

Monoamine oxidase: associations with alcohol dependence, smoking and other measures of psychopathology

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ABSTRACT

Background. Many reports have appeared on associations between platelet monoamine oxidase (MAO) activity and susceptibility to psychiatric conditions; principally alcohol dependence but also conduct disorder, other drug use and depression. Recently, it has become apparent that MAO activity is inhibited by some component of cigarette smoke, and smokers have low platelet MAO activity. Since the prevalence of smoking is higher in many of the conditions in which MAO has been implicated, the MAO susceptibility associations may be partly, or entirely, false.

Methods. We have measured platelet MAO in 1551 subjects, recruited from the Australian NHMRC Twin Registry, who have provided information on alcohol use and dependence, smoking, conduct disorder, depression, attempted suicide, panic disorder and social phobia.

Results. Current smoking reduced platelet MAO activity in a significant and dose-related manner, with no evidence of lower MAO in ex-smokers or in non-smoking subjects with co-twins who smoked. Alcohol use and lifetime DSM-III-R alcohol dependence history were not associated with MAO activity when smoking was taken into account. Depression, panic disorder and social phobia showed no significant associations with platelet MAO activity. Subjects with a history of serious attempts at suicide had low platelet MAO activity; but although the difference from controls was as great as the reduction associated with smoking it was not significant after correction for smoking effects.

Conclusions. Although synaptic MAO activity undoubtedly plays a role in psychopathology, the concept that platelet MAO activity is a direct genetic marker of vulnerability to alcohol dependence cannot be sustained.

INTRODUCTION

Monoamine oxidase (Enzyme Commission 1.4.3.4 (MAO) is central to a number of neurotransmitter functions and psychiatric disorders; it plays a significant role in serotonin metabolism and in modulating serotonergic transmission (Weyler *et al.* 1990; Chen & Shih, 1998; Lenders *et al.* 1998). Hypotheses have

been put forward associating variation in MAO activity with susceptibility to numerous types of psychopathology.

MAO in humans is found in two isoenzyme forms; MAO A and MAO B. Both are coded by genes on the X chromosome at Xp 11, and show 70% homology (Chen & Shih, 1998). Studies *in vivo*, with patients lacking MAO A or B or both, have shown that absence of MAO A leads to greater change in neurotransmitter metabolism than absence of MAO B (Lenders *et al.* 1996). Both isoenzymes have wide tissue distribution,

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but only MAO B is found in blood cells (lymphocytes and platelets). Because it has been impossible in the past to study MAO in living human brain, many studies have used platelet MAO as a surrogate. Recently, positron emission tomography (PET) methods have been developed for estimating MAO activity *in vivo* (Bench *et al.* 1991; Fowler *et al.* 1996, 1998). Because these techniques are not suited to large numbers of subjects, most studies on associations between MAO activity and psychopathology or personality still involve the measurement of platelet enzyme activity.

The use of platelets assumes that the enzyme activity in these cells parallels that in neural tissue. Although brain and platelet MAO B 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). Nevertheless, many studies have found associations between human platelet MAO B activity and psychiatric syndromes.

Monoamine oxidase activity and alcohol dependence

There have been multiple reports that platelet MAO activity is decreased in alcohol dependent subjects compared with controls, and this has the characteristics of a 'trait marker' in that it persists through periods of abstinence from alcohol (Major & Murphy, 1978; Sullivan *et al.* 1978). In some reports (Major & Murphy, 1978; Sullivan *et al.* 1979; Alexopoulos *et al.* 1983), platelet MAO activity was found to be lower in alcohol dependent subjects with affected relatives. This has reinforced the concept that MAO is a marker of genetic susceptibility. When alcoholics are classified by Cloninger's typology (Cloninger *et al.* 1981; Cloninger, 1987), low MAO is claimed to be a feature of the early-onset, 'male' Type 2 alcoholism (Hallman *et al.* 1990; Sullivan *et al.* 1990; Von Knorring *et al.* 1991; Sherif *et al.* 1992; Devor *et al.* 1994; Von Knorring & Oreland, 1996; Virkkunen & Linnoila, 1997), although low activity has also been reported in female alcoholics (Yates *et al.* 1990; Hallman *et al.* 1991).

Features of Type 2 alcoholism include early onset, poor impulse control and social problems such as violence while intoxicated (Devor *et al.* 1994; Von Knorring & Oreland, 1996). A role for MAO A in inhibition of violent behaviour is

likely because a rare deletion of part of that gene in several male members of a Dutch family was linked with sporadic violence (Brunner *et al.* 1993). However, subjects with deletion of part of the MAO B gene, which results in absence of MAO B activity, do not show mental or behavioural abnormality (Lenders *et al.* 1996).

