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The dopamine D2 receptor mediates approach-avoidance tendencies in smokers

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Abstract

Dopamine D2 receptors (DRD2) have been strongly implicated in reward processing of natural stimuli and drugs. By using the Approach-Avoidance Task (AAT), we recently demonstrated that smokers show an increased approach bias toward smoking-related cues but not toward naturally-rewarding stimuli. Here we examined the contribution of the DRD2 Taq1B polymorphism to smokers' and non-smokers' responsivity toward smoking versus naturally-rewarding stimuli in the AAT. Smokers carrying the minor B1 allele of the DRD2 Taq1B polymorphism showed reduced approach behavior for food-related pictures compared to non-smokers with the same allele. In the group of smokers, a higher approach-bias toward smoking-related compared to food-related pictures was found in carriers of the B1 allele. This pattern was not evident in smokers homozygous for the B2 allele. Additionally, smokers with the B1 allele reported fewer attempts to quit smoking relative to smokers homozygous for the B2 allele. This is the first study demonstrating that behavioral shifts in response to smoking relative to natural rewards in smokers are mediated by the DRD2 Taq1B polymorphism. Our results indicate a reduced natural-reward brain reactivity in smokers with a genetically determined decrease in dopaminergic activity (i.e., reduction of DRD2 availability). It remains to be determined whether this pattern might be related to a different outcome after psychological cessation interventions, i.e. AAT modification paradigms, in smokers.

Keywords: nicotine, smoking, approach-avoidance, dopamine D2 receptor, DRD2 Taq1B polymorphism

1. Introduction

According to dual-process models, addictive behaviors occur as a consequence of an imbalance between a slowly operating *reflective* instance and a fast, *approach-oriented* or impulsive instance [1, 2]. The latter includes automatic approach biases toward drug-related cues which represent important triggers for both the initiation of drug intake and the "urge" to continue chronic drug use. In recent years, new paradigms have been developed for both the assessment and modification of such drug-cue induced automatic approach tendencies in the context of different addictions. The Approach-Avoidance Task (AAT) [3] has been used to measure existing approach biases in heroin [4], cannabis [5], alcohol [6] and nicotine addiction [7]. Likewise, several training versions of the AAT exist, which have been successfully employed to reduce approach biases toward addictive stimuli and to increase efficacy of conventional cessation interventions [8, 9] (for a review see: [2]).

We have recently examined approach biases for smoking-related and naturally-rewarding cues in smokers by means of the AAT [10]. We demonstrated that smoking is associated with a stronger approach bias for smoking-related pictures relative to naturally-rewarding cues, in particular pictures of highly palatable food [10]. Although imaging studies already suggested a decrease in natural reward responsivity in the course of various addictions, our findings provide the first behavioral evidence for a shift in responsivity to drug cues at the expense of naturally-rewarding stimuli in smokers [11, 12]. Research on the functional significance and the underlying neuronal mechanisms mediating this shift in reward reactivity in addiction is still limited. However, it has been proposed that adaptations in meso-corticolimbic dopamine signaling are likely to contribute to a decrease in motivational and behavioral responses to drugs and natural rewards in the course of an addiction [13-15]. For instance, a diminished activation of meso-striatal and meso-corticolimbic brain regions in response to natural reinforcers in detoxified cocaine addicts has been demonstrated [16]. Likewise, monetary rewards which activate typical dopaminergic

regions including the striatum and the prefrontal cortex in non-smokers are ineffective in activating the same reward circuits in smokers [17].

