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A longitudinal examination of adolescent response inhibition: Neural differences before and after the initiation of heavy drinking

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Abstract

Rationale—Response inhibition abnormalities contribute to several maladaptive behaviors commonly observed during adolescence, including heavy drinking.

Objectives—The present study aimed to determine whether abnormalities in brain response during response inhibition predate or follow adolescents' transition into heavy drinking, which is pivotal in identifying the neural antecedents and consequences of adolescent alcohol use.

Methods—Longitudinal functional magnetic resonance imaging (fMRI) acquired during a response inhibition task was collected on adolescents before the onset of heavy drinking, and then again on the same scanner approximately 3 years later. Adolescents who transitioned into heavy drinking (n=20) were matched to continuously nondrinking adolescents (n=20) on baseline and follow-up demographic and developmental variables.

Results—During no-go relative to go trials, participants showed responses common to inhibitory circuitry: frontal (e.g., pre-supplementary motor area), temporal, and parietal regions. A repeated measures analysis of covariance revealed that adolescents who later transitioned into heavy drinking showed less fMRI response contrast at baseline than continuous nondrinkers in frontal, parietal, subcortical, and cerebellar regions ($p < .01$, clusters > 756 microliters), then increased activation after the onset of heavy drinking in frontal, parietal, and cerebellar areas.

Conclusions—Future heavy drinkers showed less activation of inhibitory circuitry before the onset of heavy drinking. After transitioning into heavy drinking, they showed more activation during response inhibition than nondrinking controls. These results contribute to the growing literature suggesting that neural vulnerabilities exist prior to the onset of substance use, and the initiation of heavy drinking may lead to additional alterations in brain functioning.

Keywords

Alcohol; inhibition; neuroimaging; heavy drinking

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Introduction

Adolescence is a developmental period between childhood and adulthood characterized by marked physiological, psychological, and behavioral changes. Adolescents experience rapid physical growth, sexual maturation, and advances in cognitive and emotional processing (Forbes and Dahl, 2010). These changes coincide with increases in substance use, with alcohol being the most widely used illegal substance among adolescents (Windle *et al*, 2008; Witt, 2010). National survey data indicate that 33% of 8th grade students have tried alcohol, and this percentage increases to 70% among 12th graders (Johnston *et al*, 2012). Of greater concern is the increase in heavy episodic drinking (i.e., consuming 5 of more drinks in a row during the previous two weeks) where prevalence rates increase from 6% to 22% for 8th and 12th grades, respectively (Johnston *et al*, 2012), as heavy episodic drinking during adolescence is associated with numerous negative effects on adolescent health and well-being, including risky sexual behaviors (Quinn and Fromme, 2010), hazardous driving (Lee *et al*, 2011), and alterations in adolescent brain development (Squeglia *et al*, 2009a).

During adolescence, the brain undergoes significant changes, and a recent longitudinal neuroimaging study suggests that heavy episodic drinking during this developmental period alters brain functioning (Squeglia *et al*, 2012a). Squeglia and colleagues (2012a) examined the effects of heavy episodic drinking on brain function during a visual working memory task, comparing brain activity in adolescents at baseline and again at follow-up (approximately 3 years later) to compare brain activity in those who transitioned into heavy drinking during adolescence (i.e., ages 13-19) to demographically matched adolescents who remained nondrinkers. Adolescents who initiated heavy drinking exhibited increasing brain activity in frontal and parietal brain regions during a visual working memory task compared to adolescents who remained nondrinkers through follow-up, who showed decreasing frontal activation, consistent with studies in typical development (Luna *et al*, 2010; Luna and Sweeney, 2004). Thus, adolescent heavy episodic drinking may alter brain functioning involved in working memory; however, additional longitudinal studies are needed to explore the effects of alcohol on neural correlates of other vital cognitive processes, such as response inhibition.

Response inhibition refers to the ability to withhold a prepotent response in order to select a more appropriate, goal-directed response (Luna *et al*, 2010; Stevens *et al*, 2007). The neural circuitry underlying response inhibition develops during adolescence (e.g., Durston *et al*, 2006; Velanova *et al*, 2008), and as such, brain response during inhibition changes during adolescence (Luna *et al*, 2010). Briefly, cross-sectional research indicates that brain activation during response inhibition transitions from diffuse prefrontal and parietal activation to localized prefrontal activation (Luna *et al*, 2010; Luna and Sweeney, 2004). Longitudinal studies report that atypical brain responses during response inhibition, despite comparable performance, is predictive of later alcohol use (Norman *et al*, 2011), substance use and dependence symptoms (Mahmood *et al*, 2012), and alcohol-related consequences (Wetherill *et al*, 2012b). Together, these findings indicate that neural substrates associated with response inhibition change over time and abnormalities in development may contribute to later substance use.