Monoamine oxidase activity, psychiatric disorders and personality

Low MAO activity has been implicated in violent criminality (Belfrage *et al.* 1992; Alm *et al.* 1994; Af Klinteberg, 1996) and suicide (Reichborn Kjennerud *et al.* 1996; Verkes *et al.* 1997, 1998). As well as evidence for low platelet MAO activity being associated with violence, homicide and suicide, the pattern of monoamine metabolites is suggestive of reduced *in vivo* MAO activity in such people; cerebrospinal fluid (CSF) 5-hydroxyindole acetic acid (5-HIAA) is lower than normal (Lester, 1995; Åsberg, 1997; Mann & Malone, 1997) and this suggests impaired central nervous system serotonin metabolism.

Involvement of MAO in mood is shown by the effectiveness of MAO inhibitors and selective serotonin reuptake inhibitors in treatment of depression (Potter *et al.* 1991; Kilts, 1994). These drugs increase the concentration of serotonin in the synapse and a similar effect might occur in people who have naturally low MAO activity; therefore subjects with high MAO activity might be predisposed to depression or to subtypes of depression. There is some experimental support for this concept but other studies have found lower MAO activity in depressed subjects than controls, and no clear pattern has emerged (Samson *et al.* 1985; Georgotas *et al.* 1986; Poirier *et al.* 1987; Haier *et al.* 1988; Meltzer *et al.* 1988; Pandey *et al.* 1992; Wahlund *et al.* 1995*a, b*; Reichborn Kjennerud *et al.* 1996).

Studies on MAO and personality have found that people with low MAO activity are more likely to undertake high-risk pastimes and to score highly for risk-taking, sensation-seeking or novelty-seeking in personality questionnaires (Shekim *et al.* 1989; Reist *et al.* 1990; Af Klinteberg *et al.* 1990; Smith, 1994; Howard *et al.* 1996).

In summary, two hypotheses have emerged; one that low activity is related to alcohol dependence, particularly Type 2 (reviewed by

Von Knorring & Oreland, 1996), and the other that it defines a more general risk for psychiatric vulnerability (proposed by Buchsbaum *et al.* 1976). However, recent evidence from both PET brain scans and *in vitro* assay of platelet MAO activity suggests that smoking is central to the question of MAO activity and its role in psychopathology, particularly alcohol dependence.

Monoamine oxidase activity and smoking

There is evidence that smoking inhibits MAO activity *in vivo* (Fowler *et al.* 1996) and *in vitro* (Yu & Boulton, 1987), and that smokers have lower MAO activity than non-smokers (Norman *et al.* 1987; Ward *et al.* 1987; Sher *et al.* 1994). The association of low MAO with alcohol dependence may, therefore, arise because smoking and alcohol dependence are strongly associated with each other (Anthenelli *et al.* 1998). On this view, the 'trait marker' character of platelet MAO activity occurs because abstinent alcoholics persist with their smoking. Other associations of MAO with psychopathology or personality characteristics may also be due to smoking.

However, several issues remain. Tobacco may act as a 'gateway drug' to other drug use, because smoking inhibits MAO and this could make other drug use more likely (Glassman & Koob, 1996). If so, the substantial natural variation in MAO between people should also be reflected in their tobacco, alcohol or other drug use. Moreover, initiation of smoking followed by lowered MAO activity could lead to perpetuation of smoking and be a mechanism of tobacco addiction. Many psychiatric patients 'self-medicate' by smoking (Berlin *et al.* 1995). Possibly they adjust the smoking dose to bring their MAO activity into some desirable range, but whether this is so and what this range might be are unclear. If smoking inhibits MAO, then the degree of inhibition should depend on the number of cigarettes used. The dose-response relationship has not yet been established.

Genetic and environmental variation in monoamine oxidase activity

The sources of variation in platelet MAO activity have been studied in several twin or family studies (e.g. Rice *et al.* 1984; Devor *et al.* 1993; Pedersen *et al.* 1993). However, none has

integrated genetic and environmental contributions to MAO activity with smoking or psychopathology measures. Smoking is itself strongly influenced by genetic factors (Heath & Madden, 1995) that may contribute to genetic variation in MAO activity. As well as estimating genetic and environmental effects, twin studies can discriminate between trait and state effects on biological markers, by studying unaffected co-twins of affected subjects (particularly monozygotic (MZ) co-twins, who are at the same genetic risk as their affected twin).

