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Authors

Schuckit, Marc A
Smith, Tom L
Paulus, Martin P
et al.

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The Ability of Functional Magnetic Resonance Imaging to Predict Heavy Drinking and Alcohol Problems 5 Years Later

Marc A. Schuckit, Tom L. Smith, Martin P. Paulus, Susan F. Tapert, Alan N. Simmons, Neil J. Tolentino, and Alexandra Shafir

Background: Low levels of alcohol responses (low LRs) are genetically influenced phenotypes that are identified before alcohol dependence and predict future heavy drinking and alcohol problems. A recent paper described 13 LR-related blood oxygen level-dependent (BOLD) response contrast patterns observed during an emotional face recognition task that might reflect cognitive processes contributing to LR and that might themselves predict adverse alcohol outcomes (Paulus et al., *Biol Psychiatry* 2012; **72**: 848). This paper evaluates the predictive implications of those functional magnetic resonance imaging (fMRI) patterns.

Methods: Of 120 subjects from Paulus and colleagues (2012), 114 (57 low and high LRs; ~50% females) were interviewed 5 years later at age 25. Correlations between baseline fMRI patterns and alcohol-related outcomes were evaluated, and regression analyses were used to determine if BOLD response contrasts incremented over LR in predicting outcomes.

Results: Baseline fMRI patterns in 5 of 13 baseline regions of interest correlated with adverse outcomes. Such patterns in insular regions, particularly the left anterior insula, and the right frontal gyrus, added to LR in predicting alcohol problems. The relationships remained robust when exact binomial procedures were used, but, reflecting the small sample size, it was not possible to adequately consider Bonferroni corrections.

Conclusions: The data suggest that fMRI BOLD response contrasts predicted heavier drinking and alcohol problems 5 years later, even after considering baseline low LRs. Future work will focus on whether fMRI results can predict outcomes in larger samples and among young nondrinkers, as well as how the imaging results increase understanding of the processes through which LR operates.

Key Words: Alcohol, Functional Magnetic Resonance Imaging, Alcohol Sensitivity, Alcohol Outcomes, Prospective, Prediction.

THE LOW LEVEL of response (low LR) to alcohol is one of several early life genetically influenced phenotypes that predict future heavy drinking and alcohol problems (King et al., 2014; Newlin and Renton, 2010; Quinn and Fromme, 2011; Schuckit, 2014). Whether measured as lower responses to oral alcohol challenges or as self-reports of more drinks required for effects (Schuckit et al., 2010), individuals with lower LRs require higher blood alcohol concentrations (BACs) for intoxication and/or to demonstrate physiological responses to alcohol. The latter include less alcohol-induced decreases in alpha activity in background cortical electroencephalograms, less prolonged P300 waves in evoked potentials, and less change in alcohol-sensitive hormones (Ehlers et al., 1999; Schuckit and Gold, 1988; Schuckit et al., 1988a,b, 2000). Low LR has a heritability of 0.40 to 0.60 (Heath et al., 1999; Luczak et al., 2002; Schuckit et al., 2001; Viken et al., 2003), and predicts higher future alcohol quantities and problems, even after controlling for earlier drinking (Chung and Martin, 2009; Quinn and Fromme, 2011; Schuckit et al., 2007, 2008; Volavka et al., 1996).

However, until recently little was known about the neural processing underlying the low LR. Thus, our group has searched for brain features potentially related to LR using functional magnetic resonance imaging (fMRI). We began with a study of drinking but nonalcohol-dependent high school students, with results indicating that the lower the LRs the greater the prefrontal activation during a no-beverage high demand visual working memory (VWM) task above and beyond any effect of VWM performance across levels of LR (Tapert et al., 2004). Those results were corroborated in a second study with college drinkers, and expanded by including an alcohol administration session where LR group differences diminished after a moderate alcohol dose (Paulus et al., 2006).

From the Department of Psychiatry (MAS, TLS, SFT, ANS, AS), School of Medicine, University of California, San Diego, La Jolla, California; Laureate Institute for Brain Research (MPP), Tulsa, Oklahoma; and Bank of America (NJT), New York City, New York.