To this end, the current longitudinal fMRI study examined the effects of initiating heavy drinking during adolescence on brain activity during response inhibition. We examined blood oxygen level dependent (BOLD) response during a go/no-go response inhibition task prior to alcohol initiation (ages 11.7-16.7), then again on the same scanner approximately 3 years later, after some adolescents had transitioned into heavy drinking. Based on our previous findings (Squeglia *et al*, 2012a), we hypothesized that adolescents who transition into heavy drinking would show reduced BOLD response during response inhibition prior to

initiating heavy drinking (baseline time point) followed by increased activation after the onset of heavy episodic drinking, as compared to adolescents who remained non-users. By identifying potential neurobiological antecedents and consequences of heavy episodic drinking, this study will extend previous research on the effects of alcohol on brain function and point to risk factors for heavy episodic drinking during adolescence.

Methods

Participants

Participants in the current prospective study (N=40) were identified from a sample of 296 adolescents participating in a neuroimaging study of neurocognition and neural functioning in youth at-risk for substance use disorders (Squeglia *et al*, 2011; (Squeglia *et al*, 2012b; Squeglia *et al*, 2009b; Wetherill *et al*, 2012a). Adolescents were recruited through flyers distributed to households of students attending local public schools and had minimal, if any, substance use at project entry (Bava *et al*, 2011; Pulido *et al*, 2009; Squeglia *et al*, 2009b). Parents and adolescents completed phone screens, and those eligible each privately completed semi-structured diagnostic interviews to confirm eligibility. Participants provided informed assent and parents provided informed consent, as approved by the University of California, San Diego Human Research Protections Program.

Baseline exclusion criteria that helped rule out potential confounds included parental history of bipolar, psychotic, or antisocial personality disorder; any indication of *in utero* alcohol, tobacco, or illicit drug exposure; complicated or premature birth (<34 weeks gestation); left-handedness; history of chronic medical illness, any neurological or *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV, American Psychiatric Association, 1994) Axis I disorder; traumatic brain injury with loss of consciousness > 2 minutes or learning disabilities; use of psychoactive medications; more than 6 lifetime alcohol, cigarette, marijuana, or other illicit drug uses, or more than 1 drink per drinking occasion; MRI contraindications (e.g., braces, positive pregnancy test); sensory impairments; and non-fluency in English. The current sample at baseline was 55% Caucasian, 20% Latino/a, 15% multiracial, 5% Asian, and 5% African American, and participants had ≤1 total lifetime drinks, ≤1 lifetime uses of marijuana, ≤1 lifetime cigarette uses, and no history of other illicit substance use. At approximately the 3-year follow-up, 20 adolescents were categorized as Heavy Drinkers, and 20 continuously non-drinking Controls (see Figure 1) were matched based on demographics (see Table 1). Of this sample, fMRI data from participants were reported on previously – 9 in Norman *et al*, 2011, 25 in Squeglia *et al*, 2012a, and 21 in Wetherill *et al*, 2012b.

Measures

Substance use—The Customary Drinking and Drug Use Record (CDDR) (Brown *et al*, 1998) assessed lifetime and past year alcohol, tobacco, and other drug use, DSM-IV abuse and dependence criteria, and other substance-related consequences. The Timeline Followback (Sobell and Sobell, 1992) assessed the participants' substance use quantity and frequency for the 30 days prior to scan sessions. Breathalyzers, urine toxicology, and parent reports on youth substance use verified adolescent self-report data.

Family background—The Hollingshead scale provided a measure of socioeconomic status that incorporates level of education and occupation of each parent (Hollingshead, 1965). The Family History Assessment Module (FHAM) (Rice *et al*, 1995) assessed DSM-IV criteria of alcohol and other drug abuse and dependence in first and second-degree relatives. Family history density was ascertained by adding 0.5 for each biological parent

and 0.25 per biological grandparent endorsed by either youth or parent as having AUD or SUD (Zucker *et al*, 1994).

