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Decreased Amygdala Activation during Risk Taking in Non-Dependent Habitual Alcohol Users: A Preliminary fMRI Study of the Stop Signal Task

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Abstract

Background and Objectives—Habitual alcohol use is prodromal to alcohol dependence. It has been suggested that impairment in impulse control contributes to habitual drinking. Little is known whether neural processes associated with impulse control is altered in non-dependent social drinkers. The current preliminary study combined functional magnetic resonance imaging and the stop signal task (SST) to address this issue.

Methods—We compared non-dependent non/light ($n = 12$) and moderate/heavy ($n = 9$) young adult alcohol drinkers in a SST, in which they were required to exercise inhibitory control during the stop trials and were engaged in a speed/accuracy trade-off during trial-to-trial go responses. Our previous studies identified neural correlates of inhibitory control and risk taking during the SST (10, 11). Furthermore, alcohol dependent patients showed altered brain activation both during inhibitory control and risk taking, compared to healthy controls (12).

Results—We showed that moderate/heavy alcohol drinkers were decreased in amygdala activation during risk taking, while indistinguishable in neural measures of inhibitory control, when compared to non/light drinkers.

Conclusions and Significance—Altered amygdala activation during risk taking may be a key neural process underlying early habitual alcohol use and a potential marker mediating transition to alcohol dependence.

Keywords

Alcohol abuse; cognitive control; go/nogo; impulsivity; response inhibition

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

INTRODUCTION

According to the National Epidemiologic Survey on Alcohol and Related Conditions, approximately 70% or 19 million of young adults in the United States consumed alcohol in the year 2004. Many of them are engaged in heavy and binge drinking and eventually become alcohol dependent. This issue is particularly salient in young adulthood, a developmental period marked with change and exploration, and when habitual and heavy alcohol use could lead to permanent impairment in brain functions (1). Understanding the psychological and neural processes leading to heavy, habitual, and eventually uncontrollable use of alcohol is thus of enormous importance to public health.

Clinical and behavioral studies have provided evidence associating behavioral impulsivity to substance and alcohol misuse. For instance, studies employing personality scales have associated impulsivity with substance use disorders (2, 3). In a sample of more than one thousand adolescents indicators of disinhibition assessed at age 11 predicted age of first drink at age 14 (4). Elkins and colleagues showed that behavioral disinhibition was distinctly associated with early onset of nicotine, alcohol, and illicit drug use (5). Impulsivity as measured by the Barratt Impulsivity Scale also distinguished between early and late onset alcoholism (6). Thus, behavioral impulsivity is a critical factor for the management of alcohol misuse.

Chronic and heavy alcohol use is known to be associated with a wide range of cognitive deficits including impairment in inhibitory control; see (7, 8) for a review. On the other hand, relatively little is known about the cerebral processes underlying early habitual use of alcohol in non-dependent drinkers. The current preliminary study represented an attempt to address this issue. In our previous work we combined a stop signal task (SST) (9) with functional magnetic resonance imaging (fMRI) and employed a novel algorithm to delineate the neural processes of inhibitory control (10). On the basis of the race model, we characterized inhibitory control in terms of the stop signal reaction time (SSRT), which describes the time for the stop signal to be processed so a response can be withheld; a long SSRT indicates poor inhibitory control. By comparing individuals with short and long SSRT, who otherwise did not differ in any other aspects of the stop signal performance, we isolated the neural correlates of inhibitory control in the region of anterior pre-supplementary motor area (preSMA) and the rostral anterior cingulate cortex (rACC). Furthermore, by imposing on the participants to be both fast and accurate, the SST introduced a component of risk, which participants may avert by slowing down, or ignore by responding “as usual,” during go trials. We observed greater activation in a number of cortical and subcortical structures including the amygdala when participants took risk as compared to when they avoided risk (11).

Using the SST, we demonstrated altered cerebral activation during cognitive control and risk taking in alcohol dependent patients (12). The central question we attempt to address in this preliminary study is whether prefrontal cortical processes during inhibitory control and/or amygdalar processes during risk taking are impaired in non-dependent habitual alcohol users.

MATERIALS AND METHODS

Subjects, Informed Consent, and Assessment of Impulse Control and Drinking Behavior

Eight non-alcohol drinking individuals and thirteen social drinkers were recruited from the University and the local community to participate in the study (Table 1). All subjects held a regular job or were full-time students, and were physically healthy with no major medical illnesses or current use of prescription medications. None of them reported having a history of head injury or neurological illness. None of the subjects reported use of illicit substances. All participants were assessed with the Barratt Impulsivity Scale (BIS-11, 13). The Human Investigation committee at Yale University School of Medicine approved all study procedures, and all subjects signed an informed consent prior to study participation.