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Reprint requests: Marc A. Schuckit, MD, Department of Psychiatry, University of California, San Diego, 8950 Villa La Jolla Drive, B-218, La Jolla, CA 92037; Tel.: 858-822-0880; Fax: 858-822-1002; E-mail: mschuckit@ucsd.edu

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The third investigation, which is the basis for the current predictive analyses, generated data for a new group of drinking but not alcohol-dependent college students who participated in 3 cognitive tasks (Paulus et al., 2012; Schuckit et al., 2012; Trim et al., 2010). The earlier papers for this project focused on cognitive tests related to executive functioning (i.e., VWM and a stop signal task), and were published sequentially as the original data developed by using smaller subsets of the subsequent final sample (Schuckit et al., 2012; Trim et al., 2010). The manuscript for which data regarding fMRI results related to an emotional face recognition paradigm utilized the largest number of subjects and was the final paper in this series. Thus, the follow-up data in the current study focus on results from subjects who participated in the emotional face recognition paradigm as reported by Paulus and colleagues (2012).

Based on prior fMRI results which were obtained with smaller samples using 2 executive functioning tasks, we hypothesized that in the context of the emotional face recognition task, low LR subjects would demonstrate higher blood oxygen level-dependent (BOLD) response contrast with placebo and lower values after alcohol, while the high LR individuals will show the opposite pattern. This may reflect a general pattern in low LR subjects of how they process information that also extends to emotional-based tasks, even after controlling for alcohol effects on cerebral blood flow (CBF; Rickenbacher et al., 2011). This pattern was predicted in brain regions related to recognition and processing of emotional faces, such as emotion processing (e.g., insula and amygdala) and in top-down emotional processing control (e.g., medial prefrontal cortex and the anterior and perigenual cingulate). In that study LR group or LR group by placebo/alcohol condition differences were found in both right and left frontal, insula, and anterior cingulate regions.

The previous findings may indicate that individuals with low LRs need greater cognitive effort to recognize relatively subtle differences across stimuli when they are tested with placebo (Paulus et al., 2012). The neurocognitive processes related to the low LR to alcohol might more closely reflect underlying mechanisms that contribute to the low alcohol sensitivity than the potentially less precise measures of the behavioral response to alcohol during a standard alcohol challenge. In addition, the finding of the need for higher levels of neural processing resources during effortful tasks with placebo may suggest that it is possible to identify individuals with low LRs before their first drink. These issues could be addressed by following participants after imaging sessions to determine if the baseline LR and fMRI patterns during placebo and alcohol sessions predicted heavier drinking and alcohol problems.

The current paper reports the results of a 5-year follow-up of 95% of the 120 individuals who completed the baseline fMRI protocol, 116 of whom were included in the analyses by Paulus and colleagues (2012). The current paper evaluates 3 hypotheses: (i) the continuous measure of LR will correlate significantly with adverse alcohol outcomes in these subjects (an evaluation necessary to adequately evaluate Hypothesis 3); (ii) fMRI patterns that were related to LR will predict future adverse alcohol outcomes; and (iii) baseline fMRI patterns reflecting higher BOLD response contrasts with placebo in subjects with low LR, especially in the insula, amygdala, and prefrontal cortex, will add to the prediction of adverse alcohol outcomes even when the low LR to alcohol is also considered.

MATERIALS AND METHODS

Participants

Data collection for the original subjects (Paulus et al., 2012) used 3 steps, following approval from the University of California, San Diego (UCSD) Human Research Protections Program. First, randomly selected 18- to 25-year-old European American (EA) and white Hispanic students received emailed questionnaires. The sample did not include Asian individuals ~40% of whom experience physiological alcohol responses that might make alcohol challenges in MRI scanners unsafe (Luczak et al., 2002), and too few minorities of other ethnic/racial groups were available to create optimally matched low and high LR pairs within the projected 120 subjects. Questionnaire items were extracted from the Semi-Structured Assessment for the Genetics of Alcoholism interview (Bucholz et al., 1994; Hesselbrock et al., 1999) covering demography, substance use, and major psychiatric disorders using DSM-IV (American Psychiatric Association, 1994). The initial evaluation of subjects' LR status was based on a median split on the Self-Report of the Effects of alcohol questionnaire (Schuckit et al., 2007, 2008). From the ~70% who responded, participants were considered for inclusion if they: (i) ever consumed a full standard drink (ethanol [EtOH]: 10 to 12 g); (ii) denied histories of brain trauma, epilepsy, or alcohol or drug dependence; (iii) denied current psychiatric disorders; (iv) were not pregnant; (v) were right handed; and (vi) had no MRI contraindications (e.g., irremovable metal).

