

Neural Correlates of Impulsivity in Healthy Males and Females with Family Histories of Alcoholism

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Individuals family-history positive (FHP) for alcoholism have increased risk for the disorder, which may be mediated by intermediate behavioral traits such as impulsivity. Given the sex differences in the risk for and clinical presentation of addictive disorders, risk for addiction may be differentially mediated by impulsivity within FHP males and females. FHP ($N=28$) and family-history negative (FHN, $N=31$) healthy, non-substance-abusing adults completed an fMRI Go/No-Go task and were assessed on impulsivity and alcohol use. Effects of family history and sex were investigated as were associations between neural correlates of impulse control and out-of-scanner measures of impulsivity and alcohol use. FHP individuals showed greater activation in the left anterior insula and inferior frontal gyrus during successful inhibitions, an effect that was driven primarily by FHP males. Higher self-reported impulsivity and behavioral discounting impulsivity, but not alcohol use measures, were associated with greater BOLD signal in the region that differentiated the FHP and FHN groups. Impulsivity factors were associated with alcohol use measures across the FHP and FHN groups. These findings are consistent with increased risk for addiction among FHP individuals being conferred through disrupted function within neural systems important for impulse control.

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INTRODUCTION

Alcohol use disorders (AUDs) are prevalent and associated with detrimental health and societal outcomes (Li, 2008). Individuals with a family history of alcoholism (family-history positive (FHP)) have increased risk for alcoholism driven by genetic and environmental factors (Lieb *et al*, 2002; Slutske *et al*, 2002). Healthy FHPs model addiction vulnerability without confounding effects of excess alcohol on cognition and brain function.

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Increased AUD risk among FHPs may be conferred via heritable impulsive tendencies (Dick *et al*, 2010; Tessner and Hill, 2010). Impulsivity is a multi-factorial construct, where distinct sub-components appear to have differential neural bases and relationships with addiction (de Wit, 2009; Lejuez *et al*, 2010; Rogers *et al*, 2010). Aspects of impulsivity may both predispose to and be exacerbated by addictive behaviors. Impulsivity predicts development of AUDs; is higher in FHPs with more alcohol-dependent relatives (ie higher family-history load); and partially mediates the relationship between FHP and alcohol and substance use disorder (for review, see de Wit, 2009; Dick *et al*, 2010; Lejuez *et al*, 2010; Verdejo-Garcia *et al*, 2008). Other less well-studied impulsivity-related constructs (eg, sensation-seeking, risk-taking, compulsivity, behavioural activation/inhibition, reward/punishment sensitivity) have been related to addiction vulnerability, and addictions therefore warrant consideration (eg, Meda *et al*, 2009).

Sex differences are important to consider as they are observable for rates, clinical presentation, and health consequences of addiction (Becker and Hu, 2008) and for alcoholism-vulnerability factors, including impulsivity components (Cross *et al*, 2011). Although males and females demonstrate heritable alcoholism risk, they may differ on

risk-transmission mechanisms (McGue *et al*, 2001; Pickens *et al*, 1991; Prescott *et al*, 1999).

Neuroimaging Go/No-Go studies have identified functional abnormalities consistent with increases in aspects of impulsivity (eg poor response inhibition) in FHPs. Healthy FHP youths display greater activity than individuals without a family history of AUDs (family-history negative (FHN)) in the middle frontal gyrus during Go/No-Go successful inhibitions (Schweinsburg *et al*, 2004). FHPs with and without AUDs and individuals without personal or family histories of AUDs were compared during fMRI Go/No-Go performance (Heitzeg *et al*, 2010). FHPs deactivated ventral caudate less than FHNs during successful inhibitions and deactivation correlated with fewer externalizing behaviors (Heitzeg *et al*, 2010). FHPs with AUDs deactivated orbitofrontal and medial prefrontal regions less than those without AUDs (with or without a family history), and activation correlated with alcohol use (Heitzeg *et al*, 2010).

In this study, we compare healthy FHP and FHN males and females on fMRI Go/No-Go, self-reported alcohol use, and extensive out-of-scanner impulsivity-related measures. Go/No-Go is a well-established measure of prepotent response inhibition, yet likely also engages cognitive processes, such as sustained attention and set maintenance (Stevens *et al*, 2007). The neural circuitry of this task has been well-characterized in healthy individuals (Stevens *et al*, 2007). Pre-specified regions-of-interest (bilateral junction of the anterior insula and inferior frontal gyrus (insula/IFG), thalamus, and left ventral caudate) were chosen for relevance to impulsivity and addiction and Go/No-Go task activation (Heitzeg *et al*, 2010; Stevens *et al*, 2007). The insula/IFG is integral to response inhibition (Garavan *et al*, 1999; Rubia *et al*, 2001; Stevens *et al*, 2007). The insula has been proposed to be relevant to addiction, given its role in interoception and integration of information from regions important for cognitive-control and affective processes (Naqvi and Bechara, 2010; Paulus, 2007). The thalamus receives input from the striatum through direct and indirect pathways, which respectively serve to disinhibit and inhibit thalamic output to the cortex, which, in turn, provides positive feedback to the striatum. Thalamic nuclei actively influence dynamics of information processing and transfer and may modify cortical activity (Haber and McFarland, 2001). The ventral striatum has long been a candidate structure for addiction vulnerability given its central role in salience-processing, reward-learning, acute response to illicit drugs and alcohol, and demonstrated abnormalities in addicted populations (Koob and Volkow, 2010). The left ventral striatum also contributes to Go/No-Go performance in a manner sensitive to FHP (Heitzeg *et al*, 2010), consistent with findings suggesting a role for the left ventral striatum in hyperactive behaviors (Martinaud *et al*, 2009).

