

Family history of alcoholism interacts with alcohol to affect brain regions involved in behavioral inhibition

David A. Kareken · Mario Dziedzic · Leah Wetherill ·
William Eiler II · Brandon G. Oberlin ·
Jaroslaw Harezlak · Yang Wang · Sean J. O'Connor

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Abstract

Rationale Impulsive behavior is associated with both alcohol use disorders and a family history of alcoholism (FHA). One operational definition of impulsive behavior is the stop-signal task (SST) which measures the time needed to stop a ballistic hand movement.

Objective Employ functional magnetic resonance imaging (fMRI) to study right frontal responses to stop signals in heavy drinking subjects with and without FHA, and as a function of alcohol exposure.

Methods Twenty-two family history-positive (FHP; age=22.7 years, SD=1.9) and 18 family history-negative (FHN;

age=23.7, SD=1.8) subjects performed the SST in fMRI in two randomized visits: once during intravenous infusion of alcohol, clamped at a steady-state breath alcohol (BrAC) concentration of 60 mg/dL, and once during infusion of placebo saline. An independent reference group ($n=13$, age=23.7, SD=1.8) was used to identify a priori right prefrontal regions activated by successful inhibition (Inh) trials, relative to “Go” trials that carried no need for inhibition [Inh>Go].

Results FHA interacted with alcohol exposure in right prefrontal cortex, where alcohol reduced [Inh>Go] activation in FHN subjects but not in FHP subjects. Within this right frontal cortical region, stop-signal reaction time also correlated negatively with [Inh>Go] activation, suggesting that the [Inh>Go] activity was related to inhibitory behavior.

Conclusions The results are consistent with the low level of response theory (Schuckit, *J Stud Alcohol* 55:149–158, 1980; Quinn and Fromme, *Alcohol Clin Exp Res* 35:1759–1770, 2011), with FHP being less sensitive to alcohol’s effects.

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D. A. Kareken (✉) · M. Dziedzic · W. Eiler II · B. G. Oberlin
Neuropsychology Section (GH 4700), Department of Neurology,
Indiana University School of Medicine, 355 W. 16th Street,
Indianapolis, IN 46202, USA
e-mail: dkareken@iupui.edu

D. A. Kareken · S. J. O'Connor
Department of Psychiatry, Indiana University School of Medicine,
Indianapolis, IN 46202, USA

D. A. Kareken · M. Dziedzic · Y. Wang
Department of Radiology, Indiana University School
of Medicine, Indianapolis, IN 46202, USA

L. Wetherill
Department of Medical Genetics, Indiana University School
of Medicine, Indianapolis, IN 46202, USA

D. A. Kareken · L. Wetherill
Department of Psychology, Indiana University, Purdue University,
Indianapolis (IUPUI), Indianapolis, IN 46202, USA

J. Harezlak
Department of Biostatistics, Indiana University School
of Medicine, Indianapolis, IN 46202, USA

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Introduction

A family history of alcoholism (FHA) doubles the risk of alcohol dependence (Nurnberger et al. 2004). Beyond the risk for alcohol use disorders, familial alcoholism is also significantly associated with impulsive and externalizing behaviors (Marmorstein et al. 2009)—behaviors thought to be relevant to drinking initiation, escalation, and treatment relapse (Perry and Carroll 2008).

One operational definition of impulsive behavior is stop-signal reaction time (SSRT), or the time needed to withdraw (Stop) a ballistic hand movement (Logan 1994; Logan et al.

1997). Distinct from delay discounting, which measures impulsive devaluing of reward as a function of time, the motor impulsiveness assessed by SSRT represents the speed (or slowness) with which an individual can accommodate an environmental demand to halt a behavior. Using the stop-signal task (SST) to quantify SSRT, Nigg et al. (2004) found that alcohol-naïve adolescent offspring of alcoholic fathers had slower SSRTs than children from control families, and that SSRT predicted aggregate future alcohol and drug problems (Nigg et al. 2006). Acheson et al. (2011) also reported more SST inhibition failures in family history-positive (FHP) adults without histories of alcohol or drug use disorders. These findings suggest that slower SSRTs in illicit substance use (Lipszyc and Schachar 2010) may be more than a toxicologic effect and reflect a pre-existing deficit in the frontal and subcortical brain systems that regulate behavioral inhibition. In imaging, a large-scale functional magnetic resonance imaging (fMRI) study of the SST (Whelan et al. 2012) found lower orbitofrontal responses related to successful inhibition in adolescents who had used illicit substances (although frequent users of illicit drugs also had higher responses in right inferior frontal cortex). In alcohol-dependent patients, Li et al. (2009) showed a reduced left frontal response in successful compared with errant stop-signal inhibition. Smokers and problem gamblers have also been shown to have less dorsomedial frontal activation during SST (de Ruiter et al. 2012). Contrary to the evidence above, however, it is of note that, in all of these imaging studies of addiction, SSRT was not different between controls and the clinical samples of interest.

Beyond its potential as a reflection of baseline behavioral impulsiveness, SSRT and inhibition success (but not choice reaction time (RT)) are worsened by alcohol intoxication (e.g., De Wit et al. 2000; Fillmore and Vogel-Sprott 1999). In turn, this aggravated motor impulsiveness (lengthened SSRT) has been found to correlate with increasingly maladaptive reward-seeking behaviors (Loeber and Duka 2009). Thus, as inhibitory control worsens during intoxication, so does ad lib alcohol consumption (Weafer and Fillmore 2008), speaking to a potential mechanism in the loss of control of drinking.

Against this background, we examined frontal lobe responses to stop-signal behavior in groups of heavy drinking subjects with and without FHA. Subjects performed the SST in fMRI during exposure to intravenously infused alcohol that was clamped at a breath alcohol concentration (BrAC) of 60 mg/dL, as well as during an intravenous infusion of placebo saline. Given alcohol's propensity to induce behavioral disinhibition, as well as the relationship between familial alcoholism and impulsive behaviors, we hypothesized that FHP individuals would be disproportionately affected by acute alcohol exposure, both in SSRT and in a right inferior frontal region implicated in behavioral inhibition

(e.g., Aron and Poldrack 2006; Congdon et al. 2010; Whelan et al. 2012).

