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GENETIC DIFFERENCES IN DRINKING HABITS, ALCOHOL METABOLISM AND SENSITIVITY IN UNSELECTED SAMPLES OF TWINS

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It is a common observation that individuals differ greatly in their consumption of alcohol and, if they do drink, in their sensitivity to it. Some people appear greatly affected by even small doses, others consume large amounts of alcohol with little apparent effect on their behaviour or performance. The causes of this normal variation both in consumption and sensitivity are of considerable interest, not least because they may provide clues to the etiology of the abnormal condition alcoholism.

Comparison of identical (MZ) and non-identical (DZ) twins is perhaps the best available design for estimating the relative contributions of environmental and genetic factors to individual differences. We have conducted a laboratory study of alcohol metabolism and psychomotor sensitivity in more than 200 twin pairs. Serum enzymes and haematological variables used to diagnose alcohol-related liver damage were also measured in these twins. Independently, we have studied drinking habits in nearly 4,000 twin pairs who responded to a mailed questionnaire. Detailed reports of these studies have appeared elsewhere and in this paper I shall highlight some of the insights we have gained into causes of normal individual differences in drinking habits, ethanol metabolism and sensitivity to alcohol, and the relationships between these variables.

Alcohol consumption

A questionnaire which included items on drinking patterns was mailed to all 5,967 pairs of adult (>18) twins

enrolled on the Australian Twin Register. Completed replies were obtained from 3,810 pairs, a 64% pairwise response rate, including 1,233 MZ female, 567 MZ male, 751 DZ female, 352 DZ male and 907 unlike sex pairs. The distribution of alcohol consumption reported by our volunteer twin sample was similar to that found in a random sample of the population surveyed by the Australian Bureau of Statistics. Because the distribution is highly skewed, genetic analysis was carried out on log-transformed scores.

Alternative hypotheses concerning the causes of individual differences in alcohol consumption were fitted to the meansquares for MZ and DZ twins. Causes considered were additive genetic variance (VA) which produces differences between MZ pairs but not within them, and is divided equally between and within DZ pairs. Two sources of environmental variance are distinguished; exogenous influences which make siblings differ from each other ("individual" or "specific" environment - E1) and those which affect both cotwins but differ between twin pairs ("shared" or "family" environment - E2). The distinction is important; E1 estimates the influence of environmental factors unique to the individual and also includes measurement error while E2 includes the influence of social and familial environments which are of primary interest to sociologists, for example. Models comprising various sensible combinations of these parameters were fitted to the data by the method of iterative weighted least squares and criteria including goodness of fit and parsimony were used to decide upon a preferred hypothesis for the cause of individual differences (see Eaves et al., 1978).

The median age of the sample was about 30 years so separate analyses were performed for twins aged 30 and under and for pairs over 30. Percentages of variance in alcohol consumption due to the three sources of variance considered are shown in Table 1 (Jardine and Martin, 1984).

TABLE 1. Sources of variance (%) for alcohol consumption

	FEMALES		MALES	
	≤30	>30	≤30	>30
Individual environment	42	45	34	49
Shared environment	-	-	21	51
Genetic	58	55	45	-

These percentages are calculated from the preferred models and since the sample is subdivided four ways, the power to detect all three sources of variance in a subgroup is low if any one source is small (Martin et al., 1978). Thus, it is unlikely that there is no influence of shared environment on females, nor of genetic factors on older males.

However, the differences in etiology between age and sex groups are highly significant and our analysis makes the point that the relative importance of genetic and environmental factors depends crucially on the group under consideration. Thus genetic factors are of major importance in determining the alcohol consumption of females, although both genetic and individual environmental variance for this measure increase considerably with age. In males, genetic differences are important when young but are increasingly overshadowed by environmental influences shared by brothers as they get older. Our results confirm the importance of genetic factors in determining individual differences in alcohol consumption and echo the results of other twin studies (e.g. Kaprio et al., 1981). The nature of environmental influences on alcohol consumption is currently under investigation in a large study of twins, their spouses, parents and other relatives, which is being conducted in Virginia (Heath et al., in progress).

