THE INHERITANCE OF ALCOHOL SENSITIVITY AND
OF PATTERNS OF ALCOHOL USE

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ABSTRACT

Compared to controls, sons of alcoholics have been reported to exhibit decreased sensitivity
to a challenge dose of alcohol (e.g. a smaller increase in body-sway: Schuckit, 1985). We
reanalyze alcohol challenge data from a general population sample of Australian twin pairs
(Martin et al., 1985a,b). By fitting direction-of-causation models, we show that in males
differences in body-sway are largely a consequence, not a cause, of differences in alcohol
consumption patterns. In females, direction-of-causation could not be resolved.

KEYWORDS

Twins; alcohol challenge; body-sway; alcohol consumption.

GENETIC CONTRIBUTIONS TO ALCOHOL SENSITIVITY

Results from twin, adoption and half-sibling studies are broadly consistent in finding a
significant genetic contribution to risk of alcoholism in males. These findings have led to
high-risk studies, comparing sons of alcoholics and controls, in an attempt to identify
variables which mediate this genetic influence. Sons of alcoholics, for example, have been
reported to exhibit a decreased reactivity to a standard dose of alcohol, whether assessed by
subjective feelings (Schuckit, 1984), increase in body-sway (Schuckit, 1985) or hormonal
changes (Schuckit et al., 1987a,b). Inherited differences in reactivity are hypothesized to
account for the increased risk in sons of alcoholics (Schuckit and Gold, 1988).

A study of psychomotor performance and subjective intoxication after a challenge dose of
alcohol (0.75g/kg body-weight), using a sample of twin pairs unselected for risk of
alcoholism, has confirmed significant genetic differences in reactivity (Martin et al.,
1985a,b). Multivariate analysis of change scores, assessing the decrement in performance from
baseline to the first testing cycle after the standard alcohol dose (Heath and Martin, 1990a),
identified two orthogonal factors. The first factor had high loadings on drinking history
(self-report average weekly alcohol consumption, measured in standard drinks), on subjective
intoxication and reported willingness to drive, and on body-sway; but a very low loading on
blood alcohol concentration (BAC). The second factor had high loadings on BAC and on tests of
psychomotor coordination (Vienna Determination Apparatus) and eye-hand coordination (pursuit
rotor), but low loadings on drinking history and subjective ratings. In females only, body-
sway also loaded on this second, BAC-sensitive factor, as well as on the first, drinking
history-sensitive factor. Multivariate genetic analysis identified two genetic factors with
loadings broadly similar to those observed in the conventional principal components analysis
(Heath and Martin, 1990a).
From these multivariate analyses, therefore, it appears that the same genetic factors which influence average weekly alcohol consumption also influence body-sway and subjective ratings after alcohol challenge. This analysis does not, however, resolve the question of direction-of-causation. It might be the case that genetically determined differences in reactivity to alcohol are leading to differences in consumption pattern (sensitivity -> consumption). Alternatively, it is possible that other inherited factors are influencing alcohol consumption patterns, and that differences in drinking history are leading to differences in reactivity to the standard dose of alcohol (consumption -> sensitivity). It would not be surprising if subjects who were light drinkers exhibited a more marked deterioration in performance after alcohol challenge than heavier drinkers. Since alcohol challenge studies are not usually performed with alcohol-naive subjects, in conventional designs this question of direction-of-causation remains an important concern. Sons of alcoholics may exhibit differences from controls merely because of differences in drinking history which have been imperfectly matched between groups. However, the availability of twin data raises the possibility of obtaining information about direction of causation which does not rely upon the availability of alcohol-naive subjects.

In previous analyses, by fitting direction-of-causation models to the data on drinking history and self-report intoxication, we have found that the major causal influence appears to be that of increased average weekly alcohol consumption leading to decreased ratings of self-report intoxication after alcohol challenge (Heath and Martin, 1990b). In this paper, we explore the causal relationship between drinking history and body-sway after alcohol challenge.