Materials and methods

Subjects

Forty-three nondependent, nontreatment-seeking, heavy-drinking subjects were recruited by the use of advertisements placed in the community. Subjects were assessed using the semi-structured assessment for the genetics of alcoholism (SSAGA; Bucholz et al. 1994), the timeline followback interview for habitual drinking (TLFB; Sobell et al. 1986), the alcohol use disorders identification test (AUDIT; Saunders et al. 1993), and urine screens for drugs of abuse. All subjects had previously participated in a larger, ongoing behavioral study in which they performed the SST during clamped alcohol and placebo exposures outside the scanner. Three subjects did not have usable imaging data because of their inability to either remain awake (one subject) or to perform the task (two subjects).

The resulting 40 subjects (Table 1) consisted of 22 individuals with positive family histories of alcoholism and 18 of whom were family history negative (FHN). FHP had at

Table 1 Subject characteristics

	FHP (<i>n</i> =22)		FHN (<i>n</i> =18)	
	Mean (SD)	<i>n</i> (%)	Mean (SD)	<i>n</i> (%)
Age	22.7 (1.9)		23.7 (1.8)	
Male (%)		12 (54.5)		11 (61.1)
Smokers ^a (%)		2 (9.1)		0 (0)
Education (years)	15.1 (1.8)		15.8 (0.8)	
Drinks/drinking day	5.1 (3.1)		5.4 (2.4)	
Heavy drinking days/week	1.5 (1.3)		1.3 (0.8)	
Drinks/week	15.1 (13.0)		13.9 (6.9)	
Age of regular drinking	18.2 (1.7)		18.3 (1.9)	
AUDIT	8.1 (2.6)		9.1 (3.2)	
SRE (first 5 times drinking)	4.4 (1.9)		4.1 (1.4)	
SRE (most recent 3 months)	5.8 (2.0)		5.4 (1.6)	
SRE (heaviest period)	7.6 (3.0)		8.6 (2.0)	

AUDIT Alcohol use disorder identification test (scores unavailable for two FHP subjects and three FHN subjects), *SRE* subjective rating of the effects of alcohol inventory, quantified as number of drinks required to obtain detectable effects rated

^a Of the two smoking subjects, one reported at 0.25 pack/day habit while the second reported a 0.3-pack/day habit. One heavy drinking day is ≥ 5 drinks for men and ≥ 4 for women (NIAAA 2005)

least one first-degree relative with probable alcoholism, and at least one other first- or second-degree relative (with one exception being a subject with four second-degree relatives), assessed using the family history (FH) assessment module of the SSAGA and interviewing only the subject (not the subjects' family members). As intended, the FH groups did not differ (p values >0.10) in age, education, drinking patterns, age at initiation of regular drinking, current AUDIT scores, or in scores on the subjective rating of the effects of alcohol inventory (Schuckit and Smith 1997). All subjects were right handed. Although we did not exclude for drug experimentation, none of the subjects had histories of drug dependence. None tested positive for drugs of abuse, except for one FHP subject who was positive for stimulants the day of his saline infusion session (prior night's use of a prescription stimulant for studying). Data were therefore analyzed with and without this subject/session.

To assist in defining regions of interest (ROIs) for analysis, we first imaged a similarly aged (23.7 years, $SD=1.8$) "reference sample" of 13 (six males) right-handed healthy community volunteers who performed the SST during fMRI without any intravenous infusions. This permitted defining a priori regions that responded to the task in an independent sample that was unrelated to those samples tested for the effects of alcohol and FHA. Although detailed TLFB results are not available for the reference sample, five described drinking two to four times per week, four drank two to four times per month, three drank once per month, and one abstained. Of those who did drink alcohol, all but one drank under five drinks per occasion, with the remaining subject drinking more than six per occasion on a weekly basis.

Stop-signal task

An SST, modeled after Rubia et al. (2003), was programmed in E-Prime 2.0 software (Psychology Software Tools Inc., Sharpsburg, PA). Each of three individual task runs consisted of 80 "Go" trials, each requiring a left or right button press on an MRI-compatible response box (Current Designs, Philadelphia, PA) to horizontal green arrows pointing either left or right; subjects were instructed to respond as quickly and as accurately as possible. An additional 40 "Stop" trials were marked by a red up-pointing arrow immediately after a Go stimulus, indicating the need to inhibit the Go response to the prior green arrow (total of 240 Go trials and 120 Stop trials). An adaptive staircase algorithm adjusted the delay between Go and Stop stimuli in 50-ms increments to target a stop inhibition rate of 50 %; in the current context, the algorithm also compensates for effects related to practice, fatigue, and intoxication. Estimated SSRT for a given subject was calculated by subtracting a subject's average stop-signal delay from that subject's x th percentile Go RT, where x corresponds to the

stop failure rate (Band et al. 2003). Thus, if a subject failed to stop on 45 % of stop trials, the Go RT subtracted from the average stop-signal delay would be the time falling at the 45th percentile of the subject's Go RT distribution. A mirror mounted on the head coil enabled subjects to view the stimuli as back-projected on a screen at the rear of the scanner bore.

Procedure

Subjects reported to the Indiana Clinical Research Center (CRC) on two mornings, between 7:00 and 9:00 a.m. (average number of days between scanning, 9.4 ($SD=6.1$), with no significant differences between the FHA groups; $p=0.30$). Subjects understood that one scan would be done with alcohol and one with saline, although they remained blinded to the infusate content on each day. After obtaining height and weight, a catheter was placed in a vein in the antecubital fossa of the subject's nondominant arm. Subjects were then fed a calorically standardized breakfast and escorted to the imaging facility between 9:00 and 11:00 a.m. Following imaging, subjects returned to the CRC for lunch and remained at the CRC until BrAC fell below 20 mg/dL (0.02 g/L).