Drinking behaviors were assessed retrospectively for the previous year for the quantity of alcohol consumption. All social drinkers consumed less than 25 drinks per month as classified by the Quantity Frequency Variability Index (14). Light, moderate, and heavy drinkers were each operationally defined as those who consumed no more than 4 drinks per month ($n = 4$), between 5 and 12 drinks per month ($n = 4$), and between 12 and 24 drinks per month ($n = 5$), respectively. Note that this classification did not follow the NIAAA Clinician's Guide; it was tentative and operational for the purpose of analysis. Participants were also asked to rate whether and how much they felt they were losing control of their drinking behavior on a Likert scale from 0 (in total control) to 10 (had completely lost control).

Behavioral Task and Experimental Procedures

We employed a simple reaction time (RT) task in this stop signal paradigm (Fig. 1). Prior to the fMRI study each subject had a practice session outside the scanner. Each subject completed four 10-min runs of the task with the SSD updated manually across runs. These methods and procedures have been described in details in our previous studies (10–12, 15).

Imaging Protocol

Conventional T_1 -weighted spin echo sagittal anatomical images were acquired for slice localization using a 3T scanner (Siemens Trio, Erlangen, Germany). Anatomical images of the functional slice locations were next obtained with spin echo imaging in the axial plane parallel to the AC-PC line with TR = 300 ms, TE = 2.5 ms, bandwidth = 300 Hz/pixel, flip angle = 60° , field of view = 220×220 mm, matrix = 256×256 , 32 slices with slice thickness = 4 mm, and no gap. Functional, blood oxygenation level dependent (BOLD) signals were then acquired with a single-shot gradient echo echo-planar imaging (EPI) sequence. Thirty-two axial slices parallel to the AC-PC line covering the whole brain were acquired with TR = 2,000 ms, TE = 25 ms, bandwidth = 2004 Hz/pixel, flip angle = 85° , field of view = 220×220 mm, matrix = 64×64 , 32 slices with slice thickness = 4 mm, and no gap. Three hundred images were acquired in each run for a total of 4 runs.

Data Analysis and Statistics

Data were analyzed with Statistical Parametric Mapping version 2 (SPM2, Wellcome Department of Imaging Neuroscience, University College London, U.K.). Details of the

spatial preprocessing of brain images were described in (10). Briefly, session data with head movement greater than 3 mm in x, y, or z dimension were excluded. Images of each individual subject were first corrected for slice timing and realigned (motion-corrected). A mean functional image volume was constructed for each subject for each run from the realigned image volumes. These mean images were normalized to an MNI (Montreal Neurological Institute) EPI template with affine registration followed by nonlinear transformation. The normalization parameters determined for the mean functional volume were then applied to the corresponding functional image volumes for each subject. Finally, images were smoothed with a Gaussian kernel of 10 mm at Full Width at Half Maximum. The data were high-pass filtered (1/128 Hz cutoff) to remove low-frequency signal drifts.

Four main types of trial outcome were distinguished: go success (G), go error (F), stop success (SS), and stop error (SE) trial (Fig. 1). A statistical analytical design was constructed for each individual subject, using the general linear model (GLM) with the onsets of go signal in each of these trial types convolved with a canonical hemodynamic response function (HRF) and with the temporal derivative of the canonical HRF and entered as regressors in the model (16). Realignment parameters in all 6 dimensions were also entered in the model. Serial autocorrelation was corrected by a first-degree autoregressive or AR(1) model. We constructed for each individual subject a statistical contrast: SS vs. SE.

In a second GLM, G, SS, and SE trials were first distinguished. G trials were divided into those that followed a G (pG), SS (pSS), and SE (pSE) trial. Furthermore, pG trials were divided into those that increased in RT (pGi) and those that did not increase in RT (pGni, 11). A pG trial was compared to all preceding pG trials during each session to determine whether it increased (pGi) or did not increase (pGni) in RT. We contrasted $pGni > pGi$ (i.e., post-go speeding > post-go slowing) for individual subjects to identify activations associated with a risk taking decision.

Random Effect Analyses

We performed the general linear modeling (GLM) to isolate the neural correlates of inhibitory control and risk taking for individual subjects. To increase the power of analysis, we contrasted non- and light social drinkers ($n = 12$) vs. moderate and heavy drinkers ($n = 9$) in second-level, group analyses. The two groups did not differ in age, years of education, or gender composition.

