Article

Association of the Serotonin Transporter Gene With Smoking Behavior

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Objective: In an ongoing molecular genetic study of temperament, participants were genotyped to examine the association of smoking with two polymorphisms of the serotonin transporter gene (SERT): the promoter region, 5-HTTLPR, and an intronic variable-number-of-tandem-repeats region (VNTR).

Method: Full information was available for 330 families, and 244 "ever smokers" were identified (54 past smokers, 190 current smokers). The average number of cigarettes smoked per day was 13.12, and the mean Fagerstrom Tolerance Questionnaire score was 4.79. Associations of genotype, Tridimensional Personality Questionnaire scores, and smoking phenotype were tested by using a robust family design with a variance-components framework and by case-control analysis.

Results: There was a significant excess of the 5-HTTLPR long allele with the 12-repeat VNTR in current smokers, past smokers, and ever smokers, compared to participants who had never smoked. The results from the population design were confirmed in the family-based analysis. No association was observed between two quantitative measures of smoking and the polymorphisms. A weak association was observed between novelty seeking and the VNTR polymorphism and between reward and 5-HTTLPR. Smokers, regardless of gender, scored significantly higher on novelty seeking and did not differ on harm avoidance or reward.

Conclusions: There was a highly significant association between SERT and the categorical definition of smoking, irrespective of dependence level, suggesting that this gene influences the initiation of smoking. Mediation analysis failed to substantiate the hypothesis that novelty seeking partially mediates the effect of SERT on smoking. SERT appears to independently contribute to novelty seeking and smoking.

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Genetic factors are important in determining the complex smoking phenotype, as shown by twin studies showing that genes partially confer susceptibility to nicotine dependence (1). As well as two genome scans (2, 3), there have been a number of tests of candidate genes (4), including the promoter region of the serotonin transporter gene (SERT) (4–9). The SERT promoter region is a 44-base-pair insertion/deletion polymorphism that was originally shown to be associated with anxiety-related personality traits (10). Indeed, an interaction of the short promoter polymorphism, anxiety-related personality traits, and smoking was observed in two studies (7, 8). Conversely, in a Japanese study it was the long promoter variant that was observed to be associated with smoking (6, 9).

We have now recruited a new group of 330 families, including 244 past and present smokers, in the framework of our continuing studies of normal personality (11), positioning us to validate previous studies showing an interaction between SERT, personality traits, and smoking behavior (7, 8). Toward this end, we genotyped this group for two SERT polymorphisms, the serotonin (5-HT) transporter linked promoter region (5-HTTLPR) and an intronic variable-number-of-tandem-repeats region (VNTR) (12). Both common repeats of the VNTR are purported to increase transcription of this gene (13). The association between smoking and SERT was analyzed both by using a case-control design and by a more robust family-based approach. Scoring allelic transmission in families (14, 15) allowed us to test association in this heterogeneous group by using both categorical and quantitative definitions of smoking.

Method

Subjects

Participants in our ongoing studies of personality (11), who are primarily but not exclusively college students at various locations in Israel and their families, are recruited by word of mouth and advertisements on campuses and at other institutions. The study group analyzed comprised 330 families, each consisting of two biological parents and two or more same-sex siblings. The subgroup of smokers in this nonclinical group was defined as participants who had smoked for at least 1 year, irrespective of level of dependence or number of cigarettes smoked. They were identified by a set of questions that subjects in the study answered, e.g., "Do you currently smoke?" and "Did you smoke in the past?"

There were 244 participants between the ages of 14 and 70 years (mean=28.91) who had ever smoked ("ever smokers"); 54 had

TABLE 1. Relation of Smoking Phenotype to Allele Frequency of Two Polymorphisms of the Serotonin Transporter Gene (SERT) in Nonclinical Subjects[a]

SERT Polymorphisms[b]	Subjects Who Never Smoked (N=486)		Current Smokers (N=190)		Past Smokers (N=54)		Total Number of Alleles
	Number of Alleles	%	Number of Alleles	%	Number of Alleles	%	
10-repeat VNTR	272	100.00	90	100.00	29	100.00	391
5-HTTLPR long allele	224	82.35	78	86.67	24	82.76	326
5-HTTLPR short allele	48	17.65	12	13.33	5	17.24	65
12-repeat VNTR	700	100.00	290	100.00	79	100.00	1,069
5-HTTLPR long allele	231	33.00	132	45.52	35	44.30	398
5-HTTLPR short allele	469	67.00	158	54.48	44	55.70	671

[a] Subjects must have smoked for at least 1 year to be considered smokers.
[b] VNTR, intronic variable-number-of-tandem-repeats region. 5-HTTLPR, serotonin transporter linked promoter region.

