

Twin Studies of Alcohol Consumption, Metabolism and Sensitivity

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Abstract: *It is a common observation that individuals differ greatly in their consumption of alcohol and, if they do drink, in their sensitivity to it. 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 studied drinking habits in 3,810 adult twin pairs who responded to a mailed questionnaire. Genetic factors are of major importance in determining the alcohol consumption of females of all ages but are modified in their expression by marriage. They are also important in young males but are overshadowed by environmental influences shared by brothers as they get older. In a laboratory study of alcohol metabolism and psychomotor sensitivity in more than 200 twin pairs we found heritabilities of 0.62 for peak BAC and 0.49 for rate of elimination. These did not differ significantly from their respective test-retest reliabilities, which were surprisingly low, indicating the importance of short-term environmental influences on ethanol metabolism. For certain psychomotor tests, particularly body sway, we found evidence that sensitivity to alcohol was strongly genetically determined. However, only 2 per cent of variance was accounted for by blood alcohol concentration. Two possible interpretations of our results are :- i) the psychomotor tests we have used have little to do with driving competence and therefore our results are irrelevant for practical purposes, or ii) roadside tests of driving competence will be a more effective preventive measure than measuring concentrations of alcohol or other drugs in the blood.*

Keywords: *Twins; genetics; alcohol drinking; alcohol — metabolism; psychomotor performance.*

Introduction

Some people appear greatly affected by even small doses of alcohol, while others consume large amounts with little apparent effect on their behaviour or performance. The causes of normal variation in alcohol consumption and sensitivity are of considerable interest, not least because they may provide clues to the etiology of the abnormal condition alcoholism. One of the best ways to investigate normal variation is with twins.

We have conducted a laboratory study of alcohol metabolism and psychomotor sensitivity in more than 200 twin pairs. 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 relationship 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. 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 1.¹

Table 1: Sources of variance (%) for alcohol consumption

	Females		Males	
	Age ≤ 30	Age > 30	Age ≤ 30	Age > 30
Individual environment	42	45	34	49
Shared environment	-	-	21	51
Genetic	58	55	45	-

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. Further investigations into the nature of environmental influences on alcohol consumption are currently 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.^{2,3} 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.

At least six assays for blood ethanol were made from finger-prick blood samples on each subject. A curve was fitted to the BACs for each subject from which was calculated the peak BAC, time to peak, and the rate of elimination. Repeatabilities (test-retest reliabilities) between occasions (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.

Heritabilities of $0.62 \pm .06$ for peak BAC and $0.49 \pm .07$ for rate of elimination were estimated and these do not differ significantly from the respective repeatabilities, suggesting that all repeatable variation between people in the way they metabolise alcohol is genetically determined. Our results are close to those of Kopun and Propping⁴ who 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 study² 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. 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 BACs,⁵ although this may change with the availability of DNA probes for these enzymes.

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. We were therefore in a position to ask whether genetic factors could be identified which affected individual differences in psychomotor response to alcohol.³ An analysis 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).

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.

The trends are striking. Before alcohol ingestion, a set of genes which affects body sway accounts for 70 per cent of variance in the sober state. One hour after ingestion these genes account for only 23 per cent of the variance and a new set of genes, whose effects are only "switched on" in the presence of alcohol, now account for 44 per cent of variance. As the influence of alcohol wears off, these genes account for less and less of the variance — 40 per cent at 2 hours and only 10 per cent 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 per cent 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 per cent of variance was

accounted for by blood alcohol concentration, and another 3 per cent 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 per cent 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 psychomotor change scores are very poorly predicted by blood alcohol concentration, at least within the range of BACs 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 psychomotor 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 BACs above or below a certain level, say 80mg/100ml? We treated each BAC reading and its associated performance measures at a given time as a separate case and calculated a discriminant function to attempt to classify BACs into three groups: 0, 1-80 and >80mg/100ml (Table 3).

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

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

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.

We conclude that our battery of tests provides only very crude predictive power about the blood alcohol concentration of individuals. Conversely and more importantly, BACs 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 that 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 BACs. 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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