CHANGES OVER TIME IN THE SELF-REPORTED LEVEL OF RESPONSE TO ALCOHOL

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Abstract — Aims: A low level of response to alcohol, or the need for a higher number of drinks for an effect, is a risk factor for alcohol use disorders. The response to alcohol is usually measured in young subjects, and changes in this phenomenon over time have rarely been evaluated. Reports that, overall, individuals are likely to become more reactive to alcohol with advancing age led to the current evaluation to determine whether the number of drinks needed for an effect decreased between the teens and age 40 in a group of men. Methods: Data were available from the 20-year follow-up of 202 men who had originally been chosen at age 20 as nonalcoholic subjects from families at high and low risk for alcoholism. The number of drinks required for effects was determined through the Self-Report of the Effects of Alcohol questionnaire (SRE) regarding their recollection of their intensity of reaction early in their drinking careers, as well as reports regarding the recent (e.g. prior 3 month) response to alcohol at the 15- and 20-year follow-ups. Results: Overall, there was a slight decrease in the drinks required for effects (SRE scores) across the three time points which became significant when recent drinking and depressant medication use were evaluated as covariates. When nonalcoholic or light-drinking subjects were evaluated separately, the decrease in the number of drinks needed for effects was more prominent. Among heavier drinkers, there was an increase in the number of drinks required for effects over time. The findings were generally similar for men with and without alcoholic relatives. Conclusions: The development of a more intense reaction to alcohol, or the need for fewer drinks for an effect, with advancing age may only be relevant to lighter drinkers. Among heavier drinkers, the finding that a higher number of drinks are required for effects may be relatively stable over time.

INTRODUCTION

Alcohol dependence is a complex genetically-influenced disorder where genes explain ~60% of the risk (McGue, 1999; Prescott and Kendler, 1999; Schuckit et al., 2001a; Schuckit, 2002). The genetic factors appear to be heterogeneous, and it is likely that separate sets of genes may impact on the risk through alcohol metabolism, behavioral and neuronal disinhibition, the predisposition to other major psychiatric disorders such as schizophrenia and manic depressive disease, as well as a person’s level of response (LR) to alcohol early in their drinking careers (Zucker, et al., 2000; Schuckit, 2002). Regarding the latter, a lower LR to alcohol (i.e. the need for more drinks to produce effects) in the late teens to early 20’s has been reported to characterize several groups at high risk for alcohol use disorders (AUDs) (e.g. children of alcoholics, Koreans, and Native Americans), and to predict repetitive alcohol problems later in life (Pollock, 1992; Volavka et al., 1996; Ehlers et al., 1999; Schuckit and Smith, 2000; Schuckit, 2002). Family, twin, and animal studies indicate that LR is genetically influenced, with genes explaining as much as 60% of the variance (Baldwin et al., 1991; Erblich and Earleywine, 1999; Heath et al., 1999; Schuckit et al., 1999; Wilhelmse et al., 2003).

The need for higher amounts of alcohol for a desired effect from early in the drinking career is hypothesized to alter a person’s cognitive expectations of how alcohol might affect them, impact on social decisions such as the choice of heavier-drinking friends, and relate to the probability of exhibiting behaviors that include the use of alcohol to cope with stress (Schuckit and Smith, 1996; Schuckit, 1998; Dodge et al., 2003; Schuckit et al., submitted for publication). Here, a social information processing bias might be created by experiences with alcohol that could contribute to developing a social milieu in which drinking more per occasion is encouraged, with subsequent physiological tolerance developing in the context of the heavier drinking, and changes in the cognitive set through which an individual determines whether their own drinking pattern is moderate or excessive. While a low LR earlier in life predicts future alcohol problems, it is not known whether this need for more drinks for effects might also contribute to the continuation of heavier drinking with advancing age.