TABLE 2. Family-Based Test of Association Between Smoking Phenotype and Two Polymorphisms of the Serotonin Transporter Gene (SERT) in Nonclinical Subjects[a]

Group and SERT Polymorphism[b]	Results of Family-Based Test of Linkage Disequilibrium (QTDT)[c]					
	Null Model		Full Model		Chi-Square Analysis	
	df	Log Likelihood	df	Log Likelihood	χ^2 (df=1)	p
Current smokers (N=190)						
10-repeat VNTR	594	282.40	593	276.01	12.79	0.0003
12-repeat VNTR	594	282.60	593	276.44	12.33	0.0004
Ever smokers (N=244)						
10-repeat VNTR	594	352.32	593	342.59	19.45	0.00001
12-repeat VNTR	594	352.33	593	342.70	19.26	0.00001
Past smokers (N=54)						
10-repeat VNTR	594	112.96	593	110.96	4.00	0.05
12-repeat VNTR	594	113.03	593	110.93	4.19	0.05

[a] Subjects must have smoked for at least 1 year to be considered smokers.
[b] VNTR, intronic variable-number-of-tandem-repeats region.
[c] Two models were evaluated with QTDT (quantitative transmission disequilibrium tests) (14, 15). In the null model, means = mu + COVARIATE_HTTLPR + AGE + BMI + Tridimensional Personality Questionnaire novelty seeking score + B, with variances = Ve + Vg + Va. In the full model, means = mu + COVARIATE_HTTLPR + AGE + BMI + Tridimensional Personality Questionnaire novelty seeking score + B + W, with variances = Ve + Vg + Va. HTTLPR, allele for the serotonin transporter linked promoter region; BMI, body mass index; *B,* between-family component of association; *W,* within-family component of association; *e,* nonshared environment; *g,* polygenic effects (function of relatedness between family members, perhaps due to polygenes); *a,* additive genetic effects. The chi-square value for determining the overall global p value was derived by subtracting the chi-square value of the null model from the chi-square value of the full model. Alleles with rare frequencies of 0.05% or less were lumped together. The individual effects for all other alleles were estimated, producing a single, global p value. A fuller explanation of these models can be found at http://www.sph.umich.edu/csg/abecasis/ and in references 14 and 15.

smoked in the past, and 190 were current smokers. For current smokers, the average number of cigarettes smoked per day was 13.12 (SD=8.65, range=1–50), and their mean score on the Fagerstrom Tolerance Questionnaire (16) was 4.79 (SD=2.37). The body mass index of the current smokers was 22.16 (SD=2.18). Only 25% of the smokers had a Fagerstrom Tolerance Questionnaire score of 6 or above, one common measurement of nicotine dependence. Similarly, only 10% of the smokers in this study smoked more than 20 cigarettes per day, and "heavy smoking" is commonly defined as more than 30 or more than 40 cigarettes per day. The lifetime duration of smoking was 6.4 years (range=1–17 years, with a minimum of 1 year of smoking). However, only 8% of the smokers had smoked for more than 10 years, reflecting the young age of this group. Overall, the smokers in this study were not "heavy smokers," and only a minority were clearly "dependent," i.e., had a Fagerstrom Tolerance Questionnaire score of 6 or higher.

Each contact person received a number of booklets (equal to the number of participating siblings), containing the Tridimensional Personality Questionnaire (17) and other self-report questionnaires, and two sterile test tubes per family member, each containing 10 cm^3 of Aquafresh mouthwash, for DNA sampling. The booklets, completed by the siblings, and the DNA mouthwashes were returned by mail or hand delivered to an office. Only siblings completed the questionnaires. The contact person received a modest monetary incentive for the family's participation. The study was approved by the local institutional review board and by the Israeli Ministry of Health Genetics Committee.

Genotyping

DNA was obtained from all family members, including parents. DNA was extracted with the Master Pure kit (Epicentre, Madison, Wis.). The 5-HTTLPR polymorphism was characterized as previously described by our laboratory (18).