We have measured platelet MAO activity in samples from 1551 adults from a community-based volunteer twin registry, who have provided detailed information on alcohol use and alcohol-related problems, smoking, and psychiatric disorders. They have also completed the Tri-dimensional Personality Questionnaire (TPQ), which assesses Novelty Seeking, Harm Avoidance and Reward Dependence.

This paper explores the relationships between variation in platelet MAO activity, smoking, and self-reports of alcohol dependence, depression, suicide attempts, panic disorder, social phobia and conduct disorder. In the case of alcohol dependence, we have tested whether low MAO activity is associated with early onset, or persistent alcohol-related problems or with family history of alcohol dependence.

METHOD

Subjects

The subjects were recruited through the Australian NHMRC Twin Registry for studies on alcohol use, alcohol dependence, and co-morbid psychiatric conditions. Inclusion criteria for this study were completion of a questionnaire in 1989, a telephone interview in 1993–4, and providing a blood sample in 1993–6. All subjects were twins, but in many cases only one member of a twin pair provided blood. Subjects who provided blood for platelet MAO determination attended blood collection sessions in Adelaide, Brisbane, Melbourne or Sydney. They gave informed consent to the questionnaires, interview and blood collection and the studies were approved by appropriate Ethics Committees.

The demographic, social, educational, psychological and alcohol-related characteristics of these twins have been described in previous

Table 1. Associations with smoking: odds ratio (OR) between never and current smokers for various conditions, with 95% confidence intervals. Smoking was associated with a significantly higher risk of conduct disorder, depression and alcohol dependence in both men and women. It was also associated with (generally non-significantly) higher risk for the other conditions

Condition	Female		Male	
	OR	95% CI	OR	95% CI
Conduct disorder	5.84	1.75–19.5	2.51	1.45–4.35
Depression (DSM-IV)	1.72	1.11–2.68	1.82	1.05–3.16
Alcohol dependence (DSM-III-R)	9.02	4.88–16.67	3.33	2.13–5.22
Serious suicide attempt	1.29	0.35–4.74	6.18	0.87–69.2
Social phobia	2.94	1.02–8.42	2.43	0.88–6.69
Panic disorder	1.53	0.59–3.97	2.20	0.68–7.09

papers, which reported on genetic influences and specific risk factors for the psychiatric conditions considered below (Heath & Martin, 1994; Heath *et al.* 1994, 1995, 1997; Baker *et al.* 1996; Madden *et al.* 1996; Posner *et al.* 1996; Slutske *et al.* 1996, 1997, 1998; Statham *et al.* 1998). Selection for platelet MAO activity determination was non-random. Because of the need to study adequate numbers of alcoholics, they are over-represented in this subgroup. MAO results were obtained on 690 men (age 44 ± 11 (s.d.) years) and 861 women (age 45 ± 11 years). Thirty-three per cent of the men and 11% of the women met DSM-III-R criteria for lifetime alcohol dependence. Twenty-two per cent of the men and 17% of the women reported themselves to be current smokers, and 28% and 19% to be ex-smokers. Their alcohol intakes were (geometric mean and 95% CIs) 6.4 (0.6 to 66) drinks per week for men and 3.1 (0.4 to 26) for women.

Diagnostic criteria and personality measures

The questionnaires and interviews that provided data used in this paper were as follows.

In 1989

The data from 1989 concerned information on current smoking status (never smoker, ex-smoker or current smoker at that time); results from the Tridimensional Personality Questionnaire (Cloninger *et al.* 1991).

In 1993–4

An adaptation for telephone administration of the SSAGA (Semi-Structured Assessment for Genetics of Alcoholism) instrument (Bucholz *et al.* 1994) was employed. This permits diagnosis

of alcohol dependence, panic disorder, social phobia, and conduct disorder by DSM-III-R criteria, and depression by DSM-IV. Questions on history of these conditions in their parents and twin siblings were also included. Subjects were asked about suicide attempts or thoughts of suicide, and the method chosen where attempts had been made (Statham *et al.* 1998). Alcohol history questions included recent (previous 12 months) quantity and frequency of use, the maximum used on any single occasion (ever and in the previous 12 months), and the number of symptoms or problems associated with alcohol. In order to test hypotheses about possible subtypes of alcohol dependence, groups with early and late onset and continuing or past problems were defined. Late onset of alcohol dependence was set at an age greater than or equal to 25 years for women and 21 years for men, at the time the diagnostic criteria were first met. Data on the largest number of drinks taken on a single occasion within the past year were used to classify subjects who had ever met alcohol dependence criteria into past and persisting problem groups. Continuing alcohol problems were assumed for women who reported more than five drinks and for men who reported more than ten drinks on any occasion in the year before the telephone interview.

