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Article

Effects of Alcohol Dependence Severity on Neural Correlates of Delay Discounting

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Abstract

Aims: The current study examines the relationship between alcohol dependence severity and delay discounting neural activation.
Methods: Participants ($N = 17$; 6 female) completed measures of alcohol use and severity and a functional magnetic resonance imaging version of a delay discounting task.
Results: Alcohol dependence severity was negatively associated with activation in superior frontal gyrus during impulsive relative to delayed decisions, and positively associated with activation in paracingulate gyrus and frontal pole in delayed relative to impulsive decisions.
Conclusions: These results indicate that alcohol dependence severity tracks closely with dysregulations in cognitive control and reward evaluation areas during impulsive and delayed decisions, respectively. Delay discounting may be a useful construct in capturing these cognitive dysregulations as alcohol use disorders become more severe.
Short summary: Among alcohol-dependent individuals, alcohol dependence severity is associated with overactivation of ventromedial prefrontal areas during delayed and underactivation of dorsolateral prefrontal regions during impulsive reward decisions.

INTRODUCTION

As alcohol use disorder (AUD) remains a public health concern, there have been concerted efforts to develop measures sensitive to AUD development and chronicity. One promising measure has been propensity for impulsive decision-making, such as a tendency to choose smaller, sooner rewards (SS) over larger, later rewards (LL). Recently, Gray and MacKillop (2015) have posited that this specific form of impulsivity, known as delay discounting, represents a potential endophenotype for addiction, including AUD.

Indeed, many studies find that individuals with AUD exhibit greater levels of impulsive choice than non-addicted individuals (Mitchell *et al.*, 2005; Bobova *et al.*, 2009). Within one prospective study that assessed behavioral impulsivity among adolescents over 2 years, delay discounting predicted a composite index of alcohol frequency and heavy use (Fernie *et al.*, 2013). Studies have also found that delay discounting is moderately heritable (Anokhin *et al.*, 2015), and that individuals with a family history of alcohol and/or other drug use disorders exhibit higher rates of delay discounting than those without such a history (Dougherty *et al.*, 2014).

Recent functional magnetic resonance imaging (fMRI) studies have begun to elucidate neural systems associated with delay discounting to explore its utility as an endophenotype for AUD, with a specific focus on activity that differentiates individuals with AUD from healthy controls. Relative to delayed decisions, impulsive decisions are associated with greater activation of the ventral striatum, medial prefrontal cortex and anterior insula. These areas have been implicated in a reward processing network, such that the strength of activation in these regions is correlated with the monetary value of stimuli (Kable and Glimcher, 2007; Carter *et al.*, 2010). These activations during SS are higher in abstinent alcohol-dependent individuals than in healthy controls (Boettiger *et al.*, 2007). For LL decisions, abstinent alcohol-dependent individuals relative to controls demonstrate

significantly higher activity in the right lateral orbitofrontal cortex (OFC; Boettiger *et al.*, 2007). Additionally, recent work posits that dorsolateral prefrontal cortex (dlPFC) may be particularly hyperactivated for male AUD individuals during delayed and cognitively difficult decisions (Amlung *et al.*, 2014). Such fronto-parietal activity is associated with cognitive control and restraint, suggesting that alcohol-dependent individuals recruit these brain regions more when making the delayed choice.

A current gap in the delay discounting literature consists of understanding the function of alcohol dependence severity. As existing neuroimaging and behavioral delay discounting studies primarily compare alcohol-dependent individuals with non-substance using healthy controls (Boettiger *et al.*, 2007, 2009) or non-dependent heavy drinkers (Amlung *et al.*, 2014), it is currently unclear whether activation for delay discounting neurobiological substrates vary as a function of alcohol dependence severity. There is evidence that delay discounting may be related to alcohol dependence by greater premorbid neurodevelopmental impulsivity that leads to earlier and greater quantities of alcohol consumption (Anokhin *et al.*, 2011). Neurotoxic effects of alcohol disproportionately affect frontal lobes (Crews and Boettiger, 2009). Therefore, neural activation during intertemporal decision-making may vary as a function of alcohol dependence severity. Further, addressing this gap is important to elucidating the predictive specificity of delay discounting as an endophenotype for AUD.

To date, only one study has explicitly examined effects of alcohol use severity on delay discounting; this study found that severity of alcohol-related problems among both treatment seeking and non-treatment seeking heavy drinkers was associated with increased activation in the anterior insula, parietal lobe, supplementary motor area, temporal gyrus and inferior frontal gyrus in LL compared to SS choices (Claus *et al.*, 2011). These results are consistent with the delay discounting literature broadly, and suggest that exaggerated recruitment of cognitive control areas during LL choices track closely with dependence severity. Replication and extension of these crucial findings are warranted. Specifically, inclusion of additional validated measures of alcohol dependence would strengthen the identified associations between dependence severity and neural activation. Further, as this previous study utilized a sample of heavy drinkers with a range of drinking behavior, examination of dependence severity among individuals who meet diagnostic criteria for AUD can elucidate neural patterns in decision-making that characterize AUD severity, as compared to heavy drinking more broadly.