To account for impulsivity's multi-factorial nature and the relevance of related constructs to addiction vulnerability, extensive out-of-scanner measures assessing impulsivity and related constructs (reward and punishment sensitivity, attention, compulsivity, risk-taking, sensation-seeking) were consolidated into five factors, based on a previously published factor analysis (Meda *et al*, 2009). Measures of age of drinking onset and past-month alcohol consumption were explored in relation to regional FHP-related differences in BOLD signal and impulsivity-related

factors. Age of drinking onset has been associated with likelihood of later alcohol dependence and its heritability is partially mediated by impulsivity and differs by sex (McGue *et al*, 2001). We hypothesized that FHPs relative to FHNs would display enhanced bilateral insula/IFG and thalamus activation, consistent with diminished inhibitory-control efficiency, and diminished ventral-striatal deactivation during Successful Inhibitions, consistent with recent findings in FHP individuals (Heitzeg *et al*, 2010). We hypothesized these patterns would be more robust in FHP males than females. Regarding secondary aims, we hypothesized that insula/IFG activity would correlate with out-of-scanner impulsivity-related measures, ventral-striatal activity would correlate with both impulsivity-related and alcohol-use measures, and alcohol-use measures would be associated with impulsivity-related measures in both the family-history groups and sexes to different degrees.

PARTICIPANTS AND METHODS

Participants

Healthy FHP and FHN adults were recruited via advertisements and word-of-mouth at the Olin Neuropsychiatry Research Center, Hartford, CT. Participants provided written informed consent in accordance with the Institutional Review Boards of Hartford Hospital and Yale University. Demographic data are in Table 1.

Criteria for FHP included a father and at least one additional first- or second-degree biological relative with current or previous alcoholism according to the Family History Assessment Module. Individuals with a maternal history of alcoholism were excluded to minimize potential confounds of fetal alcohol exposure. FHN participants reported no first- or second-degree relatives with current or previous alcoholism from a family size of at least three first-degree relatives. Exclusion criteria for FHP and FHN groups included lifetime alcohol abuse or dependence, other substance use disorders (except nicotine dependence), and DSM IV-TR Axis 1 psychiatric disorders, as assessed by the Structured Clinical Interview for DSM-IV (SCID-I/NP; First *et al*, 2007), urine screens indicating pregnancy or recent drug use, or ethanol-positive breathalyzer results.

A 'family-history load' metric weighted AUD relatives according to the estimated shared genetic material (eg, first-degree 0.5, second-degree 0.25) and summed weighted scores for all AUD relatives (Stoltenberg *et al*, 1998) (Table 1).

Timeline follow-back assessed the total number of standard drinks in the past 30 days (henceforth 'past-month drinks'). Age of onset of regular (monthly) alcohol use (henceforth 'drinking-onset age') (Table 1), nicotine-dependence, and lifetime marijuana, cocaine, heroin, and amphetamine use were assessed (Supplementary Table S3). NIAAA Task Force on Recommended Alcohol Questions (October 15–16, 2003) (ie frequency of past-year drinking episodes; number of drinks on a typical drinking day; number of binge-drinking episodes) data are presented in Supplementary Table S1.

Table 1 Demographics, Alcohol Use and In-Scanner Behavior

Background	FHP			FHN		
	Total	M	F	Total	M	F
N	28	11	17	31	13	18
Age (mean (SD))	29.75 (11.49)	26.18 (6.40)	32.06 (13.52)	33.32 (13.49)	31.15 (13.90)	34.89 (13.35)
<i>Race and ethnicity (N (%))</i>						
Caucasian	25 (89)	10	15 (88)	28 (90)	10 (77)	18 (100)
African American	3 (11)	1 (9)	2 (12)	1 (3)	1 (8)	0
Asian American	0 (0)	0 (0)	0 (0)	2 (7)	2 (15)	0
Hispanic Ethnicity	4 (14)	1 (9)	3 (18)	0 (0)	0 (0)	0 (0)
<i>Alcohol measures (mean (SD))</i>						
Family-history load	0.98 (0.42)	0.89 (0.13)	1.04 (0.53)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Past-month drinks ^a	11.14 (14.59)	12.82 (14.03)	10.06 (15.26)	15.44 (17.88)	24.36 (20.31)	9.31 (13.45)
Drinking-onset age	19.17 (2.08)	18.55 (2.82)	19.69 (1.70)	19.81 (3.19)	19.10 (2.77)	20.25 (3.44)
<i>In-scanner: fMRI Go/No-Go task (mean (SD))</i>						
Correct 'go' RT	381.12 (54.57)	371.88 (41.67)	387.48 (62.43)	386.72 (37.30)	385.47 (31.16)	387.62 (42.05)
False alarm RT	336.49 (34.97)	339.32 (34.88)	334.54 (36.03)	342.33 (26.05)	346.88 (31.33)	339.05 (21.85)
Correct hits	0.97 (0.07)	0.95 (0.11)	0.99 (0.01)	0.99 (0.01)	0.99 (0.02)	1.00 (0.01)
False alarms	0.40 (0.20)	0.40 (0.18)	0.39 (0.21)	0.32 (0.12)	0.37 (0.10)	0.28 (0.12)
Signal detection (d')	0.57 (0.22)	0.54 (0.24)	0.60 (0.21)	0.68 (0.12)	0.62 (0.10)	0.72 (0.12)

FHP = family history of alcoholism; FHN = no family history of alcoholism.