Response Inhibition—The SS and SE trials were identical in stimulus condition, with SS trials involving inhibition success and SE trials involving inhibition failure. The contrast $SS > SE$ thus engaged processes related to response inhibition and was used in the random effect analysis (10). We compared the two groups for $SS > SE$ in a covariance analysis, accounting for median go trial RT and stop success rate. In addition to voxelwise whole brain exploration, we also performed region of interest (ROI) analysis based on our previous findings (10). We used MarsBaR (17) to compute for each individual subject the effect size of activation change for functional ROIs derived from our published studies. The effect size rather than mean difference in brain activation was derived in order to account for individual differences in the variance of the mean. These ROIs included two regions related to response

inhibition (10): pre-supplementary motor area (pre-SMA, $x = -4$, $y = 36$, $z = 56$, 832 mm^3) and the rostral anterior cingulate cortex (rACC, $x = -8$, $y = 40$, $z = 20$, $1,088 \text{ mm}^3$).

Risk Taking—We compared the two groups for the contrast pGni > pGi. In ROI analysis, we focused on two regions related to risk taking identified from our recent work (11): amygdala ($x = -16$, $y = -4$, $z = -16$, 704 mm^3) and the posterior cingulate cortex (PCC, $x = -4$, $y = -40$, $z = 44$, 960 mm^3).

RESULTS

Behavioral Performance

The two groups of subjects did not differ in stop signal performance (non/light vs. moderate/heavy) including: median go trial reaction time (506 ± 126 vs. 554 ± 106 ms, $p = .37$, two-tailed two-sample t test), go success rate (97.2 ± 2.8 vs. $97.5 \pm 2.1\%$, $p = .82$), stop success rate (49.0 ± 3.0 vs. $50.7 \pm 1.7\%$, $p = .14$), stop signal reaction time (225 ± 24 vs. 222 ± 38 ms, $p = .86$), fore-period effect (effect size: 2.97 ± 1.73 vs. 2.37 ± 1.09 , $p = .38$; 18, 19), and post-error slowing (effect size: 1.57 ± 1.65 vs. 2.04 ± 1.43 , $p = .50$; 20, 21). Additional analyses indicated that performance of our subjects was well tracked by the staircase procedure. These findings included that subjects succeeded in approximately half of the stop trials; and showed a significant linear correlation between the RT of stop error trials and the stop signal delay (p 's < .0001, $.70 < R$'s < .93, Pearson regression; 9).

Whole Brain and Region of Interest (ROI) Analyses

We applied the same threshold of $p < .001$, uncorrected, and 5 voxels in the extent of activation to all second level whole brain analyses.

Non/light drinkers and moderate/heavy drinkers did not differ significantly in regional brain activations during inhibitory control or risk taking, on the basis of whole brain analysis. However, we performed region of interest analysis and computed the effect size of $SS > SE$ for the pre-SMA and rACC masks (inhibitory control), as well as the effect size of pGni > pGi for the amygdala and posterior cingulate cortex masks (risk taking). The results showed that moderate/heavy drinkers and non/light drinkers did not differ in pre-SMA or rACC activation during inhibitory control; preSMA: mean (95% confidence interval [CI]): .035 (-1.410 – 1.479) for non/light drinkers vs. $-.571$ (-2.007 – $.865$) for moderate/heavy drinkers; rACC: $-.868$ (-2.064 – 0.328) for non/light drinkers vs. -2.063 (-4.047 – $.081$) for moderate/heavy drinkers. However, compared to non/light drinkers, moderate/heavy drinkers demonstrated significantly lower amygdala activation during risk-taking: 2.819 (1.660 – 3.977) for non/light drinkers vs. $.631$ ($-.921$ – 2.184) for moderate/heavy drinkers; and a trend toward lower PCC activation: 1.990 (1.078 – 2.902) for non/light drinkers vs. $.583$ ($-.893$ – 2.060) for moderate/heavy drinkers. These latter results were also confirmed by a non-parametric test ($p < .02$, amygdala; $p = .102$, PCC, Mann Whitney U Test, Fig. 2).

DISCUSSION

The current preliminary findings showed that amygdala activation was decreased during risk-taking decisions in the stop signal task in non-dependent heavy drinkers, compared to

non-or light alcohol drinkers. On the other hand, the two groups did not differ in prefrontal cortical activation during inhibitory control. These results stand in contrast to our earlier report of altered cerebral processes for both constructs in alcohol dependent patients (12).

A recent study specifically addressed the neural processes of risk taking in young adults at high risk of alcoholism (22). Employing fMRI and comparing nonabusing young adults with a family history of alcoholism and high in disinhibition measures and those with a negative family history and low in disinhibition measures, these investigators probed limbic system reactivation to recognition of fearful faces vs. geometric objects. The results showed that subjects with negative family history had robust activation to the faces in the region of bilateral amygdalar complexes, while subjects with positive family history had no such activation. Furthermore, the BOLD signal in the region of the amygdala was negatively correlated with self-report scores of disinhibited temperament. It was suggested that amygdalar hypo-responsiveness and a failure to avoid risky decisions increased the person's liability for alcohol abuse (22). Another recent study examined neural responses of adolescent children of alcoholics to negative emotional stimuli (23). Compared to children who were vulnerable, those who were resilient—categorized on the level of problem drinking over the course of adolescence—demonstrated greater prefrontal, insula/putamen, and amygdala activation to emotional stimuli (23). Altogether, the current results along with the latter two studies consistently suggest that greater amygdala activation during cognitive/affective processing confers advantage in decision making upon individuals vulnerable to alcohol misuse.