In step 2, subjects were contacted and the study was explained, with ~90% of those eligible agreeing to participate. To corroborate their preliminary LR status, the subjects received laboratory-based alcohol challenges (males: 0.75 ml/kg EtOH; females: 0.70) (Breslin et al., 1997) with both subjects and researchers blind to the contents (Mendelson et al., 1984). LR was measured using the Subjective High Assessment Scale consisting of 13 items graded on a 39-point scale for both positive (e.g., feeling high or intoxicated) and negative (e.g., feeling confused or nauseous) alcohol effects (Eng et al., 2005).

In step 3, 2 fMRI sessions scheduled within consecutive weeks on nonconsecutive days were given using, in random order, alcohol (same doses as in prior sessions) or placebo. Twenty minutes after drinking, subjects entered a 3 T GE CXK4 Magnet scanner (General Electric Medical Systems, Milwaukee, WI) and participated in the task near the usual time of the peak breath alcohol levels, ~60 minutes after drinking.

Baseline Task

An emotional face-processing task (Hariri et al., 2005) was administered, in which subjects were presented, 3 times each in random order, a 5-second exposure to 3 faces (a target and 2 probes), and told to match emotional expressions (happy, angry, or fearful) of targets and probes, with interspersed 12-second fixation periods between each face or control task. There were 18 trials (3 blocks of 6 trials) over 512 seconds.

The imaging session consisted of a 10-second 3-plane scout scan and a sagittally acquired spoiled gradient recalled sequence (FOV = 25 cm, matrix = 192 × 256, 172 sagittally acquired slices 1-mm thick, TR = 8 ms, TE = 3 ms, flip angle = 12°). Moreover, 256 axially acquired T2*-weighted echo-planar images (EPIs) were gathered (FOV = 23 cm, matrix = 64 × 64, 30 slices 2.6-mm thick, gap = 1.4 mm, TR = 2,000 ms, TE = 32 ms, flip angle = 90°) with an 8-channel brain array coil.

Follow-Up Evaluations for the 120 Original Subjects

At baseline, subjects gave permission for follow-up, and supplied birthdates, addresses, and how to reach additional individuals likely to know their future whereabouts. With UCSD Human Research Protections Program approval, ~5 years later individuals were re-contacted for 1-hour phone interviews regarding interval events, for which they were paid $125. A close relative or friend received $100 for a separate 1-hour phone interview about the subject.

Of the 120 participants, 114 (95%) individuals (57 matched low and high LR pairs) were evaluated. Similar to baseline, interval questions covered demography, alcohol quantities, and alcohol-related problems that included the 11 DSM-IV abuse and dependence items plus blackouts, morning drinking, efforts to stop drinking, alcohol interfering with relationships, self-help group attendance, and receiving professional help for alcohol-related difficulties.

Baseline fMRI Data Analyses

Image Analysis Pathway. Analysis of Functional NeuroImages (AFNI) software package was used to evaluate basic structural and functional images (Cox, 1996), while a multivariate regressor approach evaluated changes in EPI intensity in relation to task characteristics (Haxby et al., 2000). Image translation and rotation relative to all other images were minimized using a 3D-coregistration algorithm for each subject (Eddy et al., 1996), including 6 motion regressors. EPI scan slices were temporally aligned following registration to ensure that different relationships with regressors did not reflect acquisition of different slices at different times during the repetition interval.

Within Subject Multiple Regressor Analyses. The orthogonal regressors of interest were the 4 images (happy, angry, fearful, and circle/oval controls) which were convolved with a gamma variate function modeling a prototypical hemodynamic response (6- to 8-second delay) and to account for temporal dynamics of the hemodynamic response (typically 12 to 16 seconds), with each convolved time series normalized as a regressor of interest (Friston et al., 1995). Along with baseline, linear, and motion regressors (roll, pitch, and yaw), the AFNI program *3dDeconvolve* determined the height of each regressor of interest for each subject time series. The main dependent measure was the voxel-wise normalized percent signal change created by dividing the regressor coefficient by the zero-order regressor (i.e., baseline). A Gaussian filter (FWHM 4 mm) was used to account for variations in anatomy across individuals. Spatially smoothed percent signal change data were transformed into anatomical magnetic resonance image Talairach coordinates.

