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Genetic and environmental influences on the association between smoking and panic attacks in females: a population-based twin study

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ABSTRACT

Background. Clinical and epidemiological studies have reported an association between lifetime cigarette-smoking and panic attacks. Several explanations for this relationship have been proposed, mostly focusing on direct causal pathways. The objective of this study was to investigate a hypothesis of shared vulnerability by examining whether panic attacks and cigarette-smoking share genetic or environmental liability factors.

Method. Questionnaire data on 3172 female–female twins (1409 complete pairs), aged 18–31 years, from a population-based Norwegian twin registry, were used to calculate the correlation between genetic factors and the correlation between environmental factors that influence lifetime measures of panic attacks and daily smoking.

Results. The best-fitting biometrical twin model suggested that genetic factors influencing panic and smoking were uncorrelated. Shared or familial environmental factors were perfectly correlated, and accounted for 75% of the association between the phenotypes. The correlation between individual environmental factors influencing the phenotypes was 0·25 (0·07–0·44). In the full model, the genetic correlation was 0·17 (0·00–1·00), and genetic and shared environmental factors respectively accounted for 18% and 61% of the co-variance between panic and smoking.

Conclusion. The results suggest that panic attacks and lifetime smoking have few or no genetic liability factors in common. The shared environmental factors that influence the two phenotypes are identical. Liability to panic attacks in females appears to be more influenced by shared environmental factors than previously indicated by univariate studies.

INTRODUCTION

Several clinical and epidemiological studies have reported a lifetime association between cigarette-smoking and panic attacks (Amering *et al.* 1998; Breslau & Klein, 1999; Johnson *et al.* 2000; Isensee *et al.* 2003). The nature of the relationship between the two disorders is, however, not well understood. Direct causal hypotheses, i.e. panic attacks increase the risk for daily smoking, and conversely daily smoking increases the risk for panic attacks, have been proposed. Results from longitudinal studies support the second hypothesis (Breslau & Klein, 1999; Johnson *et al.* 2000; Isensee *et al.* 2003), but the existence of a second, reverse pathway of prior panic and secondary nicotine dependence can not be ruled out (Isensee *et al.* 2003). A third possibility is that both panic and smoking are influenced by a third factor that increases the

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vulnerability to both disorders. It has been shown that the association between smoking and depression arises largely from genetic factors that predispose to both conditions (Kendler *et al.* 1993). It has recently been suggested that neuroticism may reflect a shared vulnerability for the co-occurrence of smoking and panic attacks (Goodwin & Hamilton, 2002). Given that neuroticism is a heritable trait (Lake *et al.* 2000), and that smoking (Sullivan & Kendler, 1999) and panic (Hettema *et al.* 2001; Kendler *et al.* 2001) are both influenced by genetic factors, the co-occurrence of the disorders could be due to a shared genetic liability. Likewise, environmental risk factors that influence both phenotypes could contribute to the observed co-variance.

Bivariate twin studies are well suited to explore the question of shared liability (Neale & Kendler, 1995). The purpose of this study was to estimate the correlation between genetic factors and the correlation between environmental factors that influence the lifetime occurrence of panic attacks and daily smoking.

METHOD

Sample

The data reported upon here are from an ongoing longitudinal study of physical and mental health in twins from the Norwegian Twin Panel, a population-based twin registry. Procedures, including zygosity determination, have been described elsewhere (Harris *et al.* 2002). The sample in the present study is from the second wave questionnaire (1998), and includes only female–female twins because the lifetime prevalence of panic attacks in males was too low (no concordant DZ pairs). The individual response rate was 71% and the pairwise response rate was 59%. The sample included 3172 twins, 764 complete monozygotic (MZ) pairs, 645 complete dizygotic (DZ) pairs and 354 single responders. Data from the incomplete pairs were used to test possible cooperation bias (see below). Mean age of the responders was 25·37 years (S.D. = 3·70; range 18–31 years).

