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ORIGINAL ARTICLE

Association of the serotonin transporter gene, neuroticism and smoking behaviours

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Abstract Cigarette consumption and smoking cessation are influenced in part by genes. Personality traits have also been implicated in the aetiology of smoking. Neuroticism, a personality trait with a heritable component, correlates well with anxiety and depression, increasing the risk of being a smoker and decreasing the chance of smoking cessation. Several prior studies in non-British populations have given conflicting results as to whether some genetic polymorphisms affect the relationship between smoking and neuroticism. This study investigated the influence of serotonin transporter (5HTTLPR) genotypes on a composite measure of neuroticism and cigarette consumption/smoking cessation in a British population. Although neuroticism was significantly associated with cigarette consumption and smoking cessation, genotype did not affect this relationship. Our results do not support initial interest in utilising 5HTTLPR genotypes in combination with neuroticism ratings for predicting outcome in smoking cessation clinical settings.

Keywords Neuroticism · Serotonin transporter gene · Smoking cessation · Cigarette consumption

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Introduction

Cigarette consumption and smoking cessation are influenced in part by genes (Carmelli et al. 1992; Heath et al. 1995). Personality traits have also been implicated in the aetiology of smoking (Patton et al. 1997).

Neuroticism, a personality trait with a heritable component (Eaves et al. 1999; Lake et al. 2000), correlates well with anxiety, depression, impulsivity and vulnerability (Eysenck and Eysenck 1975), increasing the risk of being a smoker and decreasing the chance of smoking cessation (Breslau et al. 1993b; McCrae et al. 1978). Depressive disorder, which is a clinical correlate of high neuroticism (Hirschfeld and Klerman 1979), has been associated with cigarette consumption and smoking cessation failure in several cross-sectional and longitudinal studies (Anda et al. 1990; Borrelli et al. 1996; Breslau et al. 1991, 1993a, 1998; Breslau 1995; Covey et al. 1990; Glassman et al. 1990). Initial attempts to discover the basis of this association focused on theories that smoking cessation leads to depression (Covey et al. 1990, 1997) or that depressed individuals smoked to improve mood (Breslau et al. 1993a). Kendler and et al. (1993b) brought some clarification in a study of 1,566 female twins, demonstrating that the association is most likely accounted for by common familial factors, probably genetic, that predisposed individuals to both traits.

The serotonin transporter gene (SERT), located on chromosome 17q11 + 2 (Heils et al. 1996; Lesch et al. 1994), has received attention as a candidate in influencing the relationship between smoking and neuroticism. Serotonin influences mood, and the serotonin transporter is the principal site of action of some antidepressants, particularly the selective serotonin reuptake inhibitors (Schloss and Williams 1998). Smoking initially activates nicotinic receptors, which then release serotonin from neurons (Li et al. 1998). Additionally, dopamine, a key neurotransmitter thought to be central to reward-driven addictive behaviours is influenced by serotonergic processes (Picciotto and Corrigall 2002). Both these processes are thought to mediate reward and lead to reinforcement of the addictive behaviour. A 44-base pair insertion-deletion polymorphism in the promoter region (5HTTLPR) was shown to alter transcription levels of SERT (Heils et al. 1996). The role of the mature protein is to clear serotonin from the synaptic cleft and recycle it back into the presynaptic neuron, regulating available serotonin in the brain. The deletion or short allele is responsible for reduced transcription compared to the insertion or long allele. These findings suggest that this polymorphism influences functional aspects of the mature serotonin transporter.

Previous studies have supported SERT's role in neuroticism (Greenberg et al. 2000; Katsuragi et al. 1999; Lesch et al. 1996; Murakami et al. 1999; Ricketts et al. 1998), although not all have done so (Ebstein et al. 1997; Jorm et al. 1998; Middeldorp et al. 2007; Willis-Owen et al. 2005). A recent meta-analysis by Munafo et al. (2004) found that possession of at least one copy of the short allele was associated with an increased risk of being a current smoker, suggesting that the short allele of SERT may be associated with reduced risk of successful smoking cessation. To our knowledge, no study to date has investigated the relationship between SERT variation and level of cigarette consumption.

