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Neural and Behavioral Mechanisms of Impulsive Choice in Alcohol Use Disorder

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Abstract

Background—Alcohol dependence has repeatedly been associated with impulsive choice, or the inability to choose large delayed rewards over smaller, but more immediate rewards. However, the neural basis of impulsive choice in alcohol use disorders is not well understood.

Methods—One hundred fifty one individuals with a range of alcohol use from social drinking to severe alcohol dependence completed a delay discounting task while undergoing functional magnetic resonance imaging (fMRI). Participants received customized trials designed to ensure an approximately equivalent number of immediate responses.

Results—Delaying gratification recruited regions involved in cognitive control, conflict monitoring, and the interpretation of somatic states. Individuals with more severe alcohol use problems showed increased discounting of delayed rewards and greater activation in several regions including supplementary motor area, insula/orbitofrontal cortex, inferior frontal gyrus, and the precuneus.

Conclusions—These results suggest that impulsive choice in alcohol dependence is the result of functional anomalies in widely distributed, but interconnected brain regions involved in cognitive and emotional control. Further, our results suggest that the neural mechanisms of impulsive choice in alcohol use disorders both overlaps with that observed in previous studies, and shows that individuals with alcohol use disorders recruit additional mechanisms when making intertemporal choices.

Keywords

Delay discounting; intertemporal choice; impulsivity; delayed gratification

Introduction

Among individuals with an alcohol use disorder (AUD), the choice between choosing to drink and not to drink is often biased towards the immediately rewarding alcohol without careful consideration of the future consequences. In fact, the inability to forgo immediate gratification (i.e. impulsive choice) is considered a core feature of alcohol use disorders (Bickel and Marsch, 2001; Redish et al., 2008).

Impulsive choice is often measured with the delay discounting task (Rachlin et al., 1991; Rachlin, 2000; Madden, 2003; Mitchell et al., 2005; Rachlin, 2000; Tesch and Sanfey,

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2008). In the task, two options are presented: a small monetary reward that available soon (e.g. \$10 now) or a larger monetary reward that is available after some delay (e.g. \$30 in 2 weeks). Impulsive choice is defined as the selection of the more immediate option. Discounting behavior is best described by a hyperbolic function (see Equation 1), where discounting is relatively small at short time delays and increases with increased time delays (Mazur, 2001).

$$V=A/1+kD \quad (\text{Eq. 1})$$

In Equation 1, V is the discounted value of the delayed reward, A is the value of the delayed reward, D is the time delay until the reward (A) could be obtained, and k is the discounting parameter that influences how much a delayed reward is discounted.

Using the hyperbolic discounting framework, several studies have shown increased discounting in alcohol abusing individuals. All individuals show some degree of impulsive choice (Green et al., 1994), but individuals who are at increased risk for developing an alcohol use disorder and also those individuals who meet criteria for alcohol dependence tend to show greater discounting of future rewards than controls. For example, increased discounting rates (k) have been found in currently using alcoholics when compared to abstinent alcoholics (Petry, 2001), early-onset vs. late-onset alcoholics (Dom et al., 2006), and family history positive vs. negative (females only, Petry et al., 2002). In addition, this increased discounting of future rewards has been observed regardless of whether participants are choosing between different amounts of money or alcohol (e.g. a drink now vs. 10 drinks in a week) (Kollins, 2003; Petry, 2001; Petry et al., 2002). Further, it has been suggested that the amount a person discounts is a stable trait, suggesting that the observed differences between alcohol dependent and non-dependent individuals are not the result of prolonged use of a substance (Ohmura et al., 2006). The role of impulsive choice is significant in alcohol dependence, and gaining a better understanding will provide key insights into the nature of the neurocognitive dysfunction associated with the disorder.

