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Association of drinking problems and duration of alcohol use to inhibitory control in non-dependent young adult social drinkers

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Abstract

Background—Deficits in inhibitory control have been widely implicated in alcohol misuse. However, the literature does not readily distinguish the effects of drinking problems and chronic alcohol use. Here, we examined how years of drinking and the Alcohol Use Disorders Identification Test (AUDIT) score each influences the cerebral responses to inhibitory control in non-dependent drinkers.

Methods—Fifty-seven adult drinkers and 57 age and gender matched non-drinkers participated in one 40-minute fMRI scan of the stop signal task. Data were pre-processed and modeled using SPM8. In a regression model, we contrasted stop and go success trials for individuals and examined activities of response inhibition each in link with the AUDIT score and years of alcohol use in group analyses. We specified the effects of duration of use by contrasting regional activations of drinkers and age-related changes in non-drinkers. In mediation analyses, we investigated how regional activities mediate the relationship between drinking problems and response inhibition.

Results—Higher AUDIT score but not years of drinking was positively correlated with prolonged stop signal reaction time (SSRT) and diminished responses in the cerebellum, thalamus, frontal and parietal regions, independent of years of alcohol use. Further, activity of the thalamus, anterior cingulate cortex, and pre-supplementary motor area significantly mediates the association, bidirectionally, between the AUDIT score and SSRT. The duration of alcohol use was associated with decreased activation in the right inferior frontal gyrus extending to superior temporal gyrus, which was not observed for age-related changes in non-drinkers.

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Conclusions—The results distinguished the association of drinking problems and years of alcohol use to inhibitory control in young adult non-dependent drinkers. These new findings extend the imaging literature of alcohol misuse and may have implications for treatment to prevent the escalation from social to dependent drinking. More research is needed to confirm age-independent neural correlates of years of alcohol use.

Keywords

cognitive control; conflict; alcoholism; neuroimaging; medial prefrontal cortex

Introduction

An extensive body of research has associated altered inhibitory control to alcohol use disorders. Studies combining brain imaging and behavioral testing characterized altered cerebral responses to inhibitory control in alcohol misuse. Overall, the literature consistently supports decreased frontal functioning in association with impulsivity and risk taking in addicted and at-risk populations. For instance, compared to non-drinkers, adolescents who showed less cerebral responses to inhibitory control were more likely to become heavy drinkers (Wetherill et al., 2013). In individuals with diminished response inhibition, implicit associations between alcohol and positive affect/arousal predicted increased alcohol use and alcohol-related problems (Houben and Wiers, 2009). In our earlier studies, alcohol dependent patients demonstrated altered prefrontal cortical activations during response inhibition and anticipation of control (Hu et al., 2015; Li et al., 2009b). In another prospective study with follow-up for four years, impaired inhibitory control in the stop signal task predicts the development of alcohol dependence (Rubio et al., 2008). Indeed, impulsivity predicts not only heavier alcohol consumption but also alcohol-related mortality rates (Blonigen et al., 2011). Together, these studies support deficits in inhibitory control as a developing sign of drinking problems and an important characteristic of alcohol dependence (Leeman et al., 2014).

An important issue in this line of work is to distinguish the impact of duration of drinking and drinking problems on inhibitory control. Alcohol is known to alter cerebral structures and functions and chronic alcohol use compromises executive functioning. However, it remains unclear whether or to what extent alcohol use impacts cerebral functions in nondependent drinking. Further, drinking problems may reflect impulsivity and risk taking that goes beyond alcohol consumption and influence a broader realm of behavior. Because deficits in inhibitory control dispose individuals to alcohol misuse and alcohol consumption further compromises this capacity, breaking the self-perpetuating link is critical to managing alcohol use behavior. It is thus important to distinguish the neural processes underlying drinking problems and the effects of chronic alcohol consumption.

The current study aims to fill this gap of research. The Alcohol Use Disorders Identification Test (AUDIT) has been commonly used to assess risky drinking behavior and to identify alcohol-related problems (Babor et al., 2001). College students with drinking problems as indicated by higher AUDIT scores showed impulsive decision making in a discounting task and diminished inhibitory control in a go/no-go task (Murphy and Garavan, 2011). The

AUDIT score has been used as an outcome measure to identify young adults who developed alcohol dependence (Foxcroft et al., 2015), and to evaluate at-risk drinking in individuals with comorbid depression (van den Berg et al., 2014) and the interactive effects of cumulative stress and impulsivity on alcohol consumption (Fox et al., 2010). By combining the AUDIT and clinical assessment of alcohol use, we may examine the effects of drinking problems and duration of use on inhibitory control.