In summary, to address gaps in the delay discounting literature regarding the effects of alcohol dependence severity, the aim of this study is to use fMRI to explore whether dependence severity is related to neural activation during SS vs LL and LL vs SS decisions among a sample of alcohol-dependent individuals. Consistent with previous work on AUD and delay discounting (e.g. Boettiger *et al.*, 2007; Claus *et al.*, 2011), we hypothesize (i) dependence severity is positively associated with activation during SS relative to LL decisions in the ventral striatum, nucleus accumbens and associated areas in the temporal lobe; and (ii) dependence severity is positively associated with activation during LL relative to SS decisions in the OFC and dlPFC.

MATERIALS AND METHODS

Participants and procedures

Participants were non-treatment seekers with AUD ($N = 17$) recruited through advertisements to examine subjective responses to alcohol. Interested individuals completed a phone screening to assess drinking patterns and psychiatric and medical conditions. Individuals eligible after this phone screening were invited to a laboratory visit. After providing written consent, participants completed individual difference measures, including all alcohol-related assessments described below. Inclusion criteria were (i) ages 21–55 years and (ii) current (i.e. past month) alcohol dependence as assessed by the Structured Clinical Interview for the DSM-IV (First *et al.*, 1996); Exclusion criteria were (i) diagnosis of major depressive disorder, bipolar disorder, psychosis or suicidal ideation, (ii) current use of illicit substances other than marijuana, verified by toxicology screening and (iii) DSM-IV diagnosis of substance abuse or dependence for any illicit substance (including marijuana) within the past 12 months.

The MRI sample of 17 alcohol-dependent individuals was selected from the full-baseline sample ($N = 295$) of a study examining subjective response to alcohol (Ray *et al.*, 2013). Participants were required to remain abstinent from alcohol for at least 24 h prior to their scan, verified by a Breathalyzer test (Draeger, Telford, PA). Participants received $190 for completion of the baseline and scanning visits. The study protocol was approved by the University of California, Los Angeles (UCLA) Institutional Review Board.

Alcohol problem severity measures

Participants completed six alcohol-related measures. A 30-day timeline follow-back (TLFB; Sobell and Sobell, 1992) assessed alcohol drinks per drinking day and percent drinking days. The Structured Clinical Interview for the DSM-IV (SCID-IV; First *et al.*, 1996) was used under the supervision of a licensed clinical psychologist to assess alcohol dependence and exclusionary psychiatric diagnoses. The DSM-IV symptom participants endorsed for alcohol abuse and dependence were tabulated for a maximum of 11 symptoms; this tabulation method has been used as a measure of AUD severity (MacKillop *et al.*, 2010; Amlung *et al.*, 2014). Participants completed the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar; Sullivan *et al.*, 1989), Alcohol Dependence Scale (ADS; Skinner and Allen, 1982), Drinkers Inventory of Consequences questionnaire (DrInC-2R; Miller *et al.*, 1995) and the Penn Alcohol Craving Scale (PACS; Flannery *et al.*, 1999). At the scanning session, no individuals reported clinically significant levels of alcohol withdrawal (CIWA-Ar scores ≤ 6).

To capture shared variance of alcohol dependence severity across these measures and reduce the number of statistical tests, we conducted a principal components analysis using promax oblique rotation across the ADS, PACS, CIWA, DSM-IV symptom count and DrInC-2R for the full-study sample ($N = 295$). This analysis yields one meaningful factor that loads highly onto all comprised scales (Moallem *et al.*, 2013).

fMRI task

In the scanner, participants completed an fMRI version of the Monetary Choice Questionnaire (MCQ), a well-validated delay discounting task (DDT; Kirby *et al.*, 1999). The task lasted 3 min and consisted of 27 trials (Fig. 1). As participants had prior experience with this task as part of the larger study, we did not conduct practice trials. Each trial began with the presentation of two values at the left and right sides of the screen, representing a variable amount of money available immediately (range = $11–80) and a greater amount available in the future with variable delay (range = $25–85, 7–186 day delays). These represented hypothetical rewards that were not tied to study payment; there is evidence that individual

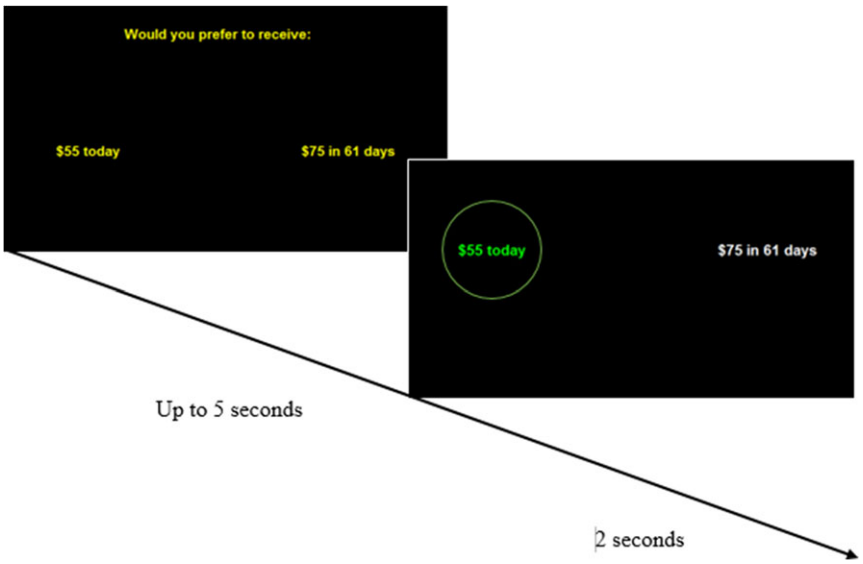

Fig. 1. Sample trial of the DDT. Participants were provided a choice between a smaller amount of money that was available sooner (SS) and a larger amount of money available after variable delay (LL). Participants were provided up to 5 s to make a decision; after the 5-s window, the chosen decision was highlighted on the screen for 2 s until the next trial began.