In 1993–6

When subjects attended for collection of a blood sample they filled in a table of their consumption of alcohol over the previous 7 days. The number of standard drinks (containing 10 g of ethanol) was calculated by summing the number of drinks across days and beverage types.

Smoking status

Validity of the 1989 smoking data (using the three categories of never, ex- or current-smoker) was established by estimating the agreement between this data and a number of post 1993 sources for some subjects, with the following results: (i) concordance with self-report at interview follow-up (1994–6); kappa 0.87 female, 0.84 male; (ii) concordance with rating by co-twin at interview follow-up, kappa 0.80 female, 0.75 male; (iii) concordance with report by spouse, kappa 0.81 female, 0.80 male. Co-twin reports within the 1989 survey showed good corroboration of respondents' self-reports, with kappa values of 0.89 for females and 0.85 for males. We concluded that the 1989 self-reports of smoking status are sufficiently valid for use in comparisons with the MAO results.

All the psychiatric conditions studied were more common among subjects who declared themselves to be current smokers in 1989 than in the never smokers. The difference was significant for conduct disorder, depression and alcohol dependence in both men and women, and for social phobia in women (Table 1).

Blood collection and platelet separation procedures

Blood was collected from an arm vein into EDTA tubes. It was centrifuged at 132 *g* (930 rpm) for 10 min and platelet-rich plasma was aspirated and centrifuged at 1370 *g* (3000 rpm) for 10 min. Plasma was removed and the platelet pellet was washed and recentrifuged twice, using 5 ml of 0.9% NaCl for each wash. The platelet isolation procedure was completed within 2 h of blood collection, and the platelet pellet was stored at -70°C until analysed. The date, time and location of blood collection were recorded.

MAO activity was measured using tyramine as substrate. Details are available from the first author. Results were expressed as nanomoles of product per hour per milligram of protein. Within-run precision of the MAO assay was assessed by measuring activity in samples from 18 normal volunteers in triplicate. The within-run precision (s.d.) was 1.4 nmol/h/mg protein at an average value of 21.1 nmol/h/mg protein (coefficient of variation 6.7%). Between-day precision was assessed by including one of three

control samples with each batch of samples analysed; the between-batch s.d. was 3.8 nmol/h/mg protein at a mean of 24.3 nmol/h/mg protein (coefficient of variation 15.8%).

Statistical methods

Differences between groups or correlations between continuous variables and MAO activity were estimated using SAS (SAS Institute Inc., Cary NC). Genetic models were fitted using Mx (Neale, 1998). Effects of dropping variables from the model on the overall goodness-of-fit were assessed by likelihood ratio chi-squared test. Because the subjects were twins, observations on different individuals are not independent for variables subject to genetic or shared environmental influences and this may lead to non-conservative *P* values. Where significant differences between groups were found using conventional statistical tests, standard errors were re-estimated, using robust variance ('sandwich') estimates (Stata Statistical Software, Stata Corporation, College Station, Texas); or by bootstrapping, using the twin pair as the unit for resampling, with 3000 bootstraps per analysis (Efron & Tibshirani, 1986), if no robust variance estimator was available for a particular statistical procedure.

Some analyses requiring listwise deletion were performed on fewer than the full set of 1551 MAO results. Numbers of subjects included are shown in the relevant Tables.

RESULTS

Sex had a highly significant effect on MAO activity ($F_{1,1549} = 85.2$, $P < 0.001$) but there was no effect of age. Mean values for women were 21.8 ± 10.5 (s.d.) nmol/mg protein/h and for men 17.4 ± 7.8 (s.d.); the variance was greater in women than men ($F_{861,690} = 1.81$, $P < 0.001$). For both men and women the distribution of results was significantly and positively skewed. Two outliers with MAO activity > 50 were excluded and results were square-root transformed before further analysis.

Because the blood samples were collected and platelets were isolated at several locations, and the MAO activity analyses were carried out in batches, we tested for effects of collection centre or analysis batch on mean MAO activity. Date of analysis had no significant effects on the