In the laboratory, the go/no-go task and stop signal task (SST) are widely used to investigate cognitive control in alcohol and substance abusers. In these behavioral tasks, the frequent “go” trials set up a prepotent response tendency that needs to be overridden occasionally when the nogo or stop signal appears. By comparing cerebral responses to the nogo or stop trials, when inhibition is required, and responses to go trials, investigators have characterized how these processes are altered in problem drinkers and those with a family history of alcohol misuse (Acheson et al., 2014; Bednarski et al., 2012; Heitzeg et al., 2010; Hu et al., 2015; Li et al., 2009b; Yan and Li, 2009). Here, we employed fMRI and the SST to examine how drinking problems, as assessed with the AUDIT, and years of alcohol use influence response inhibition and cerebral activities to response inhibition. Because years of alcohol use is highly correlated with age, we recruited a group of demographics matched non-drinkers for comparison in order to address the specific effects of duration of alcohol use.

Methods

Participants, assessments, and behavioral task

One-hundred-and-fourteen adults (66 females; 30.3 ± 11 years of age) participated in this study. This was a new cohort; none of the individuals participated in our earlier studies (Bednarski et al., 2012; Yan and Li, 2009). All participants signed a written consent after they were given a detailed explanation of the study in accordance with a protocol approved by the Yale Human Investigation Committee. All participants were without major medical, neurological, or psychiatric conditions, denied use of illicit substances, and tested negative in urine toxicology screen on the day of fMRI. All completed questionnaires to assess alcohol use, including duration (years) of regular use and detailed alcohol use behavior over the past year. Participants were also evaluated with the AUDIT (Babor et al., 2001). Individuals' AUDIT score was calculated from the sum of 10 self-report questions regarding the 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 scores indicating a greater risk for having or developing an alcohol use disorder. None of our participants met the diagnostic criteria for alcohol abuse or dependence, according to the Structured Clinical Interview for DSM-IV (First et al., 2002). Fifty-seven participants were identified as social drinkers and the rest as non-drinkers.

All participants performed a stop signal task or SST (Hu and Li, 2012; Li et al., 2009a), in which go and stop trials were randomly intermixed in presentation with an inter-trial-interval of 2 seconds (s). A fixation dot appeared on screen to signal the beginning of each trial. After a fore-period varying from 1 s to 5 s (uniform distribution), the dot became a circle – the “go” signal – prompting participants to quickly press a button. The circle

disappeared at button press or after 1 s if the participant failed to respond. In approximately one quarter of trials, the circle was followed by a 'cross' – the stop signal – prompting participants to withhold button press. The trial terminated at button press or after 1 s if the participant successfully inhibited the response. The time between the go and stop signals, the stop signal delay (SSD), started at 200 ms and varied from one stop trial to the next according to a staircase procedure, increasing and decreasing by 67 ms each after a successful and failed stop trial. With the staircase procedure we anticipated that participants would succeed in withholding the response half of the time. Participants were trained briefly on the task before imaging to ensure that they understood the task. They were instructed to quickly press the button when they saw the go signal while keeping in mind that a stop signal might come up in some trials. In the scanner, they completed four 10-minute sessions of the task, with approximately 100 trials in each session.

Behavioral data analysis

A critical SSD was computed for each participant that represents the time delay required for the participant to successfully withhold the response in half of the stop trials, following a maximum likelihood procedure. Briefly, SSDs across trials were grouped into runs, with each run being defined as a monotonically increasing or decreasing series. We derived a mid-run estimate by taking the middle SSD (or average of the two middle SSDs when there was an even number of SSDs) of every second run. The critical SSD was computed by taking the mean of all mid-run SSDs. It was reported that, except for experiments with a small number of trials (< 30), the mid-run measure was close to the maximum likelihood estimate of X50 (50% positive response; i.e., 50% stop success in the SST). The stop signal reaction time (SSRT) was computed for each participant by subtracting the critical SSD from the median go trial reaction time.

Imaging protocol and spatial preprocessing of brain images

Conventional T1-weighted spin-echo sagittal anatomical images were acquired for slice localization using a 3T scanner (Siemens Trio). Anatomical images of the functional slice locations were obtained with spin-echo imaging in the axial plane parallel to the Anterior Commissure-Posterior Commissure (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. A single high-resolution T1-weighted gradient-echo scan was obtained. One hundred and seventy-six slices parallel to the AC-PC line covering the whole brain were acquired with TR = 2530ms, TE = 3.66ms, bandwidth = 181 Hz/pixel, flip angle = 7°, field of view = 256×256 mm, matrix = 256×256, 1mm³ isotropic voxels. 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 = 2000 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. There were three hundred images in each session for a total of 4 sessions.

Data were analyzed with Statistical Parametric Mapping (SPM8, Wellcome Department of Imaging Neuroscience, University College London, U.K.). Images from the first five TRs at

the beginning of each session were discarded to enable the signal to achieve steady-state equilibrium between radio frequency pulsing and relaxation. In the pre-processing of BOLD data, images of each participant were realigned (motion-corrected) and corrected for slice timing. A mean functional image volume was constructed for each participant for each run from the realigned image volumes. These mean images were co-registered with the high resolution structural image and then segmented for normalization to an MNI (Montreal Neurological Institute) EPI template with affine registration followed by nonlinear transformation. Finally, images were smoothed with a Gaussian kernel of 8 mm at Full Width at Half Maximum. Images from the first five TRs at the beginning of each trial were discarded to enable the signal to achieve steady-state equilibrium between radio frequency pulsing and relaxation.