discount rates and neural correlates do not differ when delay discounting decisions are for hypothetical vs real rewards (Lagorio and Madden, 2005; Bickel *et al.*, 2010; Matusiewicz *et al.*, 2013). Left–right placement of the immediate amount was randomized throughout the task to reduce visual order effects. Participants chose between the two stimuli by pressing a button on a response pad corresponding to the left–right placement of their choice; choosing the immediate and delayed amount represented SS and LL decisions, respectively. Presentation of the stimuli and response interval was 5 s. A jittered 2-s delay followed each response period, during which the participant's choice on the screen was highlighted.

Discount rates were calculated using a one-parameter hyperbolic model. This parameter, k, is characterized by the equation: $V_d = V/(1 + kd)$. V_d is the present discounted value of the reinforcer, V is the objective value of the reinforcer, k is a constant that reflects the rate of discounting and d is the temporal delay to the delivery of the reinforcer (Mazur, 1987). Therefore, k measures tendency to prefer SS to LL decisions; steep discounting rates correspond to short reward delay.

Presentation of all stimuli and response collection were programmed using E-Prime 2.1. Visual stimuli were presented using MRI-compatible goggles (Resonance Technologies, Van Nuys, CA).

MRI acquisition

Neuroimaging was conducted using a 3-T Siemens Trio MRI scanner at the UCLA Ahmanson-Lovelace Brain Mapping Center. The protocol began with structural scans, followed by the DDT. A T_2-weighted, high-resolution, matched-bandwidth (MBW), anatomical scan and a magnetization-prepared rapid-acquisition gradient echo (MPRAGE) were acquired for each participant for registration (TR, 1.9 s; TE, 2.26 ms; FOV, 250 mm; matrix, 256 × 256; saggital plane; slice thickness, 1 mm; 176 slices). The orientation for MBW and echoplanar image (EPI) scans was oblique axial to maximize brain coverage. The DDT scan included 105 functional T_2*-weighted EPIs (slice thickness, 4 mm; 34 slices; TR, 2 s; TE, 30 ms; 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 for equilibrium effects.

Preprocessing and registration

FSL 4.3.10 (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) was used for preprocessing and image analyses. Motion correction was conducted using the Motion Correction Linear Image Registration Tool (McFLIRT) with the estimated motion parameters entered as covariates in the model. Skull and non-brain tissue removal was conducted with the Brain Extraction Tool (BET). Images were smoothed using a full width at half maximum Gaussian Kernel (5 mm) and high-pass filtered (100 s cutoff) in the temporal domain using a Gaussian weighted straight line with the FMRI Expert Analysis Tool (FEAT, version 5.98). The EPI images were first registered to the MBW, then to the MPRAGE using affine linear transformations. Finally, registration to standard MNI (Montreal Neurological Institute, MNI avg152 template) space for group-level analyses was refined using FSL's FMRIB's nonlinear image registration tool (FNIRT). Three participants were excluded from further analysis; one participant exhibited excessive motion (exceeding 3 mm of translation), and two participants yielded below an *a priori* defined minimum of 5 SS or LL responses for the SS vs LL contrast, yielding a full-data sample of 17 participants.

Analytic plan

DDT responses were classified as SS or LL. The number of SS decisions out of 27 trials ranged from 5 to 22, and participants averaged 16.1 SS and 10.2 LL responses. As the distribution of individual hyperbolic discount rates (k) is typically skewed, we conducted a natural log transformation of discount rates, which is consistent with the majority of delay discounting studies (Simpson and Vuchinich, 2000). Whole-brain analyses were conducted in a multilevel mixed-effects analysis, with participants as a random variable. SS and LL regressors were created in FEAT by convolving double-gamma hemodynamic responses to stick functions representing trial

onsets and response duration plus 2 s that the response was highlighted. Temporal derivatives were included as covariates to improve response sensitivity. Contrasts of SS vs LL and LL vs SS were created to examine activation to impulsive and delayed decisions, respectively.