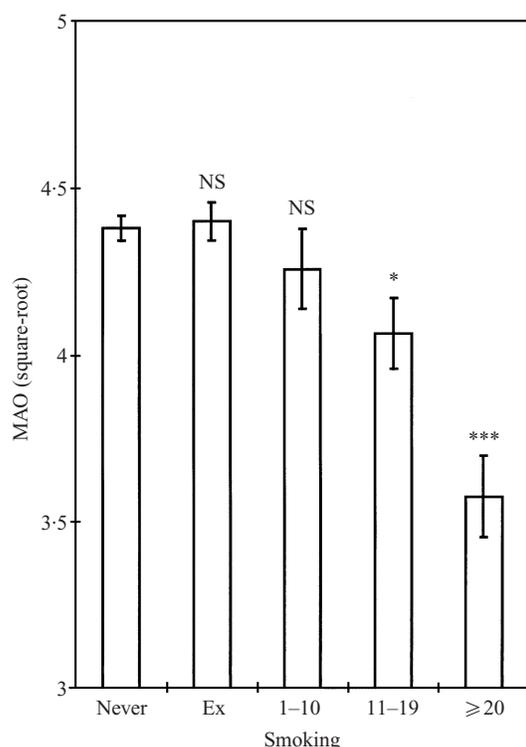


FIG. 1. Effects of smoking status on platelet MAO activity (square-root transformed data, adjusted for sex, age and EPQ N score). Smoking status is shown as Never, Ex-Smoker or Current-Smoker, and for Current Smokers the number of cigarettes used per day. Error bars show standard errors for each group and significances are shown as difference from the Never Smoker group (*** $P < 0.001$, ** $P < 0.01$, NS $P < 0.05$).

results ($P = 0.20$) but the location of blood collection had a highly significant effect ($P < 0.0001$).

Smoking

Compared to never smokers, current smokers showed low platelet MAO activity, whereas ex-smokers did not. When the number of cigarettes per day was used to categorize the current smokers, increasing cigarette use was associated with progressively lower MAO activity (Fig. 1). The point at which the decrease in MAO compared to non-smokers became significant depended on the variables included in the model; when sex and EPQ N-score (see below) were included and adjustment was made for the twin structure of the study group, subjects who were ex-smokers or who smoked up to 10 cigarettes

per day showed non-significant differences in MAO activity. Subjects smoking 11–19, or ≥ 20 cigarettes had significantly lower MAO activity than never-smokers ($P = 0.011$ and $P = 0.001$ respectively).

Comparisons of MAO activity were also made between groups of non-smokers categorized according to the smoking status of their co-twins (Fig. 2). If a low MAO predisposes to smoking by being a genetic risk factor, non-smokers with a smoking twin (especially a smoking MZ twin) would have lower MAO activity than non-smokers with non-smoking twins. Each of the non-smoking groups had significantly higher MAO results than the smokers (all P values at least < 0.05), but there were no significant differences between non-smokers with and without smoking twins, either in the MZ or the DZ groups (all P values > 0.2).

Current or past alcohol dependence

Subjects with a history of alcohol dependence, especially those who reported excessive drinking in the previous year, had significantly lower MAO results but this finding did not persist when allowance was made for smoking status. Table 2 shows that subjects with lifetime alcohol dependence and also excessive drinking on at least one occasion within the past year had lower MAO activities than the control group when smoking status was not considered as a covariate. This effect was abolished when smoking was entered into the model. Subjects who had at some time fulfilled alcohol dependence criteria, but who had not exceeded the limits set for excessive drinking in the past year, had MAO values not significantly different from controls. The age of onset of alcohol dependence did not affect MAO activity either before or after adjusting for the effects of smoking.

There was little evidence that non-dependent subjects at high genetic risk through having an alcohol-dependent co-twin had low platelet MAO activity. In Fig. 3, it will be seen that never-alcohol-dependent subjects with an affected MZ co-twin had lower MAO activity than unaffected subjects with an unaffected MZ co-twin (square-root transformed MAO activity \pm s.e.m. 3.91 ± 0.14 v. 4.24 ± 0.06), but this was not true for DZ twin pairs (4.48 ± 0.14 v. 4.11 ± 0.08 for female pairs and 4.25 ± 0.15 v.

