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Fronto-striatal functional connectivity during response inhibition in alcohol dependence

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ABSTRACT

Poor response inhibition has been implicated in the development of alcohol dependence, yet little is known about how neural pathways underlying cognitive control are affected in this disorder. Moreover, endogenous opioid levels may impact the functionality of inhibitory control pathways. This study investigated the relationship between alcohol dependence severity and functional connectivity of fronto-striatal networks during response inhibition in an alcohol-dependent sample. A secondary aim of this study was to test the moderating effect of a functional polymorphism (A118G) of the μ-opioid receptor (*OPRM1*) gene. Twenty individuals with alcohol dependence (six females; 90% Caucasian; mean age = 29.4) who were prospectively genotyped on the *OPRM1* gene underwent blood oxygen level-dependent functional magnetic resonance imaging while performing a Stop-Signal Task. The relationship between alcohol dependence severity and functional connectivity within fronto-striatal networks important for response inhibition was assessed using psychophysiological interaction analyses. Analyses revealed greater alcohol dependence severity was associated with weaker functional connectivity between the putamen and prefrontal regions (e.g. the anterior insula, anterior cingulate and medial prefrontal cortex) during response inhibition. Furthermore, the *OPRM1* genotype was associated with differential response inhibition-related functional connectivity. This study demonstrates that individuals with more severe alcohol dependence exhibit less frontal connectivity with the striatum, a component of cognitive control networks important for response inhibition. These findings suggest that the fronto-striatal pathway underlying response inhibition is weakened as alcoholism progresses.

Keywords Alcohol dependence, fMRI, functional connectivity, impulsivity, response inhibition, Stop-Signal Task.

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INTRODUCTION

Increased impulsivity is implicated in the development and maintenance of substance use disorders (e.g. Volkow & Baler 2012). The mechanisms underlying the association between alcohol use and impulsivity are complex, and while high levels of impulsivity may serve as a predisposing etiological factor, long-term exposure to drugs of abuse can lead to neuro-adaptation in the prefrontal cortex (PFC) and striatum, diminishing the brain's ability to stop an impulsive response (Jentsch & Taylor 1999; de Wit 2009).

The fronto-striatal system has a prominent role in inhibitory control of impulsive responses (Jentsch & Taylor 1999). Dysfunction of this system is associated with multiple pathological states involving excessive impulsive behavior, including attention deficit hyperactivity disorder (Rubia *et al.* 2005) and Tourette's syndrome (Marsh *et al.* 2007). Neuro-imaging studies of Stop-Signal Tasks (SSTs) have identified several brain regions subserving the ability to stop an impulsive response, including components of fronto-basal ganglia circuitry implicated in the development of substance abuse. SSTs are designed to elicit a 'race' between two response tendencies, 'going' and 'stopping' (Logan 1994), with the Go process activating fronto-striatal-pallidal regions and the Stop process activating the inferior frontal gyrus (IFG), subthalamic nucleus (STN) region, pre-supplementary motor area (pre-SMA), globus pallidus pars interna, parietal cortex and insula (Aron & Poldrack 2006). Human and animal studies suggest that response inhibition is mediated by a fast hyperdirect pathway in the right hemisphere connecting the IFG, the pre-SMA and the STN (Aron & Poldrack 2006). Moreover, evidence from pre-clinical rodent models (Eagle & Robbins 2003) and functional connectivity analyses in

healthy adults (Duann *et al.* 2009) provide support for the involvement of an indirect pathway connecting the cortex and caudate in successful response inhibition. Pre-clinical data suggest that functional activity in the striatum is also directly influenced by input from the cortex (Brown, Smith & Goldbloom 1998). Effective connectivity analyses found evidence supporting the complimentary actions of the hyperdirect and indirect pathways to implement successful inhibition of a prepotent response. These findings indicate that successful inhibition of the primary motor cortex relies on efficient fronto-basal ganglia communication and implicate a top-down controlled inhibitory process (Jahfari *et al.* 2011). Likewise, fronto-putamen connectivity has been identified as important for successful response inhibition (Zandbelt & Vink 2010). Specific to addiction, the transition from PFC to striatal control over responding, and from ventral to more dorsal striatal subregions, has been proposed as the mechanism subserving the transition from voluntary/goal directed to more habitual drug-seeking behavior (Everitt & Robbins 2005). Thus, SST performance and related neural markers may be promising measures of risk for substance abuse (Nigg *et al.* 2006).

Several reports implicate decreased response inhibition in alcohol dependence, as measured behaviorally by the Continuous Performance Task (Bjork *et al.* 2004), Go/No-Go tasks (Kamarajan *et al.* 2005), and time required to cancel an initiated response in SSTs (Goudriaan *et al.* 2006); but see less supportive studies (Lawrence *et al.* 2009; Courtney *et al.* 2012). To date, however, only one SST brain activation study has been conducted with alcohol-dependent participants. In this study, the neuroimaging measures of response inhibition, post-error behavioral adjustment and error processing, were found to differentiate abstinent alcohol-dependent patients and healthy controls. More specifically, the authors observed decreased dorsolateral PFC activation during response inhibition and post-error slowing, which is in accord with the transition from PFC to striatal control over responding and further implicates the role of efficient fronto-striatal connectivity in supporting response inhibition (Li *et al.* 2009).