Data are presented as means (SD) or N (%). Reaction times (RTs) are reported in milliseconds. Correct hits and false alarms are reported as proportion of total 'go' and 'no-go' trials, respectively. Signal detection (d') is calculated as the difference between proportion correct hits and proportion of false alarms. For other substance use measures, see Supplementary Table S3.

^aIndicates a statistically significant (uncorrected $p < 0.05$) sex difference overall, due to males reporting more past-month drinks than females regardless of family-history status. No other significant effects of family history, sex or family history-by-sex interactions were observed.

Out-of-scanner Assessments of Impulsivity and Related Constructs

Five impulsivity-related factors were calculated from the primary outcome measures of self-report scales and computerized risk/reward decision-making tasks; Factor 1: 'Self-reported Behavioral Activation', Factor 2: 'Self-reported Impulsivity', Factor 3: 'Self-reported Compulsivity and Reward/Punishment Sensitivity', Factor 4: 'Behavioral Temporal Discounting' and Factor 5: 'Behavioral Risk-Taking' (Table 2, Supplementary Table S4). Methods for calculating factor scores were based on a large principal component analysis conducted previously in a healthy sample (Meda *et al*, 2009). All participants were asked to complete five self-report scales (Barratt Impulsivity Scale Version 11 (BIS-11), Behavioral Inhibition System/Behavioral Activation System (BIS/BAS), Padua Inventory, Zuckerman Sensation-Seeking Scale Version 5 (SSS-V), Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ)) and two computerized risk/reward decision-making tasks (Balloon Analogue Risk Task (BART), Experiential Discounting Task (EDT)). Thirteen primary outcome measures were derived from these self-report and behavioral measures (Table 2, Supplementary Table S4). Primary outcome measures for each individual were converted to z-scores then multiplied by the factor weights from the study by Meda *et al* (2009) 'healthy-subject-only' principal component analysis to calculate five summary

impulsivity factors for each individual (see Table 2, Supplementary Tables S4, S5 for complete factor analytic methods). All primary outcome measures contributed to each factor (Supplementary Table S5), but factor labeling and identification was based on outcome measures with factor weightings of ≥ 0.5 (Table 2, Supplementary Table S5). When data were missing, the factor it primarily contributed to (weighting ≥ 0.5) was not calculated for that subject but the remaining four factors (to which the missing component measure contributed less significantly) were calculated for that subject using the group mean for the outcome measure in place of that individual's score (Supplementary Tables S4, S5).

ANOVAs with family-history status and sex were conducted for the demographic and alcohol-use measures (Table 1) and out-of-scanner impulsivity-related factors (Table 2, Supplementary Table S4). Chi-square tests compared sex distribution across groups. Where necessary, data were transformed to meet parametric assumptions or Mann-Whitney *U* tests were utilized.

Imaging Protocol

Participants were scanned at the Olin Neuropsychiatric Research Center with a 3-Tesla head-only MRI scanner (Allegra; Siemens, Erlangen, Germany) equipped with 40-mT/m gradients and a standard quadrature head-coil. Functional imaging data were acquired using an echoplanar

Table 2 Out-of-Scanner Impulsivity Factors

Out-of-scanner behavioral and self-report measures of impulsivity and related constructs		
Factor labels and description	Instrument: measure	Factor weight
F1. 'Self-reported behavioral activation' Measures of fun-seeking, reward-responsiveness and drive which make up the 'behavioral activation scale' within BIS/BAS.	BIS/BAS: BAS Fun Subscale	0.85
	BIS/BAS: BAS Reward Subscale	0.79
	BIS/BAS: BAS Drive Subscale	0.72
F2. 'Self-reported impulsivity' All three impulsivity factors from Barratt Impulsivity Scale (BIS-I I), including tendency to act without pre-planning, inability to withhold pre-potent motor responses and poor sustained attention, as well as the total score from Zuckerman's Sensation-Seeking Scale (SSS-V).	BIS-II: Non-planning Impulsivity Subscale	0.85
	BIS-II: Attentional Impulsivity Subscale	0.78
	BIS-II: Motor Impulsivity Subscale	0.55
	SSS-V: Total Score	0.50
F3. 'Self-reported compulsivity and reward/punishment sensitivity' Measures of sensitivity to punishment and reward (SPSRQ) as well as a scale of compulsive thoughts, worries and behaviors (Padua Inventory).	SPSRQ: Punishment Summary Score	0.82
	PI: Total Score	0.73
	SPSRQ: Reward Summary Score	0.50
F4. 'Behavioral temporal discounting' A computerized behavioral measure of 'impulsive choice' or the tendency to prefer a smaller immediate over a larger delayed reward (EDT), and a self-report measure of 'behavioral inhibition' (BIS/BAS).	EDT: Total Area Under the Curve	0.81
	BIS/BAS: BIS Subscale	0.52
F5. 'Behavioral risk-taking' A computerized behavioral measure of 'risky' decision-making (BART) where more pumps may result in greater payout or may result in a 'bust' where no money is paid.	BART: Adjusted Average Pumps Per Trial	0.87

BIS/BAS: Behavioral Inhibition System/Behavioral Activation System; BIS-I I: Barratt Impulsivity Scale (Version I I); SSS-V: Zuckerman Sensation-Seeking Scale (Version 5); SPSRQ: Sensitivity to Punishment and Sensitivity to Reward Questionnaire; PI: Padua Inventory; EDT: Experiential Discounting Task; BART: Balloon Analogue Risk Task.