Imaging Subjects were imaged on a Siemens (Siemens Healthcare, Erlangen, Germany) 3 T Magnetom Trio-Tim scanner using a 12-channel head coil array. Three echo-planar imaging (EPI) scans measured SST responses (193 blood oxygenation level-dependent (BOLD) volumes; gradient echo; repetition time, 2,000 ms; echo time, 29 ms; flip angle, 76°; 35 interleaved 3-mm-thick axial slices; acquisition matrix, 88×88; 2.5×2.5×3.0 mm³ voxels; GRAPPA acceleration factor 2; and 3D prospective acquisition correction algorithm). In addition, five 5.45-min-long pulsed arterial spin labeling (PASL) scans measured regional cerebral blood flow (rCBF; ml/100 g/min) using a one-compartment model (Wang et al. 2003): (1) at baseline (before infusion), (2–3) twice during the ascending limb, (4) once after reaching the intended brain alcohol concentration target, and (5) once after BOLD imaging. These data were collected to assure that alcohol infusion did not significantly affect global rCBF, effectively decoupling the BOLD signal from neural responses (see below). PASL scans were acquired using the Siemens product sequence with a Q2TIPS PICORE (Luh et al. 1999) labeling scheme, as detailed in Wang et al. (2011) with a 64-label-control pair readout (gradient-echo single-shot EPI; 18 ascending slices; matrix, 64×64; 3.75×3.75×6 mm³ voxels; same acceleration as BOLD; and including prospective motion correction). In addition, high-resolution (MP-RAGE sequence with 1×1×1.2 mm³ voxels) anatomical images were obtained for each subject to facilitate transformation to a common stereotactic system and to segment out gray matter tissue.

Alcohol infusion Subjects were intravenously infused with either alcohol (6 % vol/vol) or saline (placebo) in randomized, counter-balanced order on each of the 2 days. Infusion pump rates were computer controlled (O'Connor et al. 1998; Ramchandani et al. 1999), with the infusion profile customized for each individual to achieve the same time-course of BrAC for all subjects: a linear ascension to 60 mg/dL in 15 min, followed by constant exposure at 60 mg/dL throughout BOLD imaging. Placebo infusion employed the same pump-rate profile as the individual's alcohol session. BrAC was measured prior to and after imaging using a forensic grade breath meter.

Between BOLD scans, subjects rated their subjective impressions of the infusion on visual analog scales, using a button box to advance a cursor along a 100-mm line. Subjects rated perceived anxiety, intoxication, number of drinks, stimulation, enjoyment of alcohol, craving for alcohol, and tiredness. For analyses of alcohol's effect on executive control, we focused on perceived intoxication, number of drinks, stimulation, and enjoyment.

Image analysis

Functional and rCBF images were pre-processed in SPM8 (Wellcome Trust Centre for Neuroimaging). Individual subject effects were estimated in fixed-effect designs where responses to the onsets of Go and Stop signal trials were modeled with a standard hemodynamic reference function. An auto-regression term and motion parameter regressors were also used. After prospective motion correction, and as calculated by Jiang et al. (1995), mean displacement (residual subject movement) was 0.11 mm (SD=0.04) during alcohol infusion, and 0.12 mm (SD=0.08) during saline, without significant differences between groups or conditions (p values > 0.5). As lesion and transcranial magnetic stimulation studies (Aron et al. 2003; Chambers et al. 2006; Floden and Stuss 2006) suggest a right-lateralized "Stop" system, we focused on right prefrontal cortex, testing for activation related to successful Inh contrasted against correct Go responses (the [Inh>Go] contrast). This contrast has also repeatedly implicated right frontal cortex in the processing of behavioral stop signals (Aron and Poldrack 2006; Aron et al. 2007; Congdon et al. 2010).

For the primary analyses, a random effects voxel-wise analysis of the [Inh>Go] contrast was conducted in SPM8 in the reference sample to first localize target functional ROIs for subsequent analysis in the two FH groups of interest. This was done using family-wise error corrected cluster statistics ($p_{FWE} < 0.05$) at a stringent voxel height threshold of $p < 0.001$ (uncorrected). These right frontal clusters of activation (Table 3) were then used as functional regions of interest from which [Inh>Go] BOLD contrasts in the FH groups were extracted with the MarsBar utility (Brett

et al. 2002). The mean [Inh>Go] BOLD contrast values in these ROIs were then analyzed in 2 (FHA) × 2 (infusion) linear mixed models (SPSS v. 20), with our principal effect of interest being the FHA × infusion interaction. A supplementary and exploratory voxel-wise analysis ($p < 0.001$, uncorrected; $k > 10$ voxels) was also done using an SPM factorial model to test for regions other than those identified by the reference group, and where FHA and infusion might interact (see Electronic supplementary material (ESM)).

Only voxels of at least 75 % gray matter tissue (Jahng et al. 2005), as determined by the SPM segmentation of subject's MP-RAGE images, were used in determining rCBF in whole-brain gray matter and right prefrontal cortex. rCBF in these volumes was analyzed using a 2 (scan) × 2 (infusion) linear mixed model, comparing the pre-infusion baseline scan to the average of the two PASL scans obtained during the clamped alcohol period (and its matched placebo). This allowed us to verify that alcohol did not significantly alter blood flow during the period in which BOLD imaging was conducted—an effect that could depress the BOLD response as an artifact of altered perfusion (e.g., Seifritz et al. 2000).

Results

Reference sample task performance

SST performance during fMRI in the reference sample was characterized by a mean of 98.5 % correct Go responses (SD=1.9 %) and 48.6 % correctly withheld stop responses (SD=2.5 %), very near the intended 50 % targeted by the task's adaptive algorithm. Mean (of intra-subject median) Go RT was 451 ms (SD=93), and SSRT was 251 ms (SD=36). This performance was highly similar to that of the FHA samples of interest during fMRI under saline infusion (see Table 2).

