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Acute Ethanol Effects on Brain Activation in Low- and High-Level Responders to Alcohol

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Abstract

Background—A low level of response (LR) to alcohol is an important endophenotype associated with an increased risk for alcoholism. However, little is known about how neural functioning may differ between individuals with low and high LRs to alcohol. This study examined whether LR group effects on neural activity varied as a function of acute alcohol consumption.

Methods—30 matched high- and low-LR pairs ($N=60$ healthy young adults) were recruited from the University of California, San Diego and administered a structured diagnostic interview and laboratory alcohol challenge followed by two fMRI sessions under placebo and alcohol conditions, in randomized order. Task performance and BOLD response contrast to high relative to low working memory load in an event-related visual working memory (VWM) task was examined across 120 fMRI sessions.

Results—Both LR groups performed similarly on the VWM task across conditions. A significant LR group by condition interaction effect was observed in inferior frontal and cingulate regions, such that alcohol attenuated the LR group differences found under placebo ($p<.05$). The LR group by condition effect remained even after controlling for cerebral blood flow, age, and typical drinking quantity.

Conclusions—Alcohol had differential effects on brain activation for low and high LR individuals within frontal and cingulate regions. These findings represent an additional step in the search for physiological correlates of a low LR, and identify brain regions that may be associated with the low LR response.

Keywords

Level of response; fMRI; visual working memory; cerebral blood flow

I. Introduction

The low level of response (LR) (or sensitivity) to alcohol is a genetically influenced characteristic that impacts on the alcoholism risk (Schuckit, 2009). The need for higher doses of alcohol for an effect is hypothesized to increase the probability of drinking more per occasion to get to a desired level of effects in both animals and humans (Barr et al., 2003; Boyce-Rustay et al., 2006; Chappel & Weiner, 2008). In humans, a low LR may

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enhance the tendency to associate with similar heavy-drinking peers, alter the effects one expects from alcohol, and increase the risk of using alcohol to deal with stress (Dodge et al., 2003; Longzak et al., 2001; Rimal & Real, 2003). While LR is only one of several markers of AUD risk, to date a low LR helped predict future heavier drinking, alcohol-related problems, and/or alcohol use disorders (AUDs), even after controlling for drinking patterns and problems at the time LR was evaluated (Heath et al., 1999; Rodriguez et al., 1993; Schuckit et al., 2008a; Volavka et al., 1996). The heritability of LR is between 40% and 60% (Heath et al., 1999; Schuckit et al., 2001), and linkage as well as association studies have identified several genetic polymorphisms likely to be associated with this low reaction to alcohol (Hu et al., 2005; Joslyn et al., 2008).

While progress is being made regarding genetic and environmental contributors to the low LR, not as much is known about the neurophysiological changes associated with this less intense response to alcohol. Alcohol has many and varied effects in the brain, including changes in diverse neurochemical systems, a substantial decrease in glucose metabolism, and increased cerebral blood flow (D'Esposito et al., 2003; Ingvar et al., 1998; Volkow et al., 2005; Wang et al., 2000). The effects of alcohol differ across brain regions, and blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) has indicated increased neuronal activity in the dorsolateral prefrontal cortex and insula, but decreased activity related to alcohol in the cingulate, precuneus, and other brain regions (Calhoun et al., 2004; Levin et al., 1998). Consistent with acute and protracted withdrawal states, alcohol dependent individuals have shown greater signal intensities on fMRI in the frontal and cerebellar regions, even after a month or more of abstinence (Desmond et al., 2003; Oscar-Berman & Marinkovic, 2003; Sullivan et al., 2002). Recent PET imaging studies have identified decreases in dopamine activity in drug abusers to be associated with decreased activity in the striatum and frontal cortex (Martinez et al., 2009; Volkow et al., 2009), however few data are available on how neural activation patterns obtained by fMRI relate to the LR to alcohol.