OPRM1 gene

Studies have found support for the modulating role of specific genetic variants of candidate genes subserving dopaminergic neuro-transmission (i.e. DRD2, DRD4 and COMT) in the neural bases of impulsivity in heavy-drinking and alcohol-dependent samples (Boettiger *et al.* 2007; Filbey *et al.* 2012). Genes that affect the endogenous opioid system (e.g. *OPRM1*) represent plausible modulators of impulsivity, as increased levels of endogenous opioids have been associated with increased impulsivity (Ray *et al.* 2012). The μ-opioid receptor, which is encoded by the *OPRM1* gene, has been identified as the primary site of action for opiates with high abuse potential (Pasternack 1993), and non-opioid drugs such as alcohol exert some of their effects through activation of these receptors (Herz 1997). The A118G polymorphism (Asn40Asp substitution) affects the receptor activity for the endogenous ligand β-endorphin, such that the G-allele binds β-endorphin three times more strongly than A-allele. Individuals with the G-allele may display behavioral differences in responses mediated by β-endorphins at the more sensitive μ-receptors (Bond *et al.* 1998) and have been shown to experience greater subjective reinforcing effects after alcohol consumption (Ray & Hutchison 2004). Pre-clinical evidence also supports the role of μ-opioid receptors in the regulation of inhibitory control (Olmstead, Ouagazzal & Kieffer 2009; Wiskerke *et al.* 2011). In particular, *OPRM1* knockout mice were found to exhibit increased motor impulsivity on a nose-poke task (Olmstead *et al.* 2009), further implicating the role of the endogenous opioid system in inhibitory control.

Studies of the opioid antagonist naltrexone (NTX), a Food and Drug Administration (FDA)-approved medication for the treatment of alcoholism, and performance on tasks assessing behavioral impulsivity found NTX reverses a morphine-induced increase in preference for small immediate rewards over larger delayed rewards in rats (Kieres *et al.* 2004) and attenuates a variety of impulse disorders in humans (Kim *et al.* 2001). To date, one study has directly assessed the relationship between endogenous opioids and impulsivity in humans with problematic alcohol use (Mitchell *et al.* 2007). Mitchell *et al.* (2007) found enhanced response control (reduced motor errors during a conflict task) in abstinent alcoholics treated with NTX. Individuals with an external locus of control showed a reduction in impulsive decision making when receiving NTX, suggesting that endogenous opioids may impair response selection during impulsive decision making, but that the effects of NTX on this process are personality-dependent and likely mediated by frontal dopaminergic transmission. Further investigation on the neural underpinnings of impulsivity, including the endogenous opioid system and frontal control systems, in alcohol dependence is warranted.

Together, pre-clinical findings and pharmacological manipulations have implicated the opioidergic system in inhibitory control. Therefore, this study examines the role of the A118G SNP of the *OPRM1* gene on fronto-striatal connectivity during response inhibition.

The present study

In summary, regions within the hyperdirect and indirect pathways implicated in successful inhibitory control may be associated with alcohol-induced neuro-adaptation

through which response inhibition becomes impaired in alcohol-dependent populations (Baler & Volkow 2006). To test this hypothesis, this study employed a clinical neuro-science approach to investigate the relationship between alcohol dependence and the neural basis of response inhibition, focusing on fronto-striatal connectivity in particular, in individuals with and without the *OPRM1* risk allele. A neuro-imaging SST protocol was administered to 20 individuals with alcohol dependence who were prospectively selected based on *OPRM1* genotype. Fronto-striatal functional connectivity during response inhibition was assessed with a psychophysiological interaction (PPI) analysis using the right putamen as a seed region to identify brain areas that correlated with activation in this striatal region during successful stopping versus going trials on the SST. The right putamen was chosen as the *a priori* seed region due to its anatomical connections with the medial PFC, orbitofrontal cortex (OFC) and dorsolateral PFC (Draganski *et al.* 2008), as well as its functional role in motor control (Alexander, DeLong & Strick 1986), including response inhibition (Aron & Poldrack 2006; Zandbelt & Vink 2010). The resulting contrasts and connectivity maps were then correlated with a measure of alcoholism severity to assess for differential functional magnetic resonance imaging (fMRI) activation in brain regions involved in inhibitory control. Specifically, we hypothesized that fronto-striatal functional connectivity important for response inhibition would be weaker in participants with greater severity of alcohol dependence. The second aim of this study was to examine the moderating role of the A118G SNP on fMRI activation during response inhibition.

MATERIALS AND METHODS

Sample characteristics

Participants were non-treatment-seeking problem drinkers ($n = 295$) recruited from the Los Angeles community through flyers and online advertisements to investigate the effect of the *OPRM1* gene on subjective responses to alcohol. The protocol was approved by the local Institutional Review Board, and following consenting procedures, participants were screened for alcohol dependence and prospectively genotyped. For the MRI portion of the study, a subsample of 20 alcohol-dependent individuals were selected to ensure equal numbers of participants with and without the minor (G) allele of the *OPRM1* gene (AA, $n = 10$; AG/GG, $n = 10$). Ethnicity was matched across groups to account for population stratification at the *OPRM1* locus. Inclusion criteria were (1) ages 21–55 years; (2) current alcohol dependence; (3) no major psychiatric disorders; (4) no current use of illicit substances (other than marijuana), verified by toxicology screening; and (5) no abuse or dependence on any illicit substance (including marijuana) as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) in the past 12 months. Abstinence from alcohol at least 24 hours prior to their scan time was required, verified by a Breathalyzer test (Dräger Medical Inc., Telford, PA, USA).

Individual difference measures

The *OPRM1* genotype groups were found to be balanced across demographic variables, as analyzed by independent *t*-tests ($P's > 0.05$; Table 1). Alcohol use was assessed using the 30-day timeline follow-back (Sobell & Sobell 1980), resulting in estimates of alcohol drinks per drinking day and percent drinking days. Alcohol dependence and the exclusionary psychiatric diagnoses were assessed using the Structured Clinical Interview for DSM-IV (First *et al.* 1995) under the supervision of a licensed clinical psychologist. DSM-IV symptoms of alcohol abuse and dependence were recorded for a total of 11 possible symptoms. All participants completed the Clinical Institute withdrawal assessment for alcohol (CIWA-Ar; Sullivan *et al.* 1989); alcohol dependence scale (ADS; Skinner & Allen 1982); drinkers inventory of consequences (DrInC-2R) questionnaire (Miller, Tonigan & Longabaugh 1995); and the Penn alcohol craving scale (PACS; Flannery, Volpicelli & Pettinati 1999). No individuals reported clinically significant levels of alcohol withdrawal

Table 1 Sample demographics by *OPRM1* genotype.