Out-of-scanner neuropsychological task and self-report questionnaire measures of interest are paired with the impulsivity-related factor for which they had a factor weighting of ≥ 0.5 , the cutoff used by Meda *et al* (2009) to identify the factors, although all measures contributed to some degree to all the five factors. Missing component measure data prevented calculation of F2 for one participant, F4 for six participants and F5 for one participant. For complete description of factors, component measures, and treatment of missing data, see Supplementary Materials and Meda *et al* (2009). Due to the contribution of EDT 'Area Under the Curve' to the calculation of F4, where a smaller area under the curve indicates more impulsive choice, smaller F4 scores also indicate more impulsivity, in contrast to the directionality of the other impulsivity-related factors. No effects of family history, sex or family history-by-sex interactions on factor scores survived corrections for multiple comparisons.

sequence with the following imaging parameters: TR = 1500 ms, TE = 27 ms, FOV = 22 cm, flip angle = 70°, acquisition matrix = 64 × 64, voxel size = 3.44 × 3.44, slice thickness = 5 mm, number of slices = 29, ascending acquisition. Six scans performed at the beginning of each session were discarded before analysis to achieve longitudinal equilibrium. Padded cushions minimized participant movement.

fMRI Task

Following 10 out-of-scanner practice trials, participants completed two runs of an fMRI Go/No-Go task (Jamadar *et al*, 2012; Stevens *et al*, 2007). Runs each consisted of 246 trials, lasted 7 min 21 s and were separated by an approximately 1-min break. Participants were asked to press a button for Go ('X', 85% of trials) and withhold responding to No-Go ('K', 15% of trials) stimuli. Instructors emphasized the importance of response speed and accuracy before task onset and between runs. Stimuli were presented randomly except 'K's were never presented consecutively. The inter-stimulus interval varied randomly between 650, 1650, and 2650 ms. Stimuli were displayed on an LCD, which projected to a screen seen by participants via a mirror attached to the MRI headcoil. The screen subtended approximately a 25-degree field-of-view.

In-scanner behavioral performance was assessed with 'Correct Hit' and 'False Alarm' mean reaction time (RT) and

signal detection index ($d' = (\text{correct hits}/\text{total 'Go' trials}) - (\text{false alarms}/\text{total 'No-Go' trials})$) (Table 1).

fMRI Analysis

Functional images were reconstructed offline and analyzed with SPM5 (Wellcome Department of Imaging Neuroscience, London, UK). Runs were separately realigned then used to create one mean functional image per run, which was spatially normalized to Montreal Neurological Institute and smoothed with a 9 mm FWHM Gaussian kernel. Where excessive motion (> 4 mm) was indicated, an artefact repair toolbox for SPM5 (ArtRepair;<http://cibsr.stanford.edu/tools/ArtRepair/ArtRepair.htm>) was employed (2 FHP, 2 FHN).

At first-level analysis, a canonical hemodynamic response with its temporal derivative was fitted to the onset of three events: 'Correct Hits' to 'Go' stimuli, 'False Alarms' (ie responses to 'No-Go' stimuli), and 'Successful Inhibitions' of responses to 'No-Go' stimuli. The remaining data not modelled into the events of interest comprised the implicit baseline. High frequency of 'Go' stimuli resulted in a saturated estimated response function for this trial type; therefore, 'Correct Hit' trials were not included in the contrasts. The contrasts of interest were Successful Inhibitions (successful inhibitions > baseline) and False Alarms (false alarms > baseline).

For second-level analysis, a general linear model was constructed using family history (FHP, FHN) and sex (M, F) as between-subject factors for each contrast. Whole-brain analyses were first thresholded at $p_{\text{uncorrected}} < 0.001$, $k = 0$. Region-of-interest analyses examining the effects of family history, sex, and family history-by-sex were carried out in SPM5 and thresholded with a small volume correction to family-wise error (FWE) corrected $p_{\text{FWE}} < 0.01$. This threshold uses Bonferroni-correction to conservatively adjust the standard $p_{\text{FWE}} < 0.05$ to account for the use of five regions-of-interest.

The five *a priori* regions-of-interest were defined with spheres (10 mm radii) at right insula/IFG (33, 21, 0), left insula/IFG (−36, 18, 0), right thalamus (9, −12, 9), left thalamus (−12, −15, 9), and left ventral striatum (−12, 24, −6) (Supplementary Figure S1). The location of the left ventral striatum region-of-interest was based on the reported peak FHP vs FHN group difference in an fMRI Go/No-Go study (Heitzeg *et al*, 2010). Other regions-of-interest locations were based on peaks reported for this Go/No-Go fMRI task in an independent sample of healthy subjects (Stevens *et al*, 2007).