Measures

Two items related to the DSM-IV 'Panic Attack' were included. The wording of the first (panic probe) was: 'Have you ever suddenly felt very frightened or had a panic attack without any reason?' The second question assessed whether attacks had been accompanied by pounding heart or increased heart rate, sensations of shortness of breath or smothering, and feeling dizzy. Individuals who responded positively to both questions were defined as having 'broad panic'. Assuming that the liability to panic is normally distributed and that our two defined categories reflect different degrees of severity of the same underlying continuum of risk, we defined an ordinal variable for panic with three categories. Individuals who only endorsed the panic probe item were given a score of 1 and those who endorsed both items, a score of 2. This was done in order to increase statistical power, which represents an important limitation in twin studies (Neale *et al.* 1994). The goodness-of-fit for this multiple threshold model was tested separately for each zygosity group. No data on the age of onset of panic attacks were obtained, but participants who endorsed the smoking item indicated at what age they started smoking daily. A dichotomous variable was used for lifetime daily smoking.

Analyses

Polychoric correlations based on maximum likelihood (ML) estimation were calculated. The raw ordinal data option in the software program Mx (Neale, 1999) was used, making it possible to test the homogeneity of thresholds within twin pairs, across zygosity and between complete and incomplete pairs. Given that familial/genetic factors are of significant etiologic importance to the symptoms or disorders of interest, a significant difference in liability-thresholds between complete and incomplete pairs indicates a cooperation bias that is correlated with the target variable (Neale & Eaves, 1993). Structural equation modeling was used to estimate the relative contribution of three factors underlying the individual variation in liability. Additive genetic factors (A) contribute twice as much to the correlation in MZ as DZ twins (because MZ twins share all their genes, while DZ twins share on average half of their genes). Shared or familial environment (C) are environmental factors that make twins similar and contribute equally to the correlation between MZ and DZ twins. Individual specific environment (E) reflects experiences not shared by the twins and therefore contributes to within-pair

Table 1. *Polychoric correlations (with 95% confidence intervals) for lifetime panic and daily smoking*

Zygosity	*n*	Prevalence [% (*n*)] Panic probe	Daily smoking	Within-person correlation	Cross-twin correlation Panic	Smoking	Cross-twin, cross-trait correlation
MZ	1528	9·2 (140)	40·0 (621)	0·35 (0·25–0·44)	0·44 (0·26–0·59)	0·79 (0·73–0·84)	0·27 (0·11–0·41)
DZ	1290	10·2 (132)	43·1 (565)	0·34 (0·24–0·44)	0·28 (0·08–0·45)	0·51 (0·41–0·60)	0·25 (0·14–0·36)

MZ, monozygotic; DZ, dizygotic.

differences in liability. Univariate analyses were followed by bivariate Cholesky decompositions (Neale & Cardon, 1992), which permit the calculation of correlations between genetic factors (r_a), shared environmental factors (r_c), and individual specific environmental factors (r_e) that influence the two phenotypes. In this model, pathways are specified so that the latent genetic and environmental variables that affect the first phenotype also affect the second phenotype. Another set of latent variables is defined to be specific for the second phenotype. The calculation of genetic and environmental correlations is independent of the ordering of the phenotypes in the model. The full model, including A, C and E (ACE model) was compared to several nested submodels. ML analyses of raw ordinal data do not directly provide an overall test of goodness-of-fit, but relative fits of nested submodels against the full model can be obtained using the χ^2 test ($\Delta\chi^2_{df}$). Models with fewer parameters are preferable if they do not result in a significantly worse fit. An alternative method, which combines parsimony and explanatory power, is Akaike's Information Criterion (AIC), calculated as $\Delta\chi^2 - \Delta 2df$ (Akaike, 1987). However, AIC used alone to determine the 'best' model could yield incorrect results (Sullivan & Eaves, 2002). The tetrachoric correlations and estimates from the full ACE model will therefore also be utilized in the interpretation of our results.