	Frequency or mean (standard deviation)	
Variable	*AA (n = 10)*	*AG/GG (n = 10)*
Age	32.1 (11.0)	26.7 (5.8)
Sex—male/female	7/3	7/3
Ethnicity		
Caucasian	9	9
African–American	1	1
Alcohol drinks per drinking day	6.9 (1.9)	5.9 (2.6)
Percent drinking days (past 30 days)	65.3% (0.6%)	58.3% (0.2%)
Withdrawal symptoms (total CIWA-Ar score)	2.5 (1.5)	2.0 (1.8)
Education (years)	15.7 (2.5)	14.3 (1.9)
Shipley IQ (standard score)	113.3 (16.5) ($n = 9$)	106.7 (22.2)
Working memory (Digit Span scaled score)	12.3 (1.9) ($n = 7$)	11.0 (3.3) ($n = 8$)
Marijuana use (none/moderate)	7/3	7/3
Cigarettes per day		
0	3	3
1 ≤10	6	6
>10	1	1
Fagerstrom test for nicotine dependence total score		
0–4 (none-low)	4	5
5–10 (moderate-high)	6	5

No group differences observed ($P's > 0.05$).

at time of assessment as indicated by CIWA-Ar score (scores ≤6).

To appropriately model the shared variance between the alcohol dependence severity indices and minimize the number of statistical tests, principal component analyses were conducted on the full sample ($n = 295$) to derive factor scores capturing alcohol dependence severity. The principal factor method (promax oblique rotation) revealed one meaningful factor (first eigenvalue = 2.749, second eigenvalue = 0.858) with each index loading onto the factor at 0.40 or greater (ADS = 0.83, PACS = 0.74, Symptom count = 0.75, DrInC-2R = 0.85 and CIWA-Ar = 0.48) and accounted for 55% of the total variance. Participants' scores on the single factor (alcohol dependence severity) were used in subsequent analyses. Participants' ADS scores were also used in subsequent analyses for comparison with the alcohol dependence severity factor results.

Stop-Signal Task

The participants performed a 6-minute variant of the SST developed for neuro-imaging protocols (Cohen *et al.* 2010). The participants had prior experience with the SST as part of the larger study for which they were recruited; thus, no practice trials were given. While scanning, each of the 128 trials began with a white circular fixation ring presented at the center of the screen for 500 milliseconds, followed by presentation of a left- or a right-pointing arrow. The participants were instructed to quickly press one of the two buttons on a response pad corresponding to the arrow direction (Go trial). During Stop trials (32 trials), an auditory stop-signal (900 Hz, 500 milliseconds) sounded at varying delays after Go stimulus onset, signaling the participant to attempt to inhibit their response. A jittered delay (0.5–4 seconds, mean = 1 seconds, taken from an exponential distribution) followed each response. The time intervals between the Go and the Stop signals [i.e. the stop-signal delay (SSD)] were determined dynamically during scanning using a staircase approach with two independent ladders. Ladder 1 started at 250 milliseconds and ladder 2 at 350 milliseconds. The SSD was either increased or decreased by 50 milliseconds in the next trial, depending on whether the participant succeeded or failed in withholding their response, respectively.

The presentation of all stimuli and response collection were programmed using MATLAB (MathWorks, Natick, MA, USA) and the Psychtoolbox (http://www.psychtoolbox.org) on an Apple MacBook running Mac OSX (Apple Incorporated, Cupertino, CA, USA). Visual and auditory stimuli were presented using MRI compatible goggles and headphones (Resonance Technologies Co., Van Nuys, CA, USA).

MRI data acquisition

Neuro-imaging was conducted using a 3 T Siemens Trio MRI scanner at the University of California, Los Angeles (UCLA) Ahmanson-Lovelace Brain Mapping Center. The protocol began with initial structural scans followed by a series of four functional runs, including the SST, an alcohol taste-cues paradigm, a delay-discounting paradigm and a risky decision-making paradigm. A T2-weighted, high-resolution, matched-bandwidth (MBW), anatomical scan and a magnetization-prepared rapid-acquisition gradient echo (MPRAGE) were acquired for each subject to enable registration [repetition time (TR): 1.9 seconds; echo time (TE): 2.26 milliseconds; field of view (FOV): 250 mm; matrix: 256×256; sagittal plane; slice thickness, 1 mm; 176 slices]. The orientation for MBW and echoplanar image (EPI) scans was oblique axial to maximize brain coverage. The SST scan included 184 functional T2*-weighted EPIs (slice thickness: 4 mm; 34 slices; TR: 2 seconds; TE: 30 milliseconds; flip angle: 90°; matrix: 64×64; FOV: 192 mm; voxel size: $3 \times 3 \times 4 mm^3$). The first six volumes collected were discarded to allow for T1 equilibrium effects.

Imaging preprocessing and registration

FSL 4.1 (FMRIB's Software Library, http://www.fmrib.ox.ac.uk/fsl) was used for the imaging analyses. Motion correction was carried out using FSL's Motion Correction Linear Image Registration Tool (McFLIRT, version 5.0, Analysis Group, FMRIB, Oxford, UK) with the estimated motion parameters entered as covariates in the general linear model. Non-brain tissue/skull removal was conducted with the brain extraction tool. The images were smoothed using a FWHM Gaussian kernel (5 mm) and high-pass filtered (100 seconds cutoff) in the temporal domain using a Gaussian weighted straight line with FSL's FMRI Expert Analysis Tool (FEAT, version 5.63, Analysis Group, FMRIB). The EPI images were first registered to the MBW, then to the MPRAGE using affine linear transformations and into standard (Montreal Neurological Institute; MNI avg152 template) space for between-subject analyses. Registration to standard space was refined by FSL's FNIRT non-linear registration (Andersson, Jenkinson & Smith 2007). One subject (G-allele carrier) was excluded from further analyses due to excessive motion (exceeding 3 mm of translation).