Development—The Pubertal Development Scale (Petersen *et al*, 1988) ascertained current level of pubertal development with five sex-specific items. Body mass index (BMI) was calculated using the standard formula incorporating height and weight. [BMI = (weight (lbs)/(height (in)^2)) * 703]

Neurocognition—At baseline, the Vocabulary subtest of the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) estimated verbal IQ, and the Wide Range Achievement Test, 3rd Edition (Wilkinson, 1993) determined reading skill level.

Psychopathology—At baseline, the Diagnostic Interview Schedule for Children Version 2.3 (DISC-2.3) assessed DSM-IV Axis I diagnoses (Shaffer *et al*, 1996). At baseline and follow-ups until age 18, the Child Behavior Checklist (CBCL) (Achenbach and Rescorla, 2001) provided a level of adolescent psychopathological syndromes (e.g., internalizing and externalizing behaviors). Similar self-report data were obtained with the Youth Self-Report (YSR) for those age 18 and under, and the Adult Self-Report (ASR) after turning 18 (Achenbach and Rescorla, 2003) to provide quantitative measures of psychopathological syndromes including externalizing and internalizing behaviors.

Experimental paradigm—An event-related go/no-go paradigm (Norman *et al*, 2011; Wetherill *et al*, 2012b) measured response inhibition during fMRI scanning. Participants viewed a serial presentation of blue shapes on a screen, comprised of 64 large circles, 16 small circles, 43 large squares, and 57 small squares with each stimulus appearing for 200 msec. Participants were instructed to press a button each time a shape appeared (go stimuli) but *not* press when shown the small square (no-go stimulus, 32% of trials). The intertrial interval was 1500 msec. Total task duration was 6 minutes and 24 seconds. Primary analyses contrasted BOLD response to the no-go (response inhibition) trials relative to the go (response selection) trials.

Procedures

Eligible youth completed baseline (i.e., prior to onset of substance use) interviews, urine toxicology, Breathalyzer screens, neuropsychological testing, and neuroimaging, and parents provided collateral reports of youth substance use, general life functioning, and behavior. Quarterly thereafter, participants completed phone interviews assessing substance use and psychological functioning. Annually after the baseline assessment, youth who transitioned into heavy drinking and a demographically matched nondrinking control completed a full follow-up assessment (see Measures) and a neuroimaging session on the same 3T scanner as used at baseline. Follow-up rates exceeded 95% at each annual time point in this project.

MR acquisition—Imaging data at baseline and follow-up were collected on the same 3.0-Tesla General Electric Excite MR system with an 8-channel phase-array head coil (General Electric Medical System, Milwaukee, WI, USA) at the UCSD Keck Center for Functional MRI. Scan sessions involved a 10-second scout scan and a sagittally acquired high-resolution three-dimensional T1-weighted anatomical image (field of view = 24 cm, 256 × 256 × 192 matrix, 0.94 × 0.94 × 1 mm voxels, 176 slices; repetition time=8 ms, echo time=3 ms, flip angle 12°, 7:19 minutes). Whole-brain echo planar images were collected axially (field of view=24 cm, 64 × 64 matrix, 3.75 × 3.75 × 3.8 mm voxels, repetition time = 2000 ms, echo time = 30 ms, 90º flip angle, 32 slices with no gap, 6:24 minutes).

Data processing and analysis—Baseline and follow-up imaging data were processed using Analysis of Functional NeuroImages (AFNI) software (Cox, 1996) (http://afni.nimh.nih.gov/). Small movements were corrected by registering image repetitions to a selected base volume using the AFNI 3D volume registration program (Cox and Jesmanowicz, 1999). Two trained raters visually inspected time series data and removed repetitions containing visible head motions. All data sets included in analyses retained >85% of repetitions.

Separate hemodynamic task response functions for inhibitions and response selection trials were calculated using deconvolution based on each participant's behavioral data, while accounting for hemodynamic delays (Bandettini *et al*, 1993) and covarying for motion and linear trends. This yielded fit coefficients representing the BOLD response across behavioral conditions. Voxel-wise fit-coefficient data were transformed to standard coordinates (Talairach and Tournoux, 1988), resampled into 3 mm^3 isotropic voxels, and smoothed spatially with a 5 mm full width at half-maximum (FWHM) Gaussian filter.