RESULTS

Lifetime prevalence was 9·9% for the panic probe ($n=315$), 6·0% for broad panic ($n=189$), and 43·2% for daily smoking ($n=1397$). Lifetime prevalence for daily smoking in participants who endorsed the panic probe question was 67·6% ($n=213$) and in individuals with broad panic, 70·9% ($n=134$). Mean age of onset for smoking was 16·31 years (S.D. = 2·62).

The multiple threshold model for panic attacks fit well in both zygosity groups ($p=0·14$ and $p=0·16$), suggesting that the two definitions of panic appear to be on the same continuum of liability. There were no significant threshold differences within pairs, across zygosity or between complete and incomplete pairs (all $p>0·05$), indicating no significant cooperation bias associated with panic or smoking.

The within-person polychoric correlations between panic and smoking [0·35 (95% confidence interval (CI) 0·25–0·44 for MZ and 0·34 (95% CI 0·24–0·45) for DZ twins] indicate a significant association between the two phenotypes (Table 1).

Cross-twin correlations for both phenotypes were higher for MZ than for DZ twins suggesting genetic influence on both panic and smoking. The significant cross-twin cross-trait correlations for both MZ [0·27 (95% CI 0·11–0·41)] and DZ twins [0·25 (95% CI 0·14–0·36)] indicate that familial factors contribute to the covariation between the phenotypes. Because the difference between MZ and DZ correlations is very small, this is most likely due to shared environment rather than genetic factors. Univariate genetic analyses with a full ACE model yielded the following parameter estimates for panic: $a^2=0·33$ (95% CI 0·00–0·59), $c^2=0·11$ (95% CI 0·00–0·45), $e^2=0·56$ (95% CI 0·41–0·74); and for daily smoking: $a^2=0·56$ (95% CI 0·34–0·80), $c^2=0·23$ (95% CI 0·01–0·42), $e^2=0·21$ (95% CI 0·16–0·27). A model specifying only A and E (AE model) fitted the data best for panic [$a^2=0·46$ (95% CI 0·30–0·60), $e^2=0·56$ (95% CI 0·40–0·70)]. For smoking, however, C could not be omitted (AE model) without a significant increase in χ^2

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Table 2. *Bivariate Cholesky-model-fitting results and correlation estimates for lifetime daily smoking and panic attacks*

Model	−2LL	$\Delta\chi^2$	Δdf	*p*	AIC	r_a (CI)	r_c (CI)	r_e (CI)
1. Full ACE	6432·12	—	—	—	—	0·17 (0·00–1·00)	1·00 (0·06–1·00)	0·22 (0·00–0·44)
2. Drop common A	6432·46	0·33	1	0·56	−1·67	—	1·00 (0·61–1·00)	0·25 (0·06–0·44)
3. Drop common C	6436·28	4·16	1	0·04	2·16	0·61 (0·38–1·00)	—	0·15 (0·00–0·37)
4. Drop common E	6435·47	3·35	1	0·07	1·35	0·41 (0·00–1·00)	0·90 (0·002–1·00)	—
5. Drop specific C for panic	6432·12	0·00	1	—	−2·00	0·17 (0·00–0·97)	1·00	0·22 (0·00–0·44)
6. Drop common A + specific C for panic	**6432·46**	**0·33**	**2**	**0·85**	**−3·67**	**—**	**1·00**	**0·25 (0·07–0·44)**
7. Drop common C + specific A for panic	6445·61	13·49	2	0·001	9·49	1·00	—	0·00 (0·00–0·20)
8. Drop common C + specific C for panic	6436·28	4·16	2	0·13	0·16	0·56 (0·38–0·81)	—	0·15 (0·00–0·37)

The best-fitting model is shown in bold type.

AIC, Akaike's Information Criterion; r_a, genetic correlation; r_c, shared environmental correlation; r_e, individual environmental correlation; CI, 95% confidence interval; −2LL, −2 log-likelihood.