Table 2 Stop-signal performance

	FHP		FHN	
	Alcohol (SD)	Placebo (SD)	Alcohol (SD)	Placebo (SD)
Go correct (%)	96.6 (4.0)	96.4 (6.4)	98.5 (1.1)	98.7 (2.0)
Stop correct (%)	50.1 (3.0)	51.7 (2.5)	49.8 (4.1)	50.0 (3.0)
Median Go RT	455 (138)	445 (123)	447 (94)	428 (86)
SSRT*, **	246 (39)	236 (23)	267 (33)	253 (22)

RT reaction time (in milliseconds), SSRT stop-signal reaction time (in milliseconds), calculated as the difference between average stop-signal delay interval (in milliseconds) and Go RT (see "Materials and methods" for details). See text for more detailed descriptions of the effects

* $p=0.037$ (main effect of FHA); ** $p=0.012$ (main effect of infusion)

Effects of alcohol: subjective perceptions, rCBF, and task performance

Breath alcohol BrAC as measured after SST in fMRI was 60.0 mg/dL (SD=7.1) on the alcohol days and insignificantly different between FHP (60.2 mg/dL, SD=6.0) and FHN (60.0 mg/dL, SD=8.5) groups.

Subjective effects As analyzed in 2 (FHA)×2 (infusion)×5 (time) linear mixed models, with infusion and time as repeated measures, there were significant main effects of infusion for perceived intoxication ($p<0.001$), number of drinks ($p<0.001$), stimulation ($p=0.001$), relaxation ($p=0.001$), and enjoyment ($p<0.001$). Infusion×time interactions were also evident for intoxication ($p<0.001$), number of drinks ($p<0.001$), stimulation ($p<0.001$), and enjoyment ($p<0.001$). Thus, as intended, infused alcohol induced a clear subjective sense of alcohol exposure. The sole effect involving FHA was an FHA×infusion interaction for relaxation ($p=0.006$), which reflected greater relaxation under alcohol in FHP (43.6, SE=3.7) than in FHN (31.1, SE=4.1), with relaxation during placebo being equivalent across FHP (29.8, SE=3.7) and FHN (29.7, SE=4.1).

rCBF For both whole brain and right frontal gray matter, there were no main effects of infusion, and most importantly, no scan×infusion interactions (p values>0.17) that would indicate an rCBF change from the pre-infusion baseline as a function of the infusate.

Stop-signal performance Analyzed in a 2 (FH)×2 (infusion) linear mixed model, a trend FHA main effect reflected small differences in percent correct Go responses between FHP (96.5 %, SE=0.7 %) and FHN (98.6 %, SE=0.8 %; $p=0.055$), although this occurred in the context of greater than 95 % mean accuracy in both groups during both infusions. The task algorithm again functioned as intended, as stop trial accuracy was almost exactly 50 % in both FHA groups in both infusions (Table 2).

Analyzed in a 2 (FH)×2 (infusion) linear mixed model, Go RT (average of intra-subject medians) was not significantly slower under alcohol (451 ms, SE=19) than under placebo (437 ms, SE=17; infusion main effect, $p=0.078$). However, there was a significant main effect of infusion on SSRT ($p=0.012$), with clamped alcohol infusion producing slower SSRTs (256 ms, SE=6) than placebo saline infusion (244 ms, SE=4). While there was a main effect of FHA ($p=0.037$), the difference was in the opposite direction than hypothesized, with FHN SSRT being slower (260 ms, SE=7) than FHP SSRT (241 ms, SE=6). There was no FHA×infusion interaction.

BOLD imaging of SST

Reference sample BOLD response to SST The reference sample showed five significant right pre-frontal clusters for [Inh>Go] (Fig. 1, top; Table 3), which were then used to define regions from which the same BOLD contrast was extracted in the FHA groups. Of note, the overall anatomic distribution of the [Inh>Go] effect in the reference sample was very similar to that of the FHN while imaged under placebo/saline (Fig. 1, bottom); the location and magnitude of these effects was unchanged when excluding the one reference subject with more hazardous drinking (>6 per occasion).

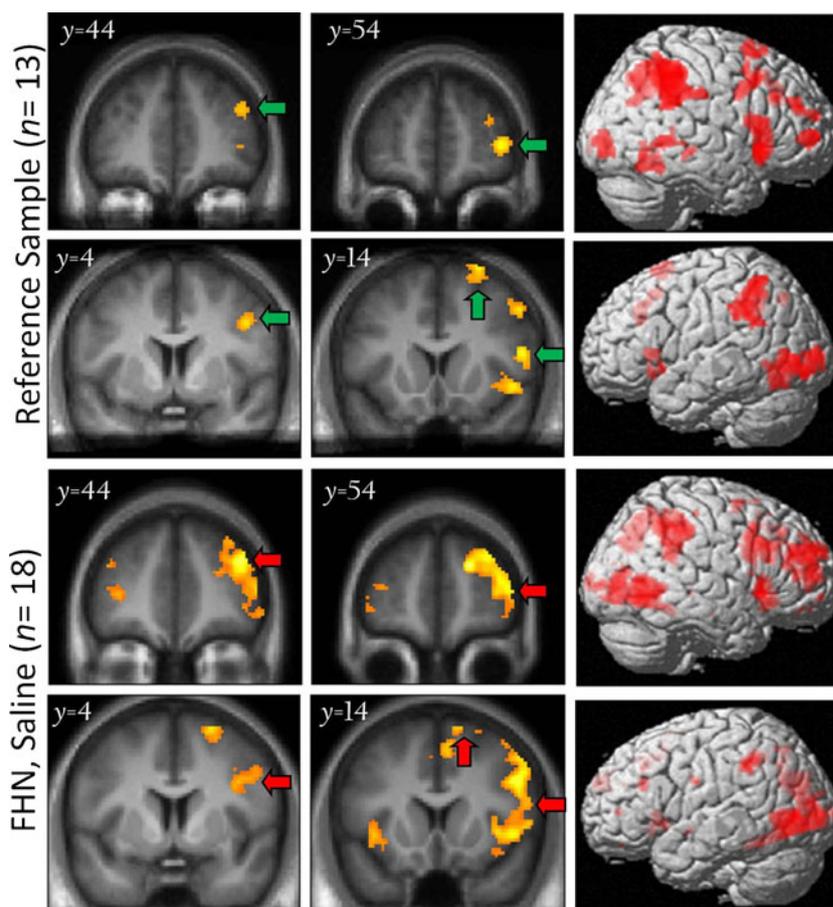
Effects of FHA and alcohol on the BOLD SST response As examined in a FHA (2)×infusion (2) linear mixed model, there were no significant FHA or infusion main effects in the five right frontal ROIs for the [Inh>Go] BOLD contrast. However, in testing the hypothesis that alcohol affected the BOLD contrast differentially by FHA, there was a significant FHA×infusion interaction ($p=0.008$) in the most anterior and inferior right frontal ROI (cluster 2 in Table 3; Fig. 2, top middle panel). This interaction reflected a significant decrease in the FHN response during clamped alcohol, as compared with placebo ($p=0.002$), but without any significant change in FHP subjects in the alcohol versus placebo comparison (see Fig. 2).