Most studies have measured LR through alcohol challenges that document changes in subjective feelings of intoxication, motor performance, and alterations in several physiological measures, but these evaluations are expensive and time consuming (Schuckit et al., 1997a; Schuckit and Smith, 2000). An alternative measure of LR uses a 12-item self-report questionnaire, asking subjects to indicate the number of drinks required for any of up to four effects during the approximate first five times of drinking alcohol and during more recent epochs such as the past 3 months (Schuckit et al., 1997a,b, 2001b; Daeppen et al., 2000). Evaluations of LR using this Self-Report of the Effects of Alcohol (SRE) instrument found that early life SRE correlated (r = −0.60) with LR from alcohol challenges, and had a retest reliability over several years reaching 0.8 (Schuckit et al., 1997a,b, 2003; Daeppen et al., 2000). SRE scores have been shown to relate in the predicted directions to a family history (FH) of alcoholism, a person’s alcohol-related problems, as well as AUDs in adolescent populations, groups in the military, and general population samples in the US and Europe. The higher scores on this measure indicate more drinks required to have an effect, implying a likely lower level of response (or lower ‘sensitivity’) for an individual during an alcohol challenge.

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No data have been published regarding changes in LR in the same person over long periods of time. There are several reasons to predict that a person’s SRE score might decrease as they age (i.e., they will report fewer drinks for an effect, or have an overall higher LR). First, LR is compared across groups at specific blood alcohol concentrations (BACs), and the BAC reached per drink is likely to increase with advancing age (Kalant, 1998; Wang et al., 2001; Lynskey et al., 2003). This may occur as a consequence of increases in the percent body fat (leading to higher BACs achieved per standard drink because of less body water, as fat contains less water than muscle), and potential decreases with advancing age in the efficiency of the liver in oxidizing substances such as alcohol. The increase in LR (or lower SRE score) with age may also relate to enhanced intensities of reaction of the brain to depressant drugs such as alcohol as a person grows older (Kalant, 1998; Wang et al., 2001). Additional data support the probability that individuals are likely to consume less alcohol with advancing years (Lynskey et al., 2003), a phenomenon that might relate to the greater effect of alcohol per drink.

The optimal way to measure changes in the LR to alcohol over time in the same individual would be to carry out alcohol challenges at different ages. The absence of data in this area may reflect the high costs in following individuals over appropriate periods of time (perhaps a decade or more), as well as the resources necessary to bring subjects back to the laboratory when they no longer live in the same city in which the initial evaluation occurred. A third problem rests with the proportion of subjects who may no longer be appropriate for direct alcohol challenges as a result of new medical conditions, the associated use of medications, and contraindications that might be related to the development of an AUD.

The self-report SRE offers a relatively inexpensive opportunity to describe a person’s perception of his or her LR to alcohol at different ages. The analyses below present such results.

**METHODS**

The subjects are 202 male probands from the San Diego Prospective Study who have completed their 20-year evaluation (Schuckit and Smith, 1996, 2000). The final follow-up rate is projected to be 97% of the 449 subjects who are still alive, with the current pool representing the subset of individuals who received SREs at both the 15- and 20-year follow-ups, and whose most recent interviews had been completed by April, 2003. The SRE questionnaire had not been developed at the time of the 10-year evaluation.

Probands had been originally preliminarily identified at approximately age 20 through questionnaires mailed to students and nonacademic staff at the University of California San Diego. Those selected included individuals who indicated a father with sufficient problems to meet the criteria for alcohol dependence in the third revised Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-III-R) (American Psychiatric Association, 1987), as well as matched family history negative (FHN) controls. All participants had experience with alcohol, and none met criteria for alcohol dependence at the time of testing. Final selection was made after a face-to-face structured interview to corroborate background data. Subjects subsequently received an alcohol challenge that included a session using 0.75 ml/kg of ethanol which was consumed over a 10 min period, and the LR evaluated over the subsequent 3 h (Schuckit and Smith, 1996, 2000).