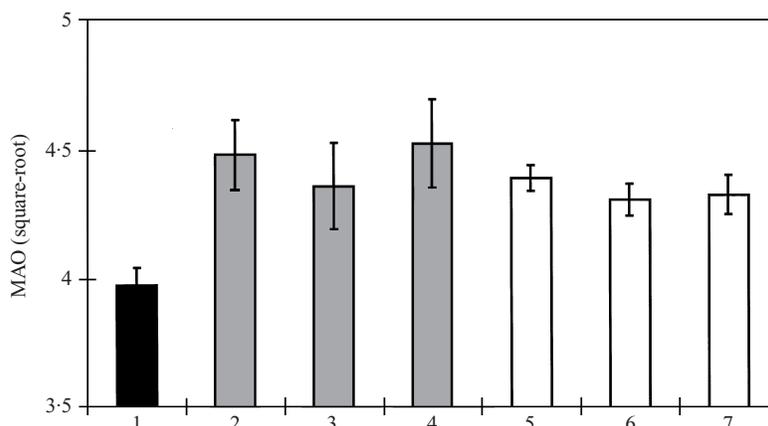


FIG. 2. Associations between subjects' or co-twins' smoking status and platelet MAO activity (square-root transformed data). Subjects are categorized as Current Smokers or Current Non-Smokers (i.e. Never or Ex-smokers), and subjects who were current non-smokers are further categorized according to the current smoking status of their co-twin and the zygosity of the twin pair (MZ monozygotic, DZ dizygotic). (Group 1, Current Smokers. Group 2, Current Non-Smokers with MZ co-twin Current Smoker; Group 3, Current Non-Smokers with DZ female co-twin Current Smoker; Group 4, Current Non-Smokers with DZ male co-twin Current Smoker; Group 5, Current Non-Smokers with MZ co-twin Current Non-Smoker; Group 6, Current Non-Smokers with DZ female co-twin Current Non-Smoker; Group 7, Current Non-Smokers with DZ male co-twin Current Smoker: i.e. ■, subject affected; ▒, subject unaffected but co-twin affected; □, both subject and co-twin unaffected.) Error bars show standard errors for each group.

Table 2. Detailed examination of the effects of alcohol dependence, categorized as early or late onset (as described in the text) and with or without reported excessive drinking in the past year (defined in the text), on square-root-transformed platelet MAO activity. Alcohol dependence effects are shown with and without correction for smoking category, as defined in the text and shown in Fig. 1. Bootstrapping was used to correct standard errors and P values for the non-independence of observations on twin pairs (P values refer to differences from the first group, subjects who had never been alcohol dependent)

	Not corrected for smoking	N	P	Corrected for smoking	N	P
Never alcohol dependent	4.323 ± 0.033	1224	—	4.134 ± 0.050	1155	—
Alcohol dependent						
No excessive drinking in past year	4.284 ± 0.087	150	0.696	4.116 ± 0.092	136	0.900
With late onset	4.280 ± 0.117	85	0.737	4.098 ± 0.121	79	0.854
With early onset	4.289 ± 0.130	65	0.818	4.140 ± 0.132	57	0.980
Alcohol dependent						
Excessive drinking in past year	4.128 ± 0.074	169	0.038	4.029 ± 0.079	158	0.426
With late onset	4.143 ± 0.113	82	0.170	4.027 ± 0.120	75	0.592
With early onset	4.114 ± 0.103	87	0.101	4.030 ± 0.097	83	0.580

4.09 ± 0.09 for male pairs). None of these differences reached statistical significance ($P = 0.126$, $P = 0.211$, $P = 0.410$, respectively). Reported parental history of alcohol dependence also had no significant effect on MAO ($P = 0.580$).

Other drug use, and psychiatric disorders

No significant associations with conduct disorder, depression, social phobia or panic disorder were detected (see Table 3). Many of these

conditions were associated with smoking (see Table 1) but all differences in MAO between groups defined by these conditions were non-significant both with and without compensation for smoking effects.

Subjects who reported past suicide attempts deemed to have been serious, had significantly ($P = 0.014$) lower MAO than subjects with no suicidal thoughts or attempts but the MAO did not decrease across other categories (thoughts of suicide, persistent thoughts of suicide and

