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Genetic Covariation of Neuroticism With Monoamine Oxidase Activity and Smoking

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Variation in the personality trait of neuroticism is known to be affected by genetic influences, but despite a number of association studies, the genes involved have not yet been characterized. In a recent study of platelet monoamine oxidase in 1,551 twin subjects, we found a significant association between monoamine oxidase activity and scores on the Eysenck Personality Questionnaire neuroticism scale. Further analyses presented here indicate that both neuroticism and monoamine oxidase activity are associated with variation in smoking habits, and that adjusting for the effect of smoking strengthens the association between MAO and neuroticism. Analysis of the genetic and environmental sources of covariation between neuroticism, smoking, and monoamine oxidase activity show that approximately 8% of the genetic variance in neuroticism is due to the same additive genetic effects that contribute to variation in monoamine oxidase activity, suggesting that variation in neuroticism is associated in part with aspects of serotonin metabolism. © 2001 Wiley-Liss, Inc.

KEY WORDS: neuroticism; MAO activity; cigarette consumption; smoking; twins

INTRODUCTION

Neuroticism, like other personality dimensions, is subject to both genetic and environmental influences [Pedersen et al., 1988; Rose et al., 1988; Eaves et al., 1989, 1999; Tambs et al., 1991; Allgulander et al., 1994; Macaskill et al., 1994; Viken et al., 1994; Jang et al., 1996; Lake et al., 2000]. This characteristic, and the causes of its variation between people, is of interest both in its own right as a stable aspect of personality and in its relationships with a number of neuropsychiatric conditions. The genes that influence neuroticism also affect the predisposition to disorders such as anxiety and depression [Jardine et al., 1984], which in turn have been associated with psychological distress [Hickie et al., 1999]. Some studies have indicated that phobias and panic disorder, while sharing a common genetic basis [Kendler et al., 1992, 1999], may be influenced by a genetic factor separate from that affecting anxiety and depression [Martin et al., 1988; Kendler et al., 1995]. However, evidence for genetic influences common to generalized anxiety disorder and panic disorder has since been reported [Scherrer et al., 2000].

So far, the identity of the genes that affect neuroticism and the relative contributions of each are unknown. Drugs that inhibit serotonin reuptake at synapses are widely used in the treatment of anxiety and depression, leading to some focus on genes coding for serotonin receptors, transporters, and enzymes. A report of a significant association between a polymorphism in the serotonin transporter gene and anxiety-related personality traits [Lesch et al., 1996] provoked a number of attempts to replicate this finding or extend it to other polymorphisms in this gene, with mixed results [Ball et al., 1997; Gelernter et al., 1998; Jorm et al., 1998; Mazzanti et al., 1998; Rosenthal et al., 1998; Deary et al., 1999; Flory et al., 1999; Gustavsson et al., 1999; Du et al., 2000; Greenberg et al., 2000; Sher et al., 2000]. Other polymorphisms in the catechol-O-methyl transferase and dopamine receptor D3 genes have also been examined for association with neuroticism, again with negative results [Henderson et al., 2000].

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Monoamine oxidase (MAO) plays a significant role in serotonin metabolism and modulating serotonergic transmission [Weyler et al., 1990; Chen and Shih, 1998; Lenders et al., 1998]. In humans, it is found in two isoenzyme forms that show 70% homology [Chen and Shih, 1998]: MAOA and MAOB. The structure of both is coded by genes on the X chromosome at Xp 11, although the genes that regulate MAO activity have not been determined despite a number of attempts using either linkage [Barnholtz et al., 1999; Juo et al., 1999; Saccone et al., 1999] or association [Garpenstrand et al., 1997; Damberg et al., 2000; Eriksson et al., 2000] techniques. Both MAOA and MAOB have wide tissue distribution, but only MAOB is found in blood cells (lymphocytes and platelets). Platelet MAO has been used in many studies as a surrogate for studying MAO in the living human brain, since even the recently developed positron emission tomography (PET) techniques [Bench et al., 1991; Fowler et al., 1996, 1998] are unsuited to use with large numbers of subjects. The use of platelets assumes that the enzyme activity in these cells parallels that in neural tissue. Although brain and platelet MAOB are identical [Chen et al., 1993], the evidence for brain-platelet activity correlation is lacking [Winblad et al., 1979; Young et al., 1986; Maetzu et al., 1997]. However, many studies have found associations between human platelet MAOB activity and psychiatric syndromes [Whitfield et al., 2000].