LR has been most classically studied through alcohol challenge paradigms where the intensity of response is evaluated every 15 to 30 minutes after the consumption of a modest dose of alcohol (Schuckit et al., 2009b). The measures of LR have included the subjective feelings of intoxication using the Subjective High Assessment Scale (SHAS), as well as electrophysiological and hormonal changes in the context of alcohol. Studies have also used a retrospective LR measure, the Self-Report of the Effects of Alcohol (SRE) questionnaire, where subjects report the number of standard (10–12 gm ethanol) drinks required during the approximate first five times of drinking to produce up to four effects of alcohol (Schuckit et al., 1997) early in the drinking career. Both LR measures have retest reliabilities of .7 or higher (Kalmijn et al., 2009; Schuckit et al., 1997), the SRE has a Cronbach alpha > .9 (Ray et al., 2007), and the ability of LR established from the two methods to predict alcohol outcomes overlaps at ~.6 (Schuckit et al., 2009b).

Our group has used fMRI to evaluate mechanisms that potentially relate to a low LR to alcohol. Tapert et al. (2004) evaluated 35 adolescents (mean age ~17 years, 63% male) from a nonclinical sample who reported experience with alcohol, and who completed the SRE. A visual working memory (VWM) fMRI paradigm developed by Luck and Vogel (1997) was used to evaluate BOLD response as a function of LR scores. A regression analysis evaluated the relationship between the BOLD signal to the memory task and SRE scores while controlling for age, gender, ethnicity, and the number of drinks per month prior to testing. Greater activation as working memory load increased in right superior frontal gyrus, right cingulate, right cerebellum, and right parahippocampal gyrus was associated with higher SRE scores (i.e., lower LR). Further analyses identified 22 regions positively associated

with a low LR (including frontal and temporal regions), and 8 regions positively linked to a high LR (including parietal regions).

A second study (Paulus et al., 2006) reported results from both alcohol challenge and placebo sessions for 10 young adult subjects (mean age 23.2 years; 40% female). The alcohol session used 0.75 ml/kg of ethanol for males and 0.68 ml/kg for females to produce similar blood alcohol concentrations (BACs) across sexes (Breslin et al., 1997). In both placebo and alcohol challenge sessions, BOLD response to the memory task (Luck & Vogel, 1997) was evaluated at the usual time of peak BAC (60 min after drinking started). In the placebo session, low LR subjects showed greater activation to increasing working memory loads than did high LR subjects in the right inferior and middle frontal gyri, right inferior parietal gyrus, right amygdala, and right parahippocampal gyrus. Alcohol did not significantly influence behavioral performance on the task, and alcohol appeared to eliminate group differences in the regions listed above.

Together, these two fMRI studies suggest that subjects with a low LR may have to exert a higher degree of mental resources to maintain task performance under normal (i.e., no alcohol challenge, or placebo) conditions, perhaps demonstrating a compromised capacity to adjust cognitive processes to contextual demands. However, these two fMRI studies were relatively small and did not control for other factors that might confound fMRI results, such as possible changes in cerebral blood flow after alcohol administration. Also, the Tapert et al. (2004) study included subjects who were not clearly low or high on LR, while the small sample of young adults from the Paulus et al (2006) study were placed into higher and lower LR categories based on a median split of the Subjective High Assessment Scale (SHAS). The current study builds upon these prior results by presenting fMRI data collected in placebo and alcohol challenge sessions from a new and much larger group of 30 young adult matched pairs ($N=60$) identified as having a clearly high or clearly low LR to alcohol. This is the first study to explicitly examine whether LR effects on neural activity vary as a function of acute alcohol consumption after controlling for cerebral blood flow changes.