METHODS

Subjects were 206 young adult twin pairs (42 monzygotic female, 42 NZ male, 44 dizygotic female, 38 dizygotic male and 39 unlike-sex pairs), aged 18-34 years, who were alcohol free at the beginning of testing, and who successfully completed the experimental protocol (e.g. did not vomit after ingestion of alcohol). Separate analyses were performed for male and for female like-sex pairs. Baseline assessments included a self-report questionnaire about average weekly consumption of beer, wine, spirits, sherry and other alcohol beverages, from which the subject's average weekly consumption in standard drinks was computed, and log-transformed; and duplicate measurements of body-sway made under two conditions, first with the subject's eyes open, and then with eyes closed. Body-sway was assessed by having the subject stand relaxed and as steady as possible on a platform, beneath which a displacement transducer was mounted, which created an electrical impulse if there was any forwards-backwards sway. Oscillations were integrated and the time taken to accumulate a given amount of sway was recorded on a polygraph. The average of two measurements was computed under each condition, and was log-transformed and adjusted for the regression of amount of body-sway on weight and height (Martin et al., 1985b). After baseline assessments, each twin was given a standard alcohol dose of 0.75g/kg body-weight, diluted to 10% (v/v) in sugarless squash, which was consumed under supervision over a 20-minute period, at a constant rate. After a further
20 minutes, the first of three hourly cycles of post-alcohol testing (including body-sway assessments) began. Our analyses focus on change scores, computed by subtracting baseline body-sway from body-sway during the first post-alcohol testing cycle. To simplify interpretation, we recoded change scores so that high scores indicate high sensitivity (i.e., a large increase in body-sway compared to baseline). Separate analyses were performed for data obtained under eyes open and eyes closed conditions.

![Path diagrams](image)

Fig. 1. Path diagrams representing (a) general bivariate model, (b) reciprocal causation model. (E, A, and C denote non-shared environmental effects, additive genetic effects and family background effects on consumption; E', A' and C' denote residual non-shared environmental effects, additive genetic effects and family background effects on alcohol sensitivity. Lower-case letters denote path coefficients whose values are to be estimated by model-fitting, e.g., e denotes the path regression of consumption on non-shared environment; see Wright, 1968; Heath et al., 1989).

For each like-sex twin group, 4x4 covariance matrices were computed, giving the variances and covariances of first twin’s average weekly alcohol consumption, first twin’s body-sway, second twin’s weekly consumption and second twin’s body-sway. Structural equation models were fitted using LISREL VII (Joreskog and Sorbom, 1988; Heath et al., 1989). Four alternative models were fitted: (i) a general bivariate model (Figure 1a), which postulates that body-sway and consumption are correlated because both are influenced by shared underlying genetic and environmental factors; (ii) a reciprocal causation model (Figure 1b), which postulates that the observed association between body-sway and consumption arises because of the reciprocal causal influence of alcohol sensitivity (assessed by body-sway) on weekly consumption and of weekly consumption on sensitivity; (iii) a model which postulates that the only causal influence is that of consumption on sensitivity (Consumption --> Sensitivity, implying i'-O in Figure 1b); and (iv) the alternative model which postulates that the only causal influence is that of sensitivity on consumption (Sensitivity --> Consumption, implying i=0). Models (ii)-(iv) can be obtained by imposing constraints on the parameters of model (i), so that each can be compared to the general bivariate model by likelihood-ratio chi-square test (Joreskog and Sorbom, 1988).

Under the general bivariate model, it is possible to estimate genetic and environmental effects which are common to both variables, as well as residual genetic and environmental effects which are specific to only one variable (sensitivity in the model presented in Fig. 1a). A model which allows for both common and specific genetic and environmental effects on both variables is not identified with only two measurements per twin. However, the choice of whether to allow for residual genetic and environmental effects on the first or second variables is arbitrary, the two models giving equivalent fits to the data. In principle, we might consider adding the reciprocal causation paths (i, i') of Fig. 1b to the general bivariate model. However, this model will not be identified if only bivariate data are available. These models are considered in greater detail, and full path diagrams for the resemblance of twin pairs are presented, in Heath and Martin (1990b; see also Heath et al., 1989).
RESULTS

Table 1 summarizes the results of model-fitting. The female like-sex twin pair data do not allow us to resolve alternative models of direction-of-causation. This is not altogether surprising, since the correlation between average weekly consumption, and change from baseline body-sway, in both eyes open and eyes closed conditions, was relatively weak in females ($r = -0.14$ and $r = -0.17$, respectively, compared with male correlations of $r = -0.34$ and $r = -0.34$).

In males, under the eyes open condition, the reciprocal causation model gave a highly significant improvement in fit over the Sensitivity $\rightarrow$ Consumption model ($\chi^2 = 10.35$, $p < 0.001$), and a marginally significant improvement in fit compared to the alternative Consumption $\rightarrow$ Sensitivity model ($\chi^2 = 3.87$, $p = 0.05$). Thus, we would prefer the reciprocal causation model over either simple model. Under the eyes closed condition, no model gave a particularly good fit to the data. The Sensitivity $\rightarrow$ Consumption model gave a significantly worse fit than the reciprocal interaction model ($\chi^2 = 6.15$, $p = 0.01$), but the Consumption $\rightarrow$ Sensitivity model did not ($\chi^2 = 2.95$, $p = 0.09$), so that we have no reason to reject the latter model.