We have recently studied the relationships between platelet MAO activity and a range of psychiatric conditions, including alcohol dependence, conduct disorder, depression, panic disorder, social phobia, and suicidality [Whitfield et al., 2000]. These relationships were strongly influenced by smoking habits, as previously noted in a study of alcoholic probands and their relatives [Anthenelli et al., 1998], with apparent associations becoming nonsignificant after allowing for the decrease in MAO activity brought about by smoking. However, a positive association between neuroticism, as measured by the Eysenck Personality Questionnaire (EPQ [Eysenck and Eysenck, 1975]), and platelet MAO was strengthened when information on smoking habits was taken into account. In this article, we present further analyses of the association between platelet MAO activity and neuroticism and their interactions with smoking and present models of the genetic and environmental contributions to these relationships.

MATERIALS AND METHODS

Subjects

Participants in this study were recruited through the Australian NHMRC Twin Registry for questionnaire- and interview-based studies on alcohol use, alcohol dependence, and comorbid psychiatric conditions. Characteristics of the sample have been described elsewhere [Heath et al., 1997; Whitfield et al., 2000]. Subjects were originally contacted via a self-report Health and Lifestyle Questionnaire mailed in 1980–1982 to all twin pairs over 18 years of age who were registered with the Australian Twin Registry (5,867 pairs). This questionnaire contained the full 90-item Eysenck Personality Questionnaire (EPQ [Eysenck and Eysenck, 1975]), including a 23-item neuroticism scale (hereafter N81). Responses were obtained from 3,808 complete twin pairs and 576 singles.

A follow-up questionnaire was mailed to the individuals who participated in the original survey (and their cotwins for incomplete twin pairs) during 1988–1990, with responses received from 3,051 complete pairs and 468 singles. This second questionnaire included the short form of the revised EPQ [Eysenck et al., 1985, with a 12-item neuroticism scale (hereafter N89), along with measures of smoking status (never smoked, ex-smoker, or current smoker) and average daily cigarette consumption (never smoked, 1–4 cigarettes, 5–10 cigarettes, 11–20 cigarettes, 21–40 cigarettes, more than 40 cigarettes). Long-term stability of smoking habits in these subjects was established through comparisons across occasions and between members of a twin pair [Whitfield et al., 2000].

From 1993 to 1995, a telephone-based semistructured interview designed to assess the physical, psychological, and social manifestations of alcoholism and related disorders (SSAGA-OZ) was administered to a subset of these twins (2,456 twin pairs and 771 individuals). Platelet MAO activity was measured via blood samples collected subsequent to this interview from 1,551 of these subjects (861 women and 690 men). Subjects meeting DSM-IV criteria for alcohol dependence are deliberately overrepresented in this subgroup due to the need to study adequate number of alcoholics. Procedures for blood collection, preparation of the platelet fraction, and measurement of MAO activity are described elsewhere [Whitfield et al., 2000].

Statistical Methods

Correlations between continuous variables and MAO activity were estimated using SAS 6.11 (SAS, Cary, NC). Due to the twin composition of the data set, observations on different individuals are not independent for variables that are subject to genetic or shared environmental influences, leading to nonconservative *P* values. In order to take this into account, 95% confidence intervals for phenotypic correlations (Table I) were calculated using bootstrapping techniques with 3,000 iterations per analysis and using the twin pair as the resampling unit [Efron and Tibshirani, 1986]. Mean differences between groups were modeled using Mx [Neale, 1999].

