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Neural Processes of an Indirect Analog of Risk Taking in Young Nondependent Adult Alcohol Drinkers—An fMRI Study of the Stop Signal Task

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Abstract

Background—Alcohol abuse and dependence are common problems in the United States that stem from a variety of factors, one of which may be a period of high level social drinking during college and early adulthood. Extant study implicates risk taking as a cognitive factor that contributes to habitual and heavy drinking. We sought to examine the neural processes of risk taking in young, nondependent drinkers.

Methods—We compared 20 young adult social drinkers with a high level of alcohol use (AH), as defined by number of drinks per month, and 21 demographically matched drinkers with low to moderate alcohol use (ALM) in a functional magnetic resonance imaging study of the stop signal task. By contrasting risk taking (speeded) to risk aversion (slowed) trials, we examined the neural correlates of risk taking. Brain imaging data were analyzed with Statistical Parametric Mapping. Regions of interest were identified and corresponding effect sizes were examined for correlations with self-reported alcohol use.

Results—The results showed that, compared with ALM, AH demonstrated decreased activation in right superior frontal gyrus and left caudate nucleus when contrasting risk taking and risk aversion trials at $p < 0.001$, uncorrected. Furthermore, examination of the effect size data showed that the extent of these decreased regional activations correlated with frequency of drinking in women, but not men.

Conclusions—These findings suggest a neural analog of nondependent, high level drinking. Specifically, high level social drinking is associated with altered activation of the caudate and superior frontal cortex, an association that appears to be stronger in women than in men and is strongly tied to the frequency of drinking. These results are relevant in understanding risk taking behavior in social drinking as well as in examining the potential path from high level social use in young adults to dangerous alcohol consumption later in life.

Keywords

Alcohol Abuse; Risk Taking; Cognitive Control; Prefrontal; Gender Difference

In a recent national survey conducted by the National Institute on Alcohol Abuse and Alcoholism, almost 5% of the population met DSM-IV criteria for current alcohol abuse or dependence (United States Department of Health and Human Services, 2004). However, the prevalence was significantly higher among college students and young adults with about 31 and 6% having met criteria for current abuse and dependence, respectively (Knight et al., 2002). When additionally taking into account approximately 1,800 deaths, 600,000 injuries, 700,000 cases of assault, 100,000 incidents of sexual abuse, 150,000 alcohol-related health problems, and 3.3 million young adults driving under the influence of alcohol annually (Hingson et al., 2002, 2009), it is not only relevant, but necessary to examine the behavior of at-risk drinkers as well as those meeting diagnostic criteria. This was a large part of the World Health Organization's 1989 initiative to develop an Alcohol Use Disorders Identification Test (AUDIT) as a means of screening for risky drinking behavior by taking into account alcohol-related problems and consumption (Babor et al., 2001). Rather than focusing on individuals with alcohol-induced health problems, at which point prevention efforts may be too late, the AUDIT seeks to intervene at a significantly earlier stage of the problem (Saunders et al., 1993). Operating under similar motivations, in this study we examined the neural processes of risk taking behavior in high level, nondependent drinkers in a sample taken from a college environment.

The construct of impulsivity is multifaceted in that it can pertain to the speed or rashness of decision making as well as one's reaction to consequences following a decision. Specifically, impulsivity can be characterized by 3 elements: (i) a quick decision made before all information has been processed; (ii) acting with disregard for potential long-term consequences; and (iii) an apparent insensitivity when exposed to negative behavioral consequences (Moeller et al., 2001). Impulsivity is commonly implicated in substance, including alcohol, abuse and dependence (De Wit, 2009; Goldstein and Volkow, 2002; Madden et al., 1997; Petry, 2001; Verdejo-Garcia et al., 2008). Further evidence suggests that impulsivity is altered not only in alcoholics (individuals meeting criteria for an alcohol use disorder), but in high level drinkers as well (Benjamin and Wulfert, 2005; Jackson and Matthews, 1988; MacKillop et al., 2007). Based upon the Moeller and colleagues' (2001) definition of impulsivity, which poses impulsivity as a manner of thinking or disregard, it can be difficult to directly measure this concept through behavioral tasks. Thus, we may also look at behavioral disinhibition as a result of increased impulsivity in go/no-go and stop signal tasks (SSTs). Furthermore, in thinking of impulsivity as a quick decision prior to gathering all information, again according to Moeller and colleagues (2001), there is an undeniable element of risk taking involved. Risk taking can be examined through tasks such as the balloon analog risk task (BART; Lejuez et al., 2002) and the Iowa Gambling Task (Bechara et al., 2001). Although behavioral inhibition has been shown to be impaired in individuals with alcohol dependence, the findings are mixed in nondependent, high level drinkers. Although some studies see a trend toward impaired response inhibition (Colder and O'Connor, 2002; Nederkoorn et al., 2009; Weafer et al., 2011), other studies find that response inhibition does not relate to social drinking (Fernie et al., 2010). On the other hand, risk taking and the more general concept of sensation seeking (Lejuez et al., 2002) consistently appear to be indicative of the level of alcohol use in high level drinkers (Fernie et al., 2010; Magid et al., 2007; Wagner, 2001; Weafer et al., 2011; Zuckerman and Kuhlman, 2000).