Statistical Procedures

QTDT (quantitative transmission disequilibrium tests) is used to analyze quantitative or discrete traits, either in nuclear families, with or without parental genotypes, or in extended pedigrees (14, 15). Since simple models of association do not provide valid tests of linkage disequilibrium when multiple offspring per family are considered, we used the robust variance-components procedures as detailed in the QTDT software package. Models for association, linkage, and linkage and association were employed.

Results

In the first analysis we used a population-based case-control design to examine the association between SERT polymorphisms (5-HTTLPR and intronic VNTR) and the smoking phenotype (Table 1). There was a significant excess of the 5-HTTLPR long allele with the 12-repeat VNTR (Pearson χ^2=15.57, df=2, p=0.0004) in both current and past smokers, compared to people who had never smoked

TABLE 3. Personality Traits of Smokers and Nonsmokers Among Male and Female Nonclinical Subjects[a]

Personality Trait and Smoking Phenotype	Men			Women			Difference Between Sexes		Difference Between Ever Smokers (current and past) and Never Smokers	
	N	Score on Tridimensional Personality Questionnaire Mean	SD	N	Score on Tridimensional Personality Questionnaire Mean	SD	F (df=1, 776)	p	F (df=1, 776)	p
Novelty seeking							0.63	n.s.	13.89	0.0001[b]
Never smokers	180	15.06	5.18	337	15.72	5.22				
Current smokers	84	17.70	5.80	115	17.57	5.20				
Past smokers	22	16.95	4.65	35	17.77	5.42				
Harm avoidance							6.56	0.01	0.06	n.s.
Never smokers	180	12.13	5.91	337	14.44	6.06				
Current smokers	83	12.19	6.25	115	14.18	6.05				
Past smokers	22	12.63	7.36	35	13.37	6.62				
Reward							35.00	0.0005	0.86	n.s.
Never smokers	180	12.77	3.97	337	14.56	3.65				
Current smokers	84	12.23	3.92	115	14.65	3.68				
Past smokers	22	12.72	4.18	35	15.65	2.97				
Persistence							1.00	n.s.	2.84	0.06
Never smokers	180	5.14	2.04	337	5.13	1.98				
Current smokers	84	4.80	1.97	115	4.72	2.15				
Past smokers	22	4.36	1.98	35	5.11	2.05				

[a] Subjects must have smoked for at least 1 year to be considered smokers. There was no significant sex-by-smoking interaction for any of the personality traits.
[b] Significant ($p<0.05$) after Bonferroni correction.

("never smokers"). When ever smokers (past and current) were compared to never smokers (data not shown), there was also a significant excess of the 5-HTTLPR long allele with the 12-repeat VNTR ($\chi^2=14.38$, df=1, p=0.0001), and the estimated risk of these polymorphisms occurring together in ever smokers was 1.37 (95% confidence interval, 1.17–1.61).

We also stratified the smokers by scores on the Fagerstrom Tolerance Questionnaire and by the number of cigarettes smoked per day. Within the group of current smokers, no association was observed between Fagerstrom Tolerance Questionnaire score (1–5 versus >5) and SERT (10-repeat VNTR: $\chi^2=0.61$, df=1, n.s.; 12-repeat VNTR: $\chi^2=0.05$, df=1, n.s.; with either the short or long 5-HTTLPR allele, respectively). Additionally, no association was observed between the number of cigarettes smoked per day (0–5, 6–15, >15) and SERT (10-repeat VNTR: $\chi^2=0.58$, df=2, n.s.; 12-repeat VNTR: $\chi^2=2.40$, df=2, n.s.; with either the short or long 5-HTTLPR allele, respectively).

Since population-based case-control designs are prone to errors due to population stratification, we also examined these findings using a robust family-based QTDT analysis. The results from the population design were confirmed in the family-based analysis (Table 2) for current smokers, ever smokers, and past smokers. Again, no association was observed between SERT VNTR (5-HTTLPR and age were covariates in the QTDT analysis) and the Fagerstrom Tolerance Questionnaire score ($\chi^2=0.03$, df=1, n.s.) or number of cigarettes smoked per day ($\chi^2=1.41$, df=1, n.s.). A marked difference in score on novelty seeking between smokers and nonsmokers (see next paragraph) provided the rationale for using this personality trait as a covariate in the QTDT family-based test of association. Body mass index was also introduced as a covariate, suggested by the association between smoking and eating (19). Both novelty seeking and body mass index increased the levels of significance, whereas when sex was entered as a covariate there was no change in significance levels.