II. Materials and Methods

Participants and Measures

Using procedures approved by the UCSD Human Research Protections Program for all steps of the investigation, 18–25-year-old students were initially identified through mailed questionnaires using alcohol questions from the Semi-Structured Assessment of the Genetics of Alcoholism (SSAGA) instrument (Bucholz et al., 1994). In addition to a brief review of demography, personal and family history of alcohol problems, and symptoms of psychiatric disorders, the questionnaire also included the 12-item SRE that asked subjects to indicate the number of standard drinks (10–12g of ethanol) needed to experience each of up to four effects (i.e., feeling effects, slurred speech, unsteady gait, and unwanted falling asleep) the first five times they consumed alcohol (Ray et al., 2007; Schuckit et al., 2009a, 2009b). SRE First Five values are generated by averaging the number of drinks needed to feel each of the up to four effects above, initially defining a low LR (i.e., needing more drinks to generate effects, which is similar to having less effect per drink) as needing ≥ 4 drinks for effects. Each low LR subject was matched with a higher LR individual (SRE score ≤ 3.5) on weight, height, frequency of alcohol use, race, gender, and other substances used. Participants were excluded if they had ever met criteria for alcohol or drug dependence, bipolar or schizophrenia disorders (American Psychiatric Association, 1994), or if they had a current medical illness or use of medications that might interfere with an alcohol challenge or brain imaging, previous head trauma with loss of consciousness >3 minutes, pregnancy, color blindness, left handedness, or fMRI contraindications (e.g., claustrophobia, irremovable metal).

Potential high and low LR subjects were scheduled for a face-to-face interview using the full SSAGA (Bucholz et al., 1994; Hesselbrock et al., 1999), including the Family History Module (FHAM; Rice et al., 1995). If deemed eligible, they were invited to participate in a traditional alcohol challenge to confirm the LR status. There, after re-reviewing recent alcohol consumption patterns and determining that BACs were zero, they consumed .70 ml/kg (for females) or .75 ml/kg (for males) of laboratory grade ethanol over ~10 minutes given as a 20%-by-volume dose ingested from a straw attached to a reservoir covered by ethanol-saturated gauze inserted into a sealed container to disguise the beverage (Mendelson et al., 1984). Then, every 15–30 minutes over the 3 hours they filled out the SHAS and breath alcohol levels were determined (Intoximeter, St Louis, MO). About 80% of those showing a clearly high or low LR to alcohol (i.e., were in the upper and lower thirds of LR scores) during this protocol were scheduled for two fMRI sessions under alcohol and placebo conditions, in randomized order. The remaining subjects did not fall into the clearly high or low LR categories. Participants were assigned to the same order of the experimental conditions as their matched counterpart.

fMRI Procedures

The alcohol and placebo fMRI sessions followed identical protocols. After abstaining from food and drink for 12 hours prior, all participants were established to have a zero breath alcohol concentration (BrAC), were given a light breakfast of toast and juice, and females took a urine pregnancy test (none were pregnant). A cannula was inserted in one arm for blood samples to assess BACs during scanning (the breathalyzer device was not permitted in the scan room). Subjects then took 10 minutes to consume either a placebo beverage (caffeine-free diet soda) with a small amount of alcohol in the straw, or the .70 to .75 mL/kg dose of ethanol described above. Participants completed a SHAS and first blood draw, and were placed into the scanner 22 minutes after the start of beverage administration, with blood samples for BAC and verbal SHAS responses collected every 22 minutes. After scanning, the cannula was removed and a breathalyzer assessed BrAC at 30-minute intervals along with continued SHAS reports. Participants were debriefed and only permitted to go home by taxi or with a driver once BrAC levels were <.01 g/dL.

Imaging data were collected at the UCSD fMRI Center with a 3-Tesla General Electric (Milwaukee, WI) CXK4 scanner using an 8-channel head array coil. Each session began with a sagittally acquired high-resolution Spoiled Gradient Recalled (SPGR) anatomical sequence (25 cm field of view; 256×256 matrix; 124 slices each 1.0 mm thick covering the whole brain; 4.8 ms echo time; and 20 ms repetition time). The memory task was administered ~50 minutes after drinking started, while BACs were likely to be rising, during T2*-weighted echo planar imaging (32 ms echo time, 90° flip angle, $3.43 \times 3.43 \times 2.6$ mm voxels with a 1.4 mm gap, 30 axial slices covering the whole brain, 2000 ms repetition time, 256 repetitions). These fMRI parameters were chosen to minimize artifacts. To control for any cerebral blood flow (CBF) differences across sessions or between groups, brain blood perfusion was measured with resting arterial spin labeling acquired by a modified Flow-Sensitive Alternating Inversion Recovery (FAIR) sequence (Liu et al., 2005). This sequence used a spatially-selective inversion pulse which extended 10 cm above and below the slab in which images were acquired. A Quantitative Imaging of Perfusion using a single-subtraction saturation pulse was used with a 22cm field of view, a 64×64 matrix, 3.2 ms echo time, 2500 ms repetition time, an inversion time of 600 ms and an inversion time 2 of 1600 ms (Wong et al., 1998).