Generalized linear models and group analyses

Our goal was to identify the neural correlates of successful inhibitory control. We distinguished four trial outcomes: go success (GS), go error (GE), stop success (SS), and stop error (SE), and modeled BOLD signals by convolving the onsets of the go signal a canonical hemodynamic response function (HRF) and the temporal derivative of the canonical HRF. Realignment parameters in all 6 dimensions were entered in the model. Serial autocorrelation of the time series was corrected by a first degree autoregressive or AR(1) model. The data were high-pass filtered (1/128 Hz cutoff) to remove low-frequency signal drifts.

In all analyses, we evaluated results at a voxelwise threshold of $p < .005$, combined with a cluster size threshold of 29 contiguous voxels (783 mm³). This combined threshold was estimated with a Monte-Carlo simulation using AlphaSim (Douglas Wand, http://afni.nimh.nih.gov/pub/dist/doc/program_help/AlphaSim.html) to yield an overall threshold of $p < .05$, corrected for multiple comparison for the whole brain. In the first level analysis, we constructed for each individual the contrast for successful response inhibition SS>GS. In the second level analysis, we conducted a one-sample t test to identify regional activations to response inhibition across all participants and compared drinkers with non-drinkers with small volume correction (SVC) for regions of interests (ROIs).

A brief justification is needed here for the use of SS>GS as our earlier studies have contrasted SS and SE trials. There are a couple of issues to consider in the use of SS>SE vs. SS>GS to identify the correlates of response inhibition. Whereas SS does not involve an overt motor response, both SE and GS do. Compared to SS, SE is highly salient and engages a wide array of cortical and subcortical structures, including the thalamus, insula, and midbrain (Li et al., 2008). In contrast, SS is more salient than GS. Thus, the question about which contrast to use in the regression against SSRT to identify the correlates of response inhibition hinges on conceptualizing the relationship of saliency response and inhibitory control. Since our earlier publications, our thinking has evolved that a critical component of motor inhibition as required of the SST is triggered by saliency processing of the stop signal (Cai et al., 2014; Cai et al., 2015; Hampshire and Sharp, 2015) and a proper contrast would have to index this saliency response. Thus, a contrast of SS>GS reflects how cerebral responses to the infrequent, stop signal “kick-start” the inhibitory process and those regional

activations in correlation with SSRT mediate this linked neural activity for successful inhibition. Conversely, a contrast of SS>SE would identify regional activities that are suppressed by saliency and undermine the link of saliency response to motor inhibition. With these considerations, it is likely that what we have seen earlier with the latter contrast primarily reflected a diminished preparatory motor activity (in the pre-SMA) during SE, as compared to SS; that is, less motor preparation is conducive to more efficient inhibitory control. Both saliency response (to the stop signal) and diminished motor preparation (as a result of response caution or top-down influence of cognitive control) are critical to successful inhibition. Both of these processes can be captured by a contrast of SS>GS, but not SS>SE. Therefore, in the current study, we have opted to employ the contrast SS>GS in data analyses. We would also like to point out here that using the contrast SS > SE revealed few significant findings either in the comparison of drinkers and non-drinkers or in the regression against SSRT.

In a linear regression of SS>GS against SSRT, we identified the correlates of response inhibition for drinkers (regression I). To examine the effects of duration of use and drinking problems on response inhibition, we regressed SS>GS against the AUDIT score and years of alcohol use in drinkers in a multiple regression (regression II). Thus, the latter model identified correlates of response inhibition each in association with drinking problems and duration of use and, by comparison with the linear regression of SS>GS against SSRT (regression I), allowed us to identify regional activities specific to response inhibition and modulated by the AUDIT score and years of alcohol use. Because the duration of drinking was significantly correlated with age (see Results), we regressed SS>GS against age to localize age-related changes in non-drinkers (regression III) and to specify regional activations to response inhibition as influenced by years of drinking (regression II) but not age.

Mediation analysis

We performed mediation analyses to test the hypothesis that regional activations mediate the association between the AUDIT score and SSRT, using the toolbox M3 developed by Wager and Lindquist (<http://www.columbia.edu/cu/psychology/tor/>). The methods were detailed in our previous work (Ide and Li, 2011). Briefly, in a mediation analysis, the relation between the independent variable X and dependent variable Y, i.e., $X \rightarrow Y$, is tested to see if it is significantly mediated by a variable M. The mediation test is performed by employing three regression equations:

$$\begin{aligned} Y &= i_1 + cX + e_1 \\ Y &= i_2 + c'X + bM + e_2 \\ M &= i_3 + aX + e_3 \end{aligned}$$