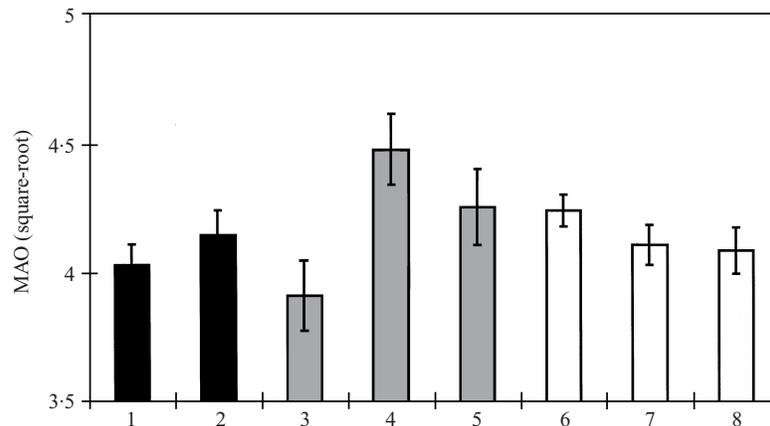


FIG. 3. Associations between subjects' or co-twins' alcohol dependence status and platelet MAO activity (square-root transformed data, corrected for sex, age and smoking effects). Subjects are categorized as ever or never alcohol dependent, and subjects who had never been alcohol dependent are further categorized according to the alcohol dependence status of their co-twin and the zygosity of the twin pair (MZ monozygotic, DZ dizygotic). (Group 1, Alcohol dependent with recent excessive drinking; Group 2, Alcohol dependent without recent excessive drinking; Group 3, Never alcohol dependent, MZ co-twin alcohol dependent; Group 4, Never alcohol dependent, DZ female co-twin alcohol dependent; Group 5, Never alcohol dependent, DZ male co-twin alcohol dependent; Group 6, Never alcohol dependent, MZ co-twin never alcohol dependent; Group 7, Never alcohol dependent, DZ female co-twin never alcohol dependent; Group 8, Never alcohol dependent, DZ male co-twin never alcohol dependent; i.e. ■, subject affected; ▒, subject unaffected but co-twin affected; □, both subject and co-twin unaffected.) Error bars show standard errors for each group.

Table 3. Effects of presence or absence of various lifetime diagnoses on square-root-transformed platelet MAO activity, without and with correction for smoking category (never, ex, or number of cigarettes per day). Bootstrapping was used to correct standard errors and P values for the non-independence of observations on twin pairs (all values are corrected for age and sex)

Condition (N of positives)	Not corrected for smoking			Corrected for smoking		
	Absent	Present	P	Absent	Present	P
Alcohol dependence (319)	4.363 ± 0.035	4.203 ± 0.061	0.032	4.150 ± 0.056	4.056 ± 0.069	0.411
Conduct disorder (135)	4.344 ± 0.034	4.126 ± 0.086	0.051	4.130 ± 0.055	3.998 ± 0.093	0.466
Depression (310)	4.328 ± 0.036	4.318 ± 0.060	0.895	4.112 ± 0.056	4.164 ± 0.071	0.657
Social phobia (35)	4.331 ± 0.033	4.030 ± 0.164	0.164	4.150 ± 0.049	4.000 ± 0.167	0.639
Panic disorder (51)	4.327 ± 0.033	4.305 ± 0.128	0.904	4.123 ± 0.054	4.136 ± 0.126	0.966
Serious suicide attempt (33)	4.337 ± 0.032	3.798 ± 0.145	0.014	4.134 ± 0.054	3.783 ± 0.146	0.334

attempts unlikely to succeed). The difference was non-significant ($P = 0.209$) when corrected for genetic similarity between the subjects and correction for smoking effects decreased the mean difference between groups.

Personality characteristics

There were no significant correlations between MAO activity and any of the TPQ variables, or with the EPQ E, P or L scales. For EPQ Neuroticism, results were available from two occasions and the association with MAO activity was significant on both. Relationships between

Neuroticism score, smoking and MAO will be reported in another paper.

Twin-pair similarities in MAO activity

Twin-pair correlations, after controlling for collection location, sex and age, were: MZ female 0.314, MZ male 0.401, DZ female 0.311, DZ male 0.214, and DZ opposite-sex 0.251. The best fit of the genetic-environmental model to the correlations estimated additive genetic variance at 0.16 (95% CI 0 to 0.44); variance due to environmental factors shared within twin pairs 0.21 (95% CI 0 to 0.39); and variance due to

unshared environment, and random effects including measurement error, 0.63 (95% CI 0.54 to 0.73). These results show that there is significant sibling resemblance in the MAO results but it is not possible to distinguish between genes and shared environments as the cause.

DISCUSSION

Alcohol dependence

The main purpose of this study was to test whether platelet MAO activity is truly a genetic marker of susceptibility to alcohol dependence, a subtype of alcohol dependence, or other common psychiatric conditions. The alternative hypothesis, that MAO is in fact a state marker of smoking and only appears to be associated with other conditions because smoking is commoner in affected subjects, now appears to be correct. Our results in this respect agree with those of Anthenelli *et al.* (1998), who found no effect of alcohol dependence on MAO once smoking and variation in site of blood collection were taken into account.

MAO decreased progressively with increasing number of cigarettes smoked (Fig. 1) and ex-smokers' results did not differ from never-smokers'. Moreover, subjects who were at an increased genetic risk of being smokers (because their genetically identical MZ twin or genetically similar DZ twin smoked) did not have low MAO. This is a useful additional test because it might otherwise be said that ex-smokers are less susceptible to smoking addiction than continuing smokers, because they had been able to give up smoking.

These results are consistent with *in vitro* studies where MAO from platelets or other sources is exposed to cigarette smoke (Yu & Boulton, 1987), and with *in vivo* studies using PET to measure brain MAO activity (Fowler *et al.* 1996). However, despite the large number of published studies on MAO and alcohol dependence or other psychopathology there are few on smoking, and those which do mention it have often failed to give the issue prominence.