Group Analysis Performed at Baseline. Anatomically constrained functional regions of interest (ROIs) were based on a priori hypotheses regarding ROIs in the insular cortex (Paulus et al., 2012), medial prefrontal cortex, and amygdala based on the Talairach atlas (Lancaster et al., 2000). A voxel-based mixed-model analysis with fixed effects of emotion type (happy, angry, and fearful), group (low and high LR), education, and response latency, with the random effects as subjects was carried out. Thirteen functionally refined clusters within these anatomical regions were defined (the volume and coordinates of the centroids in Talairach space are given in Table 2). The volume minimum for these functional ROIs were determined through threshold adjustment based on Monte Carlo simulations (conducted via AFNIs in Alpha Sim, a threshold p of 0.05, 2-tailed) guarded against identifying false positive areas of activation. Percent signal change for the contrasts of interest were extracted from each of the 13 previously defined ROIs (Paulus et al., 2012; Table 2) and used in the statistical analysis. All analyses covaried for both CBF (overall blood flow differences in ml/100 g/min for placebo vs. alcohol sessions) and for usual drinks per occasion.

Follow-Up Statistical Analyses

Using the Statistical Package for the Social Sciences (SPSS Inc., 2009), comparisons of items across low and high LR subjects and between baseline and follow-up data used dependent samples t-tests for continuous variables, and the Wilcoxon-signed ranks test (reported as a Z statistic) for dichotomous items. Relationships between baseline BOLD response contrasts and outcomes were evaluated through scatterplots and with Pearson's product moment correlations. Logistic hierarchical and 2 types of backward elimination regression analyses (used to evaluate a modest-sized set of prior-selected variables allowing identification of the most robust predictors of outcomes) evaluated Hypothesis 3 regarding whether BOLD response contrast for any ROIs predicted alcohol outcomes above and beyond the variability predicted by LR. This included an augmented backward elimination (ABE) regression (Dunkler et al., 2014) that uses both significance and change-in-estimate criteria to diminish any bias from selecting only 1 among a set of correlated variables. The alcohol outcomes were not always normally distributed, a problem addressed by square root transformations.

Recognizing both that multiple testing was involved in these analyses and that the sample was modest-sized, Type 1 errors were evaluated using the exact binomial procedure. This approach was chosen to correct for multiple testing because Bonferroni corrections are overly conservative (Bland, 2000), especially for modest-sized samples.

RESULTS

Subjects at Baseline and Outcome

Table 1 presents the demography and substance use characteristics for the 114 followed participants divided into high and low LR groups at baseline. At *study entry*, the LR groups were similar on demography and most alcohol use characteristics. Regarding baseline alcohol problems, while no person met criteria for alcohol dependence, 40% ever experienced alcohol-related blackouts, 6% needed more alcohol to experience effects (tolerance), and ~3% each ever consumed more drinks than intended, missed social occasions because of drinking, and/or had alcohol interfere with school or work. During the *follow-up*, both lower and higher LR subjects increased drinking frequencies, maximum quantities, and alcohol problems. Regarding problems during the follow-up, 70% had 1+ blackouts, 45% drank more than intended, ~25% each spent more time drinking than planned or drank before noon, and ~15% each reported tolerance, noted that alcohol had interfered with work/school, or that they ever skipped important activities in order to drink.

Table 1. Baseline and Follow-Up Demography and Substance Use for 114 Subjects Divided (Median Split) into Alcohol Challenge-Based Low and High Level of Response (LR) to Alcohol

	Low LR (n = 57)		High LR (n = 57)					
Demography	Baseline	Follow-up interval	Baseline	Follow-up interval	t-Test/χ^2 low vs. high LR baseline	t-Test/χ^2 low vs. high LR follow-up	t-Test/Z alcohol-related changes from baseline to follow-up	
Age	19.8 (1.54)	24.9 (1.78)	19.9 (1.37)	25.2 (1.66)	−0.58	−0.87	NA	
Female %	50.9		54.4		0.14	NA	NA	
Years education	13.5 (1.12)	16.4 (1.13)	13.8 (1.21)	16.3 (1.17)	−1.28	0.16	NA	
Alcohol use							Low LR	High LR
Usual frequency	6.9 (4.33)	11.5 (6.59)	6.5 (5.11)	11.0 (7.47)	0.70	0.57	−4.81***	−4.49***
Usual quantity	3.7 (1.61)	3.5 (1.80)	3.3 (1.86)	3.3 (1.39)	1.29	0.60	−2.72**	−4.03***
Maximum quantity	10.1 (3.81)	10.9 (4.69)	8.5 (4.13)	10.1 (4.18)	2.40*	0.98	−2.97***	−4.80***
% Any of 17 alcohol problems	49.1	86.0	38.6	77.2	1.28	1.46	−4.38***	−4.49***
Mean # 17 problems	0.7 (0.92)	2.6 (2.24)	0.4 (0.60)	2.5 (2.77)	1.46	1.09	−7.28***	−7.50***

