

Using fMRI to demonstrate tolerance to the rewarding and anxiolytic effects of alcohol in heavy drinkers

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Tolerance to a drug can be defined as a markedly diminished effect with continued use of the drug. While development of tolerance to the subjective effects of alcohol has been demonstrated in heavy drinkers, neural correlates of tolerance have not been adequately characterized. This study characterizes the BOLD response to intravenous alcohol administration in mesocorticolimbic and visual-emotional brain structures of social drinkers (SDs) and heavy drinkers (HDs), in order to investigate if tolerance to alcohol's rewarding and anxiolytic effects can be observed in the brain using BOLD signal.

In this study, HDs were defined as individuals who regularly drank between 20-40 standard alcoholic beverages per week, while SDs drank an average of 1-14 drinks per week. We intravenously infused both groups with 6%v/v ethanol or placebo (saline), in counter-balanced order according to an infusion-rate profile based on a physiologically-based pharmacokinetic model for alcohol, to achieve a target blood alcohol concentration of 0.08 g%. During the alcohol infusion, participants underwent functional magnetic resonance imaging (fMRI) scans in which they viewed threatening and non-threatening emotional facial images.

Among SDs, we found greater activation to fearful faces than neutral faces in the bilateral amygdala during the

placebo infusion. When the SDs received alcohol, there was no difference in amygdala reactivity between fearful and neutral stimuli (fig. 1 A,B), likely due to alcohol's anxiolytic effect. In the HDs, alcohol did not attenuate response to fearful faces, partially because this group exhibited a blunted response to fearful faces during saline administration. Furthermore, alcohol activated the bilateral nucleus accumbens in the SDs, but not in the HDs (fig. 1 C,D). This may be related to differences in subjective intoxication ratings between the two groups; SDs reported significantly higher intoxication ratings than HDs during the scan (fig. 2). As expected, self-ratings of intoxication correlated with striatal activation in the left nucleus accumbens ($r^2 = 0.37, p = 0.012$), suggesting that activation in this area may reflect subjective experience of pleasure and reward during intoxication (fig. 3).

This study confirmed our hypothesis that at equivalent blood alcohol concentrations, HDs would experience reduced subjective effects of intoxication, and demonstrate lower neural activation than SDs in reward-related brain regions. The

correlation between nucleus accumbens activation to alcohol and subjective intoxication ratings suggests that striatal activation may be necessary for the perception of alcohol's euphoric effects. Furthermore, the attenuated amygdala response to fearful faces in the SDs during the alcohol condition was not observed in the HDs, suggesting that this group may not experience the anxiolytic effects of alcohol at this dose. This is the first fMRI study to clearly demonstrate an effect of drug tolerance in the brain, and may lead to an increased understanding of how the neural correlates of intoxication may contribute to alcohol addiction.

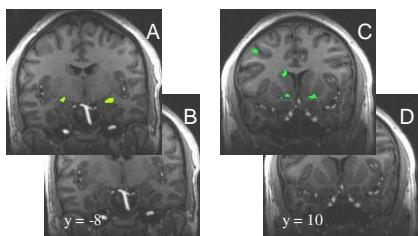


Fig 1. During the placebo condition (A), social drinkers had greater activation to fearful than neutral faces in the amygdala ($p < 0.005$). Under the alcohol condition (B), the fearful faces did not elicit greater activation. Heavy drinkers did not show greater activation to fearful compared to neutral faces in either condition (data not shown). (C) Social drinkers had greater activation during the alcohol than the placebo session in the nucleus accumbens ($p < 0.005$). The heavy drinkers did not show differences in activation between sessions (D).

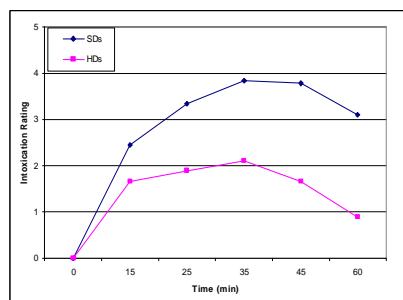


Fig 2. Participants rated on a scale of 0-5 how intoxicated they felt at each time point during the fMRI scan. The SDs reported significantly higher intoxication than HDs ($p < 0.05$).

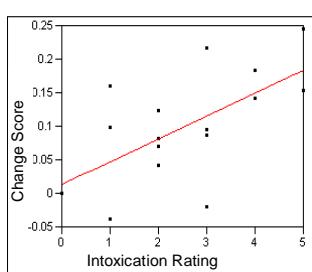


Fig 3. Significant positive association between subjective intoxication ratings and activation in the nucleus accumbens (-15, 10, -5). Change scores were calculated by subtracting percent signal change during the placebo from the alcohol condition.