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Prospective Associations between BOLD Markers of Response Inhibition and the Transition to Frequent Binge Drinking

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Abstract

Background—Altered brain activation during response inhibition has been linked to a greater risk for alcohol and other substance use behaviors in late adolescence. However, the ability of neural markers of response inhibition, acquired during adolescence, to temporally predict the transition from less frequent and lower quantity alcohol use to high-risk, frequent (≥weekly) binge drinking behavior remains unclear.

Methods—Adolescents (N=29; 9 females) were selected from a larger ongoing longitudinal study to include those who transitioned to at least weekly binge drinking (≥5/4 alcoholic drinks for males/females per occasion) over a 15-year follow-up period. Prior to the onset of weekly binge drinking (mean age=18.0), participants underwent a functional MRI including a Go/No-go task. Whole-brain activation from the no-go correct rejection vs. no-go false alarm contrast was used to predict time to transition to frequent binge drinking.

Results—Less no-go correct rejection vs. no-go false alarm activation in a cluster including the precentral gyri, insula, and inferior frontal gyri predicted a more rapid transition into frequent binge drinking (voxel-wise alpha < 0.001, cluster-wise alpha < 0.05, cluster threshold ≥ 18 voxels).

Conclusions—Results from this study are supported by literature suggesting that fronto-insular involvement is important for successful inhibition and cognitive control. Altered brain activation during response inhibition may thus represent neural antecedents of impulse regulation difficulties related to alcohol consumption. The magnitude of this activation provides temporal information that may be used to inform and optimize timing of interventions aimed at preventing the escalation and transition to problematic drinking for youth who have already begun to engage in drinking behaviors.

Keywords

Binge drinking; adolescence; longitudinal; response inhibition; fMRI

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INTRODUCTION

Alcohol remains the most commonly used substance of abuse during adolescence and young adulthood. The act of binge drinking, often defined as the consumption of greater than either 4 or 5 drinks in a given drinking episode, is of particular concern in youth given the host of associated negative consequences (for a review see Courtney and Polich, 2009) and potential for neurological alterations to the developing adolescent brain (Ruan et al., 2019). Approximately 17% of 12th graders and 33% of college-aged young adults (modal ages 19–22) reported recent binge drinking, defined as the consumption of 5 or more drinks in a row at least once in the two weeks prior to assessment (Miech et al., 2017, Schulenberg et al., 2018). Notably, almost 1% of adolescents aged 12 to 17 and 10% of young adults aged 18 to 25 engage in binge drinking episodes frequently, averaging more than once per week over the previous 30 days (Substance Abuse and Mental Health Services Administration, 2018). Frequent binge drinking (binging ≥ once per week in the previous year) during adolescence is associated with elevations in multiple risk factors, including adolescent drug use, antisociality, and parent alcoholism (Chassin et al., 2002), as well as a number of negative consequences in adulthood such as alcohol use disorder diagnosis, drug use, psychiatric morbidity, homelessness, legal problems, accidents, and lower social class (Viner and Taylor, 2007). Importantly, many of these elevated risks are greater for those who frequently binge drink during adolescence, as opposed to those who are infrequent/moderate binge drinkers (Chassin et al., 2002), suggesting that the frequency with which one binges during adolescence is an important factor in future alcohol-related outcomes. Thus, given the known neurotoxicity of alcohol at higher doses (for reviews see Oscar-Berman and Marinkovic, 2007, Sullivan and Pfefferbaum, 2005), efforts to predict who is at risk of drinking at these frequent high levels during the critical period of neurodevelopment are warranted.

A hallmark characteristic of the binge drinking episode is the apparent loss of control over ones' alcohol intake. In line with this, diminished inhibitory control (i.e., the capacity to voluntarily regulate or inhibit prepotent behavioral or attentional responses) during adolescence is consistently implicated as a risk factor for future alcohol and substance use (for a review see Casey, 2015). Successful inhibitory control likely involves the ventral attention, fronto-parietal and fronto-striatal networks, including regions such as the inferior frontal gyrus extending to the insula, cingulate and paracingulate gyri, superior parietal gyrus, and basal ganglia structures (Zhang et al., 2017, Morein-Zamir and Robbins, 2015), suggesting deficiencies in these networks may serve as correlates of alcohol-related risk prior to binge drinking onset (Whelan et al., 2014).