Here, we propose using the SST in an functional magnetic resonance imaging (fMRI) study. We will examine risk taking behavior during this task as an indirect analog of the risk taking behavior seen in high level habitual drinkers. Successful performance in the SST requires prepotent, habitual behaviors to be inhibited. Importantly, by dictating the participants to respond both quickly and accurately, we also introduced a distinct element of risk in the SST. Thus, speeding up, as compared with slowing down, in response to a go stimulus, can

be conceived as taking a risk that the stop signal would not come up (Li et al., 2009a,b; Yan and Li, 2009). In other words, the participant is risking making an error to achieve speedy performance. We sought to investigate the findings of a clear association of increased risk taking with increased alcohol use in nondependent drinkers in the context of the SST. Given that the relationship of post-go speeding (as compared to slowing) in the SST has yet to be firmly established as representative of risk taking, we will also discuss these findings in relation to the existing risk taking literature.

MATERIALS AND METHODS

Subjects and Assessment

Study participants were recruited from flyers posted in and around college campuses in the greater New Haven, Connecticut area. Commonly posted areas included gymnasiums, lecture halls, community bulletin boards, and campus bookstores at community, state, and private colleges. Although participants were not required to be enrolled in college classes, they were required to meet an age requirement of <35 years old and to have been recruited from the aforementioned target area. We anticipated that the location restriction would provide a sample from a “college environment” including full and part-time college students, students living on and off campus, as well as friends of college students.

Forty-one social drinkers aged 18 to 34 years were invited and paid to participate (Table 1). All participants completed questionnaires regarding their alcohol use over the past year. Alcohol use data were collected for 2 factors: self-reported AUDIT scores and self-reported drinking behavior, which was framed on a monthly basis. AUDIT scores are calculated from the sum of 10 self-report questions regarding level of alcohol use, alcohol-related problems, and concern expressed by others for one's drinking behavior. Each question receives a score ranging from 0 to 4, with higher numbers corresponding to a greater level of risk for having or developing an alcohol use disorder. Similarly, the higher the total score obtained, the greater the risk. Although the AUDIT literature suggests a total score of 4 or 8 for women and men, respectively, as “positive” and, therefore, warranting further screening for abuse and dependence (Babor et al., 2001), another study has tested and validated scores of 6 as indicative of “hazardous” drinking. The Aertgeerts and colleagues' (2000) study was limited, however, in only assessing college-aged men. The study cited a sensitivity of approximately 80% for abuse and dependence, implying that the AUDIT has the potential for misclassification (Aertgeerts et al., 2000). In an effort to prevent individuals who either scored falsely high on the AUDIT (individuals who had risky behavior on rare occasions, but not overall) or deceptively low scores (individuals who drank frequently in large quantities without acknowledgment of alcohol-related problems), we chose our groups based only on self-reported monthly drinking totals, but also report AUDIT scores.

Both our confidence in the accuracy of recruitment combined with the large range of drinking quantities endorsed by participants, led us to conclude that the sample accurately mirrored the population. Under this assumption, the sample composition drove our grouping criteria. We divided the population into approximately equal sized groups to create a low to moderate level alcohol consumption (ALM) group and a high level (AH) group. The primary factor in creating these groups was the monthly drinking total for each participant. However, rather than performing a median split on the entire group, we also took into consideration the difference in classification of consumption levels according to gender. Specifically, women can drink less than men, but still be classified as having the same level of risk for alcohol use disorders. The discrepancy in consumption by gender is also accounted for in the AUDIT, NIAAA Clinician's Guide, and other sources. Ultimately, the median split performed separately for each gender yielded the creation of 2 groups: AH: 9 men, 24 ± 4 years of age; and ALM: 6 men, 25 ± 4 years of age. A median split by gender

was appropriate given the bimodal distribution found within each gender group. Specifically, the ALM female group has a mean of 3 and median of 4, whereas the AH female group has a mean of 25 and median of 24 drinks. Similarly, the ALM male group has a mean of 6 and median of 4, whereas the AH male group has a mean and median of 35 drinks. Although each of the 4 aforementioned groups is slightly skewed, the distributions are approximately normal in shape as shown by the approximate alignment of mean with median. These post hoc groupings based upon the sample composition generated a cutoff of 10 or more and 17 or more drinks per month for women and men, respectively, as “high level” and less as “low to moderate level” social drinking. To contextualize these grouping methods, we next provide comparisons with standard assessment tools.

Notably, we utilize a wider range for our high level drinkers group as compared with the National Institute on Alcohol Abuse's guideline for “drinking too much” of >4 drinks on any occasion (3 for women) and/or exceeding 14 (7 for women) drinks in 1 week (United States Department of Health and Human Services: NIH, NIAAA, 2005). We chose not to use these guidelines for the monthly totals, which would yield >28 drinks per month for women and >56 for men, because we believe there is an important behavioral gap between “drinking too much” and drinking socially at a “high level.” In fact, only 3 of our women and 0 of our men would fit the criteria of “drinking too much.” Furthermore, the groupings do not directly mirror the AUDIT findings, but are quite similar. Based on the AUDIT scores, the AH group was comprised of 70% scoring positive and 85% exhibiting “hazardous” drinking behaviors based on a cutoff of 6 for both men and women, adapted from the Aertgeerts and colleagues' (2000) work. Thus, the AH group captures what we believe to be “high level” drinkers based on the sample composition, although not all are drinking at a “hazardous level.” The fact that our high level group is based upon a definition that is easier to reach potentially allows us to conclude that differences exist even before drinking becomes hazardous. Conversely, the ALM group contained 95% *not* scoring positive and 91% *not* exhibiting hazardous behavior. Closer examination of the small percentage of cases scoring positive on the AUDIT, but fitting into our “low to moderate level” group, reveal that these participants were forthcoming about a single, heavy drinking event in the past year. We feel that this single event does not mirror their typical pattern of behavior and, thus, they would likely be misclassified by the AUDIT tool.