Given FHA group differences in SSRT, we also examined the same linear mixed model using SSRT as a covariate. Although the SSRT covariate was significant ($p=0.048$), the FHA×infusion remained significant ($p=0.029$). However, there was also a significant FHA×session×SSRT interaction ($p=0.013$). The nature of this three-way interaction involving the covariate was such that during placebo infusion, SSRT was negatively correlated with the [Inh>Go] BOLD contrast in FHP ($r=-0.50$, $p=0.019$) but not in FHN ($r=-0.01$, $p=0.975$; Fig. 3, left). Thus, within FHP a smaller inferior right prefrontal [Inh>Go] BOLD contrast was associated with a longer SSRT. Under alcohol, however, there was no correlation between SSRT and the [Inh>Go] contrast in FHP ($r=0.12$, $p<0.6$), although there was a significantly negative correlation between SSRT and [Inh>Go] in FHN ($r=-0.67$, $p=0.002$; Fig. 3, right).

After re-analysis of the fMRI data without the subject who tested positive for stimulants during the placebo session, the FHA×infusion interaction remained significant, both without ($p=0.009$) and with the SSRT covariate ($p<0.028$). Re-analysis of the data when covarying for group differences in perceived relaxation during infusion also did not change the significance of the FHA×infusion interaction.

Exploratory voxel-wise analyses Voxel-wise analysis ($p<0.001$, uncorrected; $k>10$ voxels) of the FHA×infusion

Fig. 1 [Inh>Go] BOLD response in the reference sample (*top*) and in family history negative (*FHN*) subjects under placebo conditions (*bottom*), with 3D rendering of activation (*right-most column*). Note lateralized effects in right frontal cortex. *Green arrows*, significant ($p_{FWE} < 0.05$) clusters of BOLD responses at height threshold $p_{uncorr} < 0.001$. *Red arrows*, clusters in FHN that correspond to (are replicated by) those of the reference group. *Left*, left in coronal slices



interaction showed right orbital-, superior-, and middle-frontal regions in which FHP were less affected by alcohol infusion (see Results Table in the ESM). This included a peak at [46, 52, and 4], which corresponds closely to the location of the a priori ROI derived from our reference sample ([40, 54, and 4]; $p_{FWE} = 0.016$, corrected for the volume that activated in the reference sample ROI; see Table 3). There were no frontal areas in which FHN had greater activation than FHP under alcohol as compared with placebo.

Table 3 Significant right frontal clusters in the reference sample

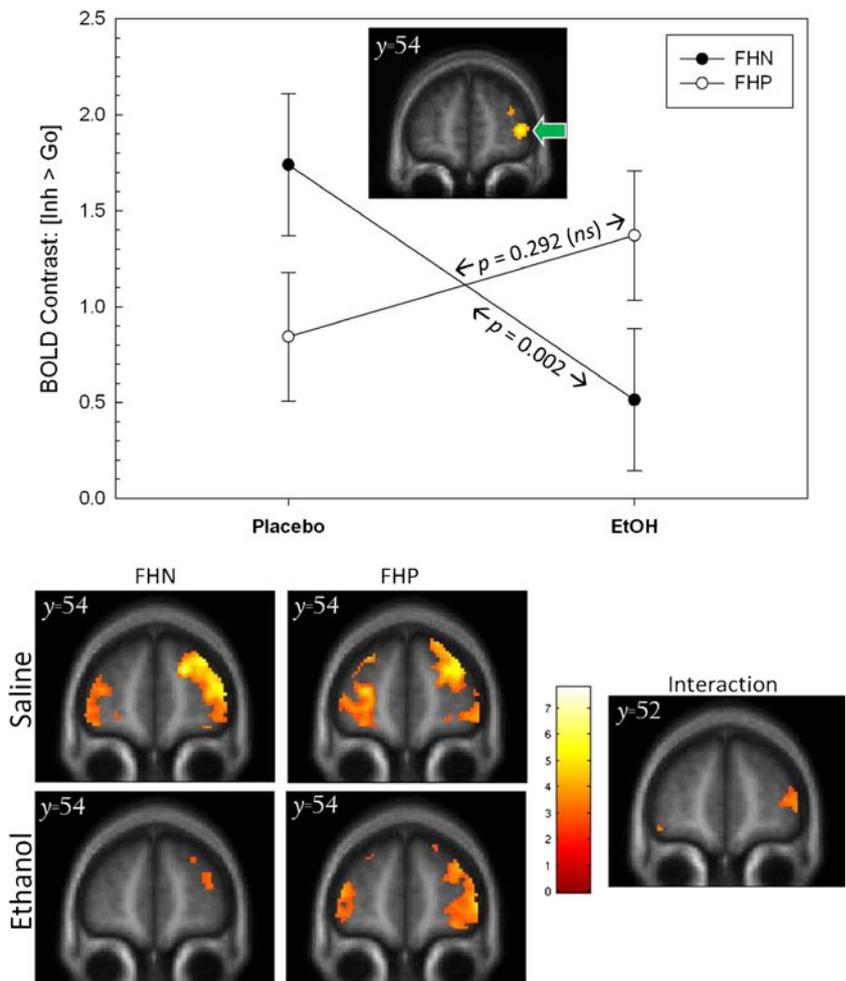
Region/cluster	MNI coordinates				
	x	y	z	Peak-Z	k
Inferior frontal gyrus ^a	54	18	14	4.61	792 ^a
Anterior, inferior frontal cortex	40	54	4	4.43	160
Superior frontal gyrus	26	14	68	4.30	143
Middle frontal gyrus	4	44	24	4.11	104
Middle frontal gyrus	44	4	34	4.05	198