where a represents $X \rightarrow M$, b represents $M \rightarrow Y$ (controlling for X), c' represents $X \rightarrow Y$ (controlling for M), and c represents $X \rightarrow Y$. In the literature, a , b , c , and c' were referred as *path coefficients* or simply *paths*, and we followed this notation. Variable M is said to be a mediator of connection $X \rightarrow Y$, if $(c - c')$ is significantly different from 0, which is mathematically equivalent to the product of the paths $a \times b$ (MacKinnon et al., 2007). If the

product of $a \times b$ and the paths a and b are significant, one concludes that $X \rightarrow Y$ is mediated by M . In addition, if path c' is not significant, it indicates that there is no direct connection from X to Y and that $X \rightarrow Y$ is completely mediated by M . Note that path b is the relation between Y and M , controlling for X , and it should not be confused with the correlation coefficient between Y and M . Note that a significant correlation between X and Y and between X and M is required for one to perform the mediation test.

Results

Behavioral performance in the stop signal task

Drinkers and non-drinkers were not different in age (mean $\pm$ standard deviation: 29.1 ± 9.6 vs. 31.5 ± 11.8 years; $p = 0.2370$, two-sample t test) or gender (22 F/35 M vs. 26 F/31 M; $p = 0.4463$, chi-square test). On average, drinkers reported a frequency of 6.9 ± 5.0 occasions of drinking per month with 2.7 ± 1.2 drinks per occasion, and 12.3 ± 10.4 years of alcohol use. Their AUDIT score was on average 4.9 ± 2.7 .

In the SST, both drinkers ($52.3 \pm 2.8\%$) and non-drinkers ($50.8 \pm 2.6\%$) succeeded in approximately half of the stop trials. Drinkers and non-drinkers did not differ in the median go trial reaction time (623.4 ± 98.6 vs. 591.3 ± 112.0 ms; $p = 0.1077$, two-sample t test) or stop signal reaction time (SSRT, 203.5 ± 39.3 vs. 209.1 ± 39.4 ms; $p = 0.4518$, two-sample t test). Stop error reaction time was significantly shorter than to go trial reaction time ($t_{drinkers} = 3.9004$, $p = 0.0002$; $t_{nondrinkers} = 3.1635$, $p = 0.0020$), suggesting that their performance was well tracked by the staircase procedure.

Table 1 shows the correlation between behavioral performance and drinking measures in drinkers. Age was significantly correlated with years of alcohol use ($r = 0.9733$, $p = 0.0000$, Pearson regression) but not the AUDIT score ($r = -0.0853$, $p = 0.5282$). Years of alcohol use and the AUDIT score were not significantly correlated ($r = -0.0173$, $p = 0.8982$). The AUDIT score but not the duration of alcohol use was positively correlated with SSRT (Table 1). That is, drinking problems was associated with prolonged SSRT and impairment in response inhibition.

Response inhibition in drinkers and non-drinkers

We first examined the extent of head motion as a confound to differences in regional BOLD signals between drinkers and non-drinkers. To quantify head motions, we computed the framewise displacement (FD) for each individual (0.1264 ± 0.0600 vs. 0.1090 ± 0.0922) and found no significant differences between the two groups ($t = 1.1957$, $p = 0.2343$). We also computed the percentage of FDs > 0.5 mm (0.0189 ± 0.0466 vs. 0.0196 ± 0.0527) (Power et al., 2012; Tomasi and Volkow 2012). These were converted to z values via Fisher's transformation and a two-sample t test again showed no differences between the two groups ($t = -0.0727$, $p = 0.9422$).

We evaluated all imaging results at a voxel threshold of $p < .005$, uncorrected, combined with a cluster size threshold of 29 contiguous voxels estimated with a Monte-Carlo simulation using AlphaSim to correct for multiple comparison across the whole brain (see Methods). One-sample t test of $SS > GS$ for all participants identified regional activations to response

inhibition for the whole brain (Figure 1a and 1b). A two-sample t test showed greater activities in the right supramarginal gyrus (SMG), superior temporal gyrus (STG), and left temporoparietal junction (TPJ) extending to the middle temporal gyrus (MTG) in drinkers as compared to non-drinkers. On the other hand, non-drinkers showed greater activation in bilateral rostral anterior cingulate cortex (rACC) than drinkers (Table 2; Figure 1c).

Relationship between drinking problems, years of use, and regional activations to response inhibition

In drinkers, the cerebellum, bilateral dorsal ACC (dACC) extending to superior frontal gyrus (SFG), bilateral thalamus, left postcentral gyrus (PoG), and right superior parietal lobule (SPL) extending to angular gyrus (AG) decreased activation to higher AUDIT score (Table 3; Figure 2a). No brain regions showed activation that positively correlated with AUDIT score. The right middle occipital cortex (MOG) increased activations to longer years of alcohol use, and the left TPJ extending to SMG, right inferior frontal gyrus (IFG) extending to STG, bilateral primary motor cortices (PMC) and PoG, left SPL bordering precuneus, and mid-cingulate cortex (MCC) decreased activations in association with longer duration of alcohol use (Table 3; Figure 2b).