All participants were screened to be free of major medical illness including past or present neurologic (e.g., epilepsy, thyroid disorders, and learning impairments) and psychiatric problems (AXIS-I disorders), denied current or past illicit substance use, and showed negative urine toxicology tests for stimulants, opioids, marijuana, and benzodiazepines at the time of fMRI. Groups did not differ in the proportion of cigarette smokers based on a Pearson chi-square test (p -value = 0.645, proportion of smokers in AH = 0.25, ALM = 0.19). Participants were further required to be free of MRI-contraindications based on the Yale Magnetic Resonance Research Center's safety guidelines. All were right-handed and used their right index finger to respond. Other than the AUDIT (Babor et al., 2001), participants were also assessed with the Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995), Alcohol Expectancy Questionnaire (Brown et al., 1987), short form Tridimensional Personality Questionnaire (short-TPQ; Sher et al., 1995), and were asked to rate how much they felt they had lost control of their drinking on a scale of 0 to 10 (0 = no loss of control, 10 = complete loss of control). Standard screening and administration of assessments were conducted by research staff holding at least a bachelor's degree in a neuroscience or psychology discipline and trained in the administration of assessments and task instructions. In the event of questionable eligibility based on medical issues, psychiatric history, or excessively high level of alcohol use, a structured clinical interview (SCID-I for DSM-IV; First et al., 2002) was administered and a board-certified psychiatrist was consulted. In the event of a subthreshold diagnosis or questionable accuracy of reported information, the

participant was not invited to participate. All subjects signed a written informed consent, in accordance to a protocol approved by the Yale Human Investigation Committee.

Behavioral Task

We employed a simple reaction time (RT) task in this stop signal paradigm (Chao et al., 2009; Duann et al., 2009; Hendrick et al., 2010; Ide and Li, 2011a,b; Li et al., 2006, 2008; Fig. 1A). There were 2 trial types: “go” and “stop,” randomly intermixed in presentation. A small dot appeared on the screen to engage attention at the beginning of a go trial. After a randomized time interval anywhere between 1 and 5 seconds (drawn from a uniform distribution), the dot turned into a circle, which served as an imperative stimulus, prompting subjects to quickly press a button. The circle vanished at button press or after 1 second had elapsed, whichever came first, and the trial terminated. A premature button press prior to the appearance of the circle also terminated the trial. Three-quarters of all trials were go trials. The remaining one-quarter were stop trials. In a stop trial, other than the fixation dot and go signal, an “X” (the “stop” signal) appeared after and replaced the go signal. The subjects were told to withhold button press upon seeing the stop signal. Likewise, a trial terminated at button press or when 1 second had elapsed because of the appearance of the stop signal. The stop signal delay (SSD) started at 200 ms and varied from 1 stop trial to the next according to a staircase procedure: If the subject succeeded in withholding the response, the SSD increased by 67 ms; conversely, if they failed, SSD decreased by 67 ms (Levitt, 1970). There was an inter-trial interval of 2 seconds. 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. Prior to the fMRI study, each subject had a practice session on the same behavioral task outside the scanner. In particular, both accuracy and response speed were emphasized to the participants (Li et al., 2008). We computed the stop signal reaction time (SSRT) for each subject's performance based on the horse race model (Logan, 1994). Effectively, the SSRT can be thought of as the time a participant requires to stop the button press after the stop signal appears. The actual computation of SSRT comes from estimating the critical SSD, which is the delay time at which a participant can correctly inhibit response to a stop signal in approximately 50% of the stop trials. SSRT is then equal to the median go trial RT minus the critical SSD. In the scanner, each subject completed four 10-minute runs of the task, with a total of 40 minutes in blood oxygen level-dependent (BOLD) scans. The between-run duration was approximately 1 minute, during which participants were instructed to close their eyes, rest, and stay still. Depending on the actual stimulus timing (trials varied in foreperiod duration) and speed of response, the total number of trials varied slightly across subjects in an experiment. On average, there were approximately 100 trials in each run, of which 75 were go and 25 were stop trials. With the staircase procedure, we anticipated that the subjects succeeded in withholding their response in approximately half of the stop trials.

