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Laterality of Cortical Response to Ethanol is Moderated by TaqIA A1 Allele

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Acute ethanol releases dopamine, implicated in drug-related reinforcement, and suppresses glucose metabolism, particularly within the right cerebral hemisphere (Volkow et al., 2008; Volkow et al., 2006). This is consistent with a predominance of left hemisphere activity being associating with positive affect or approach, and right hemisphere predominance with negative affect/avoidance (Davidson, 2002; Tomer et al., 2008). Despite substantial evidence linking the TaqI DRD2 A1 allele with lower dopaminergic tone and greater vulnerability to alcoholism (Noble, 2000), its role in modulating acute effects of alcohol is unknown. We hypothesized that in individuals with the A1 allele, acute ethanol would improve mood and alter relative hemispheric activity.

Twelve healthy right-handed white men (mean age [sd]= 29.0 [5.0]) with no history of psychiatric diagnosis or dependence on alcohol had TaqI A DRD2 alleles assessed from blood. Six had the A1A2 genotype (A1+) and six the A2A2 genotype (A1-). In two order-counterbalanced [F-18]fluorodeoxyglucose (FDG) positron emission tomography (PET-Siemens ECAT EXACT HR+ tomography; CTI, Knoxville, TN) sessions 10 ± 8 days apart, globally-scaled counts served as a surrogate marker of relative glucose metabolism while participants performed a 35-min auditory vigilance task. Five min before testing, participants drank 250-ml of diet soda containing either 0.75 g/kg body weight or a trivial dose of ethanol, and self-rated their anxiety and fatigue (McNair et al., 1971). Five min after task initiation, FDG (≤5 mCi, ≤185 MBq) was injected intravenously. PET images were acquired for 30 min, and analyzed via statistical parametric mapping software (SPM5; <http://www.fil.ion.ucl.ac.uk/spm/software/spm5/>), as previously detailed (London et al., 2004). Individual hemispheric comparisons of relative activity within lateral cortex also analyzed 56 anatomical regions-of-interest (ROIs) from a parcellation of MNI-space (Tzourio-Mazoyer et al., 2002). We hypothesized that presence of the A1 allele would influence effects of ethanol on laterality ($[\text{Right}/(\text{Left}+\text{Right})] \times 100_{\text{ethanol}} - [\text{Right}/(\text{Left}+\text{Right})] \times 100_{\text{placebo}}$). Within-subject hemispheric differences were assessed with t-tests.

Wilcoxon Signed-Rank tests assessed group differences. Correlation analysis quantified the relationship between ethanol-related change in mood and laterality.

Task performance

Both allelic groups performed the vigilance task accurately (98.0 - 99.3% correct). Reaction time increased (Placebo +190 ms; Ethanol +301 ms) from measurement taken at 15 min to 30 min ($t_{1, 10} = 87.46$, $p < 0.001$), suggesting some vigilance decrement over time.

SPM analysis

Initial visualization ($p < 0.05$) revealed opposite effects of ethanol on laterality in the two groups (Figure 1a). Using a $p < 0.001$ alpha level (Figure 1b), A1- men had 587 left hemisphere voxels in 17 clusters where activity was higher after ethanol than placebo, but only 5 small right hemisphere clusters. A cluster extending from the left middle/inferior temporal gyrus to the middle occipital gyrus was significant for whole-brain corrected spatial extent (419 voxels, $p < 0.0005$). In contrast, there were only 4 small clusters with lower activity after ethanol than placebo, as compared to 866 right hemisphere voxels in 15 clusters. Two right hemisphere clusters were significant for volume-corrected spatial extent. One extended from pre/postcentral gyrus to the inferior parietal lobule (328 voxels, $p = 0.001$), and the other from inferior frontal gyrus to superior temporal gyrus (213 voxels, $p = 0.008$).

A1+ men showed the opposite pattern. There were 9 small left hemisphere clusters where relative activity was higher after ethanol than placebo, as compared to 440 right hemisphere voxels in 13 clusters. A cluster in the right caudate nucleus was significant for whole-brain corrected spatial extent (166 voxels, $p = 0.027$). There were 101 left hemisphere voxels in 4 clusters where relative activity was lower after ethanol than placebo, as compared to 2 small right hemisphere clusters.

ROI analysis

Two-tailed t-tests compared mean activity values between the hemispheres in each ROI (Figure 2A). The right hemisphere was more active after placebo for both A1- (24 of 28 ROIs, four with $p < 0.05$), and A1+ men (21 ROIs, eight with $p < 0.05$). Ethanol reversed rightward laterality in A1- ($L > R$ in 24 ROIs), but not A1+ men ($R > L$ in 24 ROIs, thirteen $p < 0.05$). Rightward preponderance was strongest in the frontal lobe (32% of ROIs, but 68% of $p < 0.05$ t-tests).