The event-related visual working memory task administered during fMRI was developed by Luck and Vogel (1997), providing an estimation of memory across increasingly challenging tasks. Each trial consisted of 2, 4, or 6 colored dots (corresponding to low, moderate, and high working memory loads), presented for 100 ms at random locations on a gray

background that was projected onto a screen. After a 900 ms delay, for 2,000 ms a new image with the same dot locations was presented where the colors of the dots were either the same or one dot was different from the prior image. Participants indicated whether the figures were the same or different for 30 trials at each level of difficulty (2, 4, and 6 dots) in random order, along with 69 interspersed similar rest trials, for a total task time of 8 minutes, 32 seconds. Performance was measured by the number of missed responses, percent correct, and reaction time for each number of dots load.

Data Processing and Analysis

Analyses focused on changes in BOLD response to 6 dots relative to 2 dots on the VWM task. All structural and functional image processing used Analysis of Functional NeuroImages software (AFNI; afni.nimh.nih.gov; Cox, 1996). To correct for head motion, each repetition was coregistered to the maximally stable base image using a 6-parameter algorithm (3dvolreg). Time series data were analyzed with a multiple regression model (3dDeconvolve) employing task regressors coding each working memory load (2, 4, 6 dot) and controlling for baseline signal, linear drift, and motion corrections applied in three rotational orientations. Task regressors were multiplied (i.e., convolved) with a modified gamma variate function (Boynton et al., 1996) that modeled anticipated hemodynamic response. Data were resampled to 4×4×4 mm voxels, a Gaussian filter (FWHM 4 mm) was applied to account for individual anatomical variations, and each subject's data were transformed to standard space (Talairach et al., 1988). Activation in each voxel during each task trial type was divided by the baseline signal to obtain percent signal change. To capture change across the working memory loads, a difference score between the smoothed percent signal change of the 6-dot load and 2-dot load was calculated for each voxel.

A replication approach was used to examine activation patterns across groups with low and high LR and across the three levels of difficulty for the memory tasks. A series of AFNI *t*-tests analyzed LR group differences in activation patterns within the eight regions of interest (ROIs) shown to differentiate LR groups in the two prior fMRI studies (Paulus et al., 2006; Tapert et al., 2004). These *t*-tests were examined separately for the placebo and the alcohol conditions.

For those regions showing significant LR group differences, follow-up 3dANOVA3s were conducted in AFNI to assess for group by condition interaction effects, again using thresholds that considered the intensity of the statistical effect of each voxel, as well as the number of contiguous voxels with the same effect, as described below. To guard against Type I error, Monte Carlo simulations (employed in the AFNI program using AlphaSim) determined the number of contiguous voxels with an effect of $p < .01$ in each voxel that would yield < 5% probability of a false-positive finding. For regions thus ascertained as significant, the average percent signal change of the 6-dot load relative to the 2-dot load was evaluated for each participant from each condition with ANCOVA to control for the effects of any demographic or substance use characteristics shown to be significantly different between LR groups. Labels for brain activation were confirmed using the Talairach Daemon software (Lancaster et al., 2000). For brain regions showing a significant BOLD response effect, we examined cerebral blood flow (CBF) using arterial spin labeling for the effect in that cluster.

III. Results

Subject Characteristics

The 30 male and 30 female subjects were 18 to 25 years old (mean=20.17, $SD=1.54$) and each had completed the interview, alcohol challenge, and 2 fMRI sessions. Reflecting the selection criteria, low LR subjects had significantly higher SRE scores (i.e., needed more

drinks to experience effects of alcohol) than those with high LR ($t(58)=6.36$, $p<.001$), but the two LR groups were similar on gender, education, height, weight, and most measures of alcohol, tobacco, and cannabis use. However, those with low LR reported higher drinks per occasion.