MNI Montreal Neurological Institute coordinate system, *k* cluster size defined at voxel height threshold, $p < 0.001$

^a Sub-peak of a larger cluster in the right insula, extending into right inferior frontal cortex

In the ROI analyses, an unexpected three-way SSRT × FHA × infusion interaction had emerged in which the correlation between SSRT and the [Inh>Go] contrast changed as a function of both FHA and infusion. In light of this, we also conducted a voxel-wise analysis to determine if there were any frontal regions in which SSRT correlated negatively with the [Inh>Go] BOLD contrast across all subjects in each of the infusion conditions. This reflects the more intuitive hypothesis that, irrespective of group membership, a slower SSRT should be related to a smaller right frontal [Inh>Go] response. During placebo infusion, there was a right inferior frontal cluster in which SSRT negatively correlated with the [Inh>Go] contrast ($p < 0.001$, $k = 20$ voxels at (48, 40, and -2), inclusively masked for the [Inh>Go] response main effect under saline; Fig. 4, *top*). During alcohol infusion, there was also negative correlation between SSRT and the [Inh>Go] contrast in a proximal right inferior frontal cluster ($p < 0.001$; $k = 30$ voxels at (48, 50, and -4), masked inclusively for the [Inh>Go] response main effect under alcohol; Fig. 4, *bottom*). Thus, across all subjects, there was an expected negative relationship in inferior right prefrontal cortex in which less [Inh>Go] activation was related to a longer SSRT. As depicted in Fig. 4, this was particularly the case with the larger range of SSRTs that emerged under alcohol infusion.

Fig. 2 *Top*, significant ($p=0.008$) infusion \times FHA interaction in the [Inh>Go] BOLD contrast within the a priori right anterior/inferior prefrontal ROI (defined by independent reference sample, *inset/green arrow* and Fig. 1). The BOLD contrast was significantly affected by alcohol in FHN ($p=0.002$) but not FHP ($p=0.29$). *FHP* family history positive for alcoholism, *FHN* family history negative for alcoholism. *Error bars* are standard errors of the mean. *Bottom*, for reference, voxel-wise display of individual group/condition effects (*left*), as well as the infusion \times family history interaction (*right*) at its peak location ($y=54$ mm); display threshold, $p<0.005$, uncorrected. Color bar reflects *t*-statistic



Discussion

The principal finding from this experiment was a significant interaction between alcohol exposure and FHA in

right prefrontal BOLD activation during motor inhibition. Compared with FHP subjects, FHN subjects had a non-significant ($p=0.10$) trend toward greater right prefrontal activation during saline infusion. During clamped alcohol

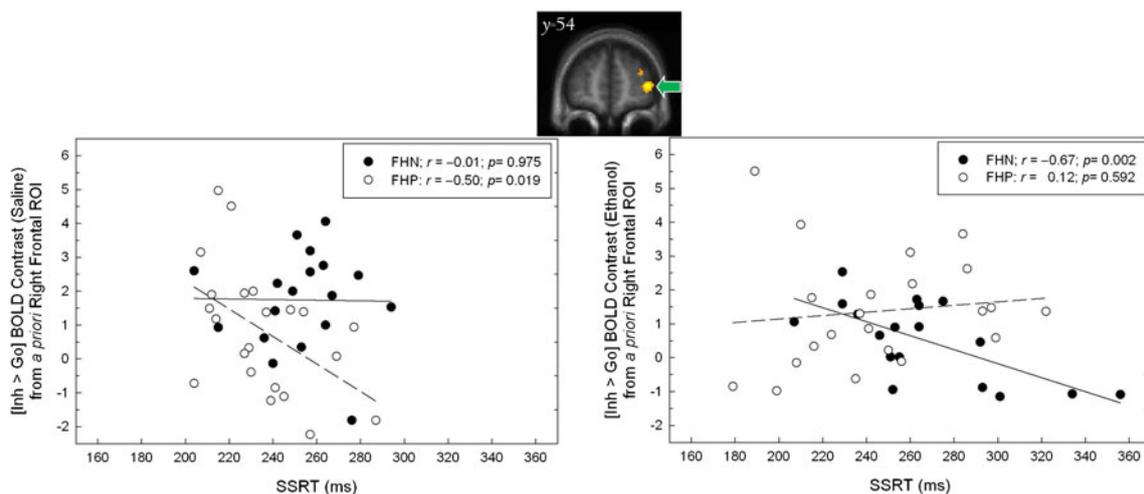
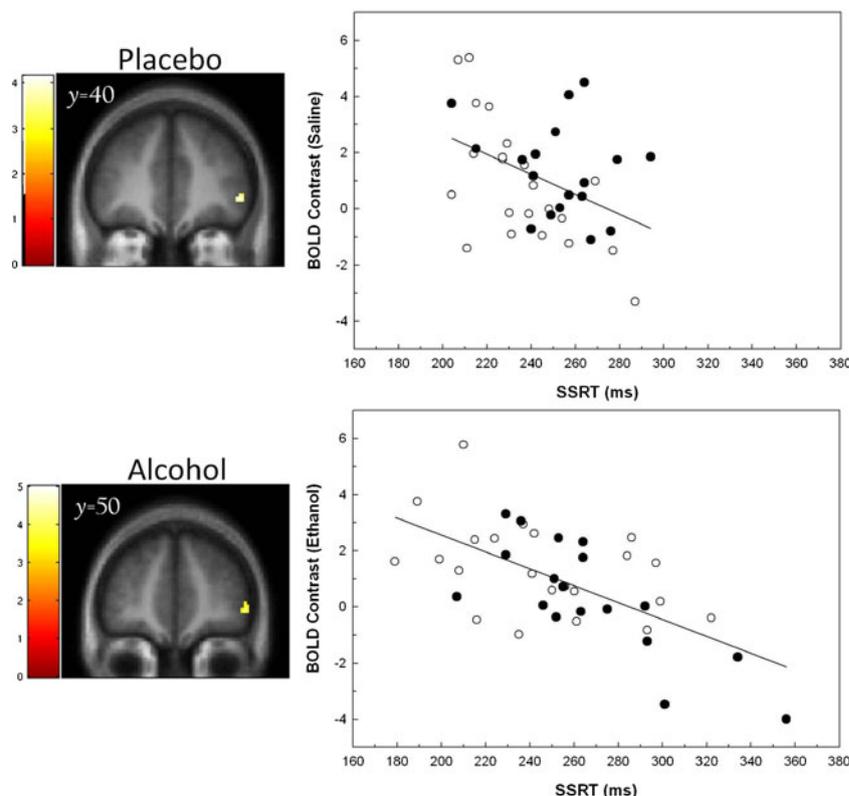