Statistical analyses—For non-imaging data, *t*-tests compared group differences in continuous demographic, substance use, and task performance variables, and chi-square tests compared groups on categorical variables. Go/no-go task performance measures were percent correct on inhibitory trials, d' (a measure of accuracy in discriminating between go and no-go stimuli)[1], and β (a measure of response bias)[2] (Green and Swets, 1966).

For imaging data, two separate analyses were conducted. First, we examined BOLD response contrast between no-go trials and go trials on whole-brain fMRI data using a single-sample *t-test* to examine activation at baseline. Second, a repeated measures ANCOVA (AFNI *3dANOVA3)* with time (baseline and follow-up) as the within-subjects factor and group (Heavy Drinker n=20 versus Control n = 20) as the between-subjects factor determines main effects of drinking group and time and their interaction, for no-go relative to go trial BOLD response contrast on whole-brain fMRI data. Lifetime marijuana, nicotine, and other illicit drug use differed between groups, and as such, these variables were composited into a lifetime substance use variable and included as a covariate. Given potential sex differences in both substance use and neural activity, sex was also included as a covariate. To control against Type I error, Monte Carlo simulations using the AFNI *3dClustSim* program were used and only clusters with a voxel threshold of p <.01 exceeding 756 μl, equal to 28 contiguous significant (α <.05) 3 mm^3 voxels were considered significant. Data representing no-go relative to go BOLD response contrasts in significant clusters for each participant were exported to PASW 18.0 (Chicago, IL) for follow-up analyses.

Post hoc analyses examined whether BOLD response change over time correlated with subsequent alcohol involvement in Heavy Drinkers (i.e., follow-up lifetime number of drinks, past year drinking days per month, past year drinks per drinking occasion, and past year maximum number of drinks during a drinking occasion). Follow-up hierarchical linear regressions assessed whether baseline activation within clusters showing significant correlations predicted follow-up alcohol consumption, after statistically controlling for baseline alcohol use, biological sex, and follow-up age.

[1] $d = \Phi^{-1}(H) - \Phi^{-1}(F)$. Φ^{-1} = z score, (H) = hit rate, (F) = false-alarm rate

[2] $\beta = e^{\left[\frac{[\Phi^{-1}(F)]^2 - [\Phi^{-1}(H)]}{2}\right]^2}$

Results

Table 1 provides baseline and follow-up descriptive information for Heavy Drinkers and Controls. Of note, the ability to inhibit prepotent responses improved with age ($p < 0.001$) with no differences in this improvement between groups (Group × Time: $p > 0.20$).

The no-go versus go contrast at baseline revealed activations consistent with meta-analyses of response inhibition (Criaud and Boulinguez, 2013; Swick *et al*, 2011) showing significant clusters of activation in inferior, superior, and medial frontal gyri, and in parietal, temporal, cerebellar, and subcortical areas ($p < 0.01$, cluster > 756 μl, see Online Resource 2).

Because Heavy Drinkers reported significantly more substance use than Controls at follow-up, a lifetime substance use composite (excluded alcohol use) and biological sex were included as covariates. A repeated measures ANCOVA revealed significant group × time interactions in 5 regions: the bilateral middle frontal gyri, right inferior parietal lobule, left putamen, and left cerebellar tonsil (see Table 2 and Figure 2). Independent samples *t*-tests probed significant group × time interactions within these 5 clusters. At baseline, Heavy Drinkers showed significantly less no-go BOLD contrast than Controls in all 5 clusters (p's < 0.05). Across adolescence, Heavy Drinkers exhibited increasing response inhibition BOLD contrast, and Controls showed attenuated response in clusters. At follow-up, Heavy Drinkers showed significantly greater response inhibition activity than Controls in 4 brain regions (p's < 0.05): bilateral middle frontal gyri, right inferior parietal lobule, and left cerebellar tonsil.

Exploratory post-hoc analyses examined whether BOLD response contrast change over time correlated with subsequent alcohol involvement in Heavy Drinkers (i.e., follow-up lifetime number of drinks, past year drinking days per month, past year drinks per drinking occasion, and past year maximum number of drinks during a drinking occasion). BOLD response contrast during no-go relative to go trials over time in the right middle frontal gyrus positively correlated with follow-up lifetime number of drinks (n =20, r = 0.65, p = 0.001) (Type I error controlled with $\alpha = 0.05/20 = 0.0025$). Follow-up hierarchical linear regressions revealed BOLD response contrast at baseline did not predict follow-up alcohol consumption after controlling for baseline alcohol, biological sex, and follow-up age at our conservative, corrected threshold ($p < 0.001$).

