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Commentary

Commentary on 'Reduced Subjective Response to Acute Ethanol Administration Among Young Men with a Broad Bipolar Phenotype'

Marc A Schuckit*,[1]

[1]*Department of Psychiatry, University of California, San Diego School of Medicine (UCSD), La Jolla, CA, USA*

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Heavy drinking and alcohol-use disorders (AUDs) are approximately 50% heritable, with the genes operating through several intermediate predisposing characteristics. Two such phenotypes are a low level of response (LR), or a low sensitivity, to alcohol and bipolar disorder (Schuckit, 2009). The low LR might enhance the quantity of drinking during an evening through the need for more alcohol to achieve desired effects coupled with the overriding desire to drink as much as is needed for those effects. Individuals with bipolar conditions might begin drinking to excess during a manic episode, but then have problems cutting back on drinking once they become euthymic, or perhaps, use alcohol to 'self medicate' irritability or depressive symptoms. It is also possible that some of the same genes contribute to both AUDs or related endophenotypes and bipolarity (Schuckit *et al*, 2003). The latter hypothesis relates well to the paper by Yip *et al* (2012), whose data suggest that some of the link between a bipolar predisposition and adverse alcohol outcomes might operate through the low LR to alcohol. This commentary gives some additional background on LR and speculates about some implications of the Yip *et al*'s results.

A low LR to alcohol that is observed at peak and falling blood alcohol concentrations (BACs) is itself 40–60% heritable, and almost all prospective studies have noted that a lower LR earlier in life runs in families and predicts later alcohol problems (eg, Quinn and Fromme, 2011; Schuckit, 2009; Schuckit *et al*, 2011). This low response can be observed through less alcohol-related changes in stress hormones and electrophysiology, as well as lower subjective feelings of intoxication (Ehlers *et al*, 2004; Schuckit and Gold, 1988). The physiological basis for LR is further supported by unique characteristics observed during functional magnetic resonance imaging (fMRI) evaluations in the context of both alcohol and placebo (Schuckit *et al*, 2012). Regarding the fMRI studies, despite similar BACs and levels of performance on the cognitive tasks, subjects with a low LR demonstrated higher brain response contrast after placebo, compared with matched high LR controls, perhaps reflecting the need to exert more cognitive effort to complete the tasks. However, following alcohol, the low LR subjects actually decreased the BOLD contrast, and perhaps the cognitive effort, associated with the tasks, whereas the high LR subjects demonstrated the opposite pattern, showing greater BOLD response contrast after alcohol.

Regarding the second phenotype, bipolar disorder as briefly described by Yip *et al*, mood-related disorders also have a long and rich history regarding their implications for future alcohol problems. The most impressive data relate to bipolar disorders, with more questionable conclusions regarding whether major depressive disorders alone are associated with an enhanced AUD risk after one control for temporary depressions only observed in the context of heavy drinking (Schuckit *et al*, 2007).

Although the low prevalence of bipolar-I disorders in the general population makes it difficult to study healthy subjects with low LR and document if they are at elevated risk for future manic episodes, Yip *et al* used a more practical approach to study the relationship between the LR and a bipolar phenotype (BPP). In their work, BPP subjects compared with healthy controls demonstrated a lower LR during alcohol challenges, perhaps suggesting that some of the associations between bipolar conditions and AUDs might operate through a low LR. Furthermore, consistent with a recent study (Quinn and Fromme, 2011), they gathered potentially important data supporting the conclusion that the impact of a low LR on future drinking may operate primarily through a perception of less effects of alcohol at peak and falling BACs, and not via higher stimulation during rising BACs combined with less sedation at falling blood levels (the absence of a 'biphasic' response). The graphs Yip *et al* use to demonstrate the BPP and control group differences in LR at similar BACs are similar to our own prior work comparing individuals with

*Correspondence: Professor MA Schuckit, Department of Psychiatry, University of California, San Diego School of Medicine (UCSD), 8950 Villa La Jolla Drive, Suite B-218, La Jolla, CA 92037, USA, Tel: + 1 858 822 0880, Fax: + 1 858 822 1002, E-mail: mschuckit@ucsd.edu
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and without an elevated AUD risk based on their family histories (eg, Schuckit and Gold, 1988; Schuckit *et al*, 2012).

Finally, I offer a brief comment on some potential implications of the Yip *et al* findings. We recently published results from a pilot prevention study with healthy, drinking, non-alcoholic matched pairs of low LR and high LR 20-year-olds. They were randomly assigned to a generic state-of-the-art protocol to prevent heavy drinking or a similar prevention approach that also taught about the low LR as a risk factor for heavy drinking. Although both low LR and high LR subjects showed the expected decreases in drinking over the subsequent 2 months of the protocol, the individuals with low LR demonstrated significantly greater decreases if they had been assigned to the LR-based sessions (Schuckit *et al*, in press). The significantly greater decreases in drinking with exposure to an LR-based prevention paradigm might generalize to another group carrying a potential high risk for future alcohol problems likely to be associated with a low LR, those with the BPP phenotype. Of course, the pilot nature of our prevention study means that a fair amount of additional work is required to test that hypothesis, but the solid methodology and careful interpretation demonstrated by the Yip *et al* indicates that such additional efforts might be well worthwhile.

DISCLOSURE

The author declares no conflict of interest. The author is solely responsible for the content of the commentary and the work is not being considered for publication by another journal.

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