Correlation Analyses

Average regional brain activity was extracted from clusters showing significant ($p_{\text{FWE}} < 0.01$) family-history group differences or family history-by-sex interactions (Table 3). Data representing the activation (in arbitrary units) of the cluster of voxels to contrasts of interest (successful inhibitions or false alarms relative to baseline) were extracted as mean cluster eigenvalues using the 'extract eigenvalues' function in SPM5. Eigenvalues were entered into SPSS 18.0 for correlations and presentation (Figures 1 and 2). Pearson's product-moment correlations evaluated associations between mean eigenvalues, impulsivity-related factors, in-scanner signal detection (*d'*), drinking-onset age, and past-month drinks. The threshold for

correlations was Bonferroni-corrected to $P \leq 0.006$ to account for the eight variables tested against each region-of-interest.

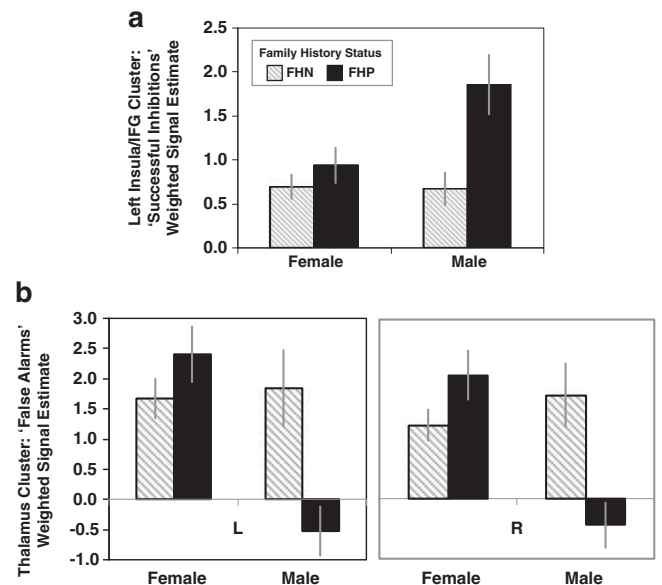


Figure 1 Effects of family history of alcoholism and sex on fMRI Go/No-Go. Bars represent the mean \pm SEM of the mean eigenvalues (presented in arbitrary units) extracted from each cluster, which reached significance ($p_{\text{FWE}} < 0.01$) within the regions of interest (Table 3). FHP = positive for family history of alcoholism; FHN = negative for family history of alcoholism; L = left; R = right; IFG = inferior frontal gyrus. (a) Hyperactivation in FHP vs FHN during successful no-go trials. The greater activity in the left insula/IFG activity during 'Successful Inhibition' trials in individuals with a family history of alcoholism (FHP) compared with those without (FHN) was primarily driven by enhanced activation in the FHP Males. (b) Family history-by-sex interaction during 'False Alarm' trials. Despite no significant main effects of family-history status or sex, the family history-by-sex interaction appeared primarily driven by diminished activity in the right and left thalamic regions in the FHP males relative to other subgroups on No-Go trials where a faulty response was made (ie 'false alarm' trials).

Table 3 fMRI Go/No-Go Group Differences

ROI	k	t	p_{FWE}	Peak voxel coordinates x, y, z		
				x	y	z
<i>Successful inhibition contrast</i>						
Main effect of family history of alcoholism (FHP > FHN)						
L insula/IFG	16	4.16	0.003	−42	15	3
R insula/IFG	2	3.53	0.015 ^a	33	12	3
Main effect of sex (Male > Female)						
L insula/IFG	2	3.52	0.015 ^a	−42	21	6
<i>False alarm contrast</i>						
Family history-by-sex interaction						
L thalamus	7	3.84	0.006	−9	−6	12
R thalamus	29	4.04	0.004	15	−15	15

Threshold of $p_{\text{FWE}} < 0.01$ Bonferroni-corrects for use of five ROIs (left IFG/insula, R IFG/insula, L thalamus, R thalamus, ventral caudate).

ROI = region of interest; k = cluster size in voxels; x, y, z = MNI coordinates of peak voxel; L = left; R = right; IFG = inferior frontal gyrus; FHP = family history of alcoholism; FHN = no family history of alcoholism.

^aIndicates clusters with trend significance, meaning they survived family-wise error correction but did not survive the Bonferroni-corrected threshold used to account for the use of multiple ROIs.