Since chronic drug use is accompanied with a progressive downregulation of dopamine D2 receptors (DRD2) in the meso-striatal brain regions [19, 20] and since DRD2 have been strongly implicated in the processing of naturally-rewarding stimuli and drugs [21], a decreased DRD2 density in addicts might account for the diminished responsivity toward natural rewards as a consequence of chronic substance use [19]. In this instance, it is well documented that polymorphisms of the DRD2 gene might represent susceptibility factors for various addictive phenotypes [21, 22]. The B1 allele of DRD2 Taq1B polymorphism in either heterozygosity or homozygosity is associated with less DRD2 density [23]. Subjects carrying the B1 allele exhibit an increased vulnerability to smoking [24, 25] and other addictive behaviors [26, 27] (for a review see: [28]) probably due to alterations in reward sensitivity [20]. With respect to processes related to smoking cessation in particular, a prominent role of the DRD2 Taq1B polymorphism has been confirmed [21, 22]. Compared to smokers homozygous for the B2 allele, smokers with the minor B1 allele show fewer attempts to quit and stronger withdrawal symptoms after quitting smoking [29, 30], and are younger at the onset of smoking [24, 25, 31] which is inversely correlated to tobacco dependence [32] and to more difficulties to quit later in life [33].

Given the important role of dopaminergic neurotransmission in reward processing of natural stimuli [16] and drugs [19] and the genetic modulation of DRD2 functionality in tobacco dependence [21, 22], we sought to determine whether the Taq1B polymorphism of the DRD2 gene affects differences in smokers' and non-smokers' approach-avoidance biases toward smoking versus natural-reward stimuli in the AAT. To this end, we reanalyzed behavioral and self-report data from our previous study examining approach-avoidance tendencies in smokers and non-smokers [10]. We expected that depending on the smoking status, carriers of the B1 allele and homozygous carriers of the B2 allele would show

differences in responsivity toward smoking-related and natural-reward stimuli in the AAT. Based on previous findings on the association between DRD2 Taq1B polymorphism and smoking behavior, a diminished approach-bias for natural rewarding cues in smokers carrying the B1 allele might be expected. Likewise, our previous finding on a stronger approach bias for smoking-related pictures relative to naturally-rewarding cues in smokers [10] should be mediated by the DRD2 Taq1B polymorphism and be more pronounced in smokers carrying the B1 allele.

2. Material and Methods

Self-report and behavioral measures obtained from participants in the Machulska et al. (2015) study were reanalyzed to examine the effect of the Taq1B polymorphism of the DRD2 gene on these measures. All subjects were genotyped at the beginning of the study. The final sample comprised 90 smokers (mean age = 26.6; 44% female; mean Fagerström Test for Nicotine Dependence Score [FTND] = 3.4), and 49 non-smokers (mean age = 23.3; 59% female). Each participant provided written informed consent for the experimental procedure and the study was approved by the local Ethics Committee of the Ruhr-Universität Bochum.

2.1 Self-report measures

Each participant completed an extensive set of questionnaires concerning her/his: (i) Current smoking status, (ii) subjective cigarette craving (ranging from 0 (“not at all”) to 5 (“very high”)), (iii) degree of nicotine dependence (FTND with a score of 0 indicating no or very weak dependence and a score of 10 indicating very high nicotine dependence [34]; German version: [35]), (iv) attitude toward smoking (items ranging from -3 and +3; [36]) and (v) smoking abstinence motivation (Stages of Change Scale [37]; German version: [38]). For full description of all questionnaires see Machulska and colleagues [10].

2.2 Automatic approach and avoidance tendencies

Automatic approach and avoidance tendencies were assessed with an adapted version of the Nicotine-Approach-Avoidance-Task (N-AAT). For a detailed task description see: [10]. Briefly, during the AAT, discrete pictures from four different categories were displayed on a computer screen: (a) smoking-related pictures, (b) shape- and color-matched pictures of tooth-cleaning, (c) pictures of highly palatable food (e.g., pizza, ice cream, etc.) and (d) shape- and color-matched neutral pictures (i.e., empty dishes). Each picture was either rotated 3° to the left or 3° to the right. Participants were instructed to pull pictures rotated to the left and to push pictures rotated to the right, as quickly and accurately as possible by using a joystick which was connected to the computer. Upon a pull movement, picture size increased, whereas upon a push movement, picture size decreased, creating a *zooming effect* [3]. Each picture from the four picture categories was presented for a total of six times (three times in pull-closer format and three times in push-away format), resulting in 192 trials.