Genotyping

Saliva samples were collected using Oragene saliva collection kits (DNA Genotek, Ontario, Canada) and sent to the UCLA Genotyping and Sequencing Core for genotyping. Polymerase chain reaction (PCR) was performed on Applied Biosystems (Carlsbad, CA, USA) dual block PCR

thermal cyclers. Single-nucleotide polymorphisms were run on an AB 7900HT Fast Real-Time PCR System and analyzed using the Sequence Detection Systems software (version 2.3, Applied Biosystems, Grand Island, NY, USA). Genotypes were automatically scored by the allele calling software, verified by visual inspection.

Statistical analyses

SST performance was assessed for the following criteria: average percent inhibition on Stop trials between 40 and 60%, response on greater than 80% of Go trials, less than 10% arrow direction errors, and greater than 50 milliseconds Stop-Signal Reaction Time (Congdon *et al.* 2010). All subjects' SST performance met the specified criteria and the staircase procedure employed resulted in participant performance at the desired 50% inhibition level (Table 2).

Whole-brain statistical analysis was performed using a multi-stage approach to implement a mixed-effects model treating participants as a random-effects variable. Explanatory variables for the SST paradigm were created by convolving stick functions representing the onset of relevant experimental events with a double-gamma hemodynamic response function in FEAT. The events modeled included Go, Successful Stopping and Unsuccessful Stopping, all with 1.5-second duration from stimulus onset. Temporal derivatives were included as covariates of no interest to improve statistical sensitivity. Null events, consisting of the jittered inter-stimulus interval when the screen was blank, were not explicitly modeled and therefore constituted an implicit baseline. The following contrasts indexed response inhibition: (1) Successful Stopping versus Go; (2) Unsuccessful Stopping versus Go; and (3) Successful Stopping versus Unsuccessful Stopping. To examine activation related to the Go and Stop processes, (1) Go versus baseline and (2) Successful Stopping versus baseline contrasts were also computed.

Second-level group analyses were conducted on contrast images transformed into standard space. Z-statistic images were thresholded with cluster-based corrections for multiple comparisons based on the theory of Gaussian random fields with a cluster-forming threshold of $Z = 2.3$ and a cluster-probability threshold of $P < 0.05$ (Worsley 2001). Alcohol dependence severity factor scores and ADS scores were modeled as explanatory variables on the whole-brain contrast maps as specified earlier. Anatomical localization of peak voxels within each cluster (maximum Z-statistics and MNI coordinates) was obtained by searching within maximum likelihood regions from the FSL Harvard-Oxford probabilistic atlas. *OPRM1* genotype (i.e. AA and AG/GG) was entered as a second-level predictor variable and examined in relation to brain activation within SST contrasts using a whole-brain approach.

Functional connectivity was assessed using PPI analysis (Gitelman *et al.* 2003), which measures coupling of brain regions during specific task conditions. To examine fronto-striatal functional connectivity during response inhibition, we examined the coupling of the right putamen and the rest of the brain within the Successful Stopping versus Go contrast. Both anatomically and functionally defined right putamen seed regions were used. To determine the anatomically defined seed for each participant, we used the high-resolution MPRAGE anatomical images, segmented on a subject-specific basis in native space using FMRIB's Integrated Registration and Segmentation Tool in FSL. For the functionally defined seed, we included voxels from the thresholded Z-statistic images for the Successful Stopping versus Go contrast that fell within the boundaries of the anatomically

Table 2 Means and standard deviations (SD) for the alcohol dependence severity measures and task-related behavioral performance by *OPRM1* genotype.

		AA		*AG/GG*	
Construct	*Variable*	*Mean*	*SD*	*Mean*	*SD*
Alcohol dependence severity	CIWA-Ar total score	2.50	1.51	2.00	1.83
	Symptom count	6.70	2.26	5.70	1.94
	ADS total score[a]	18.80	5.55	15.40	4.65
	DrInC-2R total score	103.20	22.17	93.80	15.39
	Dependence severity factor[a]	0.4957	0.9378	−0.0327	0.6415
Stop-Signal Task (SST)	MGRT	472.60	89.49	497.50	103.37
	Mean SSD	297.51	50.45	308.13	90.78
	% inhibition	50.94	6.24	50.30	6.66
	% Go responding	99.90	0.32	98.02	4.06
	SSRT	175.09	42.52	189.38	40.75

[a]Variables used in brain activation correlations. Mean Stop-Signal delay (SSD) was calculated as the time delay required to succeed in withholding a response on 50% of the Stop trials. Stop-Signal reaction time (SSRT) was estimated for each participant by subtracting the average SSD from the median Go reaction time (MGRT). No group differences observed (P's > 0.05). ADS = alcohol dependence scale; CIWA-Ar = Clinical Institute withdrawal assessment for alcohol; DrInC-2R = drinker inventory of consequences.

defined putamen. The anatomically and functionally defined left putamen seed regions were also determined using the same methods. The average time course of the right and left putamen were extracted from motion-corrected, high-pass filtered image data (the same pre-processing steps as outlined earlier). The PPI analysis was conducted using both Statistical Parametric Mapping (SPM) and FSL's FEAT. The model was identical to the first-level model described earlier with the inclusion of three additional regressors: 'psychological', 'physiological' and 'psychophysiological interaction'. These regressors were generated separately by computing three vectors using the PPI algorithms implemented in SPM5 (http://www.fil.ion.ucl.ac.uk/spm/software/spm5). The psychological vector was specified by a delta function with Successful Stopping events represented by 1 and Go events represented by −1 (zero centered), the physiological vector estimated 'neural' activation of the right putamen via hemodynamic deconvolution of the average pre-processed time course, and the PPI vector was the product of these two. The three vectors were convolved with a hemodynamic response function prior to inclusion in the FEAT model. A whole-brain contrast image for the PPI was computed from this model and submitted for second-level group analyses described earlier.