Alcohol Concentrations and Subjective Response

The BAC values across the ~ 3 hours were similar for the 2 LR groups, as shown in Figure 1. ANOVA revealed a significant time effect ($F(8,51)=139.34$, $p<.001$), but no group effect ($F(1,58)=2.07$, $p=.16$) or LR group by time interaction ($F(8,51)=.81$, $p=.60$).

Figure 2 demonstrates the expected significant LR group differences on the subjective high (SHAS) measure following alcohol. Here, ANOVA was significant for time ($F(8,51)=51.57$, $p<.001$), LR group ($F(1,58)=32.85$, $p<.001$), as well as the LR x time interaction ($F(8,51)=11.63$, $p<.001$). These SHAS scores were significantly different between groups at all time points, including the time of SHAS peak (6.61 ($SD=5.29$) vs. 14.99 ($SD=7.75$) across low and high LR subjects ($F(1,58)=23.95$, $p<.001$).

Performance on the VWM Task

Table 2 shows the performance for the 6-dot (i.e., high working memory load) trials of the memory task. Here, alcohol significantly increased the number of misses ($t(58)=-2.56$, $p=.01$) and decreased the percent correct responses ($t(58)=2.21$, $p=.03$) for both LR groups, but did not influence reaction time. In addition, the two LR groups did not differ from each other on any of these measures after placebo or following alcohol. While, as implied from these findings, a follow-up ANOVA considering the memory load (2/4/6 dots) and condition (alcohol versus placebo) revealed significant main effects on all three outcome measures of performance, there was no significant interaction between the number of dots and alcohol vs. placebo condition (i.e., alcohol had a consistent effect on performance regardless of task difficulty).

Replication of LR Group Differences in fMRI Response

The first group of results in Table 3 describes fMRI clusters that had significant LR group differences for signal change to the 6-dot load versus the 2-dot load, as shown in prior work (Paulus et al., 2006; Tapert et al., 2004). For each cluster with prior LR group differences, the table lists the volume of the cluster and the anatomical location (Talairach coordinates). The final two columns of Table 3 give the average 6-dot relative to 2-dot values for high and low LR groups. Data are provided for regions where the group differences were significant at a voxel-wise $p < .01$ and corrected volume-wise $p < .05$.

As shown near the top of Table 3, for the placebo condition, in the right inferior frontal region, low LR subjects had greater task activation (i.e., 6dot > 2dot) on the working memory task as the number of dots increased, while the high LR subjects showed no change across levels of task difficulty. In the right cingulate region, both groups showed less activation (2dot > 6dot) as the number of dots increased, and this effect was greater for low LR individuals. In the middle frontal gyrus, low LR individuals showed less activation with greater working memory difficulty (i.e., with 6 dots), while high LR individuals exhibited the opposite pattern.

The middle rows in Table 3 describe fMRI results following alcohol. While low LR subjects showed less activation as load increased (2-dot>6-dot) in all five clusters with significant LR group differences, high LR subjects showed the opposite pattern (6-dot>2-dot) in four of five regions. Only in the right inferior parietal region did both groups show less activation as load increased.