($\Delta\chi^2 = 4{\cdot}28$, $p = 0{\cdot}04$). Model-fitting results and correlation estimates from the Cholesky analyses (with smoking ordered first) are presented in Table 2.

The common genetic path could be dropped from the full ACE model without a significant increase in χ^2 (model 2), but a model where the common shared environmental pathway was set to zero was rejected by the χ^2 test (model 3). Dropping specific C for panic (model 5) increased fit in terms of AIC value. In a model where the specific A for panic was dropped (not shown in table), the common genetic path (and thus the genetic correlation) was estimated to be zero. A model forcing r_a to be one by dropping both A for panic and common C (model 7) was firmly rejected by the χ^2 test. A model specifying A, C and E for smoking and only A and E for panic (model 8) did not fit the data well. The best-fitting model specified no specific shared environmental influences on panic and no common genetic pathway (model 6). This suggests that the shared environmental factors that affect lifetime daily smoking are identical to those affecting lifetime panic ($r_c = 1$), and common shared environmental factors accounted for 75% of the co-variance between the two phenotypes. The genetic factors affecting smoking and panic were distinct, i.e. specific to each phenotype ($r_a = 0$) in this model. Individual specific environmental factors affecting the two phenotypes overlap to a small degree [$r_e = 0{\cdot}25$ (95% CI 0·07–0·44)]. In the full ACE model, r_a was 0·17 (95% CI 0·00–1·00), and genetic factors accounted for 18% of the co-variance between panic and smoking. Shared environment factors were perfectly correlated and accounted for 61% of the correlation between the phenotypes. Parameter estimates for smoking in the bivariate ACE model were identical to those found in the univariate analysis. For panic they were: $a^2 = 0{\cdot}24$ [common $a^2 = 0{\cdot}01$ (95% CI 0·00–0·16), specific $a^2 = 0{\cdot}23$ (95% CI 0·00–0·46)]; $c^2 = 0{\cdot}20$ [common $c^2 = 0{\cdot}20$ (95% CI 0·07–0·46), specific $c^2 = 0{\cdot}00$ (95% CI 0·00–0·34)]; and $e^2 = 0{\cdot}57$ [common $e^2 = 0{\cdot}03$ (95% CI 0·00–0·11), specific $e^2 = 0{\cdot}54$ (95% CI 0·39–0·70)]. Parameter estimates for panic in the best-fitting model were: $a^2 = 0{\cdot}15$ (95% CI 0·00–0·37), $c^2 = 0{\cdot}25$ (95% CI 0·12–0·43) and $e^2 = 0{\cdot}58$ [common $e^2 = 0{\cdot}04$ (95% CI 0·002–0·11), specific $e^2 = 0{\cdot}54$ (95% CI 0·40–0·63)].

DISCUSSION

The main findings in this study were that genetic factors that influence panic and daily smoking appear to be distinct (best-fitting model) or weakly correlated (ACE model), and that shared environmental factors influencing the two phenotypes are identical.

Our results do not support a hypothesis of substantial common genetic liability for the two phenotypes, and indicate that the relationship between smoking and panic is different from the relationship between smoking and depression, where the association between the disorders appear to result solely from genes that predispose to both conditions (Kendler *et al.* 1993). The hypothesis that neuroticism may reflect a shared vulnerability for the co-occurrence of smoking and panic (Goodwin & Hamilton, 2002) was not supported since neuroticism appears to be influenced by genetic and individual

environmental factors but not by shared environmental factors (Lake *et al*. 2000).