Longitudinal functional magnetic resonance imaging (fMRI) studies of adolescents have identified several neural aberrations during inhibition, as measured on the Go/No-go task, as significant predictors of greater alcohol and substance use, even in the absence of behavioral differences on the tasks (Norman et al., 2011, Mahmood et al., 2013, Wetherill et al., 2013). Specifically, greater left angular gyrus and less ventromedial prefrontal blood-oxygen-level-dependent (BOLD) activation during no-go correct rejection vs. go trials in 16 to 19 year-olds was found to predict higher levels of alcohol and substance use and dependence symptoms over an 18-month follow-up. This effect was especially pronounced for

adolescents who were high frequency substance users at baseline (Mahmood et al., 2013). In an analysis of 12–14 year-olds scanned prior to the onset of alcohol use and followed up about 4.2 years later, less BOLD response in regions including the right inferior frontal gyrus, left dorsal and medial frontal areas during no-go correct rejection vs. baseline trials was found to differentiate between those who transitioned to alcohol use from those who remained continuous controls (Norman et al., 2011); however, the activation in those regions was found to be associated with attention problems at follow-up, and not substance use outcomes per se, suggesting the groups may have differed on multiple related factors. In an additional longitudinal analysis of 11–16 year-olds, with follow-up approximately 3 years later, adolescents who transitioned into drinking by follow-up exhibited less BOLD response during no-go correct rejection vs. go trials at baseline in bilateral middle frontal gyri, left putamen, right inferior parietal lobule, and left cerebellar regions. Yet increased activation was observed after the onset of heavy drinking in all regions except the putamen, as compared to matched continuous non-drinkers who displayed decreased activation in these regions at follow-up (Wetherill et al., 2013). These results suggest alcohol-exposure may increase engagement of these neural networks in order to successfully inhibit prepotent responses; however, the degree of alcohol exposure required to produce this change has yet to be investigated.

Taken together, the current literature implies the presence of a pre-existing neural inhibition risk profile for future alcohol and substance use, along with a potential for additional alcohol and substance-related disturbances in normal neural inhibitory maturation processes. However, the neural underpinnings subserving the transition from moderate, arguably even “normative”, alcohol use behavior in adolescence to the extremely high-risk pattern of frequent binge drinking have not been determined. Thus, the present study seeks to prospectively predict the time to transition to high-risk frequent binge drinking (averaging ≥ once per week for at least one year) from the neural patterns of successful inhibitory control in a single sample of adolescents who were already engaged in moderate alcohol use. Given the broad set of inhibitory-related regions identified in the earlier literature, a whole-brain exploratory approach was used for the present analysis, with a general hypothesis of alcohol risk-related activation to fall within the fronto-parietal and fronto-striatal networks. No directionality was hypothesized for the present analyses given the mixed results of the literature and the novelty of the current inquiry.

MATERIALS AND METHODS

Participants & Procedures

Current study data was culled from a larger, ongoing longitudinal substance use and neuroimaging project (NIAAA R01 AA013419). Participants at baseline were healthy 12–14 year-olds, recruited through schools in the San Diego area, with very minimal to no experience with alcohol or drugs. Exclusionary criteria for the parent study at baseline included: premature birth prior to the 35^{th} gestational week; report of prenatal alcohol (>2 drinks during a given week) or illicit drug exposure; history of any DSM-IV (American Psychiatric Association, 2000) Axis I or neurological disorder; psychoactive medication use; loss of consciousness (>2 minutes) or head trauma; learning disability or mental retardation;

chronic medical illness; history of alcohol use (≥10 total drinking days, or > 2 drinks per week in lifetime); history of drug use (≥5 lifetime cigarette uses, ≥3 experiences with cannabis in lifetime or use in the past 3 months, or any other intoxicant use); non-correctable sensory problems; and inadequate English comprehension. Exclusionary criteria at each follow-up time-point consisted of endorsement of an emergent Axis I disorder as measured by a structured diagnostic interview (Shaffer et al., 2000). Participants were asked to refrain from alcohol and substance use for at least 24 hours prior to all baseline or follow-up assessments, verified via breath alcohol concentration and urine drug screen. The University of California San Diego Human Research Protections Program approved the study protocol and procedures (for additional methods see: Squeglia et al., 2009, Nguyen-Louie et al., 2015, Courtney et al., 2018).