Table 1. Results of fitting direction-of-causation models to body-sway data

<table>
<thead>
<tr>
<th>Model</th>
<th>EYES OPEN CONDITION</th>
<th>EYES CLOSED CONDITION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td></td>
<td>d.f.</td>
<td>$\chi^2$</td>
</tr>
<tr>
<td>Consumption $\rightarrow$ Sensitivity</td>
<td>13</td>
<td>14.15</td>
</tr>
<tr>
<td>Sensitivity $\rightarrow$ Consumption</td>
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<td>20.63</td>
</tr>
<tr>
<td>Reciprocal causation</td>
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<td>10.28</td>
</tr>
<tr>
<td>General bivariate model</td>
<td>11</td>
<td>10.24</td>
</tr>
</tbody>
</table>

Table 2 summarizes the parameter estimates obtained when the reciprocal causation model was fitted to the male like-sex twin data. It should be noted that these values have been standardized to give unit total variance for each variable, so that the magnitude of genetic and environmental parameters for consumption and for sensitivity, and the magnitude of the reciprocal paths, can be directly compared. Under both conditions, the causal path from weekly consumption to body-sway (i) is substantial and negative, indicating that increased consumption is leading to decreased sensitivity to ethanol challenge, whereas the reciprocal path (i') is opposite in sign.

Table 2. Standardized parameter estimates under reciprocal causation model: males

<table>
<thead>
<tr>
<th></th>
<th>Consumption parameters</th>
<th>Sensitivity parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>e</td>
<td>h</td>
</tr>
<tr>
<td>Eyes open</td>
<td>0.61</td>
<td>0.99</td>
</tr>
<tr>
<td>Eyes closed</td>
<td>0.67</td>
<td>0.91</td>
</tr>
</tbody>
</table>

DISCUSSION

For female like-sex pairs, our results are inconclusive. This probably reflects the weaker association between drinking history and post-alcohol body-sway in females compared to males (Martin et al., 1985b). Our ability to resolve hypotheses about direction of causation is reduced as the association between two traits weakens. Other analyses suggest that there may be important sex differences in the determinants of post-alcohol body-sway. In a multivariate analysis of performance decrement after alcohol, we found that body-sway in females had high loadings on both a BAC-sensitive factor, and on a drinking history-sensitive factor. In males, in contrast, body-sway measures loaded primarily on the drinking history-sensitive factor (Heath and Martin, 1990a).

In males, the results of model-fitting indicate that the major cause of the association between average weekly consumption and body-sway was the influence of consumption on body-sway, not the influence of reactivity to alcohol (as indexed by body-sway) on consumption. Under the eyes closed condition, there was no significant evidence for a reciprocal influence of body-sway on consumption. Under the eyes open condition, a significant reciprocal
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Influence was found, but was opposite in sign to what might have been predicted (e.g., Schuckit, 1985). Increased reactivity leading to increased consumption! When a reciprocal interaction model was fitted to the eyes closed data, the same pattern of reciprocal causation was observed. Similarly, in previously presented analyses of self-report intoxication after alcohol challenge (Heath and Martin, 1990b), we found that in males, although the major causal influence was that of increased average weekly consumption leading to decreased intoxication ratings, the reciprocal path was again opposite in sign to what had been predicted (Schuckit, 1984), increased reactivity again leading to increased consumption! A similar trend was observed in females, but as in the body-sway analyses presented here, there was insufficient power to resolve alternative hypotheses.

Is it possible that differences in body-sway after alcohol between sons of alcoholics and controls are largely a consequence of imperfectly matched differences in drinking history? Differences in sampling strategy (the twin pairs in our sample were unselected for risk of alcoholism) and differences in assessment protocol limit our ability to generalize from these findings to research using a high-risk paradigm. Nonetheless, these results, taken in conjunction with analyses of other variables that have appeared to discriminate sons of alcoholics and controls (Heath and Martin, 1990a,b), emphasize the need for careful assessment of the contribution of drinking history to performance after a standard dose of alcohol.

It should be noted that, even after allowing for the causal influence of drinking history on body-sway, our parameter estimates (Table 2) indicate that residual genetic variation in post-alcohol body-sway is found (i.e., $h^2 > 0$). For body-sway in the eyes open condition, this residual genetic variation accounts for only 4% of the total variance; whereas in the eyes closed condition residual genetic effects account for a more substantial 13% of the total variation. These findings may be contrasted with our previously reported results for post-alcohol intoxication ratings in males, where, after allowing for the causal influence of drinking history on intoxication rating, we found no residual genetic influence on the intoxication ratings (Heath and Martin, 1990b).

ACKNOWLEDGEMENTS

Data analyses were supported by ADAMHA grants AA07728, AA07535, DA05588 and MH0828. Data collection was supported by a grant from the Australian Associated Brewers to Dr. Martin and to Drs. Oakeshott, Gibson, and Starmer (whose role we acknowledge). We are grateful to Michael Hodge for his assistance with the data analyses for this paper.

REFERENCES