Shared environmental factors influencing both panic and smoking represent the main common source of liability in our study, accounting for 75% of the correlation between the phenotypes in the best-fitting model. This may seem surprising given that most previous univariate twin studies have concluded that the liability to panic is due largely to additive genetic effects and individual specific environment (Hettema *et al*. 2001; Kendler *et al*. 2001). However, results from these studies were limited by low statistical power and associated instability of parameter estimates. For example, in order to have 80% power to detect shared environmental effects of 20% for a disorder with 10% prevalence and 40% heritability, assuming a p level of 0·05, approximately 10 000 pairs would be required (Neale *et al*. 1994). A recent simulation study has also shown that in twin modeling, attempts to achieve parsimony by reducing the number of parameters often result in inaccurate representation of the trait under study. Parameter estimates based on tetrachoric correlations or estimates from the full ACE model are generally more accurate (Sullivan & Eaves, 2002). For these reasons it is possible that previous population-based twin studies have failed to detect shared environmental effects, even though a range of diagnostic approaches to panic disorder, panic-disorder-like syndromes and multiple threshold models have been applied to increase prevalence and statistical power. In the most recent twin study of panic (3194 pairs of both sexes, including 1027 female–female pairs), AE models fit the data best for all panic disorder definitions. However, in the ACE models estimates for c^2 ranged from 0·00 (95% CI 0·00–0·27) to 0·20 (95% CI 0·00–0·48) and heritability estimates from 0·18 (95% CI 0·00–0·62) to 0·34 (95% CI 0·00–0·46) (Kendler *et al*. 2001). Combining a disorder with relatively low prevalence (panic) with a disorder with high prevalence (smoking) in a bivariate analysis can increase the statistical power to detect genetic or environmental effects in the low-prevalence disorder. This applies for genetic variance if the genetic correlation (r_a) between the disorders is high, and for shared environmental effects if the shared environmental correlation (r_c) is high (M. C. Neale, personal communication, 2003). In this study, the correlation between shared environmental effects for the two phenotypes was very high ($r_c = 1$). It is therefore not unlikely that the bivariate ACE model in our study yields better parameter estimates for panic than those found in previous univariate analyses, suggesting that shared environmental factors contribute almost as much as additive genetic factors to twin resemblance for panic.

The models used in this study only explore the degree to which the two phenotypes share liability factors (phenotypic causation is not included in the models). The simplest interpretation of our results is that the same shared environmental factors directly influence both panic and smoking, thereby contributing to the correlation between the phenotypes. Although shared environmental influences have consistently been found for the initiation of tobacco use and, to a lesser extent, for nicotine dependence (Sullivan & Kendler, 1999), our knowledge about the specific environmental factors involved is limited because, as in this study, shared environment is parameterized as a latent variable that is not based on measured items. Since we have even less information on shared environmental factors associated with panic attacks, it is difficult to speculate regarding specific shared environmental factors that could contribute to both phenotypes in an additive fashion. However, aspects of religiosity (e.g. social religiosity) have been found to influence the risk for internalizing disorders, nicotine dependence and substance use disorders (Kendler *et al*. 2003), and could be one of the more important familial-environmental factors that affect the risk for both daily smoking and panic.

Although the cross-twin cross-trait correlations were significant and indicate that shared liability factors exist, this does not rule out a direct causal relationship between smoking and panic. Previous studies reveal that nicotine in low doses seems to have an anxiolytic effect whereas high doses increase anxiety, and that in chronic users tolerance is developed to nicotine's anxiolytic action, and withdrawal is associated with an anxiogenic response (Cheeta *et al*. 2001). The possibility of causal pathways in the lifetime association between the two phenotypes should be further explored with structural equation modeling and longitudinal data (Neale & Kendler, 1995).

However, the assumption of a purely additive relationship between smoking and panic could be misleading. Given that studies exploring the temporal relationship between the disorders suggest that daily smoking increases the risk for later panic (Breslau & Klein, 1999; Johnson *et al*. 2000; Isensee *et al*. 2003), it is possible that smoking increases the risk for panic attacks only in genetically sensitive individuals. This would be a gene by environment interaction (G × E) effect, and should be explored in future studies. The simplest approach would be to use smoking as a dichotomous variable, but the best alternative is to use smoking as a continuous moderator because this approach provides greater statistical power, and non-linear effects can be detected (see Purcell, 2002). Interaction between genetic and environmental effects can lead to biased estimates in standard twin models, depending on whether the environmental variables are shared (C) or non-shared (E). In short, A × C interaction acts like A, and A × E interaction acts like E (Purcell, 2002).