2.3 Genotyping

All participants were informed to refrain from eating food and drinking beverages apart from water approximately. 60 minutes prior to the study. DNA samples were collected using Oragene saliva kits (DNA Genotek, Ottawa, Canada). DNA extraction and genotyping was performed using established procedures according to the manufacturer's protocol. The DRD2 Taq1B polymorphism was genotyped by LGC Genomics (Hoddesdon, UK) using KASP technology with validated arrays. Five participants (all smokers) could not be genotyped, giving a total sample of 134 participants and a genotyping success rate of 96.4%.

2.4 Data preparation and statistical analysis

The Hardy-Weinberg exact test was used [https://www.cog-genomics.org/software/stats] to analyze whether the genotype distribution is in Hardy-

Weinberg equilibrium. Chi-square tests were used for the statistical analysis of allele frequencies and the distribution of genotypes in smokers and non-smokers.

Genotype was defined using a dominant model: Homozygotes for the minor B1 allele (B1/B1) were grouped together with heterozygotes (B1/B2) and compared to homozygotes for the major B2 allele (B2/B2).

Individual AAT bias scores were calculated for each participant. First, error trials were removed and AAT-bias scores were calculated by subtracting median reaction times (RTs) for pulling a picture from median RTs for pushing a picture for each of the four picture categories, separately (*median RTpush – median RTpull*; see: [10]).

To examine whether the genotype contributed to differences in smokers' and non-smokers' AAT bias scores, a 2 (genotype: B1 allele carriers versus B2 homozygotes) x 2 (smoking status: smoker versus non-smoker) x 4 (picture category: nicotine-related versus tooth-cleaning versus food-related versus neutral pictures) mixed design ANOVA was conducted. Significant main effects and/or first-order (two-way) interactions were investigated with simple effect analyses. To investigate the second-order (three-way) interaction, two separate 2 x 4 ANOVAS were conducted with genotype removed and smoking status (smoker versus non-smoker) as the main between-subjects factor. To account for multiple testing, a more conservative level of significance was applied, using the Bonferroni correction for multiple (n) testing ($p_{corrected} = p_{uncorrected}$ x n). Separate univariate ANOVAS were used to determine genetic influences on smokers' smoking history and behavior, i.e. subjective craving, degree of nicotine dependence, motivation to quit smoking and attempts to quit smoking during the last 12 months. Again, Bonferroni correction was used to ensure that the cumulative Type I error was below $\alpha = .05$. Analyses were performed using IBM SPSS Statistics for Windows 23.

3. Results

3.1 Genotyping

Genotyping resulted in two subjects (both smokers) homozygous for the B1 allele, 39 subjects with the heterozygous B1B2 genotype (26 smokers and 13 non-smokers), and 93 subjects homozygous for the major B2 allele (57 smokers and 36 non-smokers). Allele frequencies were .15 for the B1 allele (for smokers .18, for non-smokers .13) and .84 for the B2 allele (for smokers .82, for non-smokers .87), respectively. No significant differences in allele frequencies were found between smokers and non-smokers (*ps* > .33). No significant deviations from Hardy-Weinberg equilibrium were detected ($p = 0.52$). Sample characteristics according to smoking status and genotype are summarized in Table 1.

3.2 Automatic approach and avoidance tendencies

Mean AAT reaction times per genotype and smoking status for pulling versus pushing a picture are summarized in Table 2. To test the effect of the DRD2 Taq1B polymorphism on automatic approach-avoidance tendencies assessed with the AAT, a 2 x 2 x 4 mixed design ANOVA with smoking status (smoker vs. non-smoker) and genotype (B1 allele carriers vs. B2 homozygotes) as between-subjects factors and picture category (nicotine-related vs. tooth-cleaning vs. food-related vs. neutral pictures) as within-subjects factor was conducted. As published previously [10], there was a significant main effect of picture category, $F(3, 128) = 10.54$, $p < .001$, $\eta^2 = .2.$, and a significant picture category x smoking status interaction, $F(3, 128) = 5.29$, $p = .002$, $\eta^2 = .11$. Furthermore, a significant *picture category x genotype interaction* was evident, $F(3, 128) = 5$, $p = .003$, $\eta^2 = .11$. Irrespective of smoking status, simple effect analyses indicated that B1 allele carriers showed a larger avoidance bias toward tooth-cleaning pictures ($M = -26$, $SD = 11$) as compared to nicotine-related ($M = 3$, $SD = 12$; *p*