LR Group x Condition Interaction in fMRI Response

The third group of results, listed at the bottom of Table 3, presents LR group by condition (alcohol versus placebo) interactions, using ANOVA. Significant interactions were found in the right inferior frontal gyrus showing increased activation with working memory load, and in the right cingulate showing greater activation at the low working memory load. These results are also shown graphically in Figures 3 and 4. Overall, a similar pattern of interaction effects was observed in both clusters, such that: (1) the high LR group had similar levels of activation across working memory loads, (2) the high LR group had similar levels of activation across conditions (alcohol and placebo), (3) the low LR group showed the greatest fMRI activation under placebo, and (4) alcohol attenuated the low LR group's increased response found under placebo. In general, these effects were more pronounced in the inferior frontal than in the cingulate region. The change in activation between 2-dot and 6-dot for the LR group under placebo was significant in the frontal ($F(1,29)=18.68, p<.001$) and cingulate ($F(1,29)=15.12, p<.01$) areas, and there was a trend for LR group differences during the 6-dot trials under placebo in the frontal cluster ($F(1,58)=3.78, p=.06$) that was not present under alcohol ($F(1,58)=.10, p=.75$). Similarly, in the cingulate the LR groups were more similar on 6-dot trials under alcohol, but the LR group differences were not significant under placebo ($F(1,58)=1.19, p=.28$) or alcohol ($F(1,58)=.02, p=.89$) conditions.

Controlling for Potential Confounds

To evaluate whether the alcohol-related effects reported above could be accounted for by differences in brain blood flow, we examined baseline perfusion using arterial spin labeling (ASL) collected during each session for each clusters listed in Table 3. There were no LR group, conditions (alcohol vs. placebo), or group x condition interactions found in the rate of cerebral blood flow for any voxel within the clusters listed in Table 3. Thus, the effects reported in Table 3 are likely to relate to changes in neuronal activity as opposed to brain blood flow.

Both age and typical quantity of drinks per occasion had differed between LR groups in Table 1. Therefore, ANCOVA models were run to control for the effects these two variables might have had on the significant LR group differences listed in Table 3. In these models, neither age nor drinking quantity was significantly related to percent signal change in any region, and all LR group differences found previously remained significant at the $p<.01$ level.

IV. Discussion

The current study evaluated possible differences between high and low LR subjects on brain activation during a working memory task. The major findings relate to two brain areas (inferior frontal gyrus and cingulate) where activation during a working memory task was the highest for subjects with a low LR under the placebo condition. Interestingly, these LR group differences under placebo were attenuated after a moderate dose of alcohol. This is the first known study to provide evidence for such brain activation differences in individuals with low versus high LRs. These data were generated through 120 fMRI sessions using placebo and alcohol challenges in 30 high LR-low LR matched pairs of healthy, non-alcoholic young adults.

Therefore, the current results corroborate the conclusions of 2 prior independent samples that activation to high working memory loads is highest for subjects with a low LR under placebo condition. The prior study that included an alcohol challenge (Paulus et al., 2006) also found that alcohol tended to attenuate these LR group differences.

We had originally predicted that people with a low LR would show modest fMRI activation after alcohol as a reflection of their less intense reaction to ethanol. However, the results of the studies to date have consistently indicated the opposite pattern. These findings underscore the fact that it can be difficult to predict specific neurochemical or electrophysiological changes in the brain based on how a person reacts or what they perceive. For example, depressive symptoms might be suspected to reflect an initial paucity of monoamines in the synapse, but there might actually be an initial overabundance of these chemicals with subsequent presynaptic changes that lead to less neurotransmitter production or postsynaptic decreases in receptor sensitivity that produce the depressive symptoms. Also, the hypothesis that a low LR to alcohol might relate to higher alcohol intake and problems was initially labeled counter-intuitive by theorists who believed AUDs always developed because of greater feelings of reward from alcohol. While further work will determine if the current fMRI results are robust, findings have been consistent enough across studies to warrant speculation on what these results might mean.