Despite many studies showing increased discounting of the future in AUD, the neural mechanisms underlying impulsive choice in AUD are not known. If impulsive choice in those with alcohol use disorders is a consequence of the alcohol use itself, then different mechanisms may be expected to produce impulsive choice in those with AUDs than in individuals without AUDs. However, if a tendency toward impulsive choice is a cause of alcohol use disorders, then similar mechanisms should underlie impulsive choice in those with and without alcohol use disorders. In one of the only studies of abstinent alcoholics and controls, Boettiger et al. (2007) used fMRI to examine delay discounting in abstinent alcoholics and controls. Participants decided whether they preferred an immediate or delayed reward, and the primary analysis focused on those brain regions that correlated with an impulsive choice ratio (ICR; i.e. the proportion of now vs. later responses). Positive relationships were found between ICR and activity in dorsal PFC, parietal cortex, and the parahippocampal gyrus, and a negative relationship was found with lateral OFC. In addition, group differences (controls > abstinent alcoholics) were observed in these regions, which complimented differences in ICR. These results suggest that differences in impulsive choice are related to impaired frontal control mechanisms rather than striatal dysfunction, which has typically been associated with reward processing (Cardinal et al., 2002; Volkow and Fowler, 2000).

To formally test the role of cortical and subcortical contributions to impulsive choice, we used fMRI to scan a large sample of individuals with varying degrees of alcohol use problems during a delay discounting task (Rachlin et al., 1991; Rachlin, 2000). The purpose

of this study was threefold. First, we examined the neural substrates of intertemporal choice by examining impulsive and non-impulsive choices. Second, we examined individual differences in discounting rates to determine those brain regions that correlate with greater impulsivity. Finally, we examined the mechanisms by which individuals with AUDs make impulsive choices. It was predicted that measures of alcohol use disorders would be associated with increased discounting as well as differential BOLD activation.

Materials and Methods

Participants

One hundred sixty heavy drinking individuals (47 females) were included in this study. Participants were recruited from the greater Albuquerque metropolitan region through advertisements placed in local print, online media, and radio advertisements, and were paid a total of \$120 for completing a baseline session during which questionnaire data was completed and a separate neuroimaging session that lasted approximately 2 hours.

The total sample consisted of both non-treatment seeking ($n=93$) and treatment seeking subjects ($n=67$) who were participating in a treatment study. For the non-treatment sample, participants had to report binge drinking (5 or more drinks per drinking occasion for men, 4 or more for women) at least 5 times in the past month. Those participants seeking treatment were required to report a desire to quit drinking to enter into the study. Participants were required to stop drinking 24 hours prior to participating in the study and were required to have a breath alcohol concentration of 0.00. Treatment seekers completed the Clinical Institute Withdrawal Assessment of Alcohol Scale (Sullivan et al., 1989) to assess acute withdrawal. To qualify for the scanning session, treatment seeking participants could not show significant signs of withdrawal. All scans on treatment seekers were baseline scans, and thus participants had not received any treatment at the time the scanning session was completed. The final sample included a range of alcohol problems (AUDIT range = 6–38), providing an ideal sample for assessing the relationships between neural correlates of impulsive choice and alcohol use problems. To that end, all participants completed a delay discounting fMRI task (see details below) to assess the neural systems that underlie impulsive choice and alcohol use problems. Subjects also completed other tasks, including an alcohol cue exposure task.

Measures

All participants completed an initial baseline session during which drinking histories were established for the past 90 days using the Timeline Follow Back method (Sobell et al., 1986). In addition, participants completed several measures of their alcohol use, comorbid substance use, and related disorders, including the Structured Clinical Interview for DSM Disorders (SCID) (First et al., 2002) and the Alcohol Use Disorder Identification Test (AUDIT, Saunders et al., 1993).

Procedure

Upon arrival to the laboratory, participants provided informed consent, and completed a baseline questionnaire session. At the beginning of the session, participants were breathalyzed and continued with filling out questionnaires only if the breath alcohol concentration was 0. Upon completion of self-report and interview based assessments, participants were invited back to the laboratory to complete an MRI session. Participants were instructed to avoid drinking alcohol for 24 hours before the scanning session, and were required to have a BrAC of 0 upon arrival for the scanning session. All treatment seeking subjects were required to have a score of less than 8 on the Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar, Sullivan et al., 1989).