Discussion

The present longitudinal neuroimaging study examined the effects of initiating heavy drinking during adolescence on brain responses during response inhibition. We hypothesized, based on previous findings (Squeglia *et al*, 2012a), that adolescents who transition into heavy drinking would show reduced BOLD response during response inhibition prior to initiating heavy drinking (baseline time point) followed by increased activation after the onset of heavy episodic drinking, as compared to adolescents who remained non-drinkers. Examining a longitudinal neuroimaging sample of youth both pre- and post-alcohol use initiation allowed us to address the etiology of neural pattern differences. Although group × time effect sizes were small, our findings suggest that differential neural activity patterns predate alcohol initiation and also arise as a consequence of heavy drinking.

We found significant drinking status × time interactions in a number of distinct and reproducible brain regions commonly associated with response inhibition. Prior to initiating substance use, adolescents who initiated heavy use showed *less* BOLD activation during inhibitory trials in frontal regions, including the bilateral middle frontal gyri, and non-frontal regions, including the right inferior parietal lobule, putamen, and cerebellar tonsil, compared

with those who continued to abstain from alcohol use. This pattern of hypoactivity among youth who later initiated heavy drinking during response inhibition is consistent with studies showing decreased activity during response inhibition predicts later alcohol use (Norman *et al*, 2011) and substance use (Mahmood *et al*, 2012). Indeed, change in BOLD response contrast over time in the right middle frontal gyrus was associated with lifetime alcohol drinks at follow-up. Together, these findings provide additional evidence for the utility of fMRI in identifying neural vulnerabilities to substance use even when no behavioral differences are apparent.

At follow up, adolescents who transitioned into heavy drinking showed *increasing* brain activation in the bilateral middle frontal gyri, right inferior parietal lobule, and left cerebellar tonsil during inhibition; whereas, non-drinking controls exhibited decreasing brain activation in these brain regions. These regions have been implicated in processes of stimulus recognition, working memory, and response selection (Criaud and Boulinguez, 2013; Noonan *et al*, 2011; Rubia *et al*, 2006), all of which are critical to successful response inhibition. Indeed, neuroanatomical models of inhibitory control highlight the importance of frontoparietal attentional control and working memory networks (Corbetta and Shulman, 2002, 2011; Munakata *et al*, 2012). These models posit that inhibition and cognitive control involve frontoparietal brain regions (i.e., connections between the middle frontal gyrus extending posteriorly to the inferior parietal lobule) when detecting and responding to behaviorally relevant stimuli. Thus, findings suggest that heavy drinkers recruit greater activity in these neural networks in order to successfully inhibit prepotent responses.

Given the longitudinal nature of the current study, it is important to consider our findings in the context of typical adolescent neural maturation. During typical neural maturation, adolescents exhibit less activation over time, as neural networks become more refined and efficient (Luna *et al*, 2010). This typical pattern of neural maturation occurred among adolescents who remained nondrinkers. Adolescents who transitioned into heavy drinking showed the opposite pattern – increasing activation despite similar performance, suggesting that alcohol consumption may alter typical neural development.

The current findings should be considered in light of possible limitations. Although heavy drinking and non-drinking youth groups were matched on several baseline and follow-up measures, heavy drinking youth reported more cannabis, nicotine, and other illicit drug use at follow-up. Differential activation remained significant after statistically controlling for lifetime substance use and such differences may contribute to our findings. Further, simultaneous substance use (i.e., use of marijuana and/or tobacco with alcohol during the same episode) might be associated with these results. Future research should explore the effects polysubstance use during the same episode compared to the effects of heavy drinking on neural responses. It is also important to note that adolescence is a period of significant inter-individual differences in neural development, and as such, we matched self-reported pubertal development and age at baseline and follow-up to address this issue. For the current sample, histograms of age distributions at baseline and follow-up are provided in Online Resource 1. Again, our groups were well matched on these variables; however, additional longitudinal research to examine the effects puberty and hormonal changes on neural functioning and response inhibition are needed.