Imaging Protocol

Conventional T₁-weighted spin echo sagittal anatomic images were acquired for slice localization using a 3-T scanner (Siemens Trio, Erlangen, Germany). Anatomic images of the functional slice locations were next obtained with spin echo imaging in the axial plane parallel to the AC-PC line with time repetition (TR) = 300 ms, time echo (TE) = 2.5 ms, bandwidth = 300 Hz/pixel, flip angle = 60, field of view = 220 × 220 mm, matrix = 256 × 256, and 32 slices with slice thickness = 4 mm and no gap. Functional, BOLD signals were then acquired with a single-shot gradient 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 = 2,004 Hz/pixel, flip angle = 85, field of view = 220 × 220 mm, matrix = 64 × 64, and 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 (SPM8; Wellcome Department of Imaging Neuroscience, University College London, London, UK). Images from the first 5 TRs at the beginning of each run were discarded to enable the signal to achieve steady-state equilibrium between radiofrequency pulsing and relaxation. 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 a Montreal Neurological Institute (MNI) EPI template with affine registration followed by nonlinear transformation (Ashburner and Friston, 1999; Friston et al., 1995a). 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 first distinguished: go success (G), go error (GE), stop success (SS), and stop error (SE) trial (Fig. 1B). Herein, we focused on post-go go (pG) trials or go trials that were preceded by another go trial. The pG trials were further divided into those that increased in RT (pGi) and those that did not increase in RT (pGni), to allow the isolation of neural processes involved in risk taking during an SST—speeding up (pGni) versus slowing down (pGi). To determine whether a pG trial increased or did not increase in RT, it was compared with the pG trials that preceded it in time during each session. The pG trials that followed the pG were not included for comparison because these subsequent pG trials could not have a causal effect on the pG trial in question, in terms of how participants adjust their response speed. A single 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 (Friston et al., 1995b). Realignment parameters in all 6 dimensions were also entered in the model. Serial autocorrelation of the time series was corrected by a first-degree autoregressive or AR(1) model (Della-Maggiore et al., 2002; Friston et al., 2000). The GLM estimated the component of variance that could be explained by each of the regressors.

In the first-level analysis, we contrasted pGni versus pGi for individual subjects. In the second-level, random effects analysis, we compared ALM and AH using the contrast $pGni > pGi$ of individual subjects in a 2-sample *t*-test (Penny and Holmes, 2004). Additional design matrices were explored using the assessment data as covariates (see below). Brain regions were identified using an atlas (Duvernoy, 2003; Mai et al., 2008). In addition to voxel-wise whole-brain exploration, we also performed region of interest (ROI) analysis using MarsBaR (Brett et al., 2002; <http://marsbar.sourceforge.net/>) to derive for each individual subject the effect size of activity change for the ROIs. Functional ROIs were defined based on activated clusters from the whole-brain analysis. All voxel activations are presented in MNI coordinates. The effect size of “risk taking” ($pGni > pGi$) for each ROI was correlated with the assessment data using a Pearson correlation.

RESULTS

Stop Signal Performance

The 2 groups did not differ in general stop signal performance, as is shown in Table 2. ALM and AH groups responded to 89.8 ± 10.4 and $89.2 \pm 7.9\%$ of go trials and to 52.6 ± 3.5 and $53.6 \pm 3.1\%$ of stop trials, respectively. These data also suggest that their overall performance was adequately tracked by the staircase procedure.

Subject pace in SST performance was consistent between the AH and ALM groups. Of all post-go trials compiled from the 4 SST runs, there were 94 ± 19 (values are mean $\pm$ standard deviation) pGi and 85 ± 24 pGni trials across AH subjects. Similarly, in ALM subjects, there were 96 ± 17 pGi and 87 ± 25 pGni trials. In slowed trials (pGi), the average increases in RT were computed at 112 ± 19 ms in AH and 114 ± 18 ms in ALM. In pGni trials, decreases in RTs were 105 ± 29 ms in AH and 101 ± 24 ms in ALM. These results indicate that AH and ALM have nearly identical numbers of pGi and pGni trials and extents of RT increase (pGi) or decrease (pGni), and thus that the resulting differences in regional brain activations could not be attributed to these variations in task outcome.

Whole Brain Results of Speeded Compared to Delayed Response

Compared with post-go go trial with an increase in RT (pGi), post-go go trials with a decrease in RT (pGni) engaged greater activity in light to moderate drinkers in bilateral middle/superior frontal gyri, bilateral inferior parietal cortices, posterior cingulate cortex, left middle temporal gyrus, left caudate head, right visual cortex, right rostral anterior cingulate cortex, and left inferior frontal cortex. Figure 2A displays an image of these results at a threshold of $p < 0.001$, uncorrected. In high level social drinkers, pGni engaged greater activity in the rostral anterior cingulate cortex (Fig. 2B). At the same threshold, no brain region showed greater activation in the contrast of risk aversion (pGi) greater than risk taking (pGni) for either group. The second-level analysis comparing the ALM and AH groups showed greater activation during risk taking (pGni > pGi) in the ALM group in left caudate nucleus including body and head, as well as the right superior frontal gyrus (SFG) at $p < 0.001$, uncorrected (Fig. 3). At the same threshold, no brain regions showed greater activation in the high level as compared with low and moderate use group during risk taking. These findings are summarized in Table 3.

In a covariance analysis, we examined the group differences using the assessment data as potential covariates. The results showed that the pattern of the differences in regional brain activations largely remained the same. In fact, with BIS-11 as a covariate, both the right SFG and left caudate remained significant at the cluster-level threshold of $p < 0.05$, corrected for family-wise errors (FWEs) (right SFG: $p < 0.011$; and left caudate: $p < 0.001$) and increased in significance in voxel peak values. Likewise, we also examined the TPQ subscores as potential covariates. Results from the novelty-seeking subscale showed that the differences in regional brain activations including the right SFG and left caudate decreased in voxel peak T value, but remained significant at $p < 0.001$, uncorrected. However, the results were no longer significant at the cluster-level threshold of $p < 0.05$, corrected for FWE or FWE of multiple comparisons (right SFG: $p < 0.126$; and left caudate: $p < 0.085$). The remaining TPQ subscales did not have significant effects on the data.