= .05), neutral (M = 21, SD = 11; $p < .001$), and, by trend, food-related pictures (M = 1, SD = 10; p = .075). Furthermore, B2 homozygotes showed a higher approach bias toward nicotine-related pictures (M = 24, SD = 8) relative to tooth-cleaning (M = -10, SD = 7; $p < .001$) and relative to neutral pictures (M = -2, SD = 7; $p < .001$). In addition, B2 homozygotes showed a larger approach bias toward food-related pictures (M = 11, SD = 6) relative to tooth-cleaning pictures (p = .01).

Smoking status differentially affected the effect of genotype on AAT biases for the different picture categories, as the *smoking status x DRD2 genotype x picture category* interaction approached significance ($F(3, 128) = 2.63$, $p = .053$, $\eta^2 = .06$). In order to obtain an accurate picture of the three-way interaction, we conducted two 2 x 4 ANOVAS for each genotype separately and with smoking status (smoker versus non-smoker) as the between subjects factor.

For the B1 allele, Bonferroni corrected analyses revealed a main effect of picture category, $F(3, 37) = 5.84$, $p_{corrected} = .004$, $\eta^2 = .32$, qualified by a significant smoking status x picture category interaction, $F(3, 37) = 4.95$, $p_{corrected} = .01$, $\eta^2 = .29$. Specifically, on a between-group level, simple effect analyses revealed that smokers carrying the B1 allele showed less approach for food images than non-smokers carrying the B1 allele ($M_{smokers+B1}$ = -16, SD = 9, $M_{non\text{-}smokers+B1}$ = 18, SD = 13, p = .03) (see Figure 1). No other between-group differences reached significance (for smoking pictures: p = .10, for tooth-cleaning pictures: p = .08, for neutral pictures: p = .62). Furthermore, on a within-group level, genotype affected approach biases in smokers in particular, evidenced by a decreased approach bias for food images (M_{food} = -16, SD = 9) relative to nicotine-related pictures ($M_{nicotine}$ = 20, SD = 12; p = .03) and relative to neutral pictures ($M_{neutral}$ = 16, SD = 11; p = .02) in smokers carrying the B1 allele. Furthermore, non-smokers with the B1 allele expressed a stronger avoidance bias for tooth-cleaning images relative to food images ($M_{tooth\text{-}cleaning}$ = -45, SD = 18; M_{food} = 18, SD = 13, p = .005) and relative to neutral images ($M_{neutral}$ = 26, SD = 16, p = .002).

Finally, no group differences in response to the four picture categories occurred for B2 homozygotes as evidenced by a non-significant interaction between smoking status and picture category ($F(3, 89) < 1$, $p_{corrected} = .86$, $\eta^2 = .03$).

3.3 Self-report measures

The DRD2 Taq1B polymorphism had no effect on craving or nicotine addiction severity (FTDN score) in smokers (see Table 1 for statistics; all $ps_{corrected} \geq 0.20$; separate one-way ANOVAs with genotype as the between-subjects factor). However, the DRD2 Taq1B polymorphism had an influence on abstinence motivation in smokers (Stages of change scale; see Table 1): Smokers homozygous for the B2 allele indicated that they had made twice as many quit attempts in the last 12 months than smokers with the B1 allele ($M_{B2smokers} = 1.9$, $SD = 1.4$; $M_{B1smokers} = 1$, $SD = 1.3$; $F(1, 82) = 8.82$, $p_{corrected} = .02$, $\eta^2 = .1$).