RESULTS

Alcohol use, dependence severity and task performance are presented in Table 2. Of note, the sample was found to have mild-to-moderate alcohol dependence as compared with other alcohol-dependent samples reported in the literature. No group differences were observed across *OPRM1* genotype for these variables (P's > 0.10). Across all subjects, behavioral performance on the task was found to be uncorrelated with alcohol dependence severity (P's > 0.10).

Response inhibition

Consistent with previous reports, the main contrast examining response inhibition (Successful Stopping versus Go) activated a broad set of brain regions including the IFG, pre-SMA, parietal cortex, putamen and insula (Aron and Poldrack, 2006) (Table 3; Fig. 1). No genotype differences were observed within this contrast. Results from other task contrasts are reported in Supporting Information Table S1.

Whole-brain correlations with alcohol dependence severity

To assess whether alcohol dependence severity is associated with response inhibition, whole-brain correlation analyses were conducted within the Successful Stopping versus Go, Successful Stopping versus Unsuccessful Stopping and Successful Stopping versus baseline contrasts. No significant correlations or genotype differences among correlations were found between alcohol dependence severity (factor scores or ADS scores) and these contrasts.

PPI analyses

Fronto-striatal functional connectivity using PPI contrasts describing the connectivity between the right putamen and the rest of the brain from the Successful Stopping versus Go contrast was estimated for all subjects. The right putamen showed significant connectivity (positive correlation) with the subcallosal/anterior

Table 3 Locations of significant activation within the Successful Stopping versus Go contrast across all subjects, whole-brain cluster-corrected at Z > 2.3, $P < 0.05$.

Successful Stopping versus Go						
Brain region	*Hemisphere*	*Cluster voxels*	*Max Z*	*X*	*Y*	*Z*
Supramarginal gyrus/angular gyrus/middle temporal gyrus	R	22 072	6.03	58	−40	6
Superior temporal gyrus, posterior division	R		5.61	60	−28	0
Caudate	R/L		3.97	−10	10	4
Thalamus	R/L		3.06	−12	0	8
Anterior insula/inferior frontal gyrus	R/L		4.56/5.27	−40/34	20/22	−2/0
Paracingulate/cingulate gyrus	R		4.17	6	16	42
Anterior cingulate gyrus	R		3.75	8	30	26
Superior frontal gyrus	R		4.62	16	16	62
Intracalcarine cortex	R		3.25	14	−86	4
Occipital cortex	R/L		4.07/4.33	12/−18	−96/−96	0/6
Supramarginal gyrus/superior temporal gyrus/planume temporale	L	7 573	5.61	−64	−44	14
Angular gyrus	L		3.20	−50	−54	54
Frontal pole	L	1 097	3.89	−32	40	34
Middle frontal gyrus	L		3.59	−36	34	34

X, *Y* and *Z* MNI coordinates indicate the location of peak voxel activation (or local maxima for subregions) within each cluster. L = left; R = right.

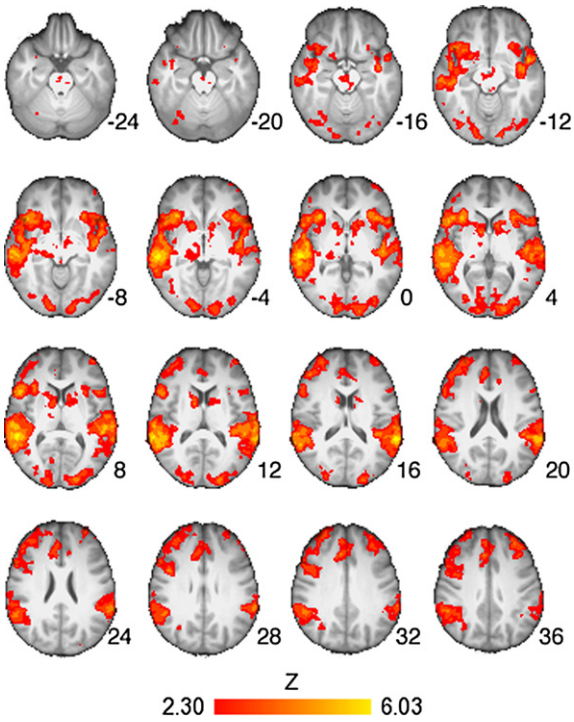

Figure 1 Brain activation for Successful Stopping versus Go contrast. Areas of activation for Successful Stopping versus Go included right inferior frontal gyrus, bilateral insula, pre-supplementary motor cortex, supramarginal gyri (see Table 3 for full list of regions). *Z*-statistic maps are whole-brain cluster-corrected, $Z > 2.3$, $P = 0.05$. Coordinates are in the MNI space, and the brain is displayed in radiological convention (left = right). MNI = Montreal Neurological Institute