All probands, both family history positive and negative, were located ~10 years after initial testing (T10), when 99.3% participated in the follow-up evaluation. Here, a face-to-face interview similar to the Structured Clinical Interview for DSM-III-R (SCID) (Spitzer et al., 1992) was used to gather data from both the subject, and separately, from an additional informant, usually the spouse (Schuckit and Smith, 1996, 2000). These interviews evaluated alcohol and drug disorders, as well as major psychiatric conditions. The subsequent follow-up at 15 years (T15) used a similar protocol, but incorporated the retrospective self-report measure of LR, the SRE, which had only recently been developed and tested. The relevant elements of the follow-up evaluations, including face-to-face interviews and SRE’s, were repeated for the ongoing 20-year (T20) protocol.

The SRE is a 12-item self-report measure that asks subjects to indicate the number of standard drinks (12 g of ethanol) required for each of up to four effects ranging from feeling intoxicated through falling asleep when they did not wish to (Schuckit et al., 1997a,b; 2003; Daeppen et al., 2000). Individuals are instructed to indicate only the numbers of standard drinks for experiences they actually had (leaving others blank) at each time point, including the approximately first five times of drinking, and the most recent 30 days or last time they had a drink. For these analyses, and for most reports in the literature, the evaluations focus on the first five and recent 30-day periods. The score for the specific time frame on the SRE is determined by summing the number of drinks required for each endorsed effect during a time frame (e.g., first five times of drinking), and dividing that by the number of effects endorsed. Thus, the larger the number of drinks required for an effect on the SRE, the lower the intensity of response to alcohol is likely to be in an alcohol challenge protocol (i.e. the self-report number of drinks correlates negatively with the LR determined on alcohol challenges).

In the current analyses, the estimated number of drinks required for the first five times of drinking was determined retrospectively at the initial administration of the SRE during T15. First five time scores were also estimated again at T20, with the two values correlating at 0.66. As the T15 rating was more proximal to the early drinking, that value was used in the analyses. At both T15 and T20, SRE scores were also determined for the number of drinks required for various effects during a recent interval (e.g., the past 3 months) prior to the 15- and 20-year follow-ups.

Data were analyzed by evaluating the pattern of SRE scores across three time points, including first five, recent experiences at T15, and recent data regarding T20. The overall change over time was determined through ANOVA for the 202 men and for relevant subgroups. Partial eta effect sizes ($\eta^2_p$) are included for relevant analyses (small ~0.05, medium ~0.06, and large ~0.15). The SRE scores over time were also compared for lighter and heavier drinkers (i.e., men whose recent maximum drinks at both T15 and T20 fell below the median versus remaining subjects), using a mixed model ANOVA, with time as the repeated measure.
RESULTS

At T20, the 202 probands had an average age of 41.1 ± 3.08 years, and 17.3 ± 2.11 years of education, 71.3% were married (or living as married), 19.3% single, and 9.4% separated or divorced. All were Caucasian, 59.4% were family history positive (FHP) for alcoholism in a first-degree relative, and 24.8% of these subjects themselves met criteria for alcohol abuse or dependence at T15, with 24.8% fulfilling criteria for these conditions during the 5-year interval before T20. Regarding religious background, 19.8% were Catholic, 29.7% were Protestant, 48.0% reported no religion, and 2.5% noted other denominations. The average weight at T15 was 180.0 ± 26.00 and at T20 was 183.5 ± 25.57 pounds, the maximum number of drinks consumed per occasion prior to T15 was 6.2 ± 4.10 and prior to T20 was 5.6 ± 3.47 drinks, while the average quantities were 2.0 ± 1.12 and 2.0 ± 1.24 drinks per occasion, and average frequencies were 12.3 ± 9.02 and 13.1 ± 9.67 drinking days per month. The proportions who had used an illicit substance prior to T15 and T20 were 21.3% and 18.3%, respectively, while 33.7% and 26.7% reported having used nicotine at the two time points. Only 2% of the men had used brain depressants (e.g. muscle relaxants) prior to evaluation at either time point.