*$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$.
Continuous variables presented as means and standard deviations.
Z = Wilcoxon signed ranks test.
Alcohol outcomes for drinking frequencies and usual quantities are for the 6 months prior to the baseline assessment and to follow-up.
Maximum drinks and problems are lifetime before baseline and for the entire follow-up interval at follow-up.

Follow-up alcohol outcomes were similar for low and high LR subjects *based on the original LR median split*. However, consistent with Hypothesis 1, as shown at the bottom of Table 2, when baseline LRs were computed as continuous measurers, lower alcohol responses correlated with higher later maximum alcohol quantities and alcohol problems.

Baseline BOLD Response Contrasts Predicting Outcomes

Table 2 addresses Hypothesis 2 regarding whether BOLD response contrasts in the 13 ROIs identified for this task in the Paulus and colleagues (2012) cross-sectional paper correlated with future alcohol quantities and/or problems. Focusing on the 2 outcomes that correlated significantly with LR in Table 2 (maximum drinks and alcohol problems) among the 9 *happy faces*-related regions, 4 (ROIs 2, 3, 8, and 9) correlated at $p \leq 0.072$ with alcohol *problem* outcomes, and among *angry faces* 1 ROI baseline BOLD response contrast (ROI 11) correlated with future *maximum* alcohol quantities at $p < 0.05$ and $p = 0.082$ for 2 baseline measures. Using the exact binomial, the probability that 5 ROIs would correlate with the 2 outcomes across 13 regions is $p < 0.05$. Within the 5 regions that correlated with an adverse outcome (ROIs 2, 3, 8, 9, and 11) there were 30 evaluations (5 ROIs with 3 conditions each [placebo, alcohol, and difference scores] across 2 outcomes), 9 of which correlated with baseline fMRI results at $p \leq 0.082$, creating a significant exact binomial that the outcome was beyond chance ($p < 0.001$). Looking at the outcome with the highest number of notable correlations with baseline BOLD response contrast values, alcohol problems, among 39 possible evaluations (13 ROIs with 3 conditions each) the chances of finding 7 correlations that related to baseline BOLD response contrast at $p \leq 0.072$ was $p < 0.02$.

Regression Analyses

The analyses next addressed Hypothesis 3 regarding whether the variances in relevant drinking-related outcomes were accounted for by baseline brain imaging even after considering baseline LR (Table 3). These evaluations began with 7 separate hierarchical regression analyses considering the baseline conditions (placebo, alcohol, or their difference score) in 5 ROIs that related to alcohol problems (the most consistent outcome). Each of these 7 regressions entered both LR the baseline BOLD response contrast value to predict follow-up alcohol problems. The top of Table 3 describes the 4 regions where the baseline BOLD response contrast values incremented over LR in predicting problems. The second step considered the fact that, with rare exceptions (data not shown), the 7 ROI BOLD response contrasts correlated significantly with each other with rs between 0.29 and 0.76. Therefore, the 4 baseline ROI values that incremented over LR and related to future alcohol problems were entered along with LR into a single simultaneous entry regression analysis, with the result that only LR entered significantly, with $R^2 = 0.21$, $p = 0.008$. Third, we noted the high correlations among the fMRI measures and the fact that when entered into a regression along with LR 4 ROIs incremented over LR in predicting alcohol outcomes, which raised the possibility that in simultaneous regressions the overlap between ROIs might disallow any one of them to enter as a significant contributor to the equation. Therefore, we carried out a backward elimination regression analysis to better determine which ROI values remained related to future alcohol problems. The results in Table 3 indicate that LR, ROI 2, and ROI 3 significantly contributed to the regression analysis, with $R^2 = 0.21$, $p = 0.001$. The backward elimination ABE approach yielded the same model with $R^2 = 0.21$, $p = 0.001$.