Figure 2 Results of the functional connectivity analysis indicating a negative relationship between fronto-striatal connectivity strength during Successful Stopping versus Go and severity of alcohol dependence. (a) Brain regions whose positive connectivity with the putamen are negatively correlated with severity (cool colors), with the main effect of connectivity overlaid (hot colors) (whole-brain cluster-corrected at $Z > 1.96$ for visualization purposes, $P < 0.05$). Regions showing significant connectivity with the right putamen include the subcallosal/anterior cingulate cortices and the paracingulate gyrus. Regions showing a negative correlation with severity were restricted to the prefrontal cortex, including the left anterior insula, bilateral inferior frontal gyri, orbitofrontal cortex, and anterior cingulate cortex. Results are from a psychophysiological interaction (PPI) analysis using the right putamen as an anatomically defined region of interest determined for each participant individually (see methods). No regions showed a positive correlation with severity. Coordinates are in the MNI space, activations are overlaid on the group mean anatomical image, and the brain is displayed in radiological convention (left = right). (b) Scatterplot (shown for visualization purposes) indicates each individual's relationship between their alcohol dependence severity index and strength of connectivity between the right putamen and frontal regions. Strength of connectivity values are the mean parameter estimates emerging from the PPI analysis (using the right putamen as a seed). These values were extracted from a mask defined by the frontal regions that showed a correlation between the PPI and severity scores [shown in (a)]. MNI = Montreal Neurological Institute

cingulate cortices (ACC) and the paracingulate gyrus (Table 4; Fig. 2a). *OPRM1* genotype was found to moderate fronto-striatal connectivity such that A-allele homozygotes exhibited less functional connectivity between the right putamen and prefrontal regions, including OFC and middle-frontal regions (parameter estimates for the cluster: A-allele homozygotes = –0.258, G-allele carriers = 0.182; Table 5).

PPI correlations with alcohol dependence severity

Whole-brain correlations of alcohol dependence severity measures (i.e. severity factor scores and ADS scores) with the PPI contrasts were performed using the anatomically and functionally defined seed regions. Regions from the anatomically defined right putamen seed analysis showing a negative correlation with severity factor scores were restricted to the PFC and included the left anterior insula, bilateral IFG, OFC and ACC (Table 4; Fig. 2). No

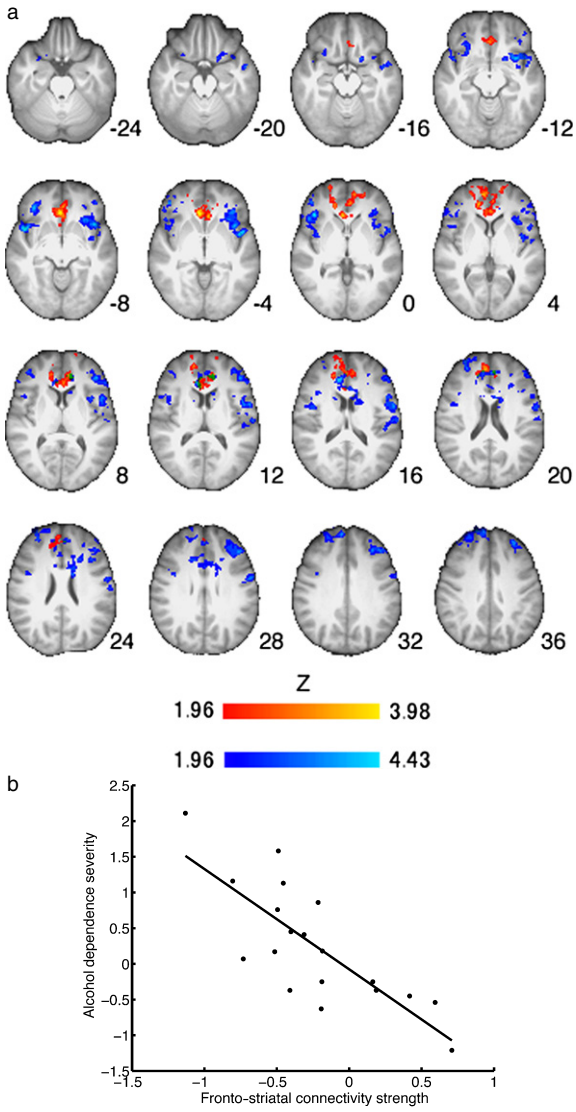

Table 4 The PPI correlation results show a negative correlation between fronto-striatal connectivity during Successful Stopping versus Go and severity of alcohol dependence (cluster-corrected at $Z > 2.3$, $P < 0.05$). No regions showed a positive correlation with severity.

PPI for Successful Stopping versus Go						
Brain region	*Hemisphere*	*Cluster Voxels*	*Max Z*	*X*	*Y*	*Z*
Subcallosal cortex	R	1525	4.00	6	30	−4
Anterior cingulate cortex	L		3.54	−2	32	6
Paracingulate gyrus	R/L		3.25/3.16	6/−6	48/54	20/2
Correlation of alcohol dependence severity factor scores with PPI for Successful Stopping versus Go						
Anterior cingulate gyrus	R	2537	3.81	10	34	16
Superior frontal gyrus	R		3.55	8	56	34
Middle frontal gyrus	L		3.29	−30	44	36
Inferior frontal gyrus	L		3.46	−44	38	8
Central opercular cortex	L	1742	3.95	−48	6	−2
Insular cortex	L		3.63	−40	16	−6
Orbitofrontal cortex	L		3.50	−36	32	−2
Precentral gyrus	L		3.40	−58	2	14
Temporal pole	R	1057	4.43	48	10	−8
Orbitofrontal cortex	R		3.58	36	38	−8
Inferior frontal gyrus/anterior insula	R		3.12	50	22	−2

X, *Y* and Z MNI coordinates indicate the location of peak voxel activation (or local maxima for subregions) within each cluster. L = left; R = right.

Table 5 Results are from the psychophysiological interaction (PPI) analysis using the putamen as an anatomically defined region of interest determined for each participant individually (see the Methods section). Clusters listed are results from comparing the slopes of correlation within each allele group. Thus, the A- versus G-allele group comparison lists regions that showed a steeper regression slope for the A- than the G-allele group. No regions showed a positive correlation with severity.