The possibility of a joint influence of variation in SERT and neuroticism in influencing smoking behaviour was initially examined by Hu et al. (2000) and, on an independent sample, by Lerman et al. (2000). Hu et al. (2000) concluded that neuroticism was positively correlated with current smoking and negatively associated with smoking cessation in individuals and siblings with short 5HTTLPR genotypes, but not in those with long 5HTTLPR genotypes. Individuals with both a short 5HTTLPR genotype and a high level of neuroticism had the greatest difficulty in quitting smoking. Later, Brody et al. (2005) examined the influence of SERT in moderating the relationship between smoking and neuroticism, in particular attempting to replicate the findings of Hu et al. (2000) and Lerman et al. (2000). Measures of neuroticism in this study were depression proneness inventory (Alloy et al. 1987), a ten-item self-report questionnaire, and the inventory to diagnose depression-lifetime (Zimmerman and Coryell 1987). No joint influence of the short 5HTTLPR genotype and neuroticism was found in this study. Furthermore, a recent study by Kremer and colleagues (Kremer et al. 2005) found that the long 5HTTLPR allele was associated with smoking and that novelty seeking mediated the effect of SERT on smoking in those with the long 5HTTLPR allele. Four studies to date have focused on the influence of SERT variants on the relationship between neuroticism and smoking and the key features of these are outlined in Table 1.

Table 1 Studies to date examining the relationship between 5HTTLPR, smoking and neuroticism

Study	Personality measure	5HTTLPR/smoking cessation	5HTTLPR influence on relationship between smoking and personality measure
(Hu et al. 2000) (USA)	NEO-PI-R	Association of short allele (0.24, $P = 0.05$)	Neuroticism positively correlated with smoking status and negatively correlated with smoking cessation in those possessing 5-HTTLPR-S genotypes.
(Lerman et al. 1998, 2000) (USA)	EPI	Not studied	Neuroticism associated with various smoking behaviours in those possessing 5-HTTLPR-S genotypes.
(Brody et al. 2005) (USA)	DPI	No association	Relationship between depression vulnerability and smoking behaviours not influenced by 5-HTTLPR genotype.
(Kremer et al. 2005) (Israel)	Novelty/sensation seeking	Not studied	Extraversion/sensation seeking associated with smoking behaviours in those possessing 5HTTLPR-L genotypes.

5HTTLPR 44-base pair insertion/deletion polymorphism of the serotonin transporter gene, *NEO-PI-R* a 240-item self-report questionnaire measuring 5 personality domains, *DPI* depression proneness Inventory, a 10-item self-report questionnaire (Alloy et al. 1987), *EPI* Eysenck personality inventory neuroticism subscale (Eysenck and Eysenck 1975), *5HTTLPR/smoking cessation* association of the serotonin transporter linked promoter region polymorphism and smoking cessation

It has been suggested that neuroticism and personality scores in combination with the 5HTTLPR genotype might in future predict the clinical efficacy of certain smoking cessation drugs (Hu et al. 2000), thereby reducing side-effects and costs associated with poorly matched treatments. Several prior studies in non-British populations (outlined in Table 1) have given conflicting results as to whether different genetic variations affect the relationship between smoking and neuroticism. This study investigated the influence of serotonin transporter (5HTTLPR) genotypes on a composite measure of neuroticism and cigarette consumption/smoking cessation in a British population.

Aims

Our study aimed to investigate the potential of using personality traits and serotonin genotype as a combined therapeutic screening tool, ultimately within clinical smoking cessation services. To do this, we investigated two hypotheses. First, that there would be an association between 5HTTLPR genotype and cigarette consumption and/or smoking cessation. Second, that the 5HTTLPR genotype would affect the relationship between a novel composite index of neuroticism (G) and cigarette consumption and/or smoking cessation and G (Sham et al. 2000).

Materials and methods

Individuals were recruited as part of a larger project, the GENESiS study (Sham et al. 2000), which examined quantitative trait loci that contribute towards anxiety and depressive disorders. Written informed consent was obtained from all participants, and a total of 35,223 adult responses were collected for the GENESiS study. Included in the questionnaire completed by all participants was a self-report measure of smoking behaviour, completed by 99% of the respondents (34,946).