Limitations

Although this is the largest study of panic attacks in female–female twins that has been published to date, statistical power is a limitation (Neale *et al*. 1994). It cannot be concluded with confidence that there are no genetic influences common to panic and smoking. The cross-twin cross-trait correlations and the full ACE model indicate that a small fraction of the genes that influence daily smoking also affect the liability to panic, but that this contributes little to the co-variance of the two phenotypes.

The analyses were based upon unvalidated questionnaire data. However, the panic items used here are similar to those previously used by Kendler *et al*. (2001), and yielded similar prevalence estimates (panic probe 12·5%, broad panic 5·5%) and heritability estimates in the univariate multiple threshold model (0·32 in the ACE model). Preliminary results from a subsample of the twins in our study currently undergoing structured psychiatric interviews ($n = 2490$) support the validity of the questionnaire items for panic. The tetrachoric correlation between the panic probe question and a lifetime diagnosis of panic disorder assessed by the Composite Diagnostic Interview for DSM-IV (WHO, 1990) on average approximately 3 years after the questionnaire was 0·66. It is important, however, to underscore that the phenotype in this study is panic attacks and not panic disorder. It is not certain that these results can be extrapolated to the full syndrome.

Our heritability estimate for lifetime smoking is also in accordance with previous studies (Sullivan & Kendler, 1999). We used a measure for daily smoking that does not distinguish between regular smoking and nicotine dependence. Although non-dependent regular smoking has been found to be significantly associated with panic attacks, the association with dependent regular smoking is much stronger (Isensee *et al*. 2003). In previous twin studies, various measures of smoking behavior have been used as proxy measures of nicotine dependence, but only one study used a direct measure of nicotine dependence (Sullivan & Kendler, 1999). Whether nicotine dependence is more heritable and less dependent on shared environment than regular smoking without dependence is not known, but higher estimates for heritability and lower estimates for shared environmental effects have been found for persistent smoking compared to smoking initiation (Sullivan & Kendler, 1999). Further studies are needed to determine whether the use of strictly defined nicotine dependence as a phenotype would yield different parameter estimates in a bivariate study with panic.

The reliability of our panic and smoking measures has not been tested. In twin studies, individual specific environment also subsumes measurement error. Heritability and shared environment are therefore proportionally deflated by decreasing reliability. However, estimates of the degree to which genetic and environmental factors influence the co-variation between smoking and panic would not be affected by measurement errors unless these errors for the two phenotypes are correlated.

Age of onset for panic attacks and panic disorder vary considerably but debut is most typical between late adolescence and early adulthood. The mean age of onset is usually in the early to middle twenties (Weissman *et al*. 1997). It is therefore likely that some of the non-cases in our study will develop panic at a later point in time. Since our models are based on lifetime diagnoses, this will increase measurement error and thus inflate our estimates of individual environmental effects and decrease estimates

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of heritability and shared environmental effects. Although age of onset for smoking is lower than for panic, the parameter estimates for lifetime daily smoking would also be influenced by the reduction in reliability due to cases not appearing until a later age. It is uncertain whether the inclusion of older age groups would alter the relationship between the phenotypes. It is possible, for example, that different genetic and environmental effects might be present in different stages in life (Sullivan & Kendler, 1999). Further research is needed to investigate if our results are to be generalized to other age groups.

Our results apply only to women. Although previous studies have not been able to demonstrate gender differences in the heritability of panic (Kendler *et al*. 2001) the statistical power has not been sufficient to conclude with confidence that differences between males and females do not exist. The question of gender differences with regard to the heritability of smoking also remains unanswered (Sullivan & Kendler, 1999).

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DECLARATION OF INTEREST

None.

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