Region of Interest Analyses and Correlations with Frequency of Drinking

Functional ROIs were created based on the whole-brain analyses. Effect size of pGni > pGi (risk taking > risk aversion) was derived for all ROIs from the 2-sample t -test. Across subjects, the effect size of this contrast correlated between the ROIs that showed differential activations between ALM and AH groups (all p -values < 0.006; pairwise Pearson regressions). Thus, in assessing whether the extent of risk tasking is related to frequency of alcohol use, we focused on the left caudate nucleus and right SFG, which showed the most significant differences between groups.

In examining the total drinks per month, the variable from which the grouping was made, it was to be expected that the linear correlation with the caudate was significant ($R = -0.345$, $p < 0.028$) and nearly significant in right SFG ($R = -0.292$, $p < 0.064$). Interestingly, we observed significant and stronger linear correlations between the frequency of drinking

(number of days per month in which at least 1 drink was consumed) and the caudate ($R = -0.387$, $p < 0.013$, uncorrected) and with the right SFG ($R = -0.385$; $p < 0.013$, uncorrected). On the other hand, a related, but distinct variable of the number of drinks per occasion was not significantly correlated with either the caudate or right SFG. We further examined such correlations with the AH and ALM groups separately, but did not find any significant linear relationships. Similarly, we sought to explore the difference between men and women taken from the combined sample of the AH and ALM groups. The moderate sample size did not allow us to directly examine the effect of gender on regional brain activations during risk taking. However, in an exploratory analysis, we correlated the monthly frequency of drinking with the effect size of the caudate and SFG separately for men and women. The results showed that this correlation was significant in women, but not in men for both the caudate (women: $R = -0.512$, $p < 0.007$; men: $R = -0.324$, $p > 0.258$) and right SFG (women: $R = -0.685$, $p < 0.0001$; men: $R = -0.184$, $p > 0.528$; Fig. 4).

The linear regression findings were slightly negatively affected by the addition of BIS-11 and TPQ subscales added individually as covariates. However, of those significant results reported, the combined sample (ALM + AH) results for right SFG and left caudate as well as the left caudate results for women remained significant at $p < 0.05$. Similarly, the right SFG results for women remained significant at $p < 0.0005$ with the addition of covariates.

DISCUSSION

Our findings showed decreased superior frontal cortical and caudate activation in the high level social drinking group compared with the low to moderate group during risk taking in the SST. Furthermore, the extent of activation during risk taking in these structures was inversely correlated with frequency of drinking in women, but not in men. These results suggest a neural analog of impulsivity in high level as compared with light or moderate social drinking.

Risky Responses to Stimuli Were Less Salient for High Level Alcohol Drinkers

The superior frontal cortices and caudate nuclei are both implicated in risk taking decisions. For instance, in a modified BART, the dorsolateral prefrontal cortex (DLPFC) and dorsal striatum, among other structures, increased in activation during voluntary risky choices (Rao et al., 2008). Risk estimation is associated with DLPFC activation during a simple gambling task (van Leijenhorst et al., 2006). Transcranial direct current stimulation of the right DLPFC enhanced conservative or risk averting choices in healthy volunteers in a decision-making task (Boggio et al., 2010; Fecteau et al., 2007). Considered along with these previous findings, the current results suggested that, compared with light and moderate drinkers, high level drinkers activated the right DLPFC to a lesser extent when taking a risk, perhaps reflecting decreased engagement in the appraisal of their risk taking behavior. This explanation appeared to be consistent with the broad literature depicting the important role of frontal cortex in exercising cognitive control during risky situations (Clark et al., 2008; Sanfey et al., 2003) and its vulnerability in substance-abusing populations (Goldstein and Volkow, 2002; Li et al., 2009b).

We can examine the caudate findings in terms of attention and saliency, in association with risk taking during the SST. Human fMRI and animal single-cell recording studies have implicated the caudate nucleus in reward and saliency processing (Carretié et al., 2009; Gerdes et al., 2011; Hikosaka, 2007; Knutson et al., 2005; Scott et al., 2006; Yamada et al., 2007; Zink et al., 2003, 2004). The SST as employed in the current study did not involve an explicit component of reward; nor were participants' monetary gain contingent upon their performance. On the other hand, the staircase procedure tracked behavioral performance and required participants to exercise a speed-accuracy trade-off, in which taking a risk by

responding faster, although not necessarily rewarding, was a highly salient, or arousing, action (Li et al., 2009a). In our study we found less caudate activation in high level drinkers as compared with light/moderate drinkers. Thus, the current findings suggest that post-go speeding in response may be less salient for high level drinkers. These results were consistent with many studies implicating the caudate nucleus and altered saliency processing in individuals who misused substances or were at risk for substance misuse (Aron et al., 2004; Bjork et al., 2008; Feldstein Ewing et al., 2011; Leland et al., 2006; Weinstein, 2010; Wilson et al., 2008). Given the relatively novel application of this task, further work is needed to examine the use of the SST in assessing salient events and risk taking. We later discuss this issue in greater detail as a limitation.