Individual contrast maps were then normalized into MNI standard space and analyzed for the entire sample. All group-level analyses utilized FLAME stage 1 (FMRIB Local Analysis of Mixed Effects; Woolrich *et al.*, 2004), which performs linear mixed-effects regression at each voxel, and accounts for within-subject variance using weighted values. *Z*-statistic images were thresholded with cluster-based corrections based on Gaussian Random Fields theory, with cluster-forming threshold of $Z = 2.3$ and a cluster-probability threshold of $P < 0.05$ (Worsley, 2001). To test our main hypotheses, alcohol dependence severity factor (ADSF) scores were modeled as explanatory variables for the whole-brain contrast maps. Ln(k) was also examined as a predictor to elucidate activation of regions associated with discount rate. Cluster activation peaks (i.e. MNI coordinates associated with maximum contrast *Z* statistics) were localized within anatomical regions defined using the FSL Harvard–Oxford cortical structural atlas. To visualize and confirm directionality of associations, percent signal change within significantly activated areas was plotted against ln(k) and the ADSF, respectively. Percent signal change was calculated for voxels within a 5-mm radius sphere from each cluster's peak for participants within respective groups.

RESULTS

Demographic, behavioral and alcohol use variables are presented in Table 1. The principal components analysis for the five alcohol indices (ADS, PACS, DSM-IV symptom count, DrInC-2R and CIWA-Ar) revealed one significant factor, using a cutoff of Eigenvalue greater than one (first Eigenvalue = 2.749, second Eigenvalue = 0.858). Each index loaded onto the factor as follows: ADS = 0.83, CIWA-AR = 0.48, DrInC-2R = 0.85, PACS = 0.74, DSM-IV symptom count = 0.75. This ADSF accounted for 55% of the variance among the measures, and was used as the sole dependence severity predictor in subsequent analyses. The ADSF was not significantly associated with the number of impulsive decisions ($r(17) = 0.39$, $P = 0.12$).

Table 1. Sample characteristics ($n = 17$)

Variable	*M* (SD)
Age	30.65 (9.24)
ADSF	0.30 (0.88)
PACS	19.59 (5.86)
DSM-IV symptom count	6.35 (2.26)
ADS	42.18 (5.73)
DrInC-2R	47.24 (20.23)
30-day TLFB % heavy-drinking days	41% (18.9)
30-day TLFB drinks per drinking day	6.17 (1.96)
Delay discounting measures	
MCQ overall k	0.05 (0.07)
MCQ ln(k)	−4.35 (1.81)
Reaction time SS (s)	2.86 (0.46)
Reaction time LL (s)	2.79 (0.55)
Variable	% (*n*)
Sex (% female)	35.3% ($n = 6$)
Race/ethnicity	
White	58.8% ($n = 10$)
Black	11.8% ($n = 2$)
Asian	5.9% ($n = 1$)
Latino	23.5% ($n = 4$)

Notes: SS = smaller sooner, LL = larger later decisions.
ADSF was calculated from the other alcohol measures and was the primary alcohol severity variable used in analyses.

The average DDT parameter, k, was 0.05, indicating that participants on average equally valued $100 today and $70 in a week. Reaction times for SS and LL decisions were not significantly different ($P = 0.74$). Additionally, there were no significant associations between ADSF and reaction time for SS and LL decisions (Ps > 0.50). ADSF was, however, marginally positively associated with natural log-transformed k values ($r(17) = 0.45$, $P = 0.07$), indicating that dependence severity was positively associated with greater individual discount rate which is consistent with both behavioral (Amlung and MacKillop, 2011) and fMRI delay discounting studies (Claus *et al.*, 2011).

Neural correlates of delay discounting

For the fMRI analyses, SS relative to LL produced significantly greater activation in the precuneus, angular gyrus and occipital cortex (Fig. 2a; Table 2a). The whole-brain analysis with discount rates as a predictor of brain response revealed that ln(k) was positively associated with increases in the precuneus, anterior insula and supplementary motor area (Fig. 2b and c; Table 2b) for SS vs LL decisions. Ln(k) was not associated with activation in areas for LL vs SS decisions.

AUD severity effects on neural correlates of delay discounting

ADSF was negatively associated with superior frontal gyrus activity in SS vs LL (Fig. 3a and b; Table 2c). In LL vs SS, ADSF was positively associated with activation in the paracingulate gyrus and frontal pole (Fig. 3c and d; Table 2c).

DISCUSSION

This study sought to elucidate the neural bases of delay discounting in a sample of alcohol-dependent individuals and specifically, to test whether alcohol dependence severity was associated with neural responses to this task. This is critical to understanding how brain activation during impulsive and future-oriented decision-making differs across levels of alcoholism severity. Results from this study have implications for delay discounting as a potential endophenotype for addiction. Behavioral results from our study found that the sample's average discounting rate is similar to those reported previously in heavy drinkers, which are elevated relative to healthy controls (Mitchell *et al.*, 2005). Individuals with more severe dependence demonstrated higher discounting rates, providing evidence that discounting rates are marginally associated with severity even among those meeting diagnostic criteria for AUD.

Across the entire sample, fMRI results indicated that impulsive relative to delayed choices activated brain areas in the parietal and occipital lobes, including the precuneus, angular gyrus and occipital cortex. These regions have widely been reported in the delay discounting literature (Bickel *et al.*, 2010; Carter *et al.*, 2010), and are involved in spatially directed attention, converging multisensory perception and visual focus (Cavanna and Trimble, 2006; Seghier, 2013), thus indicating our findings converge with previous studies of neural activation during delay discounting.