Data for the current project was selected among the first 15 years of annual follow-up assessments. Participants were included in the present analysis if they: (1) transitioned to frequent binge drinking, averaging ≥ one binge episode per week for at least a one-year period, at any point during the 15-year follow-up period, and (2) provided usable neuroimaging data within 3 years of their 18th birthday. fMRI Go/No-go data was selected from available scan time points to be closest to their 18th birthday and prior to their transition to frequent binge drinking (mean age at scan = 18.0, SD = 1.3; N = 29; see Table 1). This time point was selected because all participants had begun moderate drinking by this time and it represented a proximal time point to the average age of transition (mean = 19.6 years old; SD = 1.6), thus reducing the potential for influence from extraneous developmental factors. Time to transition to frequent binge drinking was calculated as the difference in time (months) between age of transition onset and age at scan. The neuroimaging data of 8 participants in this sample are also included in the report by Wetherill et al., 2013.

Measures

Youths were administered comprehensive interviews at baseline, including the assessment of demographics, living situations, and alcohol and drug use. The Hollingshead Index of Social Position score (Hollingshead, 1965), an index of socioeconomic status (SES), was calculated for each subject using parental socioeconomic background information (i.e., educational attainment, occupation, and salary of each parent) to characterize the youth's rearing environment. Higher values indicate lower SES (possible range 11–77). Corroborative information from an informant (a biological parent in the majority of cases) was used to support youth report on demographic background and family history topics. The annual follow-up assessments were similarly structured.

The Customary Drinking and Drug Use Record structured interview (Brown et al., 1998) was used to assess history of alcohol consumption and alcohol-related problems, as well as additional substance use information. For the purposes of this study, a binge drinking episode was defined as the consumption of ≥5 alcoholic drinks for males, or ≥4 drinks for females, in a single occasion.

Imaging

Consistent with previous analysis on the parent data set (Wetherill et al., 2013), imaging data were collected using a 3.0 Tesla General Electric short bore Excite-2 system with an eight-channel phase-array head coil. A high-resolution T1-weighted sequence including a sagittally acquired spoiled gradient recalled sequence (256 × 256 × 192 matrix, .94 × .94 × 1mm voxels, field of view [FOV] 24cm, 176 slices, repetition time=8ms, inversion time=450ms, echo time=25ms, flip angle 12°, 7:26 minutes) was acquired. BOLD signal was measured with T2*-weighted axially acquired echo-planar images (64 × 64 matrix, 3.75 × 3.75 × 3.8mm voxels, FOV=24cm, 32 slices, echo time=30ms, repetition time=1,500ms, flip angle 90°, task time: 6:24 minutes). Field maps with two different echo times were used to measure signal dropout and field inhomogeneities. Field maps were applied to the BOLD signal to minimize signal dropouts and warping. Stimuli for the task were back-projected from a laptop to a screen at the foot of the scanner bed and were visible via an angled mirror attached to the head coil. Task performance and behavior was recorded using a fiber-optic response box compatible with MRI (Current Designs, Pittsburgh, PA).

Response inhibition was assessed during scanning via an event-related Go/No-Go paradigm (see Norman et al., 2011, Wetherill et al., 2013 for additional task details). The task consisted of a serial presentation of blue shapes, which included 64 large circles, 16 small circles, 43 large squares, and 57 small squares. The duration of each stimulus was 200ms and the intertrial interval was 1,500ms. Participants were asked to press a button each time a large circle, small circle, or large square shape was presented (go stimuli) but to withhold their response when a small square was presented (no-go stimulus, 32.0% of trials). Baseline constituted ~114 seconds scattered throughout the task. Primary analyses contrasted BOLD response during no-go correct rejection (successful response inhibition) trials (86.9% of no-go trials; SD=10.0%) relative to no-go false alarm (unsuccessful response inhibition) trials (13.1% of no-go trials). The no-go correct rejection versus go contrast was also evaluated. Correct rejections were determined by the absence of a motor response during no-go trials. False alarms were defined as a button press following a no-go stimulus.