4. Discussion

The present study sought to determine the role of the DRD2 Taq1B polymorphism on approach-avoidance biases toward smoking-related and natural-reward stimuli in smokers and non-smokers. To this end, we reanalyzed data from our recent study [10] to examine the contribution of the DRD2 gene on approach-avoidance tendencies in smokers and non-smokers.

While we did not find a genotype-mediated difference in approach-avoidance behavior in the entire sample, we found genotype x smoking status interactions with respect to specific approach biases towards smoking-related relative to natural-reward related stimuli. In particular, smokers carrying the B1 allele showed a reduced approach behavior for natural rewarding (food) stimuli compared to non-smokers with the same allele. The DRD2 Taq1B polymorphism, however, did not influence responsivity toward different picture categories in the AAT in non-smokers. Interestingly, in the group of smokers, a higher responsivity toward

smoking-related relative to food-related pictures in the AAT was found in carriers of the B1 allele. Such a pattern was not found in smokers homozygous for the B2 allele. This pattern of findings suggests that the B1 allele in combination with smoking behavior is associated with a decreased sensitivity to naturally-rewarding stimuli (i.e., pictures of highly palatable food). Furthermore, as an important addition to previous results [10] that indicated a shift in approach-bias toward smoking-related stimuli relative to natural-reward stimuli, we found that this shift was limited to smokers with the B1 allele. Our findings are indicative of a genetic contribution to individual variability in approach-avoidance behavior towards naturally-rewarding and smoking-related stimuli in smokers similar to previous findings in hazardous drinkers [6].

Several previous studies confirmed a close relation between polymorphisms in the DRD2 gene and tobacco addiction. In this instance, both the B1 allele of the Taq1B polymorphism of the DRD2 gene and the minor A1 allele of the adjacent ankyrin repeat and kinase domain containing 1 (ANKK1) gene are found in higher frequency among polysubstance abusers [39, 40], cocaine-dependent subjects [41, 42] and smokers relative to non-smokers [24]. A reduced density of dopamine receptors has been reported for both, the minor A1 allele of the ANKK1 gene and the minor B1 allele of the DRD2 gene [23]. Reduced DRD2 availability has been linked to the reward deficiency syndrome [43] which is characterized by an increased likelihood to develop impulsive or addictive behaviors [21], but also to more difficulties to abstain from addictive behavior. Here we add new data suggesting that differences in approach-avoidance tendencies might contribute to these previous findings regarding the relationship between DRD2 availability and nicotine addiction.

Previous imaging studies have already suggested an increased threshold for activation of reward circuits in response to monetary [17] or food reward in tobacco smokers [18]. Our results indicate that such altered responsivity to natural rewards can also be detected on the behavioral level (by means of the AAT) which, however, is related to individual differences

in DRD2 availability. A reduced sensitivity to food-related pictures was only found in smokers carrying the B1 allele which is associated with lower DRD2 availability. Similar to other drugs, chronic tobacco use leads to a dysregulation of dopaminergic neurotransmission in meso-corticolimbic areas [15]. These include increases in dopamine cellular activity after acute tobacco consumption, but also a downregulation of dopaminergic activity in response to natural reinforcers [15]. Neuroimaging studies [44] suggest that the orbitofrontal cortex is a central structure responsible for an increased salience attribution to drug cues at the expense of natural rewards in the course of addictions. Interestingly, reductions in DRD2 go along with decreased metabolism in prefrontal cortical regions [45]. Thus, in smokers a reduction in DRD2 density in combination with a decreased prefrontal activity might lead to an aberrant salience attribution toward drug cues versus food cues representing an important neuroadaptive change in the mesolimbic dopaminergic function [15]. However, our findings only partially support this conclusion since smokers with the B1 allele did not show a reduced responsivity (approach tendency) towards smoking-related cues. This might be due to the fact that we used a sample of moderate smokers with a mean FTND score of 3.4. Since the AAT is a measure of impulsive tendencies and the prefrontal cortex has been linked to impulse control [2], a disruption of prefrontal control due to reduced DRD2 availability might lead to a greater imbalance between executive and impulsive instances in heavy smokers only [1]. This, in turn could lead to a more pronounced approach-bias toward smoking cues compared to other cues. Indeed, evidence from animal and human data suggests a strong negative association between DRD2 availability and control of impulsivity [46]. Future studies combining AAT and imaging techniques [47] in heavy smokers genotyped for the Taq1B polymorphism of the DRD2 gene could be helpful to get more insight into the possible neuronal underpinnings.