Fig. 3 Relationship between stop signal reaction time (*SSRT*) and the BOLD contrast [Inh>Go] during alcohol and placebo (saline) infusion in the right prefrontal ROI derived from the reference group (voxel

map, *top*; *green arrow*; also see Fig. 1). Separate regression lines reflect trends for FHN (*solid*) and FHP (*dashed*)

Fig. 4 *Left*, voxel-wise analyses of the relationship between SSRT and BOLD contrast [Inh>Go] during placebo (saline; *top*) and alcohol (bottom) infusion. Display threshold $p < 0.001$, $k > 10$ voxels, masked for the [Inh>Go] main effect in each of the respective infusions. *Right*, plots that illustrate the relationships between SSRT and the BOLD contrast as extracted from the clusters displayed in the voxel-wise maps at *left*. *Solid circles*, FHN; *open circles*, FHP



infusion, however, this right frontal activation in FHN was significantly reduced, while in FHP activation remained essentially unchanged. Moreover, there was a significant negative correlation between SSRT and the right prefrontal BOLD response. That is, those subjects with a smaller right prefrontal [Inh>Go] BOLD response also tended to need more time (had a longer SSRT) to successfully inhibit their behavioral responses. This negative correlation between SSRT and inferior right prefrontal activity, also reported by others (see Congdon et al. 2010), provides confidence that activity in right inferior prefrontal cortex was related to inhibitory behavior—particularly so when SSRT was lengthened by alcohol infusion.

Impulsive, externalizing behaviors are associated with FHA (Marmorstein et al. 2009). As one operational definition of impulsive behavior, SSRT does appear to be related to both FHA and drinking in some larger behavioral studies (Nigg et al. 2004; Nigg et al. 2006). Meta-analyses suggest that substance dependent patients do have a mild deficit in SSRT (Lipszyc and Schachar 2010; but also see Whelan et al. 2012 for contradictory findings). Correspondingly, frontal deficits in the BOLD response to stop signals also appear affected in substance use disorders (Whelan et al. 2012; Li et al. 2009; de Ruiter et al. 2012). Although the SST specifically targets the attempt to stop an already initiated motor impulse, others have used the Go/NoGo paradigm to study brain regions involved in behavioral inhibition as a function of FHA. Schweinsburg et al. (2004) reported that FHP

youths (as compared with FHN youth) had smaller left middle frontal gyrus responses in successful No-Go trials. Heitzeg et al. (2010) reported that only those FHP subjects with alcohol related problems had Go/No-Go activation differences when compared with either FHP or FHN without alcohol-related difficulties. In this latter study, however, FHP subjects with alcohol problems had *greater* left middle and medial frontal activation related to No-Go responses, while FHN subjects had greater Go-related activation in the ventral caudate. Jamadar et al. (2012) also found greater FHP activation (in the anterior cingulate) during correct No-Go trials when compared with FHN, although memantine (an *N*-methyl-D-aspartate glutamate receptor antagonist) reduced No-Go responses in the left cingulate and caudate regions of FHP subjects, while it did not in FHN. As far as we know, however, the data that we report here represent the first study of differences in frontal activation in the stop signal paradigm as a function of both FHA and alcohol exposure. While we found only an insignificantly smaller difference in frontal responses to correct stop signal responses in FHP subjects, which is consistent with the Go/No-Go data of Schweinsburg, et al. (2004), only FHN subjects' frontal activation was significantly reduced by alcohol.

Schuckit et al. (1980) first proposed that individuals with FHA are less sensitive to alcohol's effects. A recent meta-analysis (Quinn and Fromme 2011) suggests that this effect is not particularly different as a function of alcohol's

stimulant and sedative effects. The same meta-analysis nevertheless found that, when compared with lower drinkers, heavier drinkers are more sensitive to alcohol's stimulant effects, and less sensitive to alcohol's sedative effects. In a closely analogous study to the research presented here, Schuckit et al. (2012) used a stop signal paradigm to study nondependent college drinkers who were stratified by level of response to alcohol. In Schuckit et al.'s (2012) BOLD response comparison that most closely matches our own findings, this group found that those with a low response to alcohol had larger left superior frontal and anterior cingulate BOLD responses to difficult (as compared with easy) stop trials when challenged with oral alcohol (and in comparison to those who reported a higher level of response to alcohol). FHA was, however, not addressed in this study. Moreover, in our work BOLD responses to successful stop trials were compared with Go trials that required no inhibition, while Schuckit et al. (2012) focused on level of difficulty within successful stop trials.