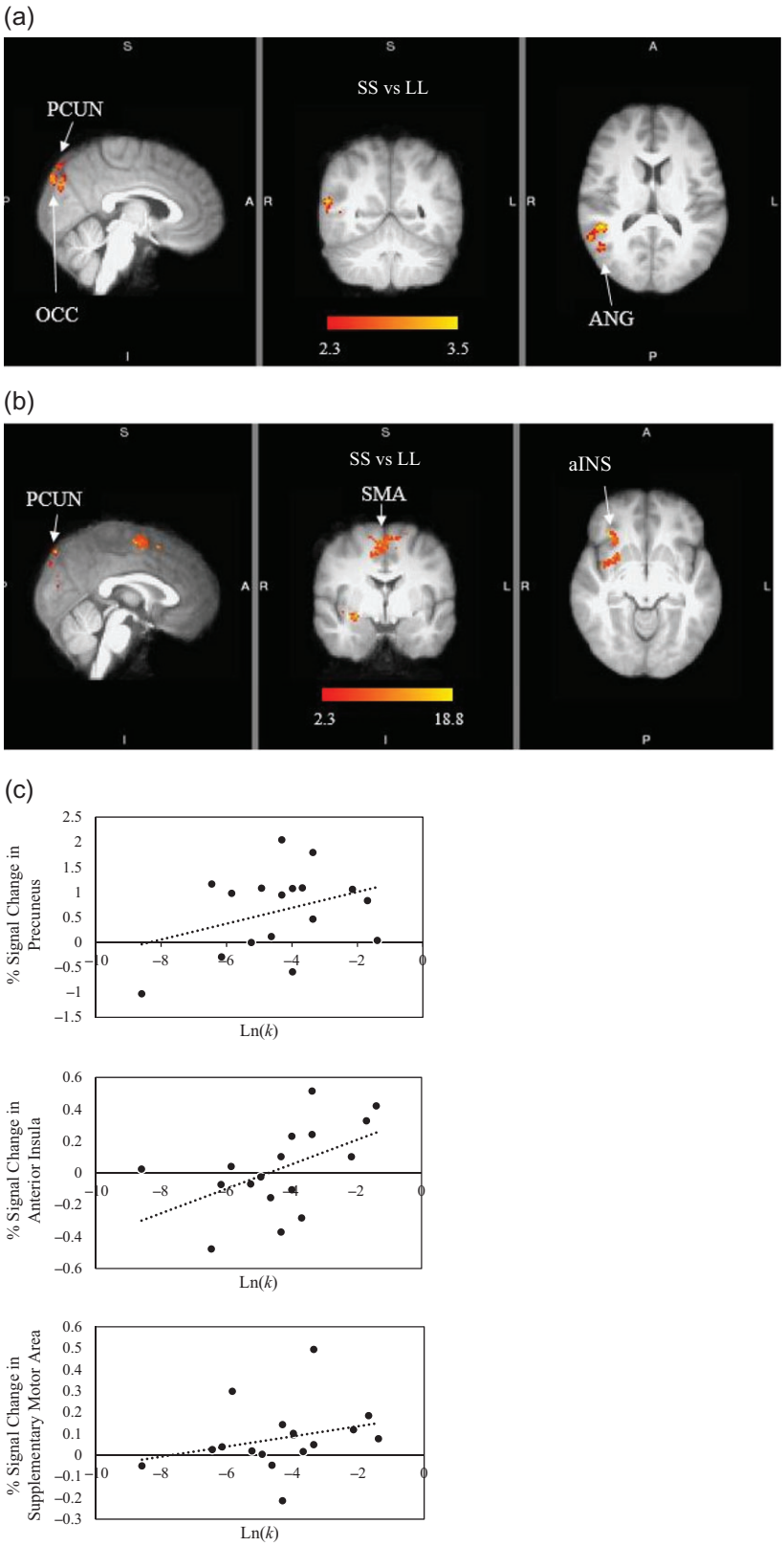

Fig. 2. Neural activation across all participants associated with impulsive vs delayed decisions and individual discount rate. (**a**) Neural activation associated with greater activation during impulsive (SS) vs delayed (LL) decisions across all participants, including occipital cortex, precuneus and angular gyrus. No regions showed significant activation for the LL vs SS contrast. PCUN = precuneus, OCC = occipital cortex, ANG = angular gyrus. (**b**) Positive association between log-transformed individuals' discounting rate (ln(*k*)) and activation during impulsive (SS) vs delayed (LL) decisions in the precuneus, anterior insula and supplementary motor area. SMA = supplementary motor area, aINS = anterior insula. (**c**) Scatterplots 1–3 visualizing each participant's log-transformed discounting rate and level of activation in (i) precuneus, (ii) anterior insula and (iii) supplementary motor area. Less positive values indicate higher delay discounting rates (i.e. greater impulsivity). No regions showed significant activation for the LL vs SS contrast. Percent signal change for each area was calculated for 5 mm sphere generated around the peak contrast of the parameter estimate.