Altered Neural Processes of Risk Taking are Related to Frequency of Drinking

The extent of activation of the caudate nucleus and SFG correlated inversely with the frequency of drinking as reported for the month prior to study across the entire cohort of subjects and, in particular, female participants. The significance of frequency and lack of significance of quantity (the average number of drinks consumed per occasion) adds to the imaging findings which only looked at total drinks per month. Our result was consistent with a recent report of Weafer and colleagues (2011). This behavioral study utilized an ocular return task to assess attentional inhibition, a go/no-go task for behavioral inhibition, and a BART task for risk taking. The investigators found quantity of drinking to be significantly correlated with behavioral disinhibition and frequency to be associated with risk taking (Weafer et al., 2011). This finding in combination with our results highlights the importance of frequency in assessing risky drinking behavior. A conclusion such as this has important applications to college alcohol awareness programs which typically target binge-drinkers as being at immediate risk of developing alcohol-related health problems. Perhaps these frequent drinkers, who consume a high level of alcohol on a monthly basis, should not be overshadowed by their more overt, bingeing classmates.

The correlation between risk taking neural processes and frequency of drinking appeared to be more significant in women. This finding suggested the importance of gender differences in the manifestation and etiology of substance, including alcohol, misuse (Fattore et al., 2008; Ferreira and Willoughby, 2008; Greenfield et al., 2010; Hensing and Spak, 2009; Li and Sinha, 2008; Schulte et al., 2009). Consistent with these findings is an earlier study that showed increased impulsivity, as assessed in choice of immediate over delayed monetary reward, in women, but not men with a paternal history of alcohol dependence (Petry et al., 2002). Other studies demonstrated that, although both men and women smokers were higher in sensation seeking than their nonsmoking counterparts, sensation seeking was only correlated with the severity of dependence in female smokers (Carton et al., 1994). Also, the association between the frequency of alcohol drinking and high-risk driving is stronger in women than in men (Lonczak et al., 2007). Taken together, these findings suggest risk taking as a unique psychological factor in high level drinking in women and add to the literature of gender differences in the risk factors of alcohol use, transition of initial use to dependence, and cognitive effects of high level drinking (Flensburg-Madsen et al., 2007; Townshend and Duka, 2005; Zilberman et al., 2003).

Addition of BIS-11 and TPQ–Novelty Seeking Scores as Covariates

The increased significance of the imaging results when BIS-11 was added as a covariate in the analysis suggested that BIS-11 (and inter-subject variation in overall impulsivity) did not account for these group differences. Likewise, we also focus on the novelty seeking subscore of the TPQ as a covariate, which decreased the significance of the imaging results such that they were no longer significant at the cluster-level. This latter result suggested that

some of the group differences may be accounted for by the personality trait of novelty seeking.

We went on to examine the linear regression analyses on the combined AH and ALM sample as well as samples divided by gender in relation to our frequency variable, with the addition of relevant covariates (BIS-11 and TPQ subscales: harm avoidance, novelty seeking, and reward seeking) added individually, such that each model had only 1 covariate. All results decreased in significance, but remained significant at least at $p < 0.05$. Therefore, although the covariates may account for the findings to some extent, the overall relationship between activation of the right SFG and left caudate to frequency of drinking, with particular respect to women, remains a robust finding. Finally, the fact that these correlations did not retain their significance when applied to the AH and ALM groups separately may be a limitation of sample size or evidence of a relationship that exists between the 2 distinct groups, but is not present along a finer continuum of drinking levels.

LIMITATIONS AND CONCLUSION

In this article, we claim our “post-go speeding > post-go slowing” contrast in the SST to be an indirect analog of risk taking behavior during activities such as high level habitual drinking. An inherent limitation that differentiates the SST from other risk taking tools is that it does not rely on reward. Importantly, however, this contrast in the SST appeared to activate many similar as well as distinct brain regions when compared with results from reward-based tasks, as we discussed previously (Li et al., 2009a). For instance, post-go speeding as compared with slowing activates predominantly left-hemispheric fronto-parietal regions, which is consistent with the literature (Drake, 1985; Drake and Ulrich, 1992; Fecteau et al., 2007; Knoch et al., 2006). However, this contrast did not activate the anterior insula, which is extensively implicated in mediating risk taking decisions in reward-related tasks (Huettel, 2006; Kuhn and Knutson, 2005; Paulus et al., 2003; Preusschoff et al., 2008). The lack of anterior insula activation in the current and our earlier work perhaps suggests that post-go speeding in the SST does not evoke anxiety or other negative sensations, as does a risk taking decision during gambling tasks. Thus, despite the motivational saliency of post-go speeding, risk taking in the SST may partake in some, but not all, of the risk-related cognitive and affective processes that have been observed in earlier work in which material loss was involved. More work is needed to substantiate the relationship of post-go speeding (as compared with slowing) as a cognitive construct to the personality trait of risk taking. In particular, future study is warranted to compare these present findings with the neural processes underlying behavioral decisions that involve explicit reward.