PPI for Successful Stopping versus Go moderated by OPRM1 *genotype*						
Brain region	*Hemisphere*	*Cluster voxels*	*Max Z*	*X*	*Y*	*Z*
A- versus G-allele						
Cerebellum	L	508	3.56	−14	−50	−24
G- versus A-allele						
Caudate	L	1067	3.80	−16	12	20
Orbitofrontal cortex	L		3.10	−24	28	2
Middle frontal gyrus	L		3.08	−26	40	16
Negative correlation of PPI for Successful Stopping versus Go with alcohol dependence severity moderated by OPRM1 genotype						
A- versus G-allele						
Superior frontal gyrus	R	715	3.82	20	66	26
Paracingulate gyrus	R		3.43	8	44	32
Middle frontal gyrus	R		3.51	28	54	24
Middle frontal gyrus	R	581	3.46	32	66	−8
Inferior frontal gyrus	R		3.42	32	58	4
Middle frontal gyrus	L	469	3.42	−24	60	−6
Subcallosal cortex	R/L	319	3.43/3.54	6/−6	18/22	−4/0
Caudate	R		3.38	10	20	−2
Orbitofrontal cortex	L		3.07	−16	22	−12
Occipital fusiform gyrus	R	347	3.72	20	−86	−18
Occipital pole	R		3.41	10	−98	−14
Lingual gyrus	R		3.06	8	−84	−14
G- versus A-allele						
Superior frontal gyrus	R/L	1561	4.20/3.93	20/−18	−8/−8	68/70
Precentral gyrus	R/L		4.02/3.82	18/−32	−20/−8	72/62
Precuneous	R		3.88	8	−46	62
Superior parietal lobule	R		3.62	34	−40	64
Superior frontal gyrus	L	273	3.68	−4	14	64

X, *Y* and Z MNI coordinates indicate the location of peak voxel activation (or local maxima for subregions) within each cluster. L = left; R = right.

regions showed a positive correlation with alcohol dependence severity. Similar results were obtained when using the functionally defined right putamen as the seed region and when using ADS scores instead of the alcohol severity factor scores (see Supporting Information Tables S2 and S3; Figures S1 and S2). Whole-brain correlations of alcohol dependence severity factor scores with the PPI contrasts using the anatomically and functionally defined left putamen as seed regions were also performed; however, consistent with the previous findings of a largely right lateralized response inhibition network (e.g. Aron & Poldrack 2006), no significantly correlated regions of activation were observed for either left seed region. The anatomically defined right putamen seed region was used for all further PPI analyses as we sought to determine fronto-striatal connectivity that was unbiased by variations in striatal functional activation. In addition, the influence of participant age was investigated through an exploratory correlation of alcohol dependence severity with the Successful Stopping versus Go PPI with the age range restricted from 21 to 33 years old (resulting in $n = 16$). The restricted age range results were found to be virtually identical to that of the full sample.

OPRM1 genotype was found to moderate the PPI and alcohol dependence severity correlation in bilateral fronto-polar cortex, superior frontal gyrus, middle frontal gyrus, IFG, right caudate, OFC and right occipital pole/fusiform gyrus, such that A-allele homozygotes exhibited a steeper regression slope describing the relationship between alcohol dependence severity and functional connectivity with the right putamen. In contrast, G-allele carriers showed a steeper slope in the superior frontal and parietal gyri, precuneus and bilateral precentral gyri as compared with A-allele homozygotes (Table 5).

DISCUSSION

This study found an association between alcohol dependence severity and fronto-striatal functional connectivity, such that individuals with more severe alcohol dependence exhibited less fronto-striatal connectivity during response inhibition on the SST. Furthermore, *OPRM1* genotype was found to moderate functional connectivity between the right putamen and prefrontal regions, as well as the correlation strength of fronto-striatal connectivity with alcohol dependence severity in frontal and posterior regions during response inhibition.

The SST has proven useful in the study of addictive disorders as a loss of cognitive control, including diminished response inhibition, has been hypothesized to accompany the transition from voluntary to compulsive drug-taking behavior (Kalivas & Volkow 2005). Differential neural activation during SST performance has been found to relate to heaviness of smoking in adolescent smokers (Galván *et al.* 2011) and risk status for alcohol use disorders (i.e. low alcohol responders; Schuckit *et al.* 2012). It has also been found to discriminate individuals with alcohol use disorders from healthy controls (Li *et al.* 2009). Results from a sample of stimulant abusers and their non-drug using siblings indicate that self-control deficits on the SST in both groups are associated with white matter disorganization in the right PFC. Furthermore, duration of drug exposure was found to have effects on white matter organization, albeit less anatomically extensive. Together, these findings suggest that deficiencies in response inhibition may represent substance-induced neuro-adaptation as well as a heritable risk marker for substance abuse (Ersche *et al.* 2012).

In the present study, alcohol dependence severity was associated with diminished fronto-striatal functional connectivity during response inhibition. Reduced fronto-striatal connectivity has been previously associated with abnormal reward prediction error signaling during decision making in alcohol-dependent individuals (Park *et al.* 2010), and desynchrony of cortico-striatal-midbrain activation in alcoholics was observed during inhibitory control on a Stroop task (Schulte *et al.* 2012), suggesting an important role of this pathway in modulating impulsive behavior. Although PPI analyses preclude determining directionality of connectivity, evidence from an effective connectivity analysis points to a top-down controlled inhibitory process, mainly directed from prefrontal regions, during successful response inhibition (Jahfari *et al.* 2011), suggesting that the negative relationship between fronto-striatal connectivity and alcoholism severity reflects weaker prefrontal control of the striatum. This is consistent with the clinically observed transition to later stages of addiction, which is marked by loss of control of a prepotent response, namely alcohol use (Kalivas & Volkow 2005).