Table 2. Areas of activation for impulsive (SS) vs delayed (LL) and delayed vs impulsive decisions

SS vs LL	*P*-value	Hemisphere	Cluster size	Max *Z*-value	MNI *X*	MNI *Y*	MNI *Z*
(a) Group							
Precuneus	0.02	R/L	367	3.05	−2	−84	48
Angular gyrus	0.038	Right	349	3.17	60	−54	16
Occipital cortex	0.036	R/L	353	3.21	2	−90	38
(b) Ln(*k*)							
Precuneus	0.025	R/L	362	3.08	−2	−84	48
Anterior insula	0.038	Right	316	18.9	28	−2	−12
Supplementary motor area	0.011	R/L	391	16.5	2	−2	56
(c) ADSF							
Superior frontal gyrus	0.017	Right	397	3.34	10	8	72
LL vs SS							
Paracingulate gyrus	0.003	Right	541	3.39	−6	36	26
Frontal pole	0.044	R/L	338	3.3	34	64	8

Notes: Analyses are whole-brain cluster-corrected at $Z > 2.3$, $P < 0.05$. Results shown for these contrasts across (a) all subjects (group), as well as effects of (b) discounting rate (ln(*k*)) and (c) ADSF.

In delayed relative to impulsive decisions, we had anticipated significant activation in OFC and dlPFC areas, which are cited in the literature for assigning representative value to stimuli and implicated in organized cognitive reasoning (Bechara, 2005). The present results indicated no significant OFC or PFC activation for this contrast. Several studies have reported activation in the dlPFC but not the OFC during difficult and/or LL vs SS decisions among substance-dependent individuals (Monterosso *et al.*, 2007; Hoffman *et al.*, 2008). Other studies found that both dlPFC and OFC are activated during LL vs SS decisions (McClure *et al.*, 2004, 2007). One study of heavy drinkers, however, found that the prefrontal cortex, cingulate cortex and precuneus are activated during delayed decisions (Claus *et al.*, 2011). Additionally, one previous study of alcohol-dependent and heavy-drinking males reported that activations for delayed vs impulsive decisions within the dlPFC, precuneus and middle occipital gyrus were non-significant after correcting for multiple comparisons (Amlung *et al.*, 2014). As delay discounting neural correlates have not been extensively studied among substance users, these mixed findings may indicate that such OFC and PFC activation during delayed decisions may not be a robust finding in these populations, or may require additional larger fMRI studies of individuals with AUD to corroborate activation in these areas.

Activation in limbic system regions (i.e. anterior insula), supplementary motor area and the precuneus was positively correlated with individual discount rate, such that higher activation in these regions was associated with steeper delay discounting. These results overall replicate the delay discounting literature. Activation in the supplementary motor area has previously been identified as activated during both impulsive (Amlung *et al.*, 2014) and delayed decisions even after controlling for motor responses during the task, and is posited to contribute to deliberative decision-making in delay discounting (Bickel *et al.*, 2010). Anterior insula and precuneus activation have also been found to correlate with impulsive responding (Bickel *et al.*, 2010), though one study found that steeper discounting was positively associated with anterior insula activation during delayed decisions (Claus *et al.*, 2011). There is additional evidence that anterior insula activity decreases as the value of delayed rewards increase (Luhmann *et al.*, 2008). As the anterior insula is frequently recruited during cognitive conflict and particularly somatosensory proprioception (Paulus, 2007; Allen *et al.*, 2016), this area may be implicated as a key neural basis for delay discounting more broadly (Carter *et al.*, 2010), as well as a region associated with how steeply alcohol-dependent individuals discount rewards during impulsive vs delayed decisions.

This study is the first to find that, among alcohol-dependent individuals, alcohol dependence severity is negatively associated with activation of cognitive control regions during impulsive decisions and positively associated with activation of reward evaluation regions during delayed decisions. Specifically, dependence severity was negatively associated with activation of dlPFC regions, such as the superior frontal gyrus (Du Boisgueheneuc *et al.*, 2006; Klein *et al.*, 2010), during impulsive relative to delayed decisions. For delayed relative to impulsive decisions, dependence severity was associated with increased activation of the frontal pole and paracingulate gyrus. These results replicate and extend the one previous study (Claus *et al.*, 2011) that had examined alcohol-related problems and delay discounting in two ways. First, the present study demonstrates that these activations are found not only in the use of screening tools such as the AUDIT, but also across six validated alcohol use and severity measures that were combined into a composite index of alcohol dependence severity. Second, these results demonstrate that the increased recruitment of ventromedial prefrontal cortex (vmPFC) areas, such as the frontal pole and paracingulate gyrus (Bechara *et al.*, 1999; Clithero and Rangel, 2014), may be required to successfully delay reward for severely dependent individuals, and that alcohol dependence severity is not related to activation of limbic regions typically associated with reward orientation during either SS vs LL or LL vs SS decisions.

Overall, activation in limbic regions during impulsive relative to delayed decisions as a function of discount rate corroborate competing systems theory (Bechara, 2005). This theory posits that intertemporal decision-making occurs in the context of competing activation in regions comprising the PFC ('executive' system) and limbic areas, including the amygdala, nucleus accumbens and related structures ('impulsive' system). Studies have expanded on the executive system and have found that the vmPFC encodes reward values, and that self-control requires modulation of vmPFC activation by the dlPFC, a region associated with working memory and cognitive flexibility (Lee and Seo, 2007; Hare *et al.*, 2009). Recent delay discounting studies have similarly found that the interactive activation of vmPFC and dlPFC (Baumgartner *et al.*, 2011; Rudorf and Hare, 2014; Saraiva and Marshall, 2015) contribute to cognitive self-regulation in decision-making.