Numerous reports have suggested differences in personality traits measured by self-report questionnaires between smokers and nonsmokers, and Table 3 presents a comparison of personality factors in nonsmokers, current smokers, and past smokers. Current smokers and past smokers scored significantly higher on the Tridimensional Personality Questionnaire trait of novelty seeking than did never smokers. There were no significant differences between past and current smokers. Smokers did not differ from never smokers on either the reward or harm avoidance measure. Smokers scored nonsignificantly lower on persistence. As observed previously in the Israeli population (20), the women scored higher than the men on both harm avoidance and reward, but we found no significant interaction between sex and smoking phenotype regarding the Tridimensional Personality Questionnaire temperament factors. Both male and female smokers scored higher on novelty seeking than sex-matched never smokers according to analysis of variance.

We next examined the relationships among the SERT polymorphisms, personality traits, and smoking phenotype. Although a strong association was observed between the SERT variants and the smoking phenotype (Table 1), only weak relationships were observed between the polymorphisms and personality traits according to the QTDT family-based analysis (Table 4). No association was detected in this study group between the SERT polymorphisms and harm avoidance, whereas a weak but significant association was observed between novelty seeking and the VNTR polymorphism. Additionally, a weak associ-

TABLE 4. Family-Based Test of Associations Among Smoking Phenotype, Personality Traits, and Two Polymorphisms of the Serotonin Transporter Gene (SERT) in 244 Nonclinical Subjects[a]

Tridimensional Personality Questionnaire Trait and SERT Polymorphism[b]	Results of Family-Based Test of Linkage Disequilibrium (QTDT)[c]					
	Null Model		Full Model		Chi-Square Analysis	
	df	Log Likelihood	df	Log Likelihood	χ^2 (df=1)	p
Harm avoidance						
5-HTTLPR						
Long allele	734	2385.77	733	2385.01	1.50	0.22
Short allele	734	2385.77	733	2385.31	0.91	0.34
VNTR						
10-repeat	727	2360.58	726	2360.52	0.12	0.73
12-repeat	727	2360.52	726	2360.45	0.14	0.70
Novelty seeking						
5-HTTLPR						
Long allele	608	1895.23	607	1894.69	1.09	0.29
Short allele	608	1895.15	607	1894.71	0.88	0.35
VNTR						
10-repeat	601	1869.27	600	1867.28	3.97	0.05
12-repeat	601	1869.26	600	1867.04	4.45	0.04
Reward						
5-HTTLPR						
Long allele	608	1689.56	607	1687.26	4.59	0.04
Short allele	608	1689.56	607	1687.34	4.44	0.04
VNTR						
10-repeat	601	1671.46	600	1671.45	0.01	0.92
12-repeat	601	1671.62	600	1671.62	0.00	1.00

[a] Subjects must have smoked for at least 1 year to be considered smokers. Both current and past smokers were classified as "ever smokers."
[b] VNTR, intronic variable-number-of-tandem-repeats region. 5-HTTLPR, serotonin transporter linked promoter region.
[c] Two models were evaluated with QTDT (quantitative transmission disequilibrium tests) (14, 15). In the null model, means = mu + COVARIATE_AGE + BMI + EVER SMOKER + B, with variances = Ve + Vg + Va. In the full model, means = mu + COVARIATE_AGE + BMI + EVER SMOKER + B + W, with variances = Ve + Vg + Va. BMI, body mass index; *B,* between-family component of association; *W,* within-family component of association; *e,* nonshared environment; *g,* polygenic effects (function of relatedness between family members, perhaps due to polygenes); *a,* additive genetic effects. The chi-square value for determining the overall global p value was derived by subtracting the chi-square value of the null model from the chi-square value of the full model. Alleles with rare frequencies of 0.05% or less were lumped together. The individual effects for all other alleles were estimated, producing a single, global p value. A fuller explanation of these models can be found at http://www.sph.umich.edu/csg/abecasis/ and in references 14 and 15.

ation was observed between the 5-HTTLPR polymorphism and reward. However, none of these associations between the SERT polymorphisms and the Tridimensional Personality Questionnaire personality traits was significant following Bonferroni correction.