As shown in Table 1, recent period SRE scores at T15 and T20 covaried with contiguous maximum drinking quantity, illicit drug use, smoking status, and use of depressant medications, but not with weight measured at the same time. In order to select the most appropriate covariates for the analyses that follow, the significant items at T15 were placed into a multiple regression analysis predicting T15 recent SRE scores, with only maximum alcohol quantities adding significantly to the equation. The procedure was then repeated for T20, and when all significant variables were considered, recent use of depressants and maximum drinks entered the equation. When T15 and T20 maximum drinks and T20 use of depressants were evaluated together, only the T15 drink and T20 drug contributed to the regression.

The solid line in Fig. 1 demonstrates the SRE scores for the T1 first five times of drinking (as measured retrospectively at T15), as well as recent SRE values at both T15 and T20 for all 202 men. The estimated ‘first five’ SRE scores reported at T15 were 3.5 ± 1.80, and at T20 the estimate of ‘first five’ was 3.2 ± 1.60 (F[1, 201] = 6.43, P < 0.02, η² = 0.03), with an overall correlation between the two of 0.66 (P < 0.001). The figure reveals a possible modest decrement in SRE scores over time, with a resulting nonsignificant overall ANOVA (F[2,402] = 1.55, P = 0.22), which remained nonsignificant when analyzed through a linear contrast (F[1, 201] = 2.43, P = 0.13). However, when the two most relevant correlates from Table 1 (recent maximum drinks at T15 and depressant medications at T20) were used as covariates, the change in SRE over time became significant both overall (F[2, 390] = 23.10, P < 0.001) and through a linear contrast (F[1, 195] = 24.55, P < 0.001).

The impact of the covariates may indicate that the relatively small amount of change in SRE scores over time shown in the top line of Fig. 1 could reflect the balance between two opposite trends. First, recent drinking and depressant drug use might relate to higher SRE scores reflecting a larger number of drinks per occasion needed for an effect. At the same time, it is possible that, as suggested in the literature, growing older might contribute to the need for fewer drinks for effects as a person ages, or that as people drink less with age or with the change in US cultural attitudes to drinking, the number of drinks needed for an effect diminishes. While the impact of cultural changes is difficult to evaluate, the possible role of recent depressant use could be addressed. This possibility was evaluated in the dotted line in Fig. 1 which describes the SRE scores after excluding the 79 individuals for whom recent drinking might contribute most to the SRE values, i.e. subjects who met criteria for alcohol abuse or dependence at any time during the follow-up. Focusing on the remaining 123 men, there was a significant decrease in the number of drinks required for an effect over time (F[2, 244] = 7.65, P = 0.001), with a medium effect size (η² = 0.06). For these 123 subjects, the mean quantity of drinks per occasion at T15 and T20 were 1.6 ± 0.81 and 1.8 ± 0.74, with a mean frequency of 10.3 ± 8.68 and 11.0 ± 9.14 days per month. Their maximum drinks at T15 were 4.6 ± 2.47 and at T20 4.5 ± 2.35. The analyses in Fig. 1 were repeated for these 123 subjects after considering the two covariates mentioned above (the maximum drinking in the prior 6 months, and the use of depressant medications) for these nonalcoholics, with results indicating an even lower P-value (F[2, 240] = 11.53, P < 0.001), as well as an increase in the effect size (η² = 0.09).