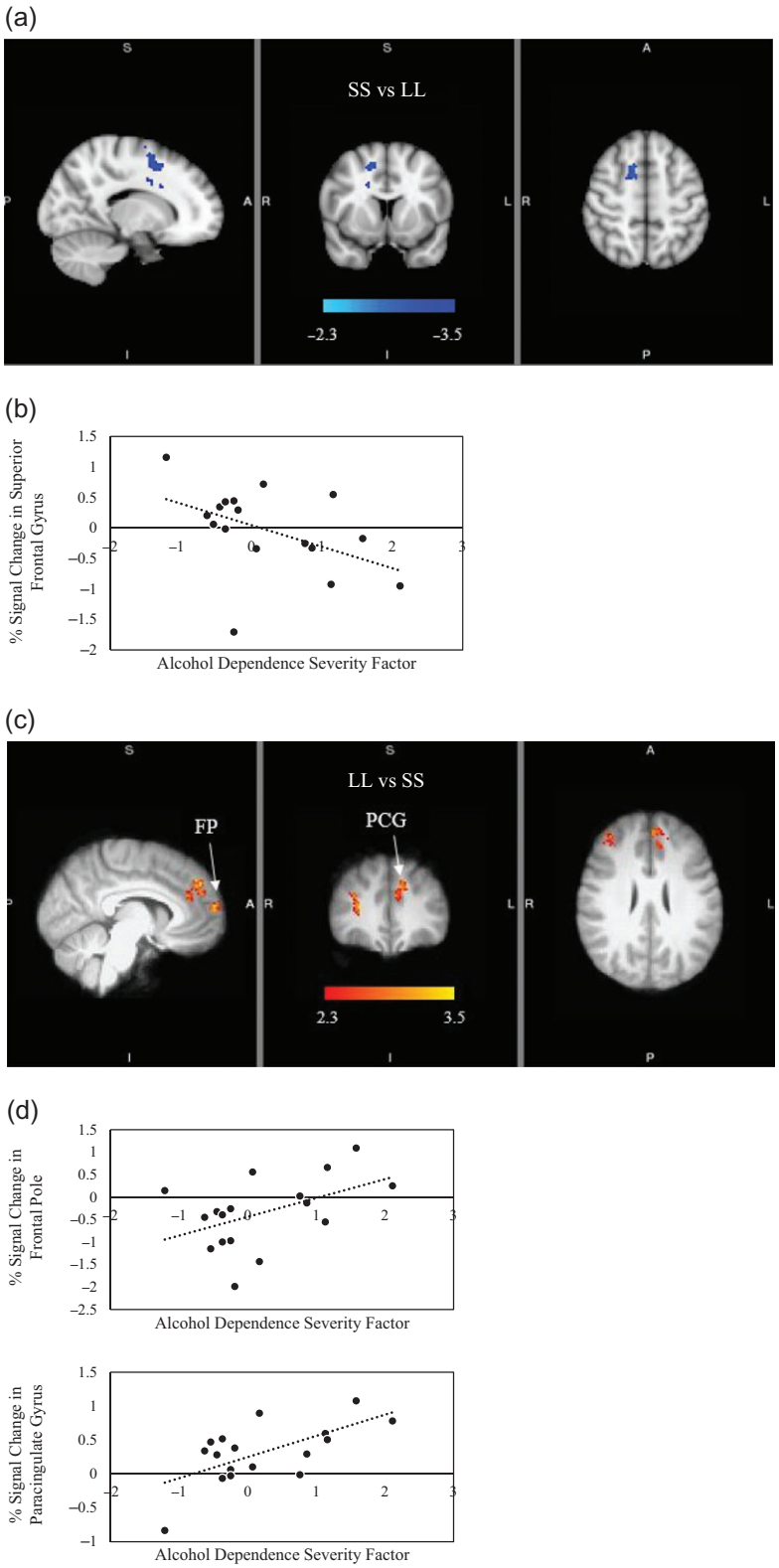

Fig. 3. Associations between alcohol dependence severity and neural activation during impulsive vs delayed and delayed vs impulsive decisions. (**a**) Negative association between individuals' ADSF and activation in the superior frontal gyrus during SS vs LL. Areas denoted in blue indicate less activation. (**b**) Scatterplot visualizing each participant's ADSF and level of activation in the superior frontal gyrus. Percent signal change for each area was calculated for 5 mm sphere generated around the peak contrast of the parameter estimate. (**c**) Positive association between individuals' ADSF and activation in the frontal pole and paracingulate gyrus during LL vs SS. FP = frontal pole, PCG = paracingulate gyrus. (**d**) Scatterplot visualizing each participant's ADSF and level of activation in the frontal pole and paracingulate gyrus.