Among our subjects, alcohol dependence was only associated with low MAO activity in the group of subjects who reported at least one episode of excessive drinking in the previous year. Thus, low MAO was probably associated

with continuing problems. However, no significant MAO-dependence associations existed once variation in smoking was taken into account. The apparent association with dependence plus recent excessive drinking is due to differences in smoking habits between ever-dependent people who do, or do not, continue to drink excessively on some occasions. There was no evidence for lower MAO in subjects with early onset of alcohol dependence. No significant associations with current alcohol intake, or family history of alcohol dependence (parental or co-twin) could be shown after allowing for the effects of smoking. MAO is not a trait marker for alcohol dependence, or a state marker of alcohol intake.

However, it might be said that the failure to find an association between alcohol dependence and MAO activity is due to the nature of the cohort studied. These subjects were recruited from a volunteer twin registry. Community-based volunteer recruitment is both a strength (because it avoids bias from clinical recruitment) and a weakness (because it selects for co-operativeness, probably excludes severely affected alcoholics, and almost certainly excludes antisocial and violent alcoholics). Although substantial numbers of subjects met the DSM-III-R criteria for alcohol dependence, only around 1% of the men had problems that were severe enough for them to have sought treatment (Heath *et al.* 1994), and who would be comparable to the 'alcoholics' in studies that recruited from clinical sources. Therefore, our results cannot entirely exclude the possibility that low MAO is a marker for 'severe alcoholism', although the paper of Anthenelli *et al.* (1998) makes this unlikely. Their study was based on recruitment from clinical sources and required multiple affected members of a family.

Another source of variation between studies may arise during blood sample processing. Both in this study and in that reported by Anthenelli *et al.* (1998), mean MAO results differed between collection centres. The most probable explanation is that small differences in the platelet preparation procedure affect the relative proportions of platelet and plasma proteins in the sample analysed. However, such variation should not affect the differences between smokers and non-smokers, or between subjects with alcohol dependence or any other condition and the relevant control group.

Platelet MAO as a general psychiatric vulnerability marker

The wider hypothesis of MAO being a marker of psychiatric vulnerability was not supported by our results. There were no significant associations with depression, panic disorder or social phobia. Conduct disorder was associated with lower MAO values but, again, this difference was not significant. The characteristics of our sample make it difficult to rule out abnormalities in MAO in patients with severe forms of these conditions, or to comment on those such as schizophrenia, which did not occur with sufficient frequency among our subjects. Nevertheless, it is clear that smoking has such major effects on MAO that all past and future studies should be assessed with due regard to its role.

Subjects who reported serious suicide attempts had low platelet MAO activity, with or without correction for smoking status. Although the difference in MAO activity between suicide attempters and other subjects was as great as that between smokers and non-smokers, it was non-significant after correcting for the non-independence of observations on twin pairs, possibly because of the small number of suicide attempters (Statham *et al.* 1998).

The interpretation of low MAO/suicide associations depends on whether suicide attempts are seen as related to depression or to violence. Depression was associated with a non-significant increase in MAO among our subjects, but other authors (Belfrage *et al.* 1992; Verkes *et al.* 1996, 1998) have seen some forms of suicide as related to violent or impulsive behaviour. Reports of platelet MAO activity in people who have attempted or completed suicide (Meltzer & Arora, 1986; Traskman-Bendz *et al.* 1992; Van Kempen *et al.* 1992; Verkes *et al.* 1996, 1998), or who have shown other forms of violent behaviour (Stalenheim *et al.* 1997), are mixed, but there is a substantial and consistent literature showing low CSF 5-HIAA concentrations in suicidal subjects (Lester, 1995; Mann & Malone, 1997). 5-HIAA is low whether or not the suicidal actions are associated with depression (Åsberg, 1997). Nevertheless, although low CSF 5-HIAA in suicidal subjects is a well established finding and is compatible with low MAO activity, it too could be due to smoking and future studies should control for this possibility.

Conclusions

MAO has been one of the more promising biological markers of psychopathology, both because of the importance of this enzyme for neurotransmitter metabolism and because of the consistency of reports of low MAO in alcoholics. This view is severely undermined by the major effects of smoking, and the association between smoking and so many of the conditions of interest. Future epidemiological, genetic or pharmacological studies on MAO and related areas of serotonin metabolism must take account of smoking, and should concentrate on severely affected individuals which we have not been able to investigate in sufficient numbers. Methodological issues also need consideration, because collection of blood and separation of platelets at multiple sites has been a significant source of variation. MAO A activity may be a fruitful area for exploration, but technical difficulties in testing large numbers of subjects with PET are likely to prove an obstacle.

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