In summary, the current data suggest that pre-existing differences in brain activity during response inhibition increase the likelihood of initiating heavy drinking, and initiating heavy alcohol consumption leads to differential neural activity associated with response inhibition. These findings make a significant contribution to the developmental and addictive behaviors fields, as this is the first study to examine neural responses differences during response inhibition prior to and following the transition into heavy drinking among developing

adolescents. Further, we provide additional support for the utility of fMRI in identifying neural vulnerabilities to substance use even when no behavioral differences are apparent. Identifying such neural vulnerabilities before associated behaviors (e.g., substance use) emerge provides an additional tool for selecting and applying targeted prevention programs. Given that primary prevention approaches among youth have not been widely effective, it is possible that targeted prevention programs for youth who are at greatest *neurobiological* risk could be a novel, effective approach. As such, our findings provide important information for improving primary prevention programs, as well as answering the question of whether neural differences predate alcohol initiation or whether differences arise as a consequence of alcohol use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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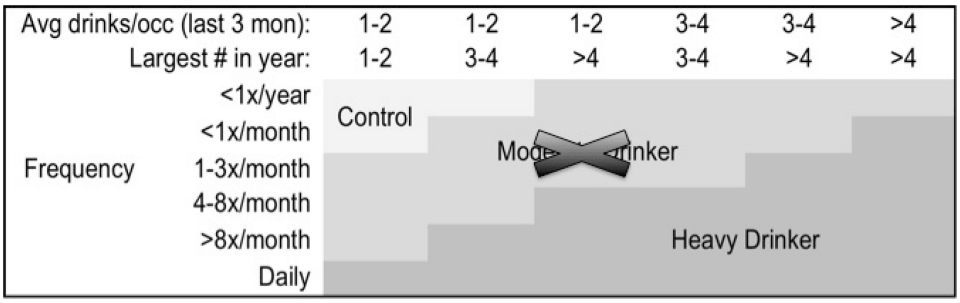

Figure 1.
Drinking classification for heavy drinking adolescents, based on Cahalan et al., 1969 and Squeglia et al., 2009. Note that Moderate Drinkers were not included in this study.

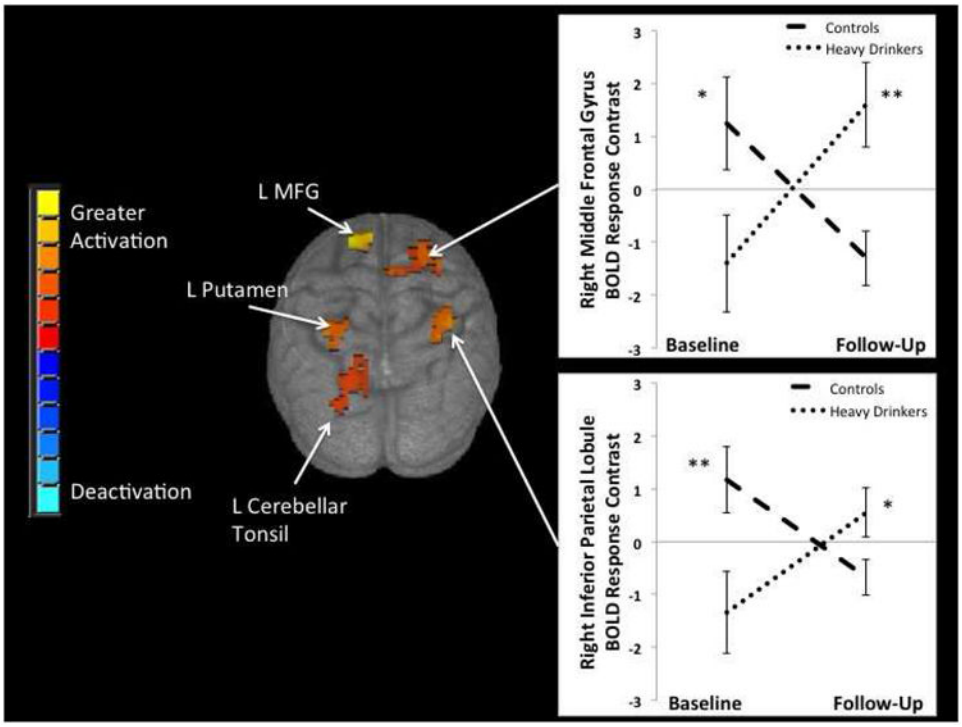

Figure 2.

Significant ($p < 0.01$, cluster > 756 microliters) group × time interactions in BOLD response contrast to no-go relative to go trials were seen in 5 clusters in frontal, parietal, cerebellar, and subcortical brain regions. Graphs are shown for two of these regions: right middle frontal gyrus and right inferior parietal lobule. Future heavy drinkers showed less BOLD response at baseline in several brain regions, but greater BOLD response at follow-up after the initiation of heavy drinking, compared to continuous non-drinking controls. MFG = Middle Frontal Gyrus, L = Left, * $p < .05$, ** $p < .01$.