Table 2. Emotional Face Recognition Task: Correlations[a] Among Baseline BOLD Response Contrasts for ROIs, and Drinking Outcomes (Maximum Quantities and 1+ Alcohol Problem) 5 Years Later for 114 Subjects

Brain region bold response contrast (Paulus et al., 2012)	Maximum quantity	Any of 17 alcohol problems
Happy face		
[1] R inferior frontal gyrus [1,792, 54/32/0]		
Placebo	−0.04	0.00
Alcohol	−0.07	0.12
Difference[b]	0.02	−0.08
[2] R middle frontal gyrus [640, 34/48/−8]		
Placebo	−0.08	−0.18† ($p = 0.062$)
Alcohol	−0.07	−0.06
Difference	−0.00	−0.07
[3] L anterior insula [576, −46/12/0]		
Placebo	−0.04	−0.09
Alcohol	0.03	0.17† ($p = 0.072$)
Difference	−0.05	−0.18† ($p = 0.059$)
[4] Anterior cingulate [960, 2/8/−8]		
Placebo	−0.02	−0.06
Alcohol	−0.03	0.06
Difference	0.01	−0.08
[5] R posterior insula [512, 50/−24/20]		
Placebo	−0.08	−0.07
Alcohol	0.01	0.07
Difference	−0.07	−0.11
[6] L inferior frontal gyrus [576, −42/28/−4]		
Placebo	0.08	0.03
Alcohol	0.02	0.08
Difference	0.08	−0.03
[7] L middle frontal gyrus [960, −34/48/−12]		
Placebo	0.03	0.04
Alcohol	−0.06	0.02
Difference	0.07	0.02
[8] R middle insula [576, 42/−4/8]		
Placebo	−0.09	−0.17† ($p = 0.069$)
Alcohol	0.07	−0.11
Difference	0.10	−0.19*
[9] L middle insula [576, −42/0/4]		
Placebo	−0.09	−0.08
Alcohol	−0.06	0.19*
Difference	−0.02	−0.18† ($p = 0.056$)
Angry face		
[10] L middle frontal gyrus [1,280, −50/20/32]		
Placebo	0.12	0.09
Alcohol	0.01	0.00
Difference	0.09	0.07
[11] R middle frontal gyrus [704, 46/12/40]		
Placebo	0.23*	0.14
Alcohol	0.07	0.14
Difference	0.16† ($p = 0.082$)	0.04
Fearful face		
[12] Anterior cingulate [576, −2/40/−8]		
Placebo	0.06	0.09
Alcohol	0.07	0.13
Difference	−0.02	−0.02
[13] L middle frontal gyrus [512, −34/52/−8]		
Placebo	0.01	0.13
Alcohol	0.02	0.01
Difference	−0.01	0.10
LR relation to outcomes	−0.20*	−0.24**

[a]Pearson Product Moment Correlations.

[b]The difference score was computed by subtracting the alcohol blood oxygen level-dependent (BOLD) response contrast value from the placebo BOLD response contrast value.

†$p \leq 0.10$, *$p \leq 0.05$, **$p \leq 0.01$.

ROI: regions of interest related to low versus high level of response (LR) in prior paper (Paulus et al., 2012).

ROI details format as per Paulus and colleagues (2012) [in parentheses are volumes in mm^3; *x*/*y*/*z* (centroid locations in Talairach coordinates)].

L, left; R, right.

Outcome time frames are the same as for Table 1.

Shaded rows highlight ROIs that relate at $p < 0.10$ or better to 1+ outcomes.

Table 3. Logistic Regressions Predicting Having any of the 17 Outcome Alcohol Problems

Variable	Odds ratio (95% confidence interval)
Simultaneous entry	
LR	0.47 (0.29 to 0.79)**
[2] R middle frontal gyrus (placebo)	0.64 (0.34 to 1.17)
[3] L anterior insula (alcohol)	1.57 (0.62 to 4.00)
[3] L anterior insula (difference)	0.93 (0.40 to 2.15)
[9] L middle insula (alcohol)	1.11 (0.46 to 2.67)
$R^2 = 0.21$ ($p = 0.008$)	
Backward elimination	
LR	0.47 (0.28 to 0.77)**
[2] R middle frontal gyrus (placebo)	0.61 (0.36 to 0.99)*
[3] L anterior insula (alcohol)	1.78 (1.02 to 3.06)*
$R^2 = 0.21$ ($p = 0.001$)	

*$p \leq 0.05$, **$p \leq 0.01$.

