

Genetically influenced responses to alcohol affect brain activation both with and without alcohol

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A low level of response (LR) to alcohol is a genetically influenced characteristic, or phenotype, that reflects at least in part a low brain response to alcohol, and carries significant risk for the later development of alcoholism. This study addressed the physiological underpinnings of a low and high LR, finding significant differences in brain activation during a cognitive task, possibly reflecting differences in the amount of brain activity used to deal with a cognitive challenge.

Results will be published in the January 2012 issue of *Alcoholism: Clinical & Experimental Research* and are currently available at Early View.

"While some genes that contribute to LR have been provisionally identified, the mechanism through which the low LR operates in the brain has not been extensively studied," explained Marc A. Schuckit, distinguished professor of psychiatry at the University of California, San Diego, and corresponding author for the study. "This report confirms prior reports from our group that used a different cognitive task to show that people with a low LR process information differently from those with a high LR even when tested with placebo. The differences between LR groups after placebo and [alcohol](#) across different cognitive tasks may help explain why low LR subjects might have more problems recognizing the effects of moderate doses of alcohol. If you aren't able to recognize the effects of lower doses of alcohol, you are more likely to

drink heavy amounts per occasion, which both directly and indirectly increases your risk for alcohol problems."

"A phenotype provides an observable window into a genetically influenced behavior, in this case, the predisposition to alcohol use disorders," added Edith V. Sullivan, a professor in the department of psychiatry and behavioral sciences at Stanford University School of Medicine. "Here, the phenotype was a behavior with a physiological basis associated with a difference in response when having alcohol in the system. This combination provides the potential of identifying individuals who are at risk for developing alcohol use disorders before they develop. This is the essence of a genetic marker for a behavior. Few markers are perfect predictors, but those that approach a genetic basis should be robust and also be related to associated behaviors that are surrogate markers for the primary behavior."

Sullivan added that this study is cutting edge in its use of differential responses to alcohol at different levels of physiological processing as a grouping variable to interpret performance measures and brain physiological responses while performing cognitive tasks in an fMRI setting.

Schuckit and his colleagues examined 98 (52 females, 46 males) young, healthy drinkers who were not alcohol dependent and who had been identified in prior testing as clearly having low or high LRs to alcohol. The subjects in the two LR groups were matched to be similar on recent drinking histories, age, gender, race, and histories of smoking and using illicit drugs. All participants were evaluated during two event-related functional magnetic resonance imaging (fMRI) sessions while performing a validated cognitive task based on the stop-signal paradigm. The two groups were given a placebo or approximately 0.7 ml/kg of alcohol (roughly the equivalent of 3 standard drinks), in random order, and treated subjects developed identical blood alcohol levels during the

sessions.

"Those with a low LR seemed to have had to exert more cognitive effort to perform a [cognitive task](#) than those with high LR's after placebo," said Schuckit. "After alcohol, the low LR subjects seemed to do the task with less effort than after placebo, while the high LR subjects had to work harder to do the task after alcohol than after placebo. So when the low LR people drink modest amounts of alcohol, they may not perceive much change in how their brain is working. Also, if a modest dose of alcohol produces a situation where you don't have to exert as much effort to think about how a challenging task needs to be done, as might be true for low LR subjects, perhaps drinking is a bit more rewarding for you compared to people who find that modest alcohol doses impair their thinking, as is seen for high LR subjects." In short, intoxication seemed to become almost a 'normalized' state for low LR individuals.

"Extrapolating from these findings allows us to speculate that adolescents who are genetically predisposed for a low response, and therefore relatively high tolerance, to drinking alcohol would have poor ability for self-correction – the lesson we have from the Stop task – and their high tolerance may enable them to drink to dangerous levels," said Sullivan.

"The real issue for clinicians is that the low LR is an important genetically influenced risk factor for later alcohol problems," said Schuckit. "These results can also inform researchers interested in how the low LR might actually work to affect how intoxicated a person might feel."

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