Within this competing systems framework, the present results suggest that impulsive regions concerned with reward orientation and representation are especially active in impulsive decisions among alcohol-dependent individuals, but these activations do not vary as a function of dependence severity. Additionally, the most dependent individuals exhibited a lack of dlPFC organized cognitive control (i.e. underactivation) during impulsive decisions and requisite vmPFC-driven reward valuation (i.e. overactivation) during delayed decisions; as alcohol dependence severity was also positively associated with individuals' discount rates, this suggests that the most severely dependent individuals exhibit elevated impulsivity via deficient regulatory functioning of the executive system rather than an over-activated limbic system. Previous studies have found that alcohol-dependent individuals demonstrate higher fronto-parietal network resting-state connectivity relative to healthy controls (Jansen *et al.*, 2015). Additionally, functional connectivity between the lateral PFC and vmPFC has been shown to mediate the relationship between measures of cognitive self-regulation and delay discounting (Guo and Feng, 2015). Within the context of these studies, the relationship between dependence severity and vmPFC/dlPFC activation during decision-making may provide support for neurobiological models that frame addiction as an allostatic phenomenon (Koob and Volkow, 2010) or a pathology of motivation and control (Kalivas and Volkow, 2005). Both models posit that the later stages of addiction are characterized by dysregulated fronto-parietal networks which contribute to a loss of cognitive control and inability to limit substance use. Both models also consolidate findings that heavily dependent individuals display sensitization toward specific drug cues rather than a generalized reward hypersensitivity (Volkow *et al.*, 2010; Goldstein and Volkow, 2011). Therefore, our results that dependence severity is not associated with activation in reward-oriented limbic areas during a monetary decision task and that the most dependent individuals exhibit executive system dysregulation in impulsive and delayed decisions are consistent with both models' predictions.

These findings also largely replicate and extend previous neuroimaging work on the relationship between alcohol dependence severity and delay discounting neural correlates. Specifically, as these patterns of activation are found across both heavy drinkers and alcohol-dependent individuals, these results not only identify brain regions associated with decision-making as it relates to alcohol dependence severity, but also support the validity of delay discounting in assessing cognitive dysregulation during decision-making across a large range of alcohol use and dependence. Corroborating this applicability and biological specificity is an important step in understanding a construct's potential as an endophenotype, and providing a foundation for testing additional endophenotype criteria, discussed further below.

The present study should be considered in lights of its strengths and limitations. As a cross-sectional study, these results cannot provide information on causality or separate effects of premorbid neurological impulsivity from the chronic consequences of alcohol use. Additionally, the small sample size may have resulted in limited power to detect effects, and may have been further limited by relatively fewer delayed trials; therefore, future studies that incorporate more participants particularly to include additional trials assessing neural correlates of delayed decisions, are needed to corroborate these results. While the task paradigm in this study elicited results that are consistent with previous delay discounting studies, there are several other DDT in the fMRI literature (e.g. Claus *et al.*, 2011) that may help to address this limitation. These tasks include greater numbers of items than the MCQ and provide an initial run to calculate individual k values. The monetary amounts used in the subsequent discounting task are then adapted to individuals' k to ensure a balanced numbers of responses for regressors of interest. Examination of these tasks in future studies may be useful with heavy substance-using populations that demonstrate higher levels of impulsivity. Another potential limitation of the implemented task is that decisions were not tied to real rewards. Although studies have not found significant differences in discount rates or neural correlates when decisions are for hypothetical vs real rewards (Lagorio and Madden, 2005; Bickel *et al.*, 2010; Matusiewicz *et al.*, 2013), some behavioral economics studies have found significantly different discount rates for hypothetical and real rewards (Camerer and Hogarth, 1999; Coller and Williams, 1999). Given this mixed literature, it is possible that these findings may not generalize for all types of delay discounting decisions.

There are several important future directions in further understanding the relationship between dependence severity and delay discounting, including dependence severity effects on variations of decision-making tasks; beyond the titrated stimuli values, it is unclear if these effects persist for non-monetary stimuli, tasks that incorporate potential for loss, and other parameters that capture real-world decision-making. There are also several ways to analyze DDT outcomes. Analyses that also examine easy vs difficult decisions (e.g. Amlung *et al.*, 2014) or incorporate beta and gamma parameters (e.g. McClure *et al.*, 2004) may be needed to fully elucidate neural bases for delay discounting in AUD individuals, as well as to elicit activation of the ventral striatum and nucleus accumbens. Relatedly, future ROI studies that focus on the OFC are warranted, as OFC activation tracks closely with magnitude of reward for healthy controls but not for heavy-drinking populations, such as cocaine users (Goldstein *et al.*, 2007). Another potential area of exploration is the impact of genetics on delay discounting as it is related to dependence severity. Given that delay discounting is posited as a potential endophenotype for addiction (Gray and MacKillop, 2015), such research is necessary to fulfill one of the core requirements for an endophenotype, namely, that the association between an endophenotype and behavior must partly derive from shared genes (De Geus and Boomsma, 2001).

In conclusion, the present results shed light on regions that are associated with dependence severity during impulsive and delayed decisions within an alcohol-dependent sample. This information is potentially useful for identifying brain regions that appear to be particularly dysregulated among individuals with more severe AUD, as such individuals may display deficits in effective cognitive control more than reward orientation, which in turn may serve as intervention targets for future treatments

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CONFLICT OF INTEREST STATEMENT

LAR has previously received study medication from Pfizer and consulted for GlaxoSmithKline. The authors have no other potential conflicts of interest to disclose.

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