Alcohol metabolism

In a laboratory study we measured psychomotor performance in 206 pairs of 18-34 year old twins before alcohol and then three times at hourly intervals after a standard dose of ethanol (0.75g/kg body weight) was ingested. Blood alcohol concentration (BAC) was measured at frequent intervals after ingestion. There were 43 MZ female, 42 MZ male, 44 DZ female, 38 DZ male and 39 DZ pairs of opposite sex. Repeat measurements were obtained for 41 of these pairs approximately four months after their first trial (Martin et al., 1985a,b).

At least six assays for blood ethanol were made from finger-prick blood samples on each subject. To correct for slight inequalities in sampling times, a curve was fitted to the BAC's for each subject from which was calculated the peak BAC, time to peak, and the rate of elimination. Repeatabilities (test-retest reliabilities) between occ-

asions (averaging 4.5 months apart) were surprisingly low. For the individual readings the average repeatability across different sampling times was only 0.64, for peak BAC 0.66, rate of elimination 0.39, and time to peak a barely significant 0.27. Since the correlation between duplicate assays of the same sample was 0.97, little of this non-repeatable variation can be attributed to errors of measurement in aliquotting or to machine fluctuations.

Genetic analysis found heritabilities of $0.62 \pm .06$ for peak BAC and $0.49 \pm .07$ for rate of elimination but no significant genetic variance could be detected for time to peak. Heritabilities do not differ significantly from the respective repeatabilities of the BAC parameters, suggesting that all *repeatable* variation between people in the way they metabolise alcohol is genetically determined. Our results are at variance with those of Vesell (1972) who estimated a heritability of 0.98 for alcohol elimination rate in 14 pairs of twins, but are close to those of Kopun and Propping (1977) who used a larger sample of 40 pairs and found a heritability of 0.41. Our much larger sample of twins confirms the extensive role of environmental influences on rates of alcohol metabolism and suggests that these are ephemeral in nature and cannot be detected systematically over a period of months.

Our subjects had been instructed to have a light, non-fatty breakfast before the trial and not to drink after midnight the previous evening. But in an effort to identify the ephemeral influences which account for so much of the variance in ethanol metabolism, we examined the relationship between BAC's and the size of breakfast eaten on the day of the trial, and also with whether the subject had consumed any alcohol the previous evening. Neither factor accounted for more than a few percent of the variance in BAC's. Larger correlations were obtained with normal weekly alcohol consumption and also with the number of years that the subject had been drinking regularly. However, these variables still only accounted for 5-10% of the variance in BAC's and in any case, we have shown that they are fairly stably reported and quite heritable, particularly in women (see above). Similarly, significant correlations were found between BAC's and physical variables including weight, adiposity and lung function, although the relationships were a complex function of age, sex and time of sampling. Once again, however, these

physical variables are fairly stable over a period of a few months, are moderately to highly heritable (Clark et al., 1980; Gibson et al., 1983), and therefore will not explain much of the ephemeral environmental variation we detected.

Our study (Martin et al., 1985a) could only provide the broadest description of major influences on alcohol metabolism, namely genetic factors and ephemeral environmental factors. We have failed to identify the nature of these environmental influences, although we have established that they are not merely due to measurement error. Further pharmacological experiments of the most traditional kind - investigations of the influence of A on B - are needed to identify and quantify these influences, which may well reside in quite subtle aspects of lifestyle, small-scale life events and associated moods.

Polygenic factors which affect drinking habits and adiposity also appear to influence ethanol metabolism but are unlikely to account for more than a small proportion of variance in the latter. There is not yet sufficient evidence of polymorphism at alcohol or aldehyde dehydrogenase loci in Europeans to account for the observed genetic variance in BAC's (Goedde et al., 1979), although this may change with the availability of DNA probes for these enzymes. Clearly, we have barely begun to explain individual differences in alcohol metabolism.