Abbreviations are the same as in Tables 1 and 2.

Independent variables were standardized for ease of interpreting odds ratios.

The last step in these analyses focused on searching for commonalities among the baseline BOLD response contrasts for the ROIs that correlated with adverse alcohol outcomes. In Table 4, columns 1 to 3 describe the 4 baseline conditions and related ROIs that were entered into the regression analysis in Table 3. Columns 4 and 5 present the baseline BOLD response contrast characteristics for those brain regions listed in the original Paulus and colleagues (2012). As shown in columns 4 and 5, in all relevant baseline conditions low LR subjects demonstrated baseline BOLD response contrasts that were higher for placebo than for alcohol, while for high LRs none demonstrated this pattern.

DISCUSSION

The data for the current analyses utilized 240 baseline placebo and alcohol fMRI sessions with 120 drinking but not alcohol-dependent young adults, which had been collected ~5 years previously, to determine whether fMRI BOLD contrasts predicted follow-up drinking-related patterns. The baseline analyses (Paulus et al., 2012) were consistent with prior investigations (Paulus et al., 2006; Tapert et al., 2004) where individuals with low LR tended to demonstrate greater fMRI BOLD response contrasts during cognitive or emotional-based tests with placebo compared to alcohol, while high LR subjects showed the opposite pattern, with no task performance differences across LR groups. The current work examines whether the neural activation to affective tasks as a function of LR status predicted drinking outcomes, and, if so, if the fMRI results added to LR in those predictions. The answer to both these questions was affirmative, although the small sample requires that these results be considered preliminary.

The first step in the current stage of this work was to determine if a lower LR related to future heavier drinking and alcohol problems (Hypothesis 1) in a manner consistent with prior work (Chung and Martin, 2009; Quinn and Fromme,

2011; Schuckit et al., 2007, 2008; Volavka et al., 1996). The results using a baseline continuous measure of LR revealed that the lower the intensity of reaction during the alcohol challenge, the higher the follow-up maximum drinks and the greater the number of alcohol problems (Table 2). These 2 outcomes have been more consistently related to earlier LR than drinking frequency or usual drinks per occasion in prior studies. The fact that a median LR split did not identify those findings may reflect the limited power of dichotomous measures.

The second hypothesis was that baseline fMRI patterns that related to a low baseline LR would predict future higher alcohol quantities and associated problems. The pattern of the current data lends support to this prediction in that baseline BOLD response contrasts in 5 of 13 regions related to at least 1 alcohol outcome 5 years later. The outcome most consistently related to baseline fMRI results was alcohol problems.

Those findings allowed for testing Hypothesis 3. Here, in 4 of the 7 baseline conditions where ROIs related to future alcohol problems, baseline BOLD response contrast predicted adverse alcohol outcome above and beyond the outcome predicted by LR alone. Backward elimination regression analyses that included LR and 4 ROIs (right middle frontal gyrus, left anterior insula, and left middle insula) indicated that activation to affective faces in the right middle frontal gyrus and the left anterior insula were the strongest predictors of future alcohol problems.

The involvement of the insular cortex in predicting drinking outcomes adds to the growing literature indicating that this region, an integrator of the body–brain connection, may be related to the motivation to use substances (Paulus and Stewart, 2014; Verdejo-Garcia et al., 2012), especially in the context of approach or avoidance behaviors. Potentially pertinent to LR processing, the insula influences the nucleus accumbens and striatum downstream, with possible impacts regarding reward-related behaviors and craving (Cho et al., 2012; Goldstein et al., 2009). The frontal systems are important in cognitive effort (Corbetta and Shulman, 2002) and affective modulation of stress (Miller and Cohen, 2001), 2 processes that may be vital to alcohol effects and recovery from their influences (Franken, 2003).

There are several potential implications of these data. First, they indicate that BOLD response contrast results related to the low LR to alcohol can predict drinking behaviors over extended periods of time. The modest proportion of the variance in predicting outcomes reported here is consistent with prior studies of heavy drinking and AUDs that underscore the importance of many genetic and environmental factors in the genesis of adverse drinking outcomes, with no one element both necessary and sufficient (Schuckit, 2014). Regarding LR, the finding that perturbations in the prefrontal and insular regions appear to be associated with both a low LR and future heavy drinking may improve our ability to more accurately identify the LR-related phenotype compared to results from alcohol challenge-related changes in subjective feelings of intoxication and related characteristics (Paulus et al., 2012). This, in turn, may open the door to a more optimal multilevel process model that helps explain at least 1 aspect of the vulnerability toward problem drinking associated with LR itself.