Smoking questionnaire Are you a smoker? (please mark the box relevant to you)

- No
- Ex-regular
- Social smoker
- Light smoker (10 or less a day)
- Moderate smoker (11–20 a day)
- Heavy smoker (more than 20 a day)

The genotyping sample for this study consisted of 1,158 unrelated individuals selected from the 0 to 10th percentile and the 90–100th percentile in the original GENESiS study. All study participants completed a structured questionnaire stratifying them into those reporting non-smoker status (n = 770), "ex-regular smoker"(n = 90), "social smoker" (n = 35), "light smoker" (10 or less cigarettes per day, n = 57), "moderate smoker" (11–20 cigarettes a day, n = 120), "heavy smoker" (more than 20 cigarettes a day, n = 42). For the purposes of smoking cessation studies, a "current smoker" group was formed comprising of the light, moderate and heavy smoker groups (n = 219) and compared with the "ex-regular smoker" group (n = 90). For the purposes of cigarette consumption studies, those in the current smoker group were stratified into two groups depending on the number of cigarettes smoked, coded as <10/day, "light group" (n = 92, comprising of "social" and "light" groups), > 10 cigs/day, "heavy group" (n = 162 comprising of "moderate" and "heavy" groups), based on a previous study which used a used a similar division (McKinney et al. 2000).

We used a neuroticism measure referred to as G in the Genesis project. G is comprised of a composite score of measurements collected from several well-validated and standardised instruments for the measurement of anxiety and depression related traits, other personality traits, and psychosocial adversity: The General Health Questionnaire (12-item version; GHQ12) was used as a test of general mental health symptoms (Goldberg et al. 1997). The short form of the neuroticism scale from the revised Eysenck Personality Questionnaire (EPQ-N) was used as a measure of trait anxiety (Eysenck et al. 1985). Short forms of two subscales were used from the Mood and Anxiety Symptoms Questionnaire to measure levels of anxious arousal (MASQ-AA), and high positive affect (Watson et al. 1995) (MASQ-HPA) (a detailed description is provided in the original GENESiS study; Sham et al. 2000). G was developed to represent a score that reflected the 'shared genetic liability' to depression and anxiety because there is evidence to suggest that, at a genetic and clinical level, depression and anxiety are closely related (Kendler et al. 1987, 1992; Roy et al. 1995). The maximum possible heritability estimate of the composite index in this sample was estimated at 42%, a result comparable to estimates given for neuroticism and depression (Kendler et al. 1993a; Sullivan et al. 2000).

Recessive, co-dominant and dominant models of interaction between genotype and neuroticism (Genotype × G) were applied. In the recessive model, individuals having two copies of the hypothesised risk allele (short allele, 5HTTLPR) and who were members of the high G group were coded as 1. Individuals possessing other genotypes and all those in the low G group were coded as 0. In the co-dominant model, those in the high G group possessing one short allele were coded as 1 and those in the high G group

with 2 short alleles were coded as 2. All others were coded as 0. In the dominant model, those in the high G group possessing one or two short alleles were coded as 1. All others were coded as 0.The individuals selected for this study were sent cotton buds to collect buccal cells with instructions on how to perform the collection. On receipt of the returned samples, DNA was extracted according to a well-validated technique (Freeman et al. 2003). Primer sequences for the 5*HTTLPR* genotyping have been previously described (Gelernter et al. 1997). Electrophoresis was performed on an ABI3100 (PE Biosystems) using standard manufacturer guidelines and the resulting genotypes were analysed with GENEMAPPER™ version 3.

Statistical analysis

Statistical analysis was performed using the statistical package STATA version 8. In order to test the association of *5HTTLPR* genotype and both smoking cessation and cigarette consumption, a chi-square test was performed. Mean G scores with corresponding confidence intervals were also calculated according to smoking cessation and the rate of cigarette consumption. The STATA 8 package also enabled a series of logistic regressions equations to be run with smoking cessation and cigarette consumption as dependent variables (each examined as separate variables), and with independent variables of 5-*HTTLPR*, G and the interaction term 5*HTTLPR**G. The package facilitated the reporting of odds ratios, corresponding 95% confidence intervals and *p*-values.

Power calculations

We performed power calculations for smoking cessation and cigarette consumption to estimate the relevance of *p*-values produced from this dataset. The genetic power calculator (http://statgen.iop.kcl.ac.uk/gpc/cc2.html) was utilised, in particular methodology for discrete traits in case control studies. Prevalences were assumed to be 0.29 (90/219) for smoking cessation and 0.64 (162/254) for "heavy group" smoker status (cigarette consumption). A heterozygous odds ratio of 3 and a homozygous risk of 5 assuming a risk allele frequency of 0.43 (from Lerman et al. 2000) was defined as the level of clinical relevance for major-effect genes.