Image Processing

Processing of imaging data was conducted using the bug-corrected version of the Analysis of Functional NeuroImages software (AFNI) (Cox, 1996). Abnormal signals and artifacts were removed from the data, and the time series data were aligned temporally and co-registered to a maximally stable base volume using an iterated least squares algorithm (Cox and Jesmanowicz, 1999). AFNI's 3dSkullStrip was used to skull strip each participant's high-resolution T1-weighted image. Participants' anatomical and functional data sets were co-registered and warped to Talairach space (Talairach and Tournoux, 1988). Functional data were resampled to $3mm^2$ voxels, and activations maps were spatially smoothed using a 5mm full-width half maximum Gaussian filter. Motion was estimated for each participant (i.e., three rotational and three linear displacement parameters) and used as a control in task analyses (Bandettini et al., 1993). 3dDespike was used to detect outliers in the motion parameters. Significant outliers in the time-series data were censored or despiked.

Analysis of time series data utilized multiple regression (3dDeconvolve) controlling for linear drift, baseline signal, and motion from 6 motion parameters calculated above. Regressors of interest (go, no-go correct rejection, no-go false alarm) and no interest (go error) convolved with a modified gamma variate function (Boynton et al., 1996) that modeled anticipated hemodynamic response. Beta weights were converted to percent signal change which were used for further analysis.

Statistical analysis

Performance measures evaluated in the Go/No-Go task included percent correct on inhibitory trials, β (a marker of response bias), and d′ (a marker of accuracy in discriminating between go and no-go stimuli) (Green and Swets, 1966).

Similar to methods previously used by the authors (Courtney et al., 2019), activation was masked by an average skull-stripped anatomical image from all participants. Whole brain, voxel-level analysis on the masked data was conducted using a paired *t*-test (AFNI 3dttest++) to contrast no-go correct rejection vs. no-go false alarm trials. To control for variability in age at scan acquisition, time to transition to frequent binge drinking (age of transition onset – age at scan) was chosen for the correlation analysis and entered as the covariate of interest in the model. The Clustsim nonparametric randomization/permutation option of 3dttest++ was used with a conservative voxel-wise alpha of 0.001 and cluster-wise alpha of 0.05, resulting in an estimated a cluster size threshold of 18 contiguous voxels. This method of Type I error control has been shown to produce false positive rates compatible with the nominal 95% confidence interval (Cox et al., 2017, Eklund et al., 2016). A second model not containing the covariate of interest was run to validate the task by showing task-relevant activation in this sample using the same Type 1 error correction as above.

RESULTS

Participants

At the time of the scan, the sample drank alcohol approximately 4 days a month and binge drank once per month. After transitioning, the sample drank approximately 14 days per month and binged 6 days per month. Roughly 10% of the sample endorsed regular use (≥1x per week, 3+ months) of tobacco and/or cannabis, in addition to alcohol, at the time of the scan (see Table 1 for participant characteristics). Consistent with previous Go/No-Go reports (Ahmadi et al., 2013, Smith et al., 2014, Norman et al., 2011, Wetherill et al., 2013, Mahmood et al., 2013), false alarm rates were not associated with age at scan, time to transition to frequent binge drinking, drinking behavior at scan, or drinking behavior at follow-up (*p*s>.34) (see Table 2 for task performance).

BOLD Response

The no-go correct rejection vs. no-go false alarm contrast revealed multiple regions related to response inhibition that surpassed thresholding: bilateral putamen, left cingulate, left postcentral gyrus, bilateral anterior cingulate (negative), and left middle temporal gyrus (see Table 3 and Figure 1).

BOLD Response and Drinking

BOLD response contrast of no-go correct rejections vs. false alarms in the precentral gyrus/insula/inferior frontal gyrus cluster correlated with time to transition to frequent binge drinking (cluster size = 24 voxels, peak Z = 4.54; see Table 4 and Figure 2). In no region did no-go correct rejection relative to go activation significantly correlate with time to transition.

DISCUSSION

As expected, successful inhibition in this sample of frequent binge drinkers was associated with activation in a number of regions previously implicated in the literature, including the fronto-striatal system (Zhang et al., 2017, Morein-Zamir and Robbins, 2015), validating the use of this paradigm in our high risk sample. In the correlation analysis, a single cluster of activation, including portions of the left insula, inferior frontal gyrus (IFG), and precentral gyrus, elicited during successful inhibitory control, was found to predict time to transition to high-risk frequent binge drinking in adolescents who were already engaged in moderate alcohol use. Specifically, greater BOLD response in this cluster predicted longer time to transition, implying that lower magnitude of activation during successful inhibition could serve as a temporal warning of future high-risk impulsive behavior.