Psychomotor sensitivity to alcohol

Twins taking part in the above experiment were trained to plateau on a variety of psychomotor tasks, measured once before and three times after alcohol ingestion at hourly intervals. The tasks had all been found from previous work to exhibit a monotonic relationship between alcohol dose and psychomotor response (Franks et al., 1976). We were therefore in a position to ask whether genetic factors could be identified which affected individual differences in psychomotor response to alcohol (Martin et al., 1985b). An analysis based on Martin and Eaves (1977) was designed which would distinguish genes affecting all four measurements of psychomotor performance on a given task (general genetic factor) from independent genes which only influenced performance on the three post-alcohol trials, but not the pre-alcohol trial (alcohol genetic factor).

Our psychomotor battery measured four essentially independent aspects of performance which we may term coordination, steadiness, cognitive and reaction time. We detected alcohol specific genetic variation for all four factors. In other words, there are genetic differences between individuals which help determine how one will perform at a given task under the influence of alcohol, and these genes are quite independent of those which determine one's general level of performance with or without alcohol. Yet another way of looking at it is that an environmental factor, alcohol, unmasks genetic variation between people which is hidden when they are sober.

The most striking example of this phenomenon in our study was the body sway task. Individuals were asked to stand with their eyes closed on a platform beneath which was a transducer which measured the amount of sway in the forward-backward dimension. Sway, not surprisingly, was a function of centre of gravity, so raw scores were corrected for height and weight before analysis. Table 2 shows for males the proportions of variance due to genetic and environmental factors at each trial.

TABLE 2. Body sway in male twins: variance (%) in performance before and after alcohol ingestion.

	Environment		Genetic	
	General	Specific	General	Alcohol
Before alcohol	4	26	70	-
1 hr after	7	26	23	44
2 hr after	21	26	13	40
3 hr after	55	13	22	10

Genetic differences are either general in influence, or only expressed after alcohol ingestion. Environmental variance is partitioned between those influences affecting performance on all four occasions (general factor) which might include sporting prowess and general state of well-being on the day, and "specific" environment which influences a particular trial and that trial only. It is significant that estimates of the specific environmental variance are very close to independent estimates of the unreliability of the measurements from the test-retest data.

Genetic variance, as discussed above, is partitioned between that due to the general factor affecting performance both before and after ingestion and the alcohol genetic factor which reflects genetic differences only exposed in the presence of alcohol. The trends in Table 2 are striking. Before alcohol ingestion, a set of genes which affects body sway accounts for 70% of variance in the sober state. One hour after ingestion these genes account for only 23% of the variance and a new set of genes, whose effects are only "switched on" in the presence of alcohol, now account for 44% of variance. As the influence of alcohol wears off, these genes account for less and less of the variance - 40% at 2 hours and only 10% 3 hours after ingestion.

Similar, though not so large, alcohol-specific genetic effects were found for the other dimensions of psychomotor performance and also for physiological variables including heart rate, blood pressure and skin temperature. Clearly there are genetic polymorphisms which have great influence on sensitivity to alcohol. To what extent are these polymorphisms the same as those reflected in genetic variation for drinking habits and ethanol metabolism ?

A first approach to this problem is to examine the correlates of change scores in psychomotor performance. We calculated the difference between performance before alcohol ingestion and 1 hour after (the time of maximum effect for most measures) and carried out stepwise multiple regression on a number of independent variables including measures of drinking habits, blood alcohol concentration at 1 hour post ingestion, and personality measures including Extraversion and Psychoticism. For body sway in males, normal weekly alcohol consumption accounted for 11% of the change score, reflecting the fact that heavier drinkers were less steady than average before alcohol, but more steady after alcohol. Only a further 2% of variance was accounted for by blood alcohol concentration, and another 3% by the number of years of regular drinking by the subject. For body sway in females, regular alcohol consumption and BAC each accounted for less than 2% of variance in the change score. For some other psychomotor tasks, notably hand-eye coordination, BAC did account for somewhat more of the variance in change score.

The striking finding remains, however, that psycho-

motor change scores are very poorly predicted by blood alcohol concentration, at least within the range of BAC's obtained in our experiment (at 1 hour, mean 89 mg/100ml EtOH, s.d. 18 for males; 95±19 in females). Our results suggest that very little of the genetic variation in psycho-motor sensitivity to alcohol can be accounted for either by variation in drinking habits or even blood alcohol concentrations. This suggests that clues to the biochemical basis of variation in alcohol sensitivity in Europeans will not be found in the early parts of the metabolic pathway.