Figure 2 takes these analyses further as the dotted line describes the SRE results for 70 light drinkers, defined as those whose maximum drinking at both T15 and T20 fell below the median. For this population, the maximum drinks in the 6 months prior to T15 was 2.9 ± 1.38, and at T20 was 2.5 ± 1.31 (F[1, 110] = 4.35, P = 0.04, η² = 0.04), with a significant decrease in the number of drinks consumed per occasion (F[1, 109] = 12.54, P = 0.001, η² = 0.11), while the average quantities were 1.6 ± 1.30 and 1.4 ± 1.04 drinks per occasion, and average frequencies were 13.8 ± 9.02 and 12.5 ± 7.72 drinking days per month. The proportions who had used an illicit substance prior to T15 and T20 were 21.4% and 19.3%, respectively, while 25.0% and 21.4% reported having used nicotine at the two time points. Only 2% of the men had used brain depressants (e.g. muscle relaxants) prior to evaluation at either time point.

### Table 1. Correlations between five characteristics and recent SRE scores at T15 and T20 for 202 men

<table>
<thead>
<tr>
<th>Variables at relevant time points</th>
<th>T15 SRE</th>
<th>T20 SRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight at follow up</td>
<td>0.09</td>
<td>−0.03</td>
</tr>
<tr>
<td>Max drinks quantity 6 months prior</td>
<td>0.55**</td>
<td>0.40**</td>
</tr>
<tr>
<td>Any illicit drug use 6 months prior</td>
<td>0.15*</td>
<td>0.18*</td>
</tr>
<tr>
<td>Any nicotine use 6 months prior</td>
<td>0.11</td>
<td>0.17</td>
</tr>
<tr>
<td>Any depressant medication use 6 months prior</td>
<td>−0.03</td>
<td>0.23**</td>
</tr>
</tbody>
</table>

*P < 0.05; **P < 0.01.
When both groups in Fig. 2 were evaluated with a mixed design ANOVA, both time (F[2, 258] = 6.62, p < 0.01), and group by time effects (F[2, 400] = 9.04, P < 0.001; \( \eta^2_p = 0.04 \)) were significant.

All of the analyses reported for the data in Figs 1 and 2 were repeated for the 120 FHP and 82 FHN subjects. Regarding Fig. 1, both FH groups demonstrated a decrease in SRE over time, but only when covariates were used (FHN: F[2, 160] = 10.54, P < 0.001 and FHP: F[2, 234] = 7.67, P = 0.001). The changes in SRE over time were significant for both FH groups among nonalcoholics, even without the use of covariates (FHN: F[2, 120] = 6.21, P < 0.01 and FHP: F[2, 116] = 5.42, P < 0.01). Regarding Fig. 2, for FHNs the lighter drinkers continued to show a decrease in SRE over time, even without the use of covariates (F[2, 62] = 5.94, P < 0.01), but no significant change over time was observed for FHP light drinkers (F[2, 68] = 0.02, P = 0.98). Both FHP and FHN heavier drinkers, however, did demonstrate the significant change over time noted in Fig. 2 (FHN: F[2, 94] = 306, P = 0.051 and FHP: F[2, 160] = 4.23, P < 0.02). Finally, regarding the analyses of FH groups separately, when the mixed design ANOVA was repeated for each family group separately, the group by time effect remained significant for both FHNs (F[2, 160] = 3.97, P < 0.03) and for FHPs (F[2, 236] = 4.98, P < 0.01), even without the use of covariates.

**DISCUSSION**

The overall goal of these evaluations was to describe changes in the self-reported number of drinks required for effects over two decades or more in 202 men. The intensity of reaction to alcohol was measured using the self-report SRE questionnaire where a lower number of drinks necessary for various effects indicates a more intense response to each drink consumed. The data generally support the hypothesis that the SRE scores decrease over time, indicating a greater effect of alcohol with advancing age.