Structural equation modeling may be used to determine which combination of additive genetic effects A, nonadditive genetic effects D, shared environment C, and nonshared environment E provides the simplest explanation for the observed data, with the limitation that shared environmental and nonadditive genetic effects are generally confounded in a study of twins reared together. The most parsimonious model is determined by comparing the relative goodness-of-fit of models as assessed by the likelihood-ratio chi-square [Neale and Cardon, 1992]. Extension to multivariate

TABLE I. Correlations Between MAO Activity in Platelets Collected 1993–1996 and EPQ-N Scores Assessed in 1981 and 1989, and 95% Confidence Intervals for Correlation Derived by Bootstrap Technique*

	Not adjusted for smoking	Adjusted for smoking
	r (95% CI)	r (95% CI)
EPQ-N scale (23 items) 1981	0.092 (0.039–0.144)	0.111 (0.058–0.163)
EPQ-R-N scale (12 items) 1989	0.044 (−0.010–0.098)	0.061 (0.005–0.115)

*All analyses include age and sex regression terms. Bootstrapping was used to correct standard errors and P values for the nonindependence of observations on twin pairs. n = 1,551.

analysis allows the determination not only of the sources of covariation but also the pattern or structure in which these differentially influence the covarying measures. The structural equation model investigated was a Cholesky decomposition of the variance/covariance matrix into additive genetic, nonadditive genetic environment, and unique environment effects. This full model was then simplified by successive dropping of nonsignificant parameters, determined by a nonsignificant increase in the likelihood-ratio chi-square.

Maximum likelihood analysis methods for ordinal raw data were used to implement the structural equation modeling in Mx [Neale, 1999] in order to avoid loss of data due to listwise deletion. This allowed us to include neuroticism and smoking behavior data on the full initial twin sample, not just those individuals for whom platelet MAO activity was measured. No difference in the mean or variance of the 1980–1982 neuroticism scores was observed between those who later participated in the 1989 study (providing information on smoking status) and those who did not for either men ($t = 1.45$, $P = 0.146$) or women ($t = 0.08$, $P = 0.936$). Similarly, no difference in neuroticism scores was observed between those for whom MAO activity was subsequently measured in 1993–1995 and those who did not participate in that part of the longitudinal study ($t = 0.42$, $P = 0.673$ for men; $t = 1.76$, $P = 0.079$ for women). Smoking status (measured in 1989) was also found to be unrelated to subsequent participation in the MAO activity phase of the study, despite overrepresentation of alcohol-dependent subjects in the subsample ($\chi^2_4 = 0.52$, $P = 0.972$ in men; $\chi^2_4 = 1.41$, $P = 0.842$ in women). Although alcohol dependence is more common in the subsample of subjects for whom MAO activity was measured than in the population, it has been demonstrated that the correlation between MAO activity and alcohol dependence becomes statistically nonsignificant once smoking status is accounted for [Whitfield et al., 2000]. Since the subsample for whom MAO activity was measured does not differ significantly from the overall sample in terms of smoking behavior, the distribution of MAO activity in the subsample is not expected to be affected significantly by ascertainment bias.

Average cigarette consumption was recorded in the questionnaire as an ordinal variable (0 cigarettes, never smoker or ex-smoker/1–4 per day/5–10 per day/11–20 per day/21–40 per day/more than 40 per day). However, the last two categories were combined in this analysis (to more than 20 per day) due to low prevalence of the highest category. The other two variables of interest (monoamine oxidase activity and neuroticism score) were converted to ordinal variables to facilitate multivariate analysis. This transformation is based on the assumption that underlying each variable is a continuum of liability that is normally distributed in the population, and on which thresholds delimiting the various categories are placed. Conversion of continuous variables (measures of neuroticism and MAO activity) to ordinal measures with five or more categories involves minimal loss of information while overcoming any distributional problems and greatly simplifying analysis of covariation with variables that are necessarily ordinal (smoking behavior). Neuroticism (N81) was converted into six categories according to total scale score (0–3/4–7/8–11/12–15/16–19/20–23), while quintiles were used to categorize MAO activity. A comparison of univariate structural equation modeling results for continuous and transformed ordinal measures of neuroticism and MAO activity is shown in Table II.