As described earlier, because years of alcohol use was significantly correlated with age, we regressed SS>GS against age in non-drinkers to identify age-related changes. The left TPJ extending to MTG, bilateral MCC, right hippocampus, right insula, right dorsal lateral prefrontal cortex (DLPFC), left precuneus, and right pre-SMA and ACC decreased activation to older age (Figure 2c). An exclusive masking with these age-related activities showed that the activations in the right IFG extending to STG in drinkers were specific to years of alcohol use.

Regional activations to drinking problems and stop signal reaction time

Behavioral analysis showed that the AUDIT score was significantly correlated with SSRT. To explore whether regional responses to the AUDIT score (Figure 3, blue, same as Figure 2a) contribute to prolonged SSRT, we regressed SS>GS against SSRT (Table 2; Figure 3, turquoise) with inclusive masking to identify voxels with overlapping representations in linear regressions of SS>GS against SSRT and against the AUDIT score (Figure 3, cyan). The results showed that the activations of the dACC extending to SFG, left MFG, pre-SMA, and thalamus increased to shorter SSRT (more efficient response inhibition) and decreased to higher AUDIT score.

We identified and combined voxels responding to both the AUDIT score and SSRT in linear regressions into a single ROI for mediation analysis. The working hypotheses were whether drinking problems lead to altered regional activations, which in turn lead to prolonged SSRT, or whether poor response inhibition alters regional activations that lead to drinking problems. Four models were built to test these hypotheses. In the first model, the AUDIT score served as the independent variable X, SSRT as the dependent variable Y, and the contrast value of voxel activity of the ROI as the mediating variable M. In the second model, SSRT served as X, the AUDIT score as Y, and voxel activity as M. In the third model, voxel activity served as X, the AUDIT score as Y, and SSRT as M. In the last model, voxel

activity served as X, SSRT as Y, and the AUDIT score as M. We did not consider the other two models in which voxel activity served as the dependent variable because, as a neural phenotype, voxel activity causes behavioral manifestations but not the other way around. However, these two models were examined for completeness.

The results showed that voxel activity exclusively mediates the relationship bidirectionally between the AUDIT score and SSRT (Figure 4; Table 4). That is, the correlation between the AUDIT score and regional activity and that between regional activity and SSRT were both significant, and the correlation between the AUDIT score and SSRT was totally accounted for by regional brain activity (see Methods). In additional analyses, we investigated whether specific brain regions contribute to this mediation. Among the four clusters, the bilateral dACC/SFG, left MFG, and pre-SMA each mediated the relationship bidirectionally between the AUDIT score and SSRT (Models 1 and 2, Figure 4). On the other hand, neither SSRT nor the AUDIT score significantly mediated the correlation between voxel activity and the other variable (Models 3 and 4, Figure 4). In the remaining two models, there were not significant mediation effects.

Discussion

Drinking problems, independent of years of use, is associated with altered inhibitory control in drinkers

We showed that drinking problems, as indexed by the AUDIT score, is associated with prolonged stop signal reaction time (SSRT) or impaired response inhibition. Furthermore, activations in bilateral dorsal anterior cingulate cortex (dACC)/superior frontal gyrus, left middle frontal gyrus, and pre-supplementary motor area during response inhibition mediate the association bidirectionally between SSRT and the AUDIT score. Although these results do not specify a unique, directional influence, they suggest shared neural substrates between drinking problems and deficits in inhibitory control.

These findings are broadly consistent with earlier studies documenting the role of the dorsomedial and superior frontal cortices in inhibitory control and compromised activations of these structures in alcohol misuse (Abernathy et al., 2010). For instance, the ACC showed greater BOLD activities in light drinkers than in heavy drinkers for correct rejections in a go/no-go task (Ahmadi et al., 2013). In another study, activity of the ACC negatively correlated with the severity of alcohol misuse during correct rejections in the go/no-go task (Claus et al., 2013). In a spatial working memory task, Vollstadt-Klein et al. (2010) reported a trend of greater ACC activity in light than in heavy social drinkers. Adolescents with a family history of alcohol use disorder also showed less activation in the ACC and medial PFC than control adolescents during a spatial working memory (Spadoni et al., 2008) and emotional Stroop task (Qiao et al., 2015). The right dorsal prefrontal cortex demonstrated less BOLD activity in adolescents with a family history of alcoholism than those without during risky versus safe selection in a Wheel of Fortune task (Cservenka and Nagel, 2012). In support of these studies, our results delineated a specific link between the prefrontal cortical activity, response inhibition, and drinking problems.

Years of alcohol use is exclusively associated with altered activation in right inferior gyrus (IFG) extending to superior temporal gyrus (STG), but not with inter-subject differences in SSRT. Although this finding suggests that duration of alcohol consumption did not influence inhibitory control, years of alcohol use may not reflect the amount of alcohol consumed or adequately capture the deleterious effects of alcohol on cerebral activities. The latter concern is also mirrored by the lack of differences in SSRT or activations in brain areas of inhibitory control between drinkers and non-drinkers. Likewise, we did not observe a significant effect of age on SSRT but our previous cohort with a wider age range clearly documented prolonged SSRT with increasing age (Hu et al., 2012). One possibility is that alcohol use of this relatively young drinker population is relatively mild; as a result, the current findings need to be interpreted specifically with these considerations.