The IFG, precentral gyrus, and insula have been consistently implicated as critical regions involved in response inhibition (Zhang et al., 2017). Although the right IFG/insula are most commonly implicated (for a review see Bari and Robbins, 2013), a number of studies have also implicated key roles for the left IFG/insula in this process (Swick et al., 2008, Meffert et al., 2016, Zhang and Li, 2012). This study provides further support for the involvement of the left IFG/insula in inhibitory control by demonstrating the predictive utility of activation in these top-down executive control regions for the onset of impulsive binge drinking behavior.

The correlation with time to transition to frequent binge drinking also supports the notion that this pattern of alcohol consumption is likely driven, at least in part, by deficiencies in inhibitory control and suggests opportunities for intervention prior to the onset of this very high-risk behavior. Inhibitory control interventions, particularly those utilizing Go/No-go paradigms, have demonstrated effectiveness for short-term health behavior change (Jones et al., 2016, Allom et al., 2016), which may be all that is needed to delay onset of this high-risk drinking pattern beyond the critical neurodevelopmental stage of adolescence.

The results of this study should be interpreted within the context of its strengths and limitations. The prospective correlational design is a strength of the study, as it avoids issues related to the selection of comparable controls and addresses the question of whether the magnitude of the BOLD signal during inhibitory control contains clinically relevant predictive information. Another strength is the well-characterized sample of frequent binge drinkers who were already engaged in moderate alcohol use at scan acquisition. Few attempts have been made to identify unique risk factors for adolescents that are already engaged in moderate alcohol use, despite the exceptionally high prevalence of adolescent alcohol users. Limitations of the study include the relatively small sample size for fMRI studies and small number of no-go false alarm trials included in the analysis. The use of

conservative statistical thresholding and the consistence of implicated regions with the extent literature on inhibitory control provides support for the validity of the results; however, additional studies using more difficult tasks (and thus greater trial numbers) within larger samples are needed to confirm these within-subjects effects. Furthermore, the sample is comprised predominately of White adolescents with high educational attainment, potentially limiting the generalizability of the results. Thus, replication within a more diverse sample of adolescents is warranted.

In conclusion, this study suggests that BOLD response in portions of the IFG, insula, and precentral gyrus during successful inhibitory control could prove valuable as a temporally specific risk marker for future frequent binge drinking behavior. Early identification of adolescents at-risk for this pattern of alcohol use is of great importance given the potential for neural consequences associated with alcohol use during neurodevelopment (Squeglia et al., 2014). The increased study of risk factors for youth already engaged in moderate alcohol use could provide additional insights into meaningful pathways for intervention that were previously overlooked.

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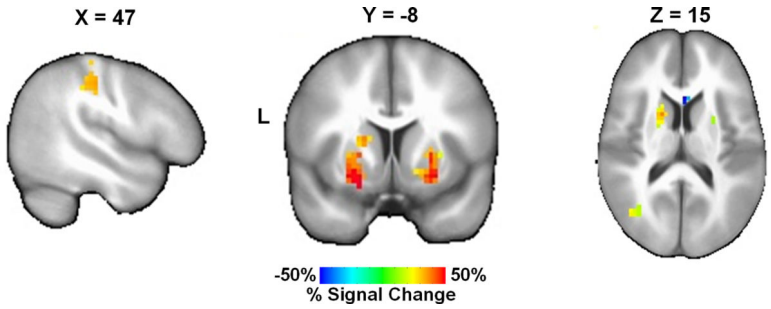

Figure 1.

Percent signal change in blood-oxygen-level-dependent (BOLD) activation to no-go correct rejection vs. no-go false alarm trials (thresholded at a voxel-wise alpha of 0.001, cluster-wise alpha of 0.05; ≥ 18 contiguous voxels).

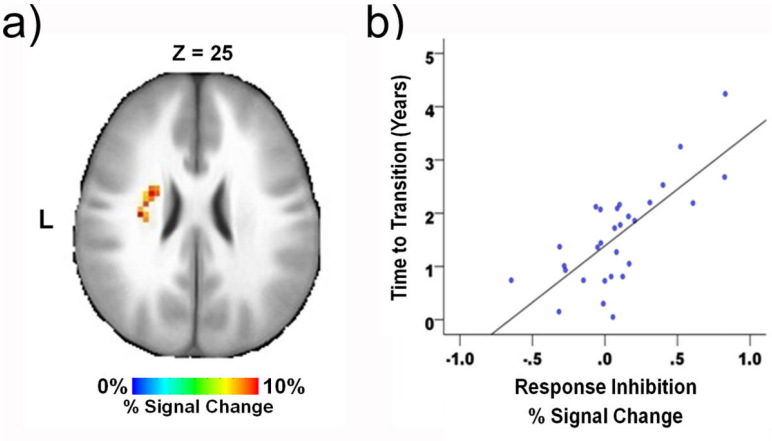

Figure 2.