Consistent with our prior fMRI studies on low responders to alcohol, the right prefrontal cortex showed greater activation in low LR individuals under placebo but not under alcohol (Tapert et al., 2004; Paulus et al., 2006). The current study extends these findings by providing support for an interaction effect in this general area, and demonstrates through arterial spin labeling that the result was not an artifact of LR group differences in cerebral blood flow. One possible explanation for the LR findings in the prefrontal cortex might be that during non-alcohol conditions the low LR group required greater activity in this region to successfully recognize similarities across visual stimuli. This might reflect a possible compromised capacity, or reduced efficiency, to adjust cognitive processes to contextual demands. Such a finding might be relatively prominent in the right inferior frontal gyrus, which, as part of the prefrontal “executive” area, consistently activates during cognitive tasks that require inhibition (Rubia et al., 2001; Rubia et al., 2003; Menon et al., 2001). This region may be part of a system that is critical for the suppression of irrelevant responses (Aron et al., 2004), helping to adjust behavior as a consequence of reinforcement learning (Rolls et al., 2008). The prefrontal cortex also appears instrumental to the reduced sensitivity of reward (Goldstein et al., 2007). Thus, a possible interpretation of the prefrontal neuroimaging findings is that individuals with low LR require more activation in this area to suppress “irrelevant” material, as compared to those with high LR. Drinking a moderate dose of alcohol attenuated this effect in low LR subjects, which may reflect less interference with inhibition and possibly greater processing efficiency after drinking. At the same time, low LR subjects may be subjectively less able to focus on the effects of alcohol itself, producing a state where there is less subjective recognition that intoxication has occurred at low to modest BACs.

A similar pattern of findings were also found to a lesser extent within the right cingulate, an area suggested to be part of a “default network” associated with increased brain activity under resting conditions, and perhaps reflecting mind wandering, planning, or self-monitoring processes (Gilbert et al., 2007; Mason et al., 2007). In the current study, low LR subjects had more BOLD response than high LR subjects at rest (i.e., greater deactivation during the 6-dot load) during the placebo condition, and this group difference was also attenuated by alcohol. One interpretation could be that alcohol resulted in decreased contextual monitoring without impacting task performance for low LR subjects as cognitive demands increased. This may illustrate a desirable effect of alcohol for low LR subjects, since it would also decrease neural activity without affecting performance.

The current data were not likely to reflect any differences between high and low LR groups on acquired tolerance to alcohol for several reasons. First, the major findings remained robust even after controlling for the modest differences between low and high LR subjects in

recent drinking quantities. Second, the major effects of LR in a recent study of 325 12–22 year olds indicated that the overall relationships between LR and the effects of alcohol remained significant after controlling for recent drinking, with results supporting the conclusion that LR and acquired tolerance are likely to be independent characteristics (Schuckit et al., 2009a).

In interpreting the current results, it is important to keep in mind the limitations of the investigation. First, only three studies, including the current work, have used fMRI to compare low and high LR subjects, and additional effort is required to determine the replicability of our findings. Second, all three studies used the same visual working memory task, and other brain activation differences might emerge when other paradigms are used. Third, while the results reported here relate to 60 individuals across 120 fMRI sessions plus an additional 60 alcohol challenges in a research laboratory, larger samples are needed to generate the greater statistical power that might be required to detect small to medium effects. Fourth, while subjects were not told whether they received alcohol or placebo, with BACs typically peaking at ~.6gm/dL at about 1 hour, it is likely that most subjects recognized the differences between the two conditions, and such recognition could influence results. Fifth, our findings were limited to the right hemisphere, which may be a function on the visual nature of the task, and it is possible that a verbal task might reveal left hemisphere findings. Finally, the current evaluations were limited to young, healthy, right-handed Caucasian men and women who were enrolled in college, and there is a need to evaluate these effects in other populations.

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FIGURE 1.

BAC over time during the fMRI session for low and high LR groups ($N=60$); 30 pairs were individually matched on age, sex, height, weight, recent drinking, smoking, and drug use. BAC= blood alcohol concentration used at baseline through 129 minutes; BrAC= breath alcohol concentration for 159 to 220 minutes. No significant group differences at any time point (p 's > .05). Error bars for ± 1 standard error of mean.

FIGURE 2. SHAS 7-item scores throughout the alcohol fMRI session, for low and high LR groups ($N=60$). SHAS-7 = Subjective High Assessment Scale scores for the 7 most informative SHAS items. Groups significantly different at each time point ($p<.001$ to $p<.01$) after alcohol administration. Error bars for ± 1 standard error of mean.

FIGURE 3.

A cluster in the right inferior frontal gyrus, highlighted here in an axial slice, showed a significant LR group by condition interaction effect on VWM task activation ($N=60$, $p<.05$, cluster size=192 μ l).