Other studies explored cerebral structural correlates that may relate to the current findings. Volumetric differences in the ACC prospectively predict alcohol-related problems in adolescence (Cheetham et al., 2014; Squeglia et al., 2014). Binge drinkers showed significantly low cortical thickness in the ACC than in light drinkers, suggesting that patterns of intermittent heavy alcohol consumption are associated with cortical thinning (Mashhoon et al., 2014). Lower gamma amino-butyric acid (GABA) and N-acetyl-aspartate (NAA) in the ACC was also reported in adult binge drinkers (Silveri et al., 2014). Together, these studies speak to the importance of the ACC as a core region for cognitive control and dysfunction of the ACC as an etiological process underlying alcohol misuse.

A consideration on the psychological constructs of SS >GS

Although the contrast of “stop success (SS) greater than go success (GS)” may reflect inhibitory control, alternative explanations including saliency response should be considered, because stop trials are infrequent as well as behaviorally relevant and thus are highly salient. The finding of greater rostral ACC (rACC) activation in non-drinkers as compared to drinkers absent a difference in SSRT may suggest an effect of alcohol use on altered saliency processing. The rACC is implicated in saliency responses in a variety of behavioral paradigms (Brazdil et al., 2007) and decreased activation in many clinical conditions including alcohol and substance use disorders (Felmington et al., 2009; Heinz et al., 2007; Moeller et al., 2014). For instance, decreased rACC response to errors is associated with impaired emotional awareness in cocaine abusers (Moeller et al., 2014) and impaired error awareness in cannabis users (Hester et al., 2009). Fein and Chang (2008) reported feedback error-related negativity (ERN) in the fronto-central region including the ACC after error trials in a Balloon Analogue Risk Task, and the magnitude of this ERN was negatively associated with family history density of alcohol problems. Smaller P3 activity was found in alcohol dependent adults than in healthy controls in the nogo condition in a go/nogo task (Colrain et al., 2011; Kamarajan et al., 2005). In contrast, the ACC showed increased response to alcohol cues in alcohol addicts, as compared to controls (Tapert et al., 2004) as well as in heavy drinkers, which diminished over time during abstinence (Brumback et al., 2015). Thus, contingent on the psychological relevance of the stimuli, ACC response to saliency may represent an endophenotype of alcohol misuse.

Limitations of the study and conclusions

There are a few limitations to consider. First, the mean AUDIT score in drinkers is lower than the range that suggests hazardous drinking. Thus, although the current results may reflect drinking problems as captured by the AUDIT score, their clinical significance remains to be clarified. Our ongoing work to follow these individuals and characterize potential changes in drinking trajectory would help in resolving this issue. Second, we attempted to distinguish the neural correlates of duration of alcohol use and age, but it is impossible to isolate one effect from the other in alcohol drinkers. Although the neural correlates of years of drinking was obtained by masking of age-related changes in non-drinkers, our best interpretation of the results would have to be considered with any confounding, interaction effects of age and alcohol use. Third, inhibitory control is a multidimensional construct that cannot be fully characterized by behavioral tasks that solely address motor response inhibition. Thus, paradigms that examine delay discounting, risky decision making, reward responsivity would need to be considered to understand the multifaceted etiologies of alcohol misuse (Moreno et al., 2012; Rossiter et al., 2012). Fourth, the SST is widely used to probe cognitive control, but the SSRT as a measure of inhibitory control appears to be noisy and not as robust when compared to the neural responses to inhibitory control. A more sophisticated approach is to estimate the distribution of SSRT, which requires a much greater number of stop trials than available from the current study. Fifth, some investigators consider AlphaSim as a liberal threshold. Thus, many of the clusters we identified here survived a corrected cluster threshold; these findings need to be replicated and confirmed in additional work. Sixth, the current results distinguish the influence of problems associated with alcohol use from the duration of drinking on the cerebral processes of inhibitory control; however, it remains unclear whether impaired inhibitory control predisposes individuals to problem drinking or results from drinking problems. To address this issue would again require longitudinal studies of both at-risk and control populations prior to the start of alcohol use, affected individuals and their non-affected siblings, as well as individuals with and without family history of alcoholism. Finally, although the participants all denied current use of illicit substance and showed negative urine screens at time of fMRI, we did not evaluate their history of illicit substance use, which may influence the current findings.

In summary, we showed that drinking problems as captured by the AUDIT score was associated with impaired inhibitory control indexed by the SSRT in social drinkers. This association manifested in decreased subcortical and cortical activities, which mediated the link between drinking problems and inhibitory control. On the other hand, years of alcohol use in social drinkers appeared to be related to decreased activities in other cerebral regions, although the confounding effect of age cannot be excluded. These findings may help elucidate the role of impaired inhibitory control in charting the trajectory of alcohol use and misuse in non-dependent drinkers.