Another potential implication of these data is highlighted in Table 4. The most consistent baseline fMRI-related pattern was that subjects with low LR were more likely than those with high LR to demonstrate higher BOLD response contrast under placebo conditions than when after drinking alcohol. This is consistent with lower alcohol responses for subjects with low LRs in prior studies evaluating alcohol responses for EEG, ERP, ACTH and prolactin (Ehlers et al., 1999; Schuckit and Gold, 1988; Schuckit et al., 1988a,b, 2000). While from this perspective the fMRI results were similar to other measures of alcohol sensitivity, it is important to note that the fMRI BOLD response contrasts added significantly to LR in predicting outcomes.

The data are also consistent with our previous interpretation (Paulus et al., 2012) that the BOLD response contrasts might indicate that individuals with a low LR may need greater cognitive effort to recognize relatively subtle differences across stimuli. This increase of neural processing resources during effortful tasks when not exposed to alcohol might indicate that it is possible to identify individuals prone to low LRs to alcohol and consumption of higher alcohol quantities even before their first drink. As shown in Table 4, among the 3 ROIs that related to future adverse alcohol outcomes, for low LRs all 3 demonstrated the pattern of placebo values being greater than alcohol values while this was not true for any of the ROIs for high LRs.

It is important to consider potential future steps for these studies. First, in light of the great expense and large amounts of staff and subject time involved in fMRI measures, it will be worthwhile to continue to search for alternate, less costly approaches that might measure phenomena that overlap with the fMRI patterns. Second, additional work is needed to further elucidate the brain mechanisms that contribute to these fMRI results and how they relate to drinking practices. Third, the current data neither definitively support nor refute

Table 4. Summary of Baseline Patterns[a] of Level of Response (LR) Group Differences for 4 Functional Magnetic Resonance Imaging Happy Face ROIs

ROI	ROI name	Condition	Low LR placebo > alcohol	High LR placebo > alcohol
2	R middle frontal gyrus	1. Placebo[b]	Yes	No
3	L anterior insula	2. Alcohol[b]	Yes	No
		3. Difference		
9	L middle insula	4. Alcohol	Yes	No

[a]Paulus and colleagues (2012).
[b]Contributed significantly to the Backward Elimination Regression.
Abbreviations are the same as in Tables 1 and 2.
ROI: regions of Interest from Tables 2 and 3.

the possibility that the relatively high BOLD response contrasts during a cognitive task after placebo can by themselves predict future low LRs and/or future heavier drinking in subjects even before their first drink. Perhaps that might be best evaluated as an add-on to prospective investigations of fMRI in the future.

This investigation has several strengths, including a 95% 5-year follow-up, and careful measures of both LR and BOLD response contrasts. At the same time it is important to recognize that the reaction to alcohol is only 1 of several intermediate phenotypes related to the AUD risk (e.g., impulsivity), and that there are several additional characteristics related to how a person reacts to alcohol, including an exaggerated alcohol response at rapidly rising BACs (King et al., 2014; Schuckit, 2014). It will be interesting to establish whether functional brain imaging might have a role in predicting drinking outcomes related to other types of LR measures and additional risk factors for AUDs (Schuckit et al., 2015). A second important caveat is that the current sample of 114 subjects is underpowered for analyses that consider 13 ROIs generating 39 values across placebo, alcohol, and a score that reflects the difference between those 2 conditions. Thus, more conservative steps to control for Type 1 errors could not be applied, and we used the less conservative exact binomial approach. As a consequence, the current results may be an overly optimistic estimate of data fit, and must be considered preliminary until larger studies are carried out (Whelan and Garavan, 2014). Third, we only studied young EA drinkers from a single university in Southern California. More work is needed to see whether similar results are applicable to other markers of risk and to alternative populations. Fourth, the focus of the work is on alcohol, as low LRs have only been found to relate to adverse alcohol outcomes and not to the use of or problems with other drugs. Finally, it is important to remember that there may be additional brain ROIs to LR and to the related prediction of adverse alcohol outcomes.

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CONFLICT OF INTEREST

No author has any conflict of interest to report.

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