When the entire group was evaluated, a significant decrease in the SRE scores over time was only observed after covarying for the recent intake of depressants, especially alcohol, benzodiazepines and muscle relaxants. These initial results indicated the possibility that there might be at least two opposing processes regarding the response to alcohol with age. Supporting this contention were results observed when the SRE scores were evaluated in nonalcoholics and, separately, in lighter drinkers. The diminution in the number of drinks required for effects was clearly observed in nonalcoholics in lighter drinkers, even without the use of covariates. However, among the heavier drinkers, an apparent increase in the number of drinks required for effects was observed over time, at least when covariates were considered. Even though the recent drinking pattern was among the covariates used in the analyses, it is also possible that changes in the alcohol consumption in the US over the last several decades (Greenfield and Room, 1997) may have contributed to drinking practices in these subjects, with subsequent lighter drinking and a loss of tolerance.

The findings for the subjects overall were generally corroborated when FHP and FHN subgroups were considered separately. The only exception occurred for data relevant to the lighter drinkers where the pattern in Fig. 2 was demonstrated for FHNs, but was not observed for FHPs. The absence of change over time for light-drinking FHPs might reflect the relatively high overall prevalence of a low LR to alcohol in FHPs (i.e. a higher SRE first five score) earlier in life, even among individuals who may have deliberately limited their alcohol intake. This might result in a maintenance of the innate high SRE values with advancing age, creating a general absence of change in SRE over time despite light drinking. This hypothesis will need to be reevaluated in another population before any solid conclusions can be drawn.

There are several implications for the results reported in this paper. First, the finding of a more intense reaction to a dose of depressants such as alcohol with advancing age (i.e. fewer drinks required for an effect) reported in the literature (Kalant, 1998; Wang et al., 2001) may primarily be true among lighter drinkers. For those who experience it, this increasing reaction might be one of several factors that contribute to the tendency for most individuals to decrease the amount of alcohol they drink per occasion as they grow older.

A second implication is that, in heavier drinkers and those with low LR’s, the intensity of response to alcohol may tend to decrease with advancing age, similar to earlier findings in nonalcoholics. However, in light drinkers, the trend observed among nonalcoholics is not found for heavier drinkers. The reasons for these opposing trends are unclear, but may be related to the different patterns of alcohol use among the two groups. Further research is needed to explore these findings and their implications for understanding the effects of alcohol on the brain.
to be a more stable trait, and might even increase a bit over time. Prior research has demonstrated that requiring more drinks for an effect (i.e. being less reactive or sensitive to alcohol) is observed in several groups at high potential risk for alcohol use disorders, and tends to predict future alcohol-related life problems (Ehlers et al., 1999; Wall et al., 1999; Schuckit and Smith, 2000). The current data indicate that individuals who reported that they required higher doses of alcohol for an effect early in their drinking careers may tend to maintain that characteristic over time. These results are consistent with the possibility that the need for more drinks for an effect might not only contribute to the onset of heavier drinking and alcohol-related life problems, but might also help perpetuate these conditions.

A third implication of the current findings relates to the optimal structure of studies attempting to understand more about changes in the response to alcohol with aging. Such epidemiological and laboratory-oriented evaluations will need to carefully control for the current intake pattern of all depressant drugs, including alcohol, and might benefit from understanding more about a person’s intensity of response to alcohol earlier in life.

To place the current data in perspective, the ideal study of changes in response to alcohol with age requires repetitive alcohol challenges over several decades. The analyses reported here used a much less expensive approach that incorporated SRE-based self-reports. While the two retrospective reports of the number of drinks required for effects early in life gathered at T15 and T20 correlated at almost 0.7, the absence of prospective data regarding this phenomenon is an important caveat. On the other hand, at least among heavier drinkers, the retrospective ‘first five times’ SRE scores appeared to be similar to those for recent reactions at both 15- and 20-year follow-ups. It is also important to note that the population evaluated here was limited to relatively well-educated Caucasian males. While this is a major subgroup in the US, it was not possible to determine the generalization of results to women and minorities. However, a recent paper demonstrated that, at least among children of alcoholics, there were no major differences in intensity of response to alcohol noted across the genders nor for Anglo versus Latino populations (Schuckit et al., in press).

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**REFERENCES**