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Figure 1.

(a) One-sample t test of drinkers; (b) One-sample t test of non-drinkers; (1c) Two-sample t test: brain regions showing greater activation in drinkers than in non-drinkers (yellow), and in non-drinkers than in drinkers (cyan). SS: stop success trials; GS: go success trials.

Figure 2.

Linear regressions: regional activations to response inhibition in association with the AUDIT score and years of alcohol use in drinkers, and activations in association with age in non-drinkers. SS: stop success trials; GS: go success trials. purple: positive correlation; blue/green: negative correlation.

Figure 3.

Regional activations negatively associated with the AUDIT score (blue, as in Figure 2a) and SSRT (turquoise) with overlapping areas (cyan, circled and labeled) in drinkers. SS: stop success trials; GS: go success trials. L: Left, MFG: middle frontal gyrus; dACC/SFG: dorsal anterior cingulate cortex/superior frontal gyrus; pre-SMA: pre-supplementary motor area.

Figure 4.

Mediation analyses testing Model 1: whether voxel activity mediates the correlation between the AUDIT score (X) and SSRT (Y); Model 2: whether voxel activity mediates the correlation between SSRT (X) and the AUDIT score (Y); Model 3: whether SSRT mediates the correlation between voxel activity (X) and the AUDIT score (Y); Model 4: whether the AUDIT score mediates the correlation between voxel activity (X) and SSRT (Y). β : regression coefficients; L: left; dACC: dorsal anterior cingulate cortex; SFG: superior frontal gyrus; MFG: middle frontal gyrus; pre-SMA: pre-supplementary motor area.

Table 1

Pearson correlation between SST measures and AUDIT, years of alcohol use, and age.

	AUDIT	Years of alcohol use	Age
median GORT	$r = -0.0822$	$r = -0.0521$	$r = -0.0747$
mean GORT	$r = -0.1010$	$r = -0.0713$	$r = -0.0877$
SSRT	$r = 0.3834^*$	$r = 0.2359$	$r = 0.1839$
GR%	$r = 0.0837$	$r = 0.1072$	$r = -0.1292$
SS%	$r = -0.0145$	$r = 0.0208$	$r = -0.0323$

Note:

* indicates significance level at 0.05; GR%: go response percentage; SS%: stop success percentage.

Table 2
Differences in regional activations to response inhibition between drinkers and non-drinkers (two-sample t-test).

Comparison	Region	Cluster Size (voxels)	Peak Voxel P Value	Voxel Z Value	MNI Coordinate (mm)		
					X	Y	Z
drinkers > non-drinkers	R SMG	362	0.0002	3.52	66	-28	37
	R STG	206	0.0003	3.40	57	-10	-11
	L TPJ/MTG	404	0.0006	3.24	-51	-46	10
non-drinkers > drinkers	L/R rACC	393	0.0009	3.11	12	35	10

Note: L: left; R: right. SMG: supramarginal gyrus; STG: superior temporal gyrus; TPJ: temporoparietal junction; MTG: middle temporal gyrus; rACC: rostral anterior cingulate cortex.

Table 3

Regional activations associated with the AUDIT score, years of alcohol use (YrsAlc), and SSRT in drinkers.

Contrast	Region	Cluster Size (voxels)	Peak Voxel P Value	Voxel Z Value	MINI Coordinate (mm)		
					X	Y	Z
AUDIT_Pos	None						
AUDIT_Neg	* L Cerebellum	396	0.0000	4.01	-36	-46	-14
	* L/R dACC/SFG	1492	0.0000	3.94	-12	23	28
	* L SFG	469	0.0000	3.90	-36	8	37
	* R Thalamus	240	0.0001	3.72	27	-22	4
	* L Thalamus	187	0.0001	3.64	-12	-10	1
	* L PoG	42	0.0003	3.41	-21	-43	61
	* L Cerebellum	63	0.0004	3.38	-6	-55	-23
	* R SPL/AG	138	0.0004	3.34	33	-70	49
YrsAlc_Pos	R MOG	30	0.0006	3.26	39	-79	13
YrsAlc_Neg	* L TPJ/SMG	94	0.0000	4.29	-66	-34	25
	* R IFG/STG	234	0.0002	3.59	48	5	10
	L PoG	43	0.0002	3.58	-39	-16	37
	L MCC	39	0.0003	3.47	-9	-19	43
	R MCC	37	0.0003	3.46	12	-25	43
	R PMC	70	0.0004	3.33	42	-10	37
	L PMC/PoG	57	0.0006	3.26	-54	-7	19
SSRT_Pos	None						
SSRT_Neg	* R SFG/MFG/ACC	526	0.0000	4.22	30	32	28
	* L SFG/MFG	138	0.0001	3.75	-30	11	22
	* R STG/MTG	139	0.0002	3.53	42	-13	-8
	* L/R Caudate/Thalamus	369	0.0003	3.40	9	-1	13