RESULTS

Phenotypic Associations

The age- and sex-adjusted correlations between MAO activity and neuroticism are given in Table I for both the full EPQ from the 1980–1982 twin survey (N81)

TABLE II. Maximum Likelihood Estimates of Sources of Variation in MAO, Neuroticism, and Cigarette Consumption With 95% Confidence Intervals*

	Measure	A	D	E
MAO (1993–1996)	Continuous	0.38 (0.29–0.47)		0.62 (0.53–0.71)
	Ordinal	0.44 (0.34–0.53)		0.56 (0.47–0.66)
EPQ-N Score (1980–1982)	Continuous	0.19 (0.01–0.36)	0.30 (0.12–0.48)	0.52 (0.48–0.55)
	Ordinal	0.24 (0.06–0.43)	0.25 (0.05–0.44)	0.51 (0.48–0.55)
Cigarette consumption (1988–1990)	Ordinal	0.71 (0.65–0.75)		0.29 (0.25–0.35)

*A, D, and E represent variations due to additive genetic effects, nonadditive genetic effects, and nonshared environmental effects, respectively.

and the revised short form of the EPQ from the 1988–1990 twin survey (N89). Adjustment for the effects of smoking on MAO activity led to significant positive associations with neuroticism at both time points. The observed correlation was stronger with the neuroticism scale scores from the full EPQ (1980–1982 survey; N81) as a result of the severe floor and ceiling effect in the distribution of the shorter N89 scale. As a result, the full EPQ neuroticism measure (N81) was used in further analyses.

Figure 1 shows the mean EPQ neuroticism score (1980–1982) by smoking status (from the 1988–1990 questionnaire) and sex. Comparison of the various groups of individuals (those who have never smoked, ex-smokers, and current smokers using 1–10 cigarettes per day, 11–20 cigarettes per day, or more than 20 cigarettes per day) reveals higher mean EPQ neuroticism scores for ex-smokers than those who have never smoked ($P = 0.025$) and even more significant mean differences between current smokers and those who have never smoked ($P < 0.001$ for all groups of current smokers for both men and women).

Figure 2 shows monoamine oxidase activity by quartiles of EPQ-N, after adjusting for the effects of smoking category, age, and sex. No difference was observed between MAO activity in the lowest two quartiles of neuroticism scores, and a nonsignificant increase in mean MAO activity was observed for those in the third quartile for EPQ-N scores. It appears that the main contribution to the significant overall correlation between neuroticism and MAO activity arises from the contrast between the subjects in the highest quartile of EPQ-N scores and those with scores below the median. However, in many studies, this positive association between neuroticism score and monoamine oxidase activity is confounded by smoking, since smoking is more common in subjects with higher neuroticism scores and also acts to decrease MAO values.

Univariate Analysis

Results of univariate structural equation modeling of ordinal measures of monoamine oxidase activity, neuroticism, and cigarette consumption are shown in Table II, along with corresponding analyses of the original continuous measures of MAO activity and neuroticism for comparison. Additive genetic variation was significant for all three variables, and nonadditive genetic effects were found to influence the EPQ-N scores. There was no evidence of significant shared environmental effects or of differences between sexes in the proportions of variance attributable to genetic and environmental influences.