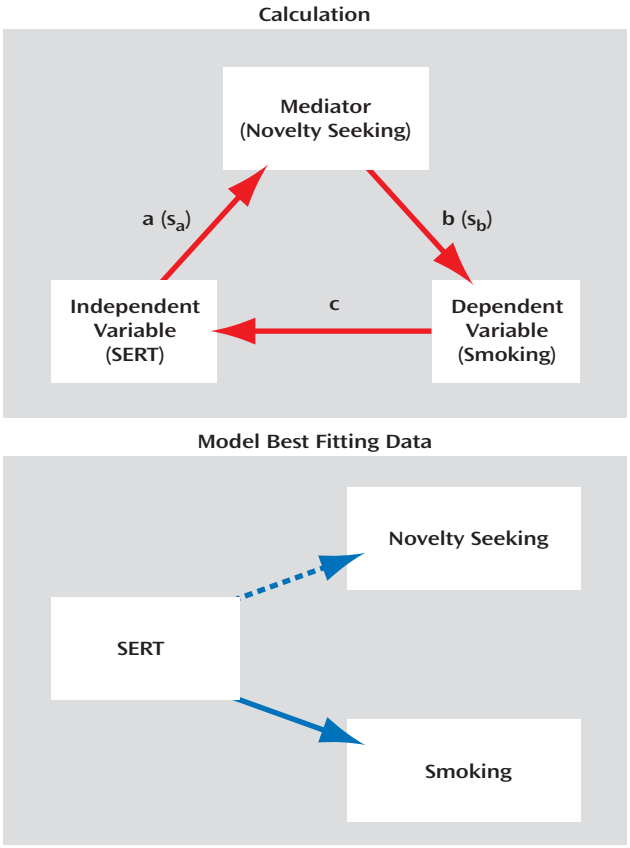
To test the hypothesis that novelty seeking mediates the effect of SERT on smoking, we used mediation analysis as described by Baron and Kenny (21) and the Sobel method (22) for significance, testing whether the mediator (novelty seeking) carries the influence of the independent variable (SERT) to smoking. The Sobel test provided no evidence for the hypothesis that novelty seeking indirectly mediates the effect of SERT on smoking (t=1.18, df=2, p=0.23). The model shown in the lower part of Figure 1 appears to best fit the data: SERT genotype independently influences smoking phenotype and, more weakly, novelty seeking.

Discussion

The main finding of the current study was a highly significant association between SERT and smoking. The long 5-HTTLPR allele with the 12-repeat VNTR conferred modest risk for smoking according to both case-control analysis and the more robust family-based design. Two previous Japanese studies (6, 9) also showed an association between the long 5-HTTLPR allele and smoking by means of a case-control design.

Many North American studies have shown that tobacco use is associated with several related personality features among adolescents and adults, including extraversion, impulsivity, risk taking, sensation seeking, monotony avoidance, novelty seeking and rebelliousness, and psychopathic and antisocial personality (23). Additionally, longitudinal studies have revealed that many of the aforementioned personality characteristics predict tobacco use (24). However, anxiety-related personality traits are also predictors of smoking behavior (25). For example, panic attacks are associated with greater risk of cigarette smoking, and neuroticism may play an essential role in this relationship (26). It appears that no single personality type generates risk for this complex phenotype, and either extraversion and neuroticism, depending on the cultural and genetic milieu, may contribute to initiation and persistence of smoking. The most notable difference between the current investigation and the American studies (5, 7, 8) is ethnicity and cultural setting, although, it should be noted, three different personality inventories were also employed, the Tridimensional Personality Questionnaire (17), Eysenck Personality Inventory (27), and NEO Personality Inventory, Revised (28). We believe it is unlikely that a difference due to the specific personality questionnaire

FIGURE 1. A Model of How Novelty Seeking Mediates the Effect of Serotonin Transporter Genotype on Smoking, Based on 244 Nonclinical Smokers[a]



[a] The independent variable is the genotype for the serotonin transporter (SERT). The mediator in this model is the score for novelty seeking on the Tridimensional Personality Questionnaire, and the dependent variable is smoking phenotype (ever smoker or never smoker). *a* is the raw (unstandardized) regression coefficient for the association between the independent variable (SERT) and mediator (novelty seeking); for these subjects, a=0.298. s_a is the standard error of *a*; in this case, s_a=0.233. *b* is the raw coefficient for the association between the mediator (novelty seeking) and the dependent variable (smoking) (when the independent variable [SERT] is also a predictor of the dependent variable [smoking]); b=0.061. s_b is the standard error of *b*; s_b=0.019. To obtain the values, 1) run a regression analysis with the independent variable predicting the mediator, which will give *a* and s_a, and 2) run a regression analysis with the independent variable and mediator predicting the dependent variable; this will give *b* and s_b. Note that s_a and s_b should never be negative. A downloadable version of the calculation for the Sobel test is available online: http://www.unc.edu/~preacher/sobel/sobel.htm.