A major limitation of the current study is the small sample size which might have limited the power to detect overall group differences. In particular the *smoking status x DRD2*

304 *genotype x picture category* approached borderline statistical significance (p=0.053).
305 According to discriminatory power analyses which we conducted a posteriori, power was
306 sufficient for detecting main effects and two-way interactions (1-ß > .80), however, the power
307 to detect a three-way interaction was indeed very small (1-ß = .65). Thus, the current findings
308 can be considered as promising, but tentative, and in need of replication with a larger sample.
309 Furthermore, it would be valuable to investigate the contribution of other dopaminergic
310 pathway genes on complex smoking behavior phenotypes since it is likely that a single-
311 nucleotide polymorphism has only small effects on smoking.

312 Nevertheless, our results may have implications for the development of more
313 optimized smoking cessation interventions. For instance, specific training programs based on
314 the AAT have been successfully employed to change maladaptive approach biases and to
315 enhance efficacy of psychological cessation interventions in smokers [48, 49]. However, not
316 all participants profit equally well from these interventions and a large proportion of ex-
317 smokers experience relapse phenomena after successful treatment [30] (see: [50] for a
318 review). The basic rationale of AAT modification paradigms is to incorporate nicotine-related
319 cues as a category of stimuli to be avoided while cues corresponding to natural rewards such
320 as palatable food or pictures of pleasant activities should be approached. Thus, in AAT re-
321 training studies for smokers, participants could be trained to abolish approach behavior
322 towards nicotine stimuli, but could concomitantly be provided with an alternative behavior,
323 i.e., approaching naturally-rewarding stimuli, or stimuli which are at least less toxic or
324 detrimental. Hence, from a theoretical perspective, training to approach naturally-rewarding
325 stimuli is equally important as training to avoid smoking stimuli. Understanding the
326 genetic/biological basis of these respective approach biases in smokers (vs. non-smokers) is
327 therefore of high interest. Based on the findings from the present study, it could be concluded
328 that AAT training programs which aim to increase tendencies to approach naturally-rewarding
329 stimuli (as an alternative category to smoking-related stimuli) in smokers would be less

efficient in B1 allele carriers or that a more extensive retraining protocol would be needed for those participants. However, it remains to be determined whether this would also be associated with a less efficient treatment outcome in smokers carrying the B1 allele relative to those homozygous for the B2 allele. Nevertheless, we found that smokers with the B1 allele underwent fewer attempts to quit smoking compared to smokers homozygous for the B2 allele which indeed suggests a more persistent course of smoking behavior. The latter finding corroborates existing literature showing a negative influence of the B1 allele of the Taq1B polymorphism on smoking severity and the ability to abstain from smoking [29, 30].

In conclusion, our results indicate a reduced natural-reward brain reactivity in smokers with the B1 allele of the DRD2 Taq1B polymorphism as evidenced with the AAT. Such a genetically determined decrease in dopaminergic activity (i.e., reduction of DRD2 availability) might result in a different outcome after psychological cessation interventions in smokers [48], which however needs to be explored in future research.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was approved by the local Ethics Committee of the Ruhr-Universität Bochum and was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki.

Informed consent All participants gave written informed consent prior to their inclusion in the study.

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Fig 1 Approach and avoidance tendencies for each of the genotypes: AAT-Bias Scores were calculated by subtracting median reaction times (RTs) for pulling a picture from median RTs for pushing a picture. * $p < .05$. Error bars include 95%-Confidence Intervals (CI).