While the direction of our findings was different from what we originally hypothesized, the data are generally consistent with the concept that FHP subjects are less susceptible to (in this case, the adverse cognitive) effects of alcohol exposure in a brain region that plays an important role in behavioral inhibition. This was the case even though the FHA groups were insignificantly different in recent drinking, and in their self-report of tolerance to alcohol in both early and later-life drinking experiences. Both groups were also not significantly different in their response to steady-state alcohol exposure during imaging, as reflected in ratings of perceived number of drinks, intoxication, stimulation, and enjoyment of the infusion. Rather, the dependent measure that proved most sensitive to the effects of alcohol across the FH groups was the right prefrontal response during successful behavioral inhibition.

Several imaging studies of FHA have focused on the reward system. For example, we (Kareken et al. 2010) reported that the aromas of preferred alcoholic drinks elicited a larger response in FHP (compared with FHN) heavy drinkers in a medial prefrontal cortical region implicated in coding subjective reward value. Others have also reported larger frontal and limbic responses in FHP subjects to alcohol-related stimuli (Tapert et al. 2003) and monetary rewards (Acheson et al. 2009; Villafuerte et al. 2012). Some studies, however, suggest that the ventral striatal response to monetary reward may be attenuated in FHP compared with FHN subjects (Andrews et al. 2011) or insignificantly different (Bjork et al. 2008). Thus, these data at least raise the possibility that FHP subjects may have brain systems that are sensitized to reward cues. It may, however, seem somewhat counter-intuitive that a resistance to becoming impulsive under alcohol intoxication (i.e., in FHP individuals) would constitute an endophenotypic risk for developing alcoholism. There are two considerations

that may make such a concept more intuitive. First, while laboratory measures of impulsive motor behavior such as the SST do correlate with the self-reported impulsive personality traits that are believed to contribute to alcoholism risk, the magnitude of this association is quite limited (Cyders and Coskunpinar 2011). Thus, it is certainly possible that an individual may habitually use poor judgment and make impulsive decisions while still possessing good motor inhibitory capacity. In that vein, there is no significant association between motor inhibition and impulsive reward choice (i.e., delay discounting; Broos et al. 2012). Having said this, a resistance to the cognitively impairing effects of intoxication may carry its own risks, as subjects may perceive a reduced vulnerability to alcohol's punishing consequences—or in this case the adverse effects in brain systems regulating behavioral control. Thus, the combination of an increased sensitivity to reward and a tolerance to alcohol's cognitively impairing effects could represent a mechanism of increased risk of progression to heavier drinking, in particular by creating expectancies in drinkers that they can increase their consumption without adverse consequences to their behavior (Vogel-Sprott and Sdao-Jarvie 1989).

Several considerations in interpreting the findings of this study deserve attention. First, the contrast that we studied was that of successful inhibition compared with Go trials in the absence of any inhibitory demand. This is a widely studied contrast that reliably produces right inferior frontal activation in this study and elsewhere (Aron and Poldrack 2006; Aron et al. 2007; Xue et al. 2008). Right inferior frontal activation from this contrast also correlates with SSRT (Congdon et al. 2010). However, some note that this BOLD contrast may instead more accurately model a right frontal attentional system involved in processing stop signals, rather than successful motor inhibition, per se (e.g., Zhang and Li 2012). Thus, there is the possibility that our data speak more to an attentional network that monitors inhibitory signals, rather than a network that directly controls motor inhibition (and, we do note that we did not find significant FHA effects when examining successful stopping compared with the baseline of failed Inh). There was also an unexpected difference between FHP and FHN subjects in SSRT that, while small in absolute magnitude, was significant and in the opposite direction (FHN > FHP) than expected (Nigg et al. 2004). Whether this difference is truly representative likely requires a larger sample for analysis. Moreover, although there was a clear effect of infusion on the SSRT response, there was no FHA × infusion interaction on SSRT to mirror the same interaction in right frontal BOLD response. Although SSRT did correlate negatively with the BOLD response in this region, it may be the case that the sample size was not large enough to detect this behavioral interaction. It is similarly unclear why there was a negative correlation between SSRT and right

prefrontal BOLD responses in the FHP under placebo but not under alcohol. Normally, a negative correlation would be expected, with a lower frontal response relating to a longer time to inhibit behavior. It can be challenging to find correlations between physiology and behavior in smaller samples (Congdon et al. 2010), and it was the case that, with voxel-wise exploration, there were similar right frontal regions in which the BOLD response negatively correlated with SSRT across both samples, and in both alcohol and placebo conditions. Thus, regional sampling error and statistical power may be considerations here. Gender effects may also be present, although the current sample size does not permit examining interactions with gender. Finally, BOLD responses can be decoupled from neuronal activity when using a vasoactive drug that significantly changes cerebral blood flow. We doubt that this played a large role in our data, as alcohol did not significantly affect rCBF in either the whole brain or in right prefrontal cortex, where FHA interacted with infusion on the BOLD response.

Conclusions

The data from this study suggest that FHA interacts with alcohol exposure in brain regions important to behavioral inhibition. In particular, the findings suggest that heavier drinking FHP subjects have right prefrontal regions that are less affected by alcohol exposure than FHN subjects who drink equivalently. The findings reinforce the concept that FHA may involve an inherent insensitivity to the adverse effects of alcohol, including in brain systems that mediate inhibitory behavior. From a clinical point of view, this reduced sensitivity could increase alcoholism risk by creating the subjective impression of an invulnerability to alcohol's adverse cognitive consequences while drinking.

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