Precisely how fronto-striatal functional connectivity becomes impaired in alcohol dependence remains unknown. The consistent finding of white matter damage, including demyelination and axonal subtraction (Kril *et al.* 1997), within chronic alcohol abusing samples represents one possible explanation for the weakened functional connectivity observed. To our knowledge, no studies have reported white matter damage directly related to fronto-striatal connectivity; however, alcohol is found to affect white matter brain regions differentially, with the frontal lobes identified as among the more compromised regions (Kril *et al.* 1997; Pfefferbaum *et al.* 1997; Harper *et al.* 2003). Thus, it is possible that alcohol-induced damage to white matter tracks directly involved in the connectivity between the frontal lobes and striatum may exist, just not at detectable levels given our current approaches. Alternatively, alcohol's desynchronizing effects within and between neural networks

(Ehlers, Wills & Havstad 2012) may be compromising fronto-striatal communication, and following prolonged use, this desynchrony may result in impaired functional connectivity between these brain regions.

While SST behavioral performance was uncorrelated with alcohol dependence severity in this sample, a larger sample may reveal behavioral differences that accompany the neural disparities observed. Conversely, the blood oxygen level-dependent signal may represent a more sensitive marker of group differences than behavioral phenotypes (i.e. task performance) and may partially explain the discrepancies in behavioral response inhibition previously observed in similar populations (Lawrence *et al.* 2009; Courtney *et al.* 2012). Thus, the correlations observed between severity and connectivity highlight a role for connectivity measures as relevant markers for alcoholism.

Genetic analyses found that G-allele carriers of the *OPRM1* gene exhibited greater functional connectivity of the putamen to the caudate, orbitofrontal and middle-frontal regions, suggesting that the A-allele homozygotes may display weaker prefrontal inhibitory control through this pathway at matched levels of clinical impairments. The cluster parameter estimates would suggest that the genotype differences observed in the fronto-striatal functional connectivity during response inhibition act to cancel each other out, resulting in no observable connectivity for these regions in the main effect analysis. This result highlights the importance of considering individual differences variables, including genotype, in addicted samples. Furthermore, *OPRM1* genotype was found to moderate the association between alcoholism severity and striatal connectivity in frontal and posterior regions. Specifically, A-allele homozygotes of the *OPRM1* gene showed a stronger negative association between alcohol dependence severity and connectivity to the right caudate and OFC during response inhibition, suggesting that the fronto-striatal pathway is more strongly affected by alcoholism in these individuals at similar behavioral levels of inhibitory control to the G-allele carriers. These results suggest that the G-allele of the *OPRM1* gene, which is typically thought of as a risk allele for a host of alcohol phenotypes, may not be a risk factor through pathways of alcoholism severity and inhibitory control. Instead, the risk conferred by the G-allele may be unique to goal-directed alcohol use mediated through neural reward processes (Ray *et al.* 2012). Thus, these different pathways influencing risk for the development and maintenance of alcoholism (i.e. reward sensitivity versus inhibitory control deficits) may account for the seemingly disparate findings.

This study must be considered in light of its strengths and limitations. The strength of this study is the well-ascertained sample of individuals with alcohol dependence. Although prospective genotyping in this study precluded the use of a control group, recent studies of response inhibition in substance users suggested the majority of variance lies within the substance-using group (Li *et al.* 2009; Filbey *et al.* 2012; Galván *et al.* 2011). Thus, the within-group analysis performed here avoids extraneous sources of variation and allows investigation of the relationship between alcohol dependence severity and fronto-striatal connectivity. The use of a factor score comprised of various clinical dimensions of alcoholism represents another significant strength. The severity factor allowed for the global examination of several important dimensions of alcoholism, including craving, DSM-IV symptoms and the experience of a host of negative consequences related to alcohol dependence, while minimizing the number of statistical comparisons. The small sample size represents a weakness of the current study. However, for the genotype analyses, the genotype-balanced sample mitigated some of the statistical power issues that may have arisen if *post hoc* genetic groupings were used. It should be noted, however, that the results obtained from the prospective genotyping groups may be different in a genetically unselected sample. Lastly, the exclusion of treatment seekers and individuals endorsing significant alcohol withdrawal symptoms led to a sample consisting of individuals with mild-to-moderate levels of alcohol dependence. Future research is needed to validate these findings in larger and more severe samples of alcohol dependence.

In conclusion, the results of this study provide the first evidence for alcoholism-mediated differences in fronto-striatal connectivity during response inhibition on the SST. These disparities are likely related to the findings of Ersche *et al.* (2012), showing poor prefrontal white matter organization related to response inhibition in substance abusing individuals and their siblings. Thus, the observed association between alcohol dependence severity and reduced fronto-striatal connectivity suggests a plausible pathway of addiction vulnerability that may be moderated by impairments in inhibitory control and genetic variation subserving those systems.

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Authors Contribution

LAR was responsible for the study concept and design. LAR and KEC contributed to the acquisition of MRI data. KEC and DGG assisted with data analysis and interpretation of findings. KEC drafted the manuscript. LAR and DGG provided critical revision of the manuscript for important intellectual content. All authors critically reviewed content and approved final version for publication.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1 Results of the functional connectivity analysis indicating a negative relationship between fronto-striatal connectivity strength during Successful Stopping versus Go and measures of alcohol dependence severity.
Figure S2 Results of the functional connectivity analysis indicating a negative relationship between fronto-striatal connectivity strength during Successful Stopping versus Go and measures of alcohol dependence severity.
Table S1 Locations of significant activation for Go versus baseline, Successful Stopping versus baseline, and Successful Stopping versus Unsuccessful Stopping contrasts across all subjects.
Table S2 Functional connectivity results for psychophysiological interaction (PPI) correlation with alcohol dependence severity factor scores using a functionally defined right putamen seed region determined for each participant individually.
Table S3 Functional connectivity results for psychophysiological interaction (PPI) correlation with alcohol dependence scale (ADS) scores using the putamen as an anatomically defined region of interest determined for each participant individually.