FIGURE 4.

A cluster in the right cingulate, highlighted here in a sagittal slice, showed a significant LR group by condition interaction effect on VWM task deactivation ($N=60$, $p<.05$, cluster size=128 μ l).

Table 1Participant demographics and substance use history ($N=30$ matched pairs)

	Low LR Subjects ($n=30$)	High LR Subjects ($n=30$)	t-statistic
SRE Score **	4.64 (1.38)	2.57 (1.12)	6.36 ($p<.001$)
% Female	50%	50%	---
Age *	19.77 (1.46)	20.57 (1.55)	-2.06 ($p=.04$)
Years of education	13.57 (0.94)	14.03 (1.03)	-1.83 ($p=.07$)
Height (inches)	68.67 (4.83)	68.30 (3.63)	.33 ($p=.74$)
Weight (lbs)	158.87 (28.92)	149.40 (21.58)	1.44 ($p=.16$)
# days/month drink	6.13 (5.08)	4.53 (4.35)	1.31 ($p=.20$)
# drinks/occasion *	3.93 (1.74)	3.03 (1.52)	2.13 ($p=.04$)
# days/month tobacco use	.93 (1.98)	.77 (1.92)	.33 ($p=.74$)
# tobacco units/occasion	.33 (0.55)	.27 (0.52)	.48 ($p=.63$)
# lifetime cannabis use occasions	9.00 (24.97)	2.60 (5.48)	1.37 ($p=.18$)

*
 $p<.05$;**
 $p<.001$

Table 2
Behavioral performance on the high working memory load (6-dot) of the VWM task ($N=30$ matched pairs)

	Placebo Condition			Alcohol Condition			Alcohol vs. Placebo
	Low LR (<i>n</i> =30)	High LR (<i>n</i> =30)		Low LR (<i>n</i> =30)	High LR (<i>n</i> =30)		
	Mean (SD)	Mean (SD)	<i>t</i> -stat	Mean (SD)	Mean (SD)	<i>t</i> -stat	<i>t</i> -stat
# Misses	.57 (0.90)	.64 (1.16)	-.28, <i>p</i> =.78	1.53 (2.79)	1.29 (1.27)	.43, <i>p</i> =.67	-2.56, <i>p</i> =.01
% Correct	82.63 (12.66)	84.18 (9.64)	-.52, <i>p</i> =.61	76.77 (15.75)	79.57 (12.39)	-.75, <i>p</i> =.46	2.21, <i>p</i> =.03
Reaction time (ms)	2478 (172)	2457 (159)	.49, <i>p</i> =.63	2496 (188)	2491 (135)	.09, <i>p</i> =.93	-.85, <i>p</i> =.40

Table 3

Clusters showing significant group differences or group x condition interaction in BOLD response to high relative to low working memory loads ($N=60$)

Anatomic Regions	Talairach coordinates					HIGH LR Mean	LOW LR Mean
	Volume (μl)	x	y	z			
<i>A priori</i> defined ROIs for placebo condition							
R inferior frontal	192	45	18	12	.00	.17	
R cingulate	256	15	-22	40	-.02	-.10	
R middle frontal	256	39	9	44	.08	-.04	
<i>A priori</i> defined ROIs for alcohol condition							
R inferior parietal	640	47	-43	27	-.02	-.17	
R inferior parietal	256	55	-32	44	.08	-.05	
R middle frontal	448	37	50	19	.14	-.04	
R middle frontal	320	37	9	52	.06	-.06	
R inferior frontal	192	41	35	7	.08	-.07	
Clusters within the <i>a priori</i> defined ROIs showing a group x condition interaction							
R inferior frontal	192	45	18	12	-	-	
R cingulate	128	12	-21	40	-	-	

ROIs= regions of interest; Talairach coordinates refer to the centroid voxel of the cluster; high LR and low LR means are the average values on the % signal change for the 6-dot to 2-dot working memory load trials. LR group differences for the clusters listed here were significant at a voxel-wise alpha of .01 and corrected volume-wise alpha of .05.