A modification of a delay discounting procedure (Rachlin et al., 1991) was used to examine intertemporal choice; all monetary choices were hypothetical and were customized based on each participant's estimated discounting parameter (see below). The primary design of the task was a 2×2, with difficulty (difficult choices vs. easy choices) and choice bias (choose early reward vs. choose later reward) manipulated. In order to avoid repeating options across many experimental trials, we used 3 levels of potential reward (small, medium, and large), 3 levels of more immediate reward time delay (today, two weeks, one month) and 2 levels of time to the delayed reward from the immediate reward (two weeks, one month). Although we manipulated trial difficulty, these analyses will not be presented here.

Initial estimate of k

During the practice, participants completed 4 sequences of trials to determine the reversal point, or the point at which the delayed value and the immediate value are considered psychologically equivalent. The values used for the practice session were delayed rewards of \$50, \$50, \$500, and \$1000 at delays of 2 weeks, 1 month, 2 weeks, and 1 month, respectively. The values used to generate the initial estimate of k were chosen to be representative of the magnitudes of values that would be encountered in the experimental task. While more trials that encompassed a greater number of delay periods for each delayed value would have provided the most stable estimate of the discounting parameter k, the number of trials used was constrained by the amount of time that was available for practice while participants were lying in the scanner. Because the use of the estimated k was successful in balancing the number of now and later responses across participants, it is reasonable to conclude that the gross estimation procedure provided a good estimate of k.

Once all four reversal points were obtained for a given participant, an initial estimate of k was derived using the hyperbolic discounting framework and was subsequently used to generate customized choice options for each participant according to the algorithm below. The initial estimation of k allowed for the generation of trial sequences that biased participants towards now or later responses and kept the number of trials within each condition approximately balanced.

Generation of intertemporal choice trials

For experimental trials, a constrained random number was generated based on the trial magnitude (small: 45–55; medium: 450–550; large: 900–1100); this value served as the delayed reward (V_D). To compute the immediate reward for a trial, the randomly chosen value was entered into the equation $V_I = x(V_D / (1 + kD))$. Depending on the difficulty and choice bias, x was 1.15, .85, 1.05, or .95 (bias now easy, bias later easy, bias now hard, bias later hard). For example, if the delayed reward was \$50 in 2 weeks and the participant's discounting rate was .01, the reversal point would be equal to $1 * (50 / (1 + .01 * 14)) = \43.85 . If the trial type was a bias now hard, the value offered immediately would be $1.05 * (50 / (1 + .01 * 14)) = \46.05 , which should be preferred by the participant over the \$50 in two weeks. If the trial type was bias later easy, the value offered now would be $.85 * (50 / (1 + .01 * 14)) = \37.28 , which should bias the participant to choose the later option of \$50 in two weeks. As part of the trial generation algorithm, we compared immediate and delayed reward values to ensure that the delayed reward was greater than the immediate reward. If the delayed reward was smaller than the immediate reward, we changed the immediate reward to a value that was \$1 less than the delayed reward. If participants made a choice that was inconsistent with the bias condition (e.g. chose Now during a bias later trial), the scaling parameter (x) was adjusted to create more disparity between the two options.

An example trial sequence is displayed in Figure 1. Participants saw two options, one more immediate and one delayed, and had up to 4 seconds to make a response with a button press.

More immediate responses were made using a button press with the right index finger and selection of the delayed response was indicated with a button press using the right middle finger; all participants used the same response mapping. After making a choice, the option selected was surrounded with a green box for 2 seconds. Following the choice, a fixation cross was shown for 2–14 seconds before the onset of the next trial; fixations were of different lengths to introduce jitter into the design (Jezzard et al., 2001).

Participants completed a total of 18 trials per condition (bias now easy, bias now difficult, bias later easy, bias later difficult) divided across 2 runs, each lasting 6 minutes 18 seconds. The same optimized trial order (generated with OptSeq (Dale, 1999)) was used for each participant.

Image acquisition

All MRI data was collected on a 3T Siemens Trio (Erlangen, Germany) whole body scanner. Participants were placed in the scanner and