used explains the contrasting results, since the personality traits of novelty seeking and harm avoidance and the NEO equivalents (extraversion and neuroticism) correlate well in most studies (29). It is not surprising that the particulars of the interaction between heritable personality traits, a complex behavioral phenotype such as smoking, and SERT differ across cultural and ethnic categories. It is intriguing that in two North American studies (5, 7, 8), in which smokers scored high on neuroticism, the short promoter variant showed an association with this phenotype, whereas in an Israeli population, in which smokers scored high on extraversion or sensation seeking, the long promoter variant was associated with smoking. Thus, the apparently opposing findings regarding which SERT promoter region allele is associated with smoking in two diverse cultural and ethnic groups are resolved by considering which personality trait (novelty/sensation seeking versus neuroticism) characterizes smokers. The role of the short allele in the North American study and the involvement of the long allele in the Israeli study therefore make biological and psychological sense.

The degree of nicotine dependence is unlikely to account for the particular SERT variant associated with smoking, since smoking habits vary considerably across studies without regard to genotype (5–9). The study by Lerman et al. (5, 7), which showed an association with the short SERT variant, included smokers who had smoked at least five cigarettes per day for at least 1 year and were likely interested in quitting. Hu et al. (8) recruited subjects who had smoked an average of 20 cigarettes per day for an average of 15 years, and in this group an association with the short SERT genotype was observed. The Japanese subjects consumed more than 25 cigarettes daily, and an association with the long SERT variant was observed. In the current investigation, the subjects smoked an average of 13 cigarettes daily and there were few "heavy" smokers, and again, an association with the long variant was observed.

We used a broad definition of smoking and studied a range of smoking phenotypes, raising the question of whether subjects within this heterogeneous group can be meaningfully compared. In the genetic analysis, however, the smoking phenotype was examined not only as a categorical trait but also as a quantitative trait. The powerful quantitative approach allowed us to test in the genetic model the degree of smoking dependence measured by number of cigarettes per day and score on the Fagerstrom Tolerance Questionnaire. However, neither quantitative measure showed any association with SERT. The highly significant association observed between the categorical definition of smoking and SERT, irrespective of dependence, suggests that this gene is more involved in the initiation of smoking than in its persistence or the level of dependence.

Short-term administration of nicotine releases serotonin, whereas long-term treatment depletes brain serotonin, and there is strong evidence that serotonergic tone plays a permissive role in the expression of nicotine's effects (30). Subjects with low serotonergic tone due to the presence of the long promoter variant may be particularly sensitive to the serotonin-releasing effects of short-term nicotine administration and thus at greater risk of developing dependence on cigarettes. Once initiated, smoking will further reduce serotonin levels, thus exacerbating the dependence on nicotine in subjects with a more transcriptionally efficient transporter gene.

Similar to other addictive drugs, nicotine is thought to affect the brain's dopaminergic reward system, which includes parts of the nucleus accumbens and amygdala

(31), and it is therefore of some interest that we observed in the current study a weak association between the Tridimensional Personality Questionnaire reward score, the 5-HTTLPR polymorphism, and smoking phenotype. Two previous studies (32, 33) demonstrated an association between polymorphisms affecting the 5-HT_{2C} receptor and the Tridimensional Personality Questionnaire reward score, and some animal data (34) also support involvement of the 5-HT_{2C} receptor in mediating mesolimbic dopamine functioning. Indeed, serotonergic activity has a dual effect on stimulation of the brain reward system in rats (35). Although the brain reward system is often associated with dopaminergic activity, key elements for the short-term reinforcing effects of drugs of abuse involve other neurotransmitters, such as opioid peptides, γ-aminobutyric acid, glutamate, and serotonin (36).

In the present study, only a weak association was observed between novelty seeking and SERT, principally with the intronic VNTR, and despite the evidence that impulsive behavior is a risk factor for smoking in the Israeli population we studied, mediation analysis (20, 21) carried out on the current data does not support the hypothesis that novelty seeking mediates the effect of SERT on smoking. SERT independently contributes weakly to novelty seeking and more strongly to the smoking phenotype. Further studies across cultural and ethnic groups are required to clarify the behavioral pathways that mediate the effect of SERT on smoking.

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