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Table 1

Baseline and follow-up demographic characteristics

		Controls (*n* = 20) *M* (SD)	Heavy Drinkers (*n* = 20) *M* (SD)
Baseline	Age (range 11.7 to 16.7)	14.1 (1.2)	14.7 (1.1)
	% female	45%	45%
	Hollingshead SES[a]	26.2 (18.0)	24.1 (17.9)
	Family history density	0.8 (0.8)	0.8 (0.8)
	Achenbach Externalizing *T*-score	39.8 (6.6)	43.1 (8.3)
	Achenbach Internalizing *T*-score	38.5 (9.3)	42.3 (10.7)
	Reading standard score	110.1 (13.0)	113.0 (6.2)
	Vocabulary T-score	53.7 (11.8)	58.3 (6.5)
	Pubertal stage	2.6 (0.6)	2.9 (0.6)
	Body mass index	21.0 (5.2)	20.2 (2.8)
	Inhibitions percent correct (%)	77.4 (1.1)	83.3 (1.1)
	D-prime (D')	3.1 (0.6)	3.1 (0.5)
	Response bias (β)	0.2 (0.2)	0.2 (0.1)
Follow-up	Age (range 14.7 to 20.6)	17.6 (1.2)	18.5 (1.8)
	Years between baseline and follow-up	3.4 (0.8)	3.3 (1.2)
	Achenbach Externalizing *T*-score	37.6 (3.9)	41.6 (13.0)
	Achenbach Internalizing *T*-score	34.8 (7.2)	38.9 (11.4)
	Past year drinking days per month***	0.0 (0.1)	2.8 (1.8)
	Past year average drinks/episode***	0.2 (0.4)	4.2 (2.1)
	Past year binge[b] episodes***	0.0 (0.0)	9.0 (13.8)
	Past year peak drinks/episode***	0.0 (0.0)	10.5 (11.3)
	Lifetime number of drinks***	0.5 (0.9)	92.3 (94.5)
	Lifetime number of cigarettes***	0.0 (0.0)	0.5 (0.2)
	Lifetime cannabis use episodes*	0.3 (1.1)	4.8 (9.1)
	Lifetime other drug use episodes***	0.0 (0.0)	0.2 (0.5)
	Days since last alcohol binge episode[c]	N/A	70
	Days since last cannabis use[c]	138	116

	Controls (n = 20) M (SD)	Heavy Drinkers (n = 20) M (SD)
Days since last other drug use[c]	N/A	131
Inhibitions percent correct (%)	86.4 (1.0)	90.6 (0.7)
D-prime (D')	3.3 (1.0)	3.8 (0.5)
Response bias (β)	0.2 (0.1)	0.3 (0.1)

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$

[a] Hollingshead SES scores typically range from 11-77, with lower scores indicating higher SES.

[b] Binge episode = 4+ drinks for females or 5+ drinks for males.

[c] Of those individuals who reported alcohol, cannabis, and/or other drug use, average number of days between date of last use and scan date.

Table 2

Drinking group × time interactions for BOLD response during inhibitory processing(*N* = 40)

Structure	BA	Volume (μl)	Peak Coordinates[c]			Group by Time[a] Effect Size η^2	*t*-test at Baseline[b]	*t*-test at Follow-Up[b]
			x	y	z			
R middle frontal gyrus	10	1,755	24	46	8	0.19**	C>HD*	HD>C**
L middle frontal gyrus	10	972	−25	38	6	0.18**	C>HD**	HD>C*
R inferior parietal lobule	40	1,458	35	−35	48	0.30***	C>HD**	HD>C*
L putamen		1,107	−29	−14	6	0.19**	C>HD**	ns
L cerebellar tonsil		1,944	−26	−38	−34	0.24**	C>HD*	HD>C**

[a] η^2 from repeated measures ANCOVA with biological sex and lifetime substance use as covariates.

[b] *t*-values from independent samples *t*-tests.

[c] Peak coordinates are in Talairach & Tournoux atlas (Talairach & Tournoux, 1988).

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$

Abbreviations. BA: Brodmann's area, C: Controls, HD: Heavy Drinkers, Ns: non-significant.