Results

In total, we collected 1,158 DNA samples from unrelated individuals selected from the 0 to 10th (n = 563, 'controls') and 90–100th (n = 595, 'cases'), percentiles of a distribution of G. The female-to-male ratio is 1.7 to 1, with 378 female and 217 male cases and 353 female and 210 male controls. G ranged from 1.4 to 3.0 standard deviations from the mean in the cases and from −1.2 to −2.9 standard deviations from the mean in the controls. The median age of the sample is 45, ranging from 20 to 67. The mean G score is 0.06. The possibility of population stratification by latent class analysis using the program L-POP (Purcell 2003) in over 400 microsatellites in approximately 724 individuals has been previously assessed in this sample (Nash 2005). No evidence of stratification was found in this population. The power calculations demonstrated that the sample size needed to ascertain the significance of association of 5HTTLPR and the smoking behaviours with an alpha value of 0.05 and 80% power was 52 for smoking cessation and 15 for cigarette consumption. This power calculation confirmed that our sample size was large enough to detect association with an acceptable level of confidence.

Self-reported smoking behaviours, G scores and serotonin transporter genotypes were determined. The serotonin transporter genotype distributions were consistent with those found in previous studies of the serotonin transporter (Brody et al. 2005; Hu et al. 2000) and Hardy–Weinberg equilibrium was confirmed (Table 2).

Potential association of genotype on cigarette consumption and/or smoking cessation

We found no association between 5HTTLPR S genotypes and cigarette consumption (Table 3).

There was also no main effect of genotype on smoking cessation (current smokers vs ex-regular smokers) (Table 4)

Table 2 5HTTLPR genotype distributions

Genotype	Frequency	(%)
Long/long	299	26.84
Short/long	564	50.63
Short/short	251	22.53
Total	1,114	100

Table 3 Association of 5HTTLPR genotype and cigarette consumption

5HTTLPR genotype	Short/short	Short/long	Long/long	Total
Light	29	43	20	92
Heavy	36	83	43	162
Total	65	126	63	254
Pearson	$\chi^2 = 2.7680$	$p = 0.251$		

Table 4 Association of 5HTTLPR genotype and smoking cessation

Smoking status	Short/short	Short/long	Long/long	Total
Ex-regular	26	45	19	90
Current	57	104	58	219

Pearson $\chi^2 = 1.0168$, $p = 0.601$

Table 5 Mean G scores according to rate of cigarette consumption

Smoking category	Mean G	*n*	95% Confidence interval
≤10 cigs/day	0.27	92	(−0.098–0.645)
>10 cigs/day	1.12	162	(0.899–1.341)

Effects of G (a novel measure of neuroticism) on cigarette consumption and/or smoking cessation

The mean G score was less in the <10 cigarettes/day than the >10 cigarettes/day groups (Table 5).

We then performed a series of logistic regression equations with the dependent variable of cigarette consumption (2 groups, <10 cigarettes/day (light)/> 10 cigarettes a day (heavy). A positive association was found between G and the rate of cigarette consumption (OR = 1.37, CI = 1.174–1.621, $p < 0.001$). However, there was no observed association between the rate of cigarette consumption and the interaction term 5HTTLPR*G for the recessive, dominant (not presented) and co-dominant (presented in Table 6).

In terms of the relationship between G and cessation, there was no main effect of 5HTTLPR genotype on smoking cessation (CI = 0.72–1.41, $p = 0.98$). Mean G scores were significantly higher in those who were continuing to smoke compared to those who had ceased smoking (Table 7). We examined the effect of genotype and G on the tendency to cease smoking once becoming a regular smoker in a logistic regression model. G had a main negative effect on smoking cessation (OR = 1.40, CI 1.28–1.53, $p < 0.001$). A recessive and dominant model investigating the interaction term of neuroticism and genotype revealed no evidence of an interaction between the 5HTTLPR × neuroticism interaction term and smoking cessation (Table 8).