Limitations of the Study, Conclusions, and Implications

This is a preliminary study that has many limitations. Firstly, the amygdala is likely to undergo marked geometrical distortion and signal dropout because of magnetic susceptibility effects from air-tissue interfaces near these regions. Secondly, altered amygdala activation has been associated with personality traits such as anxiety or psychopathy, which was not assessed in the current study. Thirdly, casual recent use of drugs or alcohol could have influenced the results because no screening was performed prior to the scan. Fourthly, cognitive control can be addressed in behavioral tasks incorporating an explicit component of reward, such as the delayed discounting task. Thus, the results obtained of the stop signal task should be considered as tentative. Fifthly, gender differences in brain activation during the stop signal task remained to be explored in relation to early habitual drinking.

Despite these limitations, the current findings present, to our knowledge, the first evidence of altered amygdala activation in early habitual drinking. Studies are warranted to examine whether decreased amygdala activation during risk taking could mediate the transition from habitual drinking to alcohol dependence. Furthermore, since amygdala is implicated in psychopathologies such as anxiety and depression, the current findings provide a venue to examine the pathogenetic processes of psychiatric conditions comorbid with alcohol misuse.

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FIG. 1.

The stop signal task (a) Stop signal paradigm. In “go” trials (75%) observers responded to the go signal (a circle), and in “stop” trials (25%) they had to withhold the response when they saw the stop signal (an X). In both trials the go signal appeared after a randomized time interval between 1 to 5 s (the fore-period or FP) following the appearance of the fixation point. The stop signal followed the go signal by a time delay—the stop signal delay (SSD). The SSD was updated according to a staircase procedure, whereby it increased and decreased by 64 ms following a stop success (SS) and stop error (SE) trial, respectively. There was an intertrial interval of 2 s. Subjects were instructed to respond to the go signal quickly while keeping in mind that a stop signal could come up in a small number of trials. With the staircase procedure, a “critical” SSD could be computed that represents the time delay required for the subject to succeed in withholding a response half of the time in the stop trials (24). The time required for the stop signal to be processed so a response is withheld (i.e., stop signal reaction time or SSRT) can be computed by subtracting the critical SSD from the median go trial RT. Generally speaking, the SSRT is the time required for a subject to cancel the movement after seeing the stop signal. A long SSRT indicates poor response inhibition. (b) An example sequence of trials to illustrate the definition of post-go slowing (risk averting) vs. post-go speeding (risk taking) in go trial reaction time.

FIG. 2.

Effect sizes of brain activity during risk taking and response inhibition. Contrasting regional brain activation during inhibitory control (pre-SMA and rACC) and risk taking (amygdala and PCC) between light (L, light gray) and heavy (H, dark gray) drinkers. Each dot represents the data of one subject. The histograms show the mean effect size of activation change for stop success > stop error (inhibitory control) and for post-go speeding > post-go slowing (risk taking). *P* values are based on Mann Whitney U test; pre-SMA = pre-supplementary motor area; rACC = rostral anterior cingulate cortex; PCC = posterior cingulate cortex. The results showed that, compared to light drinkers, heavy drinkers were significantly impaired in amygdala activation during risk taking. However, both pre-SMA and rACC also diminished in activation during inhibitory control. Thus, the lack of significant differences in inhibitory control needs to be replicated in a larger sample of subjects.

TABLE 1

Demographics of the subjects

Subject characteristic	Non- or light drinkers (n = 12)	Moderate and heavy drinkers (n = 9)	<i>p</i> value
Men/women	7/5	6/3	.36 ^a
Age (years)	27.8 ± 4.1	28.3 ± 5.5	.78 ^b
Ethnicity			
Caucasian	9 (75.0%)	9 (100.0%)	.27 ^c
African American	1 (8.3%)		
Asian	2 (16.7%)		
Education (years)	16.7 ± 1.8	17.3 ± 1.0	.33 ^b
Average number of days of alcohol use/month prior to study	1.3 ± 2.0	10.3 ± 4.4	<.0001 ^b
Average number of years of alcohol use	2.2 ± 3.4	6.1 ± 1.3	<.005 ^b
Subjective rating of loss of control	.08 ± .29	1.22 ± 1.72	<.04 ^b
BIS-11 rating	49 ± 6	55 ± 8	<.07 ^b

Note: Values are mean ± SD;

^a binomial test;

^b 2-sample *t* test;

^c Pearson chi-square test.