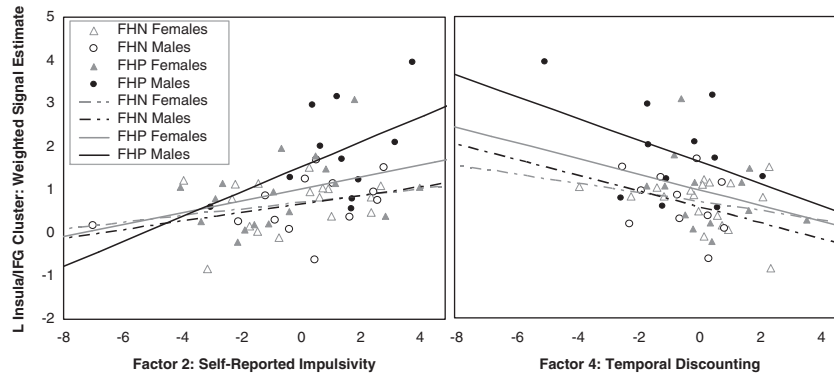


Figure 2 Left insula/IFG fMRI activity associated with greater impulsivity. Left insula/IFG activity during ‘Successful Inhibitions’ is associated with greater impulsivity on Factor 2 Self-Reported Impulsivity and Factor 4 Temporal Discounting. fMRI activity represents the mean eigenvalue (presented in arbitrary units) extracted from the cluster within the left insula/IFG region of interest, which was significantly more activated during Successful Inhibitions in the FHP relative to FHN group (Table 3, Figure 1). Larger Factor 2 scores are primarily driven by higher BIS-11 scores, while smaller Factor 4 scores are primarily driven by smaller area under the curve on a delay discounting task, both of which indicate greater impulsivity. Although the association is strong in the sample overall (Factor 2: $r_{58} = 0.41$, $p = 0.001$; Factor 4: $r_{53} = -0.37$, $p = 0.006$) in both cases, the association is strongest in FHP Males (solid black line, filled circles), less robust in FHP Females (solid grey line, filled triangles), and weakest in FHN males (dotted black line, empty circles) and females (dotted grey line, empty triangles).

To assess whether the relationships between impulsivity-related and alcohol measures were influenced by family history or sex, correlations between impulsivity-related and alcohol variables were investigated within family history and sex groups. The relative strengths of the correlations were compared across subgroups using Fisher’s *Z*-transformation.

RESULTS

Demographics, Alcohol Use, Impulsivity-Related Factors and In-Scanner Behavior

Family-history groups did not differ in sex distribution ($X^2 = .04$, $p = 0.84$) and FHP males and females did not differ in family-history loading (Mann-Whitney *U* Test, $p = 0.50$). There were no significant effects of family history, sex, or family history-by-sex on age, drinking-onset age, or in-scanner reaction time for correct ‘Go’ or incorrect ‘No-Go’ (ie ‘False Alarm’) trials. There were no significant effects of family history or family history-by-sex on past-month drinks. A sex effect reflected women drinking less than men ($F = 5.52$, $p = 0.02$) (Table 1). Effects of family history and sex on out-of-scanner impulsivity-related factors did not survive corrections for multiple comparisons (Table 2, Supplementary Table S4).

fMRI Results

Effects of task were consistent with previous publications with this task (Stevens *et al*, 2007) with ‘Successful Inhibitions’ and ‘False Alarm’ contrasts engaging frontal, parietal, striatal, and thalamic regions (Supplementary Figure S2, Supplementary Table S2).

fMRI Group Differences

During ‘Successful Inhibitions’, FHPs demonstrated hyperactivity relative to FHNs in the left insula/IFG. Trends towards effects of family history in the right insula/IFG (FHP > FHN) and sex in the left insula/IFG (males >

females) did not survive Bonferroni’s correction for multiple regions-of-interest (Table 3, Figure 1).

During ‘False Alarms’, despite no significant or trend main effects of family history or sex, there were significant family history-by-sex interactions in the right and left thalamus. To investigate interactions, mean eigenvalues extracted from significant clusters were compared. Bilaterally, significant family history-by-sex interactions were driven by sex differences in FHPs (Right: $t = 4.18$, $p < 0.001$; Left: $t = 4.41$, $p < 0.001$) but not FHNs (Right: $t = -0.92$, $p = 0.36$; Left: $t = -0.26$, $p = 0.79$), and family-history differences within males (Right: $t = 3.24$, $p = 0.004$; Left: $t = 3.03$, $p = 0.006$) but not females (Right: $t = -1.69$, $p = 0.101$; Left: $t = -1.32$, $p = 0.198$) (Table 3, Figure 1). No other family history, sex, or family history-by-sex effects for ‘Successful Inhibition’ or ‘False Alarm’ contrasts survived corrections for multiple comparisons.

Associations between fMRI, Impulsivity-Related and Alcohol Measures

The fMRI signal eigenvalues extracted from the left insula/IFG cluster significantly correlated with higher Self-Reported Impulsivity (F2) ($r_{58} = 0.41$, $p = 0.001$) and Temporal Discounting (F4) ($r_{53} = -0.37$, $p = 0.006$; Figure 2). The strength of these correlations between fMRI signal and impulsivity factors did not significantly differ by family history or sex. No other correlations between fMRI cluster activity and impulsivity factors or drinking measures approached statistical significance.

‘Past-month drinks’ was associated with Temporal Discounting (Factor 4) ($r_{42} = -0.42$, $p = 0.006$), and the strength of the association did not significantly differ by family history or sex.

DISCUSSION

We examined impulsivity, alcohol use measures, and fMRI Go/No-Go BOLD activation patterns in pre-selected

regions-of-interest in healthy individuals with and without a family history of alcoholism but no personal histories of alcohol/substance use disorders. Main effects of task were consistent with previous publications (Stevens *et al*, 2007). While successfully inhibiting responses on 'No-Go' trials, FHPs activated the left insula/IFG region more robustly than FHNs, and this effect was more pronounced in FHP males than females. While failing to inhibit responses, family history-by-sex interactions in the bilateral thalamus reflected similar levels of thalamic activation in FHN males and females but exaggerated activation in FHP females and deactivation in FHP males. Activity in the left insula/IFG cluster correlated with aspects of impulsivity, which, in turn, were associated with alcohol use measures.