Discussion

In our British Caucasian sample, we found that our results concur with those of previous studies for the basic relationship between neuroticism and smoking. As our neuroticism (G) scores increased, participants were more likely to consume more cigarettes and less likely to have ceased smoking. However, we found no association of

Table 6 Logistic regression, cigarette consumption as dependent variable, independent variables, G, 5HTTLPR, interaction term 5HTTLPR × G

Order of entry of set	Predictor variable	*Z*	Odds ratio	95% CI for exp (*B*)	*p*-value
1	5-HTTLPR		1.514092	0.832–2.754	0.174
2	G	3.92	1.379634	1.174–1.621	0.000
3	5HTTLPR*G	−0.33	0.6295945	0.040–9.873	0.742

Dependent variable: cigarette consumption

Table 7 Mean G scores according to successful/unsuccessful smoking cessation

Smoking cessation	Mean G	*n*	95% Confidence interval
Unsuccessful cessation (current smoker)	0.814	219	0.614–1.014
Successful cessation (ex-regular smoker)	0.300	90	0.163–0.545

Table 8 Logistic regression, smoking cessation as dependent variable, independent variables, G, 5HTTLPR, interaction term 5HTTLPR × G

Order of entry of set	Predictor variable	*Z*	Odds ratio	95% CI for exp (*B*)	*p*-value
1	5-HTTLPR	0.649	0.880	0.508–1.520	0.508
2	G	−0.460	0.834	0.722–0.964	0.014
3	5HTTLPR*G	−0.560	0.475	0.036–6.319	0.573

Dependent variable: smoking cessation

5HTTLPR genotypes with either cigarette consumption or smoking cessation. Crucially, there were no interactive effects of 5HTTLPR genotypes and G scores influencing cigarette consumption or smoking cessation. These results fail to replicate the positive finding from Hu et al. (2000) and Lerman et al. (2000). Our findings are in accordance with those of Brody et al. (2005) where the authors found no association between 5HTTLPR genotype, neuroticism and smoking cigarette consumption/smoking cessation. In a related randomised nicotine replacement trial, Munafo et al. (2006) also failed to find an association between 5HTTLPR genotype and smoking cessation.

Our measure of neuroticism is novel, and provided a new opportunity to test important associations between 5HTTLPR genotypes, neuroticism and smoking where previously there has been little consensus. The current study population is British Cauacasian; studies to date have been based in either the US (Hu et al. 2000; Lerman et al. 2000) or Israel (Kremer et al. 2005). Kremer et al. (2005)

highlighted how genetic population differences and differences in personality factors might explain opposing results regarding which 5HTTLPR allele is associated with smoking behaviours. Hu et al. (2000) found a negative association between short 5HTTLPR genotype and smoking cessation, supporting the hypothesis that the S genotypes conferred increased risk for smoking cessation and, furthermore, there was a positive interaction with neuroticism in those individuals possessing the S genotypes. However, the Israeli study (Kremer et al. 2005) found the opposite association of the l allele with smoking status and neuroticism. The results of the Israeli group are consistent with those of two previous studies on smoking behaviour by Japanese groups, implicating the l allele in smoking behaviours.

The heterogeneity of neuroticism measures between studies may account for a lack of concensus between results. Kremer et al. (2005) drew attention to the fact that, in North American studies where individuals scored high on neuroticism measures, the 5HTTLPR short allele tended to be associated with smoking behaviours. They noted that in the only other non-US study (in Israel), the 5HTTLPR long allele was associated with smoking variables in individuals scoring high on extraversion or sensation seeking.

Our sample used G as a measure of neuroticism, a novel composite score comprising of four questionnaires. We also selected individuals from the extremes of G from an overall sample of over 35,000 individuals. This is the first study of its kind to use the combination of questionnaires (EPQ-N, GHQ-12, MASQ-AA and MASQ-HPA) to derive a gross neuroticism/anxiety score (G) and to investigate the relationship of this score to smoking phenotypes. Kremer and colleagues have argued as to why the level of dependence in different samples is unlikely to be an important confounder in population-based smoking studies. They cite the considerable variation in levels of nicotine dependence across studies without any observed connection with genotype as adequate evidence (Arinami et al. 1999; Hu et al. 2000; Ishikawa et al. 1999; Lerman et al. 1998, 2000).

We failed to find an association between cigarette consumption and the serotonin transporter gene, and found no evidence of the serotonin transporter gene influencing the relationship between smoking cessation/cigarette consumption and neuroticism as measured by G. We therefore conclude that the interaction of the 5HTTLPR genotype and neuroticism (as measured by G) does not influence cigarette consumption or smoking cessation in unrelated individuals selected from a large community sample. We also found no evidence of an association between serotonin transporter variants and cigarette consumption/smoking cessation. Consequently, our study does not support initial interest in utilising serotonin transporter genotypes in combination with neuroticism ratings for predicting outcome in the smoking cessation clinical settings.

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