a) Percent signal change in blood-oxygen-level dependent (BOLD) activation to no-go correct rejection vs. no-go false alarm trials which correlated with time to transition to frequent binge drinking (thresholded at a voxel-wise alpha of 0.001, cluster-wise alpha of 0.05; ≥ 18 contiguous voxels); b) Average percent signal change extracted from the cluster identified in the whole-brain analysis and plotted against time to transition. Cluster activation estimates were extracted for visualization purposes only - no statistics were calculated on the extracted datapoints to avoid potential inflation of the correlation estimate.

Table 1.

Sample demographics.

	Time Point	
	Frequency or Mean (SD)/[Range]	
Variable	**Scan**	**Follow-Up**
Total N	29	29
Age (years)	18.0 (1.3) [16.2–20.9]	19.6 (1.6) [17–23]
Time to transition (years)	1.6 (0.9) [0.1–4.2]	
Sex		
- Male	20	
- Female	9	
Race/Ethnicity		
- White	22	
- Asian	1	
- Mixed	6	
Education (years completed)	11.3 (1.2) [9.0–14.0]	13.6 (1.4) [11.0–16.0]
Hollingshead Index - Socioeconomic Status	24.1 (14.9) [11.0–65.0]	26.5 (18.0) [11.0–65.0]
Alcohol use (previous year)	4.5 (3.0)	6.4 (2.5)
- Drinks per drinking day	4.5 (3.0) [1.0–12.0]	6.4 (2.5) [3.0–12.0]
- Drinking days per month	3.8 (4.6) [<1.0–20.0]	13.7 (9.1) [1.7–30.4]
- Binge days per month	1.4 (2.3) [<1.0–11.6]	5.6 (4.4) [4.0–19.5]
Other substance use (≤1x per week, 3+ months)		
- Tobacco	4	9
- Cannabis	3	14

Table 2.

Go/No-go task performance.

Variable	Mean (SD)
% Correct rejection – inhibitory trials	86.9% (0.1)
% False alarm – inhibitory trials	13.1 % (0.1)
Trial discrimination accuracy - d’	3.5 (0.6)
Response bias - β	0.33 (0.4)

Table 3.

Clusters of significant BOLD activation to no-go correct rejection vs. no-go false alarm trials from the whole-brain analysis (thresholded at a voxel-wise alpha of 0.001, cluster-wise alpha of 0.05; ≥ 17 contiguous voxels).

		Talairach Coordinates			
Region (peak)	**Cluster Voxels**	**X**	**Y**	**Z**	**Peak Z**
L putamen	80	−19.5	4.5	−12.5	4.86
R putamen	71	22.5	4.5	−9.5	4.68
L fusiform gyrus, extending into parahippocampal gyrus	41	−22.5	−37.5	−15.5	4.09
L postcentral gyrus, extending into inferior parietal lobule	40	−52.5	−28.5	41.5	4.15
R fusiform gyrus, extending into inferior temporal gyrus	31	43.5	−55.5	−9.5	4.29
R parahippocampal gyrus, extending into culmen	31	4.5	−43.5	−3.5	4.06
L/R posterior cingulate extending into culmen	23	−1.5	−55.5	5.5	4.17
L middle temporal gyrus, extending into middle occipital gyrus	22	−40.5	−67.5	20.5	3.99
L caudate extending into putamen	20	−16.5	7.5	14.5	4.71
R/L anterior cingulate	20	1.5	16.5	20.5	−3.95

Table 4.

Cluster of significant BOLD response from the whole-brain analysis (no-go correct rejection vs. no-go false alarm) that correlated with time to transition to frequent binge drinking (thresholded at a voxel-wise alpha of 0.001 and cluster-wise alpha of 0.05; ≥ 18 contiguous voxels).

		Talairach Coordinates			
Region (peak)	**Cluster Voxels**	**X**	**Y**	**Z**	**Peak Z**
L precentral gyrus, including insula and inferior frontal gyrus	24	−34.5	1.5	23.5	4.54