How well does psychomotor performance discriminate between groups with different blood alcohol levels ?

As already noted, we observed low correlations between psychomotor performance and BAC after alcohol ingestion. We may ask how well these psychomotor measures discriminate between persons with BAC's above or below a certain level, say 80mg/100ml.

One hour after alcohol, 59 males had BAC's lower than 80mg/100ml and 139 had BAC's greater than this level. The best discriminant function of performance variables measured at this time only classified 60% of these cases correctly. At other times in both males and females the best discrimination achieved between groups was only 71%. Thus at any given time, the fact that an individual had a BAC greater or less than 80 was a very poor guide to his performance on our battery of tests.

This result may arise from a restriction of range in both performance measures and BAC's at a given time. Consequently we recalculated the discriminant function by regarding each BAC reading and its associated performance measures at a given time as a separate case. The sets of observations are thus not independent since each individual is now regarded as four "cases" but the analysis should afford the maximum opportunity for performance measures to discriminate between the two classes of BAC's over a wide range of values, including the pre-alcohol values at which BAC was zero. Since the aim was to discriminate between BAC's greater or less than 80, regardless of sex, all 412 individuals were included in the analysis, generating 1648 "cases".

At least one variable from each of the four groups of psychomotor measures contributed to the discriminant function and two measures each from the Body Sway and Pursuit Rotor tests which appear to be the most discriminating tasks. Although the function made a highly significant discrimination between groups either side of the BAC of 80mg/100ml, there is a great deal of overlap between the two groups. About 29% of cases with actual BAC's <80 performed sufficiently badly to fall into the group predicted to be >80, while 34% with actual BAC's >80 performed sufficiently well that they were predicted to fall into the low BAC group. Only 69% of cases were correctly classified.

A further discriminant analysis attempted to classify BAC's into three groups: 0, 1-80 and >80 mg/100ml and the classification results are shown in Table 3.

TABLE 3. Classification results for discriminant analysis between blood alcohol concentrations of 0, 1-80, >80mg/100ml on the basis of psychomotor performance scores.

		Predicted Group			
		0	1-80	>80	N
Actual	0	72.5%	18.0%	9.5%	411
	1-80	33.1%	32.1%	34.8%	202
Group	>80	19.3%	19.8%	60.9%	653

54% of cases correctly classified

Of those who were actually completely sober, 9.5% of cases performed sufficiently badly that they were predicted to have BAC's >80, while of those who actually did have BAC's >80, 19.3% were predicted to fall into the sober group. Overall, only 54% of cases were correctly classified.

We conclude that our battery of tests provides only very crude predictive power about the blood alcohol concentration of individuals. Conversely and more importantly, BAC's in the considerable range that we have observed are a poor predictor of psychomotor performance on our battery of tests. This range was 0-162mg/100ml,

including 412 zero readings; the mean of non-zero readings is 83 and s.d. 17. This is the range of blood alcohol concentrations which is the main focus of legislative and police attention in attempts to lower the road toll.

Two possible interpretations of our results are:- i) the battery of psychomotor tests we have used have little to do with driving competence and therefore our results are irrelevant for practical purposes, or ii) preventive action would be better aimed at testing driving competence than measuring concentrations of alcohol or other drugs in the blood. It is ironic than the traditional test for drunkenness in many countries, in which the suspect was asked to walk a white line (a task closely related to our body sway test), was superseded by blood alcohol testing. Perhaps those interested in road safety should be pressing for roadside psychomotor testing rather than for lower and lower legal BAC's. If the psychomotor tasks we used in our study have any correlation with driving safety, such legislation penalises many drivers who are competent and leaves unpenalised many others who are not.

In conclusion, our studies have shown the important role played by genetic differences in determining how much people drink and how they are affected by alcohol. In an ideal world each individual would determine his own level of responsible drinking - but then this ignores individual differences in responsibility and judgement !

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