Our hypotheses that FHPs would show neuroimaging results consistent with diminished efficiency relative to FHNs in neural systems important for aspects of impulse control, and that this effect would be more pronounced in FHP males than females, was supported by the finding of increased left insula/IFG activity during successful inhibition in the FHP group, primarily driven by FHP males, and the association between greater activity in this cluster with higher out-of-scanner impulsivity scores. Hypothesized main effects of family history were not observed in other regions-of-interest.

Sex Differences in Effects of Family History

Historically, the possibility of sex differences in vulnerability mechanisms for addictions has been underemphasized; previous, similar studies have mostly not addressed this, perhaps, in part, because of sample size limitations. Family history appeared to influence the neural correlates of response inhibition more in males. As FHP females and males were well matched for family-history loading and other demographic factors, these findings may be consistent with FHP females requiring greater family-history loading to confer similar degrees of risk as males. Alternatively, if sexes differ in risk-transmission mechanisms, FHP females may demonstrate equally or more substantially disrupted function than males in neural circuitry engaged by different cognitive processes than those tapped by Go/No-Go.

Females reported fewer past-month drinks. However, the lack of associations between alcohol and fMRI measures in this sample suggests sex differences in alcohol use were unlikely to account for fMRI sex differences in FHPs.

Anterior Insula/IFG and Impulsivity-related Constructs

Neuroimaging, stimulation, and lesion studies implicate the anterior insula/IFG in response inhibition with support for a right-dominated network (eg, Aron *et al*, 2003; Garavan *et al*, 1999), which also engages the left insula/IFG to a lesser degree (eg, Rubia *et al*, 2001; Stevens *et al*, 2007). Go/No-Go activates a bilateral, yet still right-dominated, network compared with more right lateralized response inhibition tasks (ie the Stop-Signal task) (Rubia *et al*, 2001; Swick *et al*, 2008). Adolescents (Stevens *et al*, 2007) and elderly (Nielson *et al*, 2002) activate a more diffuse network during successful inhibition, including greater recruitment of the left prefrontal cortex, compared with young and middle-aged adults. This may suggest that normally right-domi-

nated tasks recruit greater engagement of left-sided networks when necessary to compensate for a less efficient right insula/IFG. Given the trend towards greater right insula/IFG in the FHP group, the significantly increased engagement of the left insula/IFG in the FHP relative to the FHN group may reflect recruitment of a more diffuse bilateral network in compensation for right insula/IFG inefficiency (Table 3).

The insula is implicated in impulsivity-related constructs, including, but not limited to, choice impulsivity (Tanaka *et al*, 2004) and risk and uncertainty assessment (Clark *et al*, 2008). These constructs, along with response inhibition, may require integration of sensory and interoceptive cues to guide cognitive and motor responses, evaluate outcomes, and adjust behavior (Brass and Haggard, 2010). Disruption to such processes may contribute to addiction vulnerability.

Insula and Addiction

Several models of addiction emphasize a role for the insula, given its ability to influence complex motivated behaviors by integrating bodily sensations, external stimuli, and motivational states while engaging executive and motor systems. Bodily sensation information, transmitted from the spinal cord via the ventromedial thalamic nucleus, is integrated with subcortical, limbic, and cortical circuitry in the anterior insula (Craig, 2002). The anterior insula and anterior cingulate have been proposed to form a 'salience network', facilitating attention to salient internal or environmental stimuli, then engaging cognitive control processes to access working memory and attentional resources by switching between central executive and default mode networks (Menon and Uddin, 2010). As reward response is influenced by homeostatic and external contexts, the insula has been proposed to contribute to complex cognitive, affective, and behavioral phenomena in addictions (Paulus, 2007), including conscious processing of pleasurable drug effects, drug cue-related craving (Garavan *et al*, 2000; Gray and Critchley, 2007; Koob and Volkow, 2010), and 'as-if' pleasure and decision-making processes weighing drug-taking positive *vs* negative consequences (Naqvi and Bechara, 2010).

Family History-by-Sex Interactions in the Thalamus

The thalamus family history-by-sex interaction was driven by sex differences in the FHP but not in the FHN group and a family-history group difference in males but not in females. The thalamus is thought to have a central role in gating information transfer along cortico-striatal-thalamo-cortical circuits and may actively modulate the resulting task-related cortical activation and deactivation patterns that signal a shift from non-task-related activity to task engagement (Haber and McFarland, 2001). Sex differences in associations between task-related activation (or de-activation) and response inhibition performance may indicate sex differences in task-related 'processing strategies' (Liu *et al*, 2012). White matter microstructural differences suggest sex differences in the thalamus's role in cortico-striatal-thalamo-cortical circuit function (Menzler *et al*, 2011). Sex differences in thalamic activation in FHP may reflect sex differences in mechanisms of addiction vulnerability.