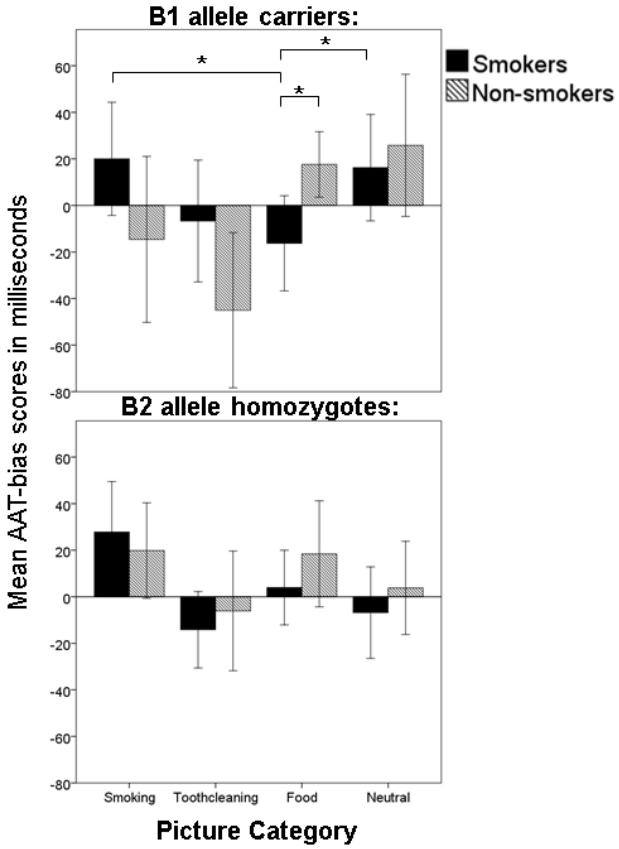

Table 1.

Mean sample characteristics and performance in the AAT separated by smoking status and DRD2 genotype.

	Smokers			Non-smokers		
	B1 allele carriers	B2 allele homozygotes	p	B1allele carriers	B2 allele homozygotes	p
N	28	57	-	13	36	-
Age	25.6 (3.3)	27.2 (7.5)	.29	24.6 (3.9)	22.9 (3.2)	.12
Gender (%female)	54	40	.25	62	58	.84
Smoking attitude	0 (.5)	-.2 (.5)	.05	-2 (.7)	-1.8 (.6)	.30
Craving	2.4 (1.3)	2.6 (1.5)	.56	0	0	-
FTND-Score	3.8 (2.5)	3.1 (2.2)	.23	-	-	-
Abstinence motivation	.7 (.9)	.9 (.8)	.36	-	-	-
Quit attempts/ last year	1 (1.3)	1.9 (1.4)	.005	-	-	-
Error rate in AAT (%)	8 (5)	8 (5)	.59	8 (3)	12 (6)	.01

Note. N = number of participants; FTND-Score = Score in Fagerström Test for Nicotine Dependence; scores in abstinence motivation vary between 0 = precontemplation/no intention to quit smoking in the following 6 months and 4 = maintenance/abstinence from smoking >6months; standard deviations are given in parentheses. Continuous variables were analyzed using univariate ANOVAs, categorical variables were analyzed using chi-square-tests. All p-values are two-tailed.

Table 2.

Mean AAT reaction times per genotype and smoking status for each picture category and response type.

	B1 allele carriers				**B2 allele homozygotes**			
	Smokers		Non-smokers		Smokers		Non-smokers	
Picture category / Response direction	pull	push	pull	push	pull	push	pull	push
Nicotine-related pictures	596 (114)	616 (114)	635 (123)	620 (118)	621 (135)	649 (124)	573 (103)	593 (85)
Tooth-cleaning pictures	607 (123)	600 (94)	646 (130)	601 (111)	638 (118)	623 (120)	585 (110)	579 (86)
Food pictures	610 (120)	594 (93)	624 (118)	642 (123)	626 (118)	630 (111)	573 (88)	592 (74)
Neutral pictures	590 (107)	606 (97)	606 (106)	632 (133)	642 (138)	635 (124)	579 (78)	582 (86)

Note. Reaction times are displayed in milliseconds. Standard deviations are given in parentheses.