Multivariate Analysis

Figure 3 illustrates the results of multivariate analysis of the cigarette consumption, MAO, and neuroticism data. The order of variables in the Cholesky decomposition has been determined by our primary interest in the influence of MAO activity on neuroticism score after controlling for the effects of smoking. Additive genetic influences on cigarette consumption (70% of variance) also have small but significant effects on monoamine oxidase activity and neuroticism score (3% and 2% of variance, respectively). After these effects are controlled for, approximately 8% of the variance in neuroticism score is due to the same additive genetic influences as MAO activity. Environmental influences on cigarette consumption

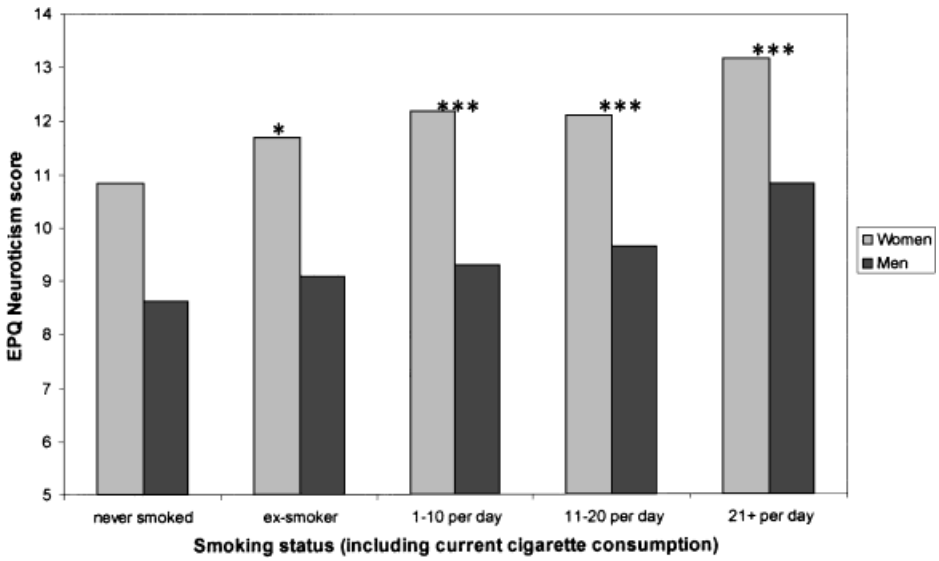

Fig. 1. EPQ-N by smoking status and sex. Groups of smoking status were: never smoked, ex-smoker, and current smoker using 1–10 cigarettes per day, 11–20 cigarettes per day, and more than 20 cigarettes per day. Statistical significance of difference from the never-smoked group indicated by asterisks: Single asterisk: $P < 0.05$; triple asterisk: $P < 0.001$. Neuroticism scores are from the 1980–1982 questionnaire (N81), while smoking status data are from the 1988–1990 questionnaire.

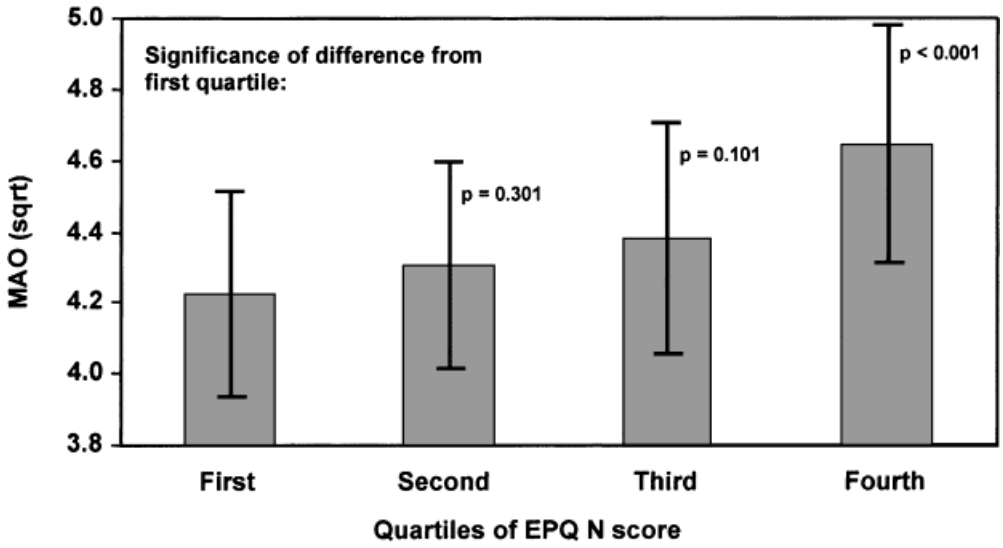

Fig. 2. MAO activity (square-root transformed) by quartiles of EPQ-N after adjusting for the effects of smoking category, age, and sex. Error bars show 95% confidence intervals for mean MAO activity for individual quartiles.

also affect MAO activity (9% of variance) but not neuroticism score.