Contrast	Region	Cluster Size (voxels)	Peak Voxel P Value	Voxel Z Value	MNI Coordinate (mm)		
					X	Y	Z
	* R Cerebellum	48	0.0004	3.32	27	-64	-26
	* L OFC	39	0.0005	3.32	-30	50	-8
	* L MCC	42	0.0005	3.28	-9	-31	40
	* L ant. Insula	42	0.0009	3.11	-27	23	-8

Note: L: left; R: right. dACC: dorsal anterior cingulate cortex; SFG: superior frontal gyrus; PoG: postcentral gyrus; SPL: superior parietal lobule; AG: angular gyrus; MCC: mid-cingulate cortex; MOG: middle occipital gyrus; TPJ: temporoparietal junction; SMG: supramarginal gyrus; IFG: inferior frontal gyrus; STG: superior temporal gyrus; PMC: primary motor cortex; MFG: middle frontal gyrus; MTG: middle temporal gyrus; OFC: orbital frontal cortex.

* indicates that the cluster survives extend threshold $p < 0.05$, FWE corrected.

Table 4

Mediation of the AUDIT score, SSRT, and co-activating cerebral activities in drinkers.

	Path <i>a</i> (X → M)	Path <i>b</i> (M → Y)	Path <i>c'</i> (X → Y)	Mediation path <i>a</i> * <i>b</i>
MODEL 1: X (AUDIT score) → Y (SSRT) mediated by M (Combined ROI)				
<i>B</i>	−0.277	−10.253	2.723	2.944
<i>p</i> -values	0.000*	0.004*	0.165	0.018*
Model 1a: X (AUDIT score) → Y (SSRT) mediated by M (ACC/SFG)				
<i>B</i>	−0.294	−8.077	3.196	2.371
<i>p</i> -values	0.001*	0.006*	0.098	0.030*
Model 1b: X (AUDIT score) → Y (SSRT) mediated by M (L MFG)				
<i>B</i>	−0.211	−10.776	3.292	2.275
<i>p</i> -values	0.001*	0.010*	0.092	0.035*
Model 1c: X (AUDIT score) → Y (SSRT) mediated by M (L Thalamus)				
<i>B</i>	−0.324	−5.228	3.873	1.694
<i>p</i> -values	0.001*	0.048*	0.052	0.085
Model 1d: X (AUDIT score) → Y (SSRT) mediated by M (pre-SMA)				
<i>B</i>	−0.243	−9.322	3.304	2.264
<i>p</i> -values	0.000*	0.016*	0.096	0.041*
MODEL 2: X (SSRT) → Y (AUDIT score) mediated by M (Combined ROI)				
<i>B</i>	−0.019	−0.695	−0.013	−0.013
<i>p</i> -values	0.000*	0.005*	0.165	0.019*
Model 2a: X (SSRT) → Y (AUDIT score) mediated by M (ACC/SFG)				
<i>B</i>	−0.021	−0.504	−0.016	0.011
<i>p</i> -values	0.000*	0.016*	0.098	0.040*
Model 2b: X (SSRT) → Y (AUDIT score) mediated by M (L MFG)				
<i>B</i>	−0.015	−0.723	−0.016	0.011
<i>p</i> -values	0.000*	0.013*	0.092	0.038*
Model 2c: X (SSRT) → Y (AUDIT score) mediated by M (L Thalamus)				
<i>B</i>	−0.020	−0.437	0.018	0.009
<i>p</i> -values	0.003*	0.013*	0.052	0.053
Model 2d: X (SSRT) → Y (AUDIT score) mediated by M (pre-SMA)				
<i>B</i>	−0.016	−0.706	0.015	0.011
<i>p</i> -values	0.001*	0.007*	0.096	0.030*
MODEL 3: X (Combined ROI) → Y (AUDIT score) mediated by M (SSRT)				
<i>B</i>	−12.589	0.013	−0.695	−0.164
<i>p</i> -values	0.000*	0.165	0.005*	0.188
MODEL 4: X (Combined ROI) → Y (SSRT) mediated by M (AUDIT score)				
<i>B</i>	−0.858	2.723	−10.253	−2.336

	Path <i>a</i> (X → M)	Path <i>b</i> (M → Y)	Path <i>c'</i> (X → Y)	Mediation path <i>a</i> * <i>b</i>
<i>p</i> -values	0.000*	0.165	0.004*	0.190
MODEL 5: X (AUDIT score) → Y (Combined ROI) mediated by M (SSRT)				
<i>B</i>	5.567	−0.016	−0.255	−0.087
<i>p</i> -values	0.003*	0.024*	0.012*	0.069
MODEL 6: X (SSRT) → Y (Combined ROI) mediated by M (AUDIT score)				
<i>B</i>	−7.838	0.017	−0.438	−0.130
<i>p</i> -values	0.001*	0.070	0.012*	0.110

Note: β: regression coefficients;

* significant at $p < 0.05$.