As with any research study that is reliant on a small sample to be representative of a greater population, our study possesses limitations due to the sample composition and means of data collection. One important limitation is our use of self-report and recall from memory data regarding the alcohol consumption questions. Although recall from memory may not be as accurate as studies which utilize an alcohol diary, the majority of our questions only required subjects to recall the past month of behavior. The remaining questions asked participants to recall only significant events during the past year such as drunk driving or black-outs. We also consider that reporting drinking behavior and corresponding problems (e.g., with the law or family) among young adults can come with a negative social stigma. All participants were encouraged to be honest when completing assessments and assured that their responses to the questions would not affect their eligibility (following the initial screening session). The reported loss of control of a modest 0.9 ± 1.6 on a 10-point scale among the AH sample consuming a striking 29.8 ± 16.1 drinks per month may be indicative of such inaccurate self-reporting. Finally, with relation to the sample, we maintain caution in

drawing conclusions about the young adult social drinking population as a whole. Although recruitment efforts focused on various college campuses, the sample likely contains elements of response and nonresponse bias that could affect the results. It is relevant to mention that the validity of our sample is of particular importance to the results given that sample composition drove the delineation of high and low/moderate groups. A larger, future study would help to validate the group delineations used here. Overall, we feel that the comparatively low threshold required for participants to reach “high level” drinking status addresses an important concept of what we call high level social drinking, which may not be equivalent to hazardous drinking. As this study takes a nontraditional approach to defining the groups, it adds to the literature in revealing differences that arise well before hazardous behavior occurs. Overall, sample bias is a limitation of any study of this nature and therefore conclusions may be taken with caution, but we do not believe that this or, the other limitations described here, detract from the validity of the results.

In addition, when considering future directions, the moderate sample size used in this study precludes additional analyses of the effects of the pattern of alcohol use, including bingeing, on regional brain activations during risk taking (Meyerhoff et al., 2004). Future studies incorporating these parameters and gender are warranted.

As a final note, we did not see significant activations in the amygdala, in contrast to expectations according to our previous results in habitual drinkers (Li et al., 2009a; Yan and Li, 2009). We speculated that the differences might reflect the characteristics of the subjects recruited for our previous study, who were mostly Yale University students and likely more emotionally tied to their performance. For instance, an anxiety trait as assessed by the Maudsley Obsessive Compulsive Inventory was significantly higher in the earlier cohort as compared with the current sample (7.0 ± 4.1 vs. 4.1 ± 3.7 , $p < 0.002$, 2-sample t -test).

To summarize, in this study we showed that the cerebral processes related to risk taking are significantly different among a cohort of healthy controls that was divided by level of social drinking. High level social drinking is associated with altered activation of the caudate and superior frontal cortex, an association that appeared to be stronger in women than in men. Such findings suggest a neural basis of risky social drinking and may also serve to improve screening measures for at-risk behavior. More accurate screening tools could in turn facilitate the prevention of escalation from habitual to dependent drinking in young, vulnerable social drinkers.

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Fig. 1.

(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 and 5 seconds (the fore-period [FP], uniform distribution) 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 67 ms following a stop success and stop error trial, respectively. There was an intertrial interval of 2 seconds. We distinguished go success (G), go error (GE), stop success (SS), and stop error (SE) trials during the task. (B) Go successes were further distinguished by their preceding trial; thus, post-go go (pG) trials were G trials preceded by a G trial, pSS trials were G trials preceded by an SS trial, and so on. Depending on whether they increased or did not increase in reaction time (RT), compared with the mean RT of all preceding pG trials, pG trials were further grouped into pGi (post-go slowing) and pGni (post-go speeding; see Materials and Methods).

Fig. 2.

Regional brain activations during risk taking in the stop signal task. **(A)** At a threshold of $p < 0.001$, uncorrected, post-go speeding as compared with post-go slowing elicited greater activation in the middle frontal gyrus, inferior parietal cortex, posterior cingulate cortex, middle temporal gyrus, rostral anterior cingulate cortex, and caudate head in the low to moderate drinking (ALM) group. **(B)** At the same threshold, post-go speeding as compared with post-go slowing elicited greater activation in the rostral anterior cingulate cortex in the high (AH) group. Blood oxygen level-dependent contrasts are superimposed on a T_1 -weighted structural image in axial sections.

Fig. 3.

At a threshold of $p < 0.001$, uncorrected, light, and moderate drinkers (ALM) showed greater activations in caudate head / body and superior frontal gyrus compared with high level drinkers (AH) during risk taking. Blood oxygen level-dependent contrasts are superimposed on a T₁-weighted structural image in axial sections.

Fig. 4.

Linear correlations of effect size for the left caudate and superior frontal gyrus (SFG) with the frequency of drinking within the past month. Data are split by gender (solid marks denote women; open marks for men) and displays the linear regression line for the data (dotted line indicates women; dashed line indicates men; solid line for all data). No covariates are included in the model shown here; however, the addition of covariates did not compromise the results. The specific effects can be found in the results and discussion sections of the text.