Lack of Family History of Alcoholism Effects in Ventral-Striatum

Contrary to our hypothesis, our family-history groups did not differ on ventral-striatal activity. Previous findings of abnormal ventral-striatal activity in adolescent/young adult FHP or alcohol-dependent individuals were often associated with high impulsivity or alcohol use (Beck *et al*, 2009; Bjork *et al*, 2008a; Bjork *et al*, 2008b; Heitzeg *et al*, 2008; Heitzeg *et al*, 2010; Wrase *et al*, 2007). The lack of ventral-striatal findings in this sample may have been due to the FHP and FHN groups' similar impulsivity and alcohol use levels. Ventral-striatal abnormalities may only be present in FHPs with high impulsivity or excess alcohol use or may partially reflect a developmental delay observable during adolescence/young adulthood.

Associations between Neural, Impulsivity-Related and Drinking Measures

Greater left insula/IFG cluster activity was associated with higher impulsivity (self-reported impulsivity and sensation seeking (F2) and steeper delay discounting (F4)). Taken together, the trend towards greater right insula/IFG recruitment (previously associated with higher self-reported impulsivity as measured by Eysenk's Impulsivity Scale (Horn *et al*, 2003)) and significantly greater left insula/IFG recruitment in FHPs, and associations between left insula/IFG activity and impulsiveness across both groups, are consistent with diminished cognitive efficiency of response inhibition processes in FHPs.

Steeper delay discounting (F4) was associated with more past-month drinking, consistent with previous research (Kollins, 2003). This impulsivity component may predispose towards alcohol use. Given the trend correlations between F4 and alcohol-onset age, an alternate explanation involving early alcohol exposure leading to increased choice impulsivity also warrants consideration (Nasrallah *et al*, 2009).

Limitations and Future Directions

Use of multiple out-of-scanner impulsivity constructs was a strength (Lejuez *et al*, 2010). However, the lack of robust effects of family history on out-of-scanner impulsivity-related factors may reflect our strict exclusion criteria for lifetime problematic alcohol use or other psychiatric disorders, which likely excluded early-onset alcoholics. These FHPs may represent a protected subset or have vulnerability for later-onset alcoholism, which is associated with less impulsivity than early-onset alcoholism (Dom *et al*, 2006). Our results may not apply to early-onset alcoholism or highly impulsive FHPs.

Findings are consistent with increased risk for addiction among FHPs conferred through diminished efficiency of neural systems important for impulse control, particularly among males. Maternal history of AUDs was an exclusion criterion to control for fetal alcohol syndrome. Genetic or environmental mechanisms of transmission of risk may differ by inheritance from same-sex or opposite-sex parents or by maternal or paternal AUDs (Lieb *et al*, 2002; Morgan *et al*, 2010). The purported risk-transmission mechanism of response inhibition inefficiency may be greater in father-to-son than father-to-daughter inheritance. The current study

only had the capacity to detect FHP or sex differences in neural systems sufficiently engaged by the Go/No-Go task and within regions-of-interest. Different neurocognitive mechanisms may be more sensitive to father-to-daughter risk transmission.

The analytic approach limited detection of potential family history or sex differences to *a priori* regions-of-interest, chosen for relevance to addiction vulnerability, impulsivity-related constructs, and Go/No-Go task engagement. However, these regions-of-interest are not the only Go/No-Go-activated regions implicated in addiction vulnerability or impulsivity-related constructs.

The finding that FHPs displayed neural markers of diminished efficiency despite minimal indications of increased impulsivity suggests that subtle alterations of neural circuitry important for response inhibition may contribute to vulnerability to addiction, despite normal impulsivity and alcohol-use behaviors. Prospective studies investigating other at-risk populations for similar vulnerability markers could inform prevention efforts by identifying at-risk individuals before problematic drinking onset. As neural vulnerabilities may persist following prolonged abstinence, they may predict risk for relapse in treatment seekers.

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DISCLOSURE

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employed by Yale University School of Medicine and VA CT Healthcare System; holds patents for the following: (1) Seibyl JP, Krystal JH, Charney DS. Dopamine and norepinephrine reuptake inhibitors in treatment of schizophrenia. Patent #:5 447 948. September 5, 1995, (2.) co-inventor with Dr Gerard Sanacora on a filed patent application by Yale University related to targeting the glutamatergic system for the treatment of neuropsychiatric disorders (PCTW 006108055A1), (3) Intranasal Administration of Ketamine to Treat Depression (patent pending). MNP reports no financial conflicts of interest with respect to the content of this manuscript yet has received financial support or compensation for the following: consulted for and advised Boehringer Ingelheim; consulted for and has financial interests in Somaxon; received research support from the National Institutes of Health, Veteran's Administration, Mohegan Sun Casino, the National Center for Responsible Gaming and its affiliated Institute for Research on Gambling Disorders, and Forest Laboratories, Ortho-McNeil, Oy-Control/Biotie, Glaxo-SmithKline, and Psyadon pharmaceuticals; participated in surveys, mailings or telephone consultations related to drug addiction, impulse-control disorders or other health topics; consulted for law offices and the federal public defender's office in issues related to impulse-control disorders; provides clinical care in the Connecticut Department of Mental Health and Addiction Services Problem Gambling Services Program; performed grant reviews for the National Institutes of Health and other agencies; guest-edited journal sections; given academic lectures in grand rounds, CME events and other clinical or scientific venues; and generated books or book chapters for publishers of mental health texts. The remaining authors declare no conflicts of interest.

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