The mean right hemisphere value in each ROI was divided by the sum of the values in both hemispheres, expressed as a percentage, and weighted by the number of constituent voxels to create multi-ROI laterality indices. The placebo value was subtracted from the ethanol value to assess group differences via Wilcoxon Rank-Sum tests. A value of 21 would indicate no overlap between groups (rank $1+2+3+4+5+6$). Ethanol decreased $R > L$ hemisphere activity more in A1- men than A1+ men across all ROIs (Rank-Sum = 22; $p < 0.01$) and within each cortical lobe (Figure 2B). The most consistent rightward laterality occurred in the frontal lobe.

Relationship between mood and laterality of brain activity

Self-reported anxiety and fatigue scores during the placebo session were summed to yield a composite score and subtracted from the corresponding score after ethanol. All A1- but only one A1+ man gave higher anxiety/fatigue ratings after ethanol than after placebo (A1-: 2.50 ± 2.07 ; A1+: -2.17 ± 3.37 ; $p = 0.008$). Effects of ethanol on mood and laterality were

correlated (Figure 3). Higher anxiety/fatigue was associated with a greater decrease in right hemisphere activity, and less anxiety/fatigue with greater decrease in left hemisphere activity.

Discussion

Ethanol releases the inhibitory neurotransmitter dopamine, and reduces glucose metabolism more in the right than left hemisphere, thereby reversing the usual rightward bias in neural activity. Could dopamine mediate this equalization of cerebral laterality? Dopaminergic asymmetry in animals predicts differences in response to both stress and drugs (Carlson and Glick, 1989). We now report the rightward bias in cortical glucose metabolism was eliminated by ethanol in men without the DRD2 A1 allele, but was increased in men with the allele.

The A1 allele increases risk for alcoholism and is associated with expression of fewer D2 receptors (Jonsson et al., 1999). Most individuals have more D₂ receptors in the right than left striatum (Carlson and Glick, 1989; Vernaleken et al., 2007), consistent with greater reduction of right hemisphere glucose metabolism by ethanol if dopamine is involved. However, D2-receptor laterality exhibits strong individual differences (Tomer et al., 2008), and has been reported to be abnormal in alcoholics (Kuikka et al., 2000). The correlated abnormalities in the effects of ethanol on relative hemispheric activity and mood may therefore be mediated by abnormal D2-laterality in A1+ men, and this may contribute to the variable findings in relating mood to cortical laterality (Reid et al., 1998). Further studies are needed to determine if abnormal cortical laterality in response to ethanol generalizes to other abused substances.

Recent studies suggest that in A1+ individuals reinforcement circuits are hyporesponsive to natural rewards like food (Stice et al., 2008), but hyperresponsive to dopamine agonists (Kirsch et al., 2006). Finding that acute ethanol improved mood more in A1+ than A1- men is consistent with proposals that low dopaminergic tone increases risk for substance abuse through self-medication of negative affect with dopamine-releasers (Noble, 2000; Volkow et al., 2004), and suggests that heightened reinforcement contributes to the increased risk for alcoholism, and possibly to the increased risk for other addictions, that have been associated with the DRD2 polymorphism (Noble, 2000; Volkow et al., 2004).

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Figure 1.

Whole-brain statistical parametric maps indicate laterality of acute ethanol effects on relative glucose metabolism varied with allelic group. (A) At $p < 0.05$, voxels with greater relative activity after ethanol are shaded red, and those with greater relative activity after placebo shaded green, superimposed over an image representing MNI space (neurological format). Results are depicted at labeled sagittal (top), coronal (center) and transaxial (bottom) slices where positive values of the x, y, and z coordinates approximately represent mm to the right, anterior and superior relative to the anterior commissure. (B) The number of voxels meeting $p < 0.001$ were summed within each cerebral hemisphere, excluding midline clusters. L = left, R = right, E = ethanol, P = placebo

Figure 2.

Anatomical region-of-interest (ROI) analyses of reconstructed activity in each scan confirm that laterality of ethanol effects varied with allelic group. (A) ROI p-values of 2-tailed t-tests comparing the cerebral hemispheres in each group and condition are segregated by lobe. Because activities in neighboring ROIs are correlated, no multiple-comparisons correction was conducted. Orange shading = R>L, blue shading = L>R, NS = p > 0.05, G = gyrus, SupFG = superior frontal gyrus, SupTG = superior temporal gyrus, MidTG = middle temporal gyrus. (B) For each cortical lobe, the index $[R/(L+R)] \times 100$ quantifies hemispheric laterality in each individual (by group) and condition. Values higher than 50% represent R>L activity. Group comparison of ethanol effects on laterality ($[R/(L+R)] \times 100_{\text{ethanol}} - [R/(L+R)] \times 100_{\text{placebo}}$) employed Wilcoxon Rank-Sum tests. Statistics and associated p-values are presented in the A1+ column.

Figure 3. Effects of ethanol on mood covaried with effects on cortical laterality (Spearman's $r = 0.605$; $p < 0.04$). The dashed line represents the best-fit solution. ELI = ethanol laterality index $[R/(L+R)] \times 100_{\text{ethanol}} - [R/(L+R)] \times 100_{\text{placebo}}$