Table 1

Subject Demographics

Subject characteristic	AH	ALM	<i>p</i> -Value
	<i>n</i> = 20	<i>n</i> = 21	
Age (years)	23.8 ± 3.7	25.0 ± 3.8	0.323 ^a
Women/men	11/9	16/6	0.231 ^b
Ethnicity			
African American	4	5	0.591 ^b
Caucasian	15	14	
Other	1	3	
Education	16.5 ± 2.8	15.3 ± 2.6	0.389 ^a
BIS-11	61.5 ± 6.4	55 ± 10.7	0.023 ^a
TPQ	5.4 ± 1.4	4.9 ± 1.5	0.294 ^a
AUDIT	7.1 ± 2.9	2.3 ± 1.9	<0.000 ^a
Total no. drinks per month	29.8 ± 16.1	4.1 ± 3.3	0.000 ^a
No. times per month	9.7 ± 5.6	1.9 ± 1.4	0.000 ^a
No. drinks per time	3.5 ± 1.4	1.9 ± 1.6	0.002 ^a
Loss of control	0.9 ± 1.6	0 ± 0	0.005 ^a
AEQ			
GP	11.1 ± 3.7	9.4 ± 4.3	0.200 ^a
SPP	20.4 ± 5.1	16.4 ± 5.9	0.036 ^a
SEXP	18.6 ± 5.2	14.4 ± 7.2	0.046 ^a
SENH	15.9 ± 4.9	14.3 ± 7.3	0.420 ^a
PA	18.0 ± 6.2	14.9 ± 6.5	0.148 ^a
TRR	16.2 ± 4.1	13.6 ± 5.6	0.120 ^a
CPI	18.5 ± 5.2	17.3 ± 7.9	0.573 ^a
CU	13.4 ± 5.1	11.1 ± 4.5	0.162 ^a

Values are mean ± standard deviation.

AH, high social alcohol use; ALM, low to moderate social alcohol use; BIS-11, Barratt Impulsivity Scale; TPQ, Tridimensional Personality Questionnaire; AUDIT, Alcohol Use Disorders Identification Test; AEQ, Alcohol Expectancy Questionnaire; GP, global positive; SPP, social and physical pleasure; SEXP, social expressiveness; SENH, sexual enhancement; PA, power and aggression; TRR, tension reduction and relaxation; CPI, cognitive and physical impairment; CU, careless unconcern.

^a2-sample *t* test.

^bChi-square test.

Table 2

Stop Signal Task Performance

	SSRT (ms)	Median go RT (ms)	%go	%stop	PES (effect size)
AH (<i>n</i> = 20)	194 ± 51	650 ± 109	89.2 ± 7.9	53.6 ± 3.1	1.94 ± 1.65
ALM (<i>n</i> = 21)	199 ± 36	624 ± 123	89.8 ± 10.4	52.6 ± 3.5	1.97 ± 1.68
<i>p</i> -Value*	0.947	0.464	0.845	0.362	0.709

All values are reported as mean ± standard deviation; Stop signal reaction time (SSRT) refers to the time a participant requires in order to refrain from making a response after the stop signal appears. The SSRT is computed by subtracting the critical stop signal delay (the estimated time delay required to achieve success in half of the stop trials) from the median go trial RT, according to the race model (Li et al., 2006; Logan, 1994). Post-error slowing (PES) describes the extent to which a participant slowed down in a go trial after they encountered an error. The effect size of the PES is computed by comparing the RT of these post-stop error go to post-go go trials (Li et al., 2008); %go and %stop refer to the overall percentage of correct go and stop trials, respectively (RT < 1s were considered go success). Data are reported for the two groups of interest: high social alcohol use (AH) and low to moderate social alcohol use (ALM).

Table 3

Regional Brain Activity During Risk-Taking

Cluster size (voxels)	Cluster-level $p_{FWE-corr}$	Voxel Z value	MNI coordinate (mm)			Side	Identified brain region	
			x	y	z			
Light and moderate drinkers								
835	0.000	4.74	-36	17	46	L	Middle frontal gyrus	
		4.62	12	23	49	R		
		4.32	-12	44	49	L		
287	0.001	4.17	-48	-55	43	L	Inferior parietal cortex	
		4.00	-39	-70	34	L		
		3.93	-33	-58	31	L		
195	0.004	3.75	-6	-37	34	L	PCC	
		3.75	0	-58	40	L/R		
		3.67	0	-46	34	L/R		
28	0.474	3.74	30	-94	1	R	Visual cortex	
		3.66	24	-100	1	R		
31	0.430	3.63	-6	44	22	L	Rostral ACC	
		3.45	-12	38	28	L		
		3.33	-12	47	28	L		
52	0.215	3.60	54	-61	37	R	Inferior parietal cortex	
		3.30	42	-64	40	R		
16	0.687	3.48	-12	20	13	L	Caudate	
13	0.748	3.47	-57	-43	-8	L	Middle temporal G	
Heavy drinkers								
50	0.204	4.07	6	32	4	L/R	Rostral ACC	
		3.47	-3	23	-8			
52	0.190	3.83	3	44	25	L/R	Rostral ACC	
		3.25	0	47	13			
		3.24	-9	38	28			
36	0.347	3.73	-9	53	-5	L/R	Rostral ACC	
		3.40	0	56	1			
Light and moderate drinkers > heavy drinkers								

Cluster size (voxels)	Cluster-level $p_{FWE-corr}$	Voxel Z value	MNI coordinate (mm)			Side	Identified brain region
			x	y	z		
130	0.026	4.16	9	-31	16	L/R	Splenium
		3.79	-6	-31	13		
		3.42	-15	-34	13		
101	0.014	4.07	-12	2	22	L	Superior frontal G
		3.87	-12	-7	25		
		3.57	-18	8	37		
126	0.029	3.94	-27	23	25	L	Caudate
		3.92	-12	17	13		
		3.72	-15	26	7		
128	0.027	3.87	24	14	34	R	Superior frontal G
		3.84	27	20	43		
		3.58	12	2	28		

MNI, Montreal Neurological Institute; PCC, posterior cingulate cortex; ACC, anterior cingulate cortex; G, gyrus.