DISCUSSION

Despite the interval of some years between the measurements of neuroticism (1980–1982 and 1988–1990), smoking behavior (1988–1990), and monoamine oxidase activity (1993–1996), the correlations between the various measures are still substantial. Monoamine oxidase activity measured in blood samples collected between 1993 and 1996 was found to be significantly associated with both the full EPQ neuroticism scale scores from 1980–1982 (10–16 years previously) and the revised short EPQ neuroticism scale scores from 1988–1990 (2–8 years previously). This association was stronger in the 1980–1982 data, when the full neuroticism scale from the EPQ was used, but both associations were strengthened after allowance for cigarette consumption. This is in contrast to the associations between MAO activity and a range of psychiatric disorders, which have been shown to become nonsignificant once smoking behavior is taken into account [Anthenelli et al., 1998; Whitfield et al., 2000].

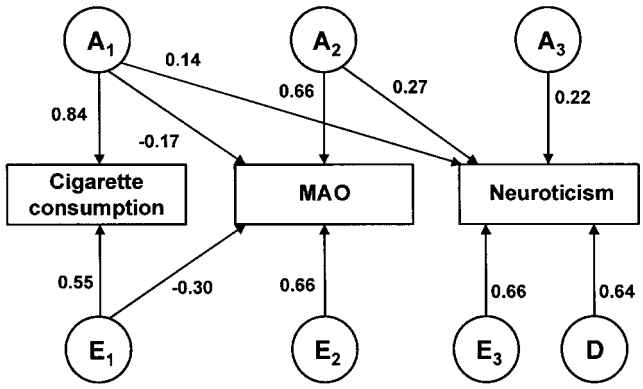

Fig. 3. Path diagram of reduced Cholesky decomposition model showing latent genetic and environmental influences (shown in circles) on the measured phenotypes of cigarette smoking, MAO, and neuroticism (shown in squares). A1, A2, and A3 are additive genetic sources of variation, while E1, E2, and E3 are nonshared environmental sources and D represents nonadditive genetic effects influencing only EPQ-N score. Numbers by paths are path coefficients and must be squared to obtain proportions of variance of the measured variable accounted for by the latent variable. Proportion of variance in neuroticism explained by genes influencing MAO (A_2) after adjustment for smoking (A_1) is $0.27^2 \sim 8\%$.

Previous research has indicated a negative correlation between monoamine oxidase activity and smoking behavior [Ward et al., 1987; Sher et al., 1994; Fowler et al., 1996; Norman et al., 1987]. However, it can now be seen from Figure 3 that this effect has both a genetic and an environmental etiology: additive genetic and environmental influences acting to increase cigarette consumption appear to decrease MAO activity. In contrast, only genetic (not environmental) effects contribute to the positive association between cigarette consumption and higher neuroticism scores.

After the effect of smoking behavior is accounted for, genes influencing MAO activity also contribute just under 8% of the variance in neuroticism. Since the broad heritability (A + D) of neuroticism (N81) in our sample is 56%, approximately 13% of the genetic variation in EPQ-N is due to genes that also act on MAO, independent of smoking behavior. In the context of genetic effects on personality, these results indicate that genes that affect MAO are candidate genes for neuroticism and possibly for the psychiatric conditions related to this personality trait. Although the identity of the genes that affect platelet MAO activity is still uncertain, our result reinforces the view that variation in serotonin metabolism and in serotonergic neurotransmission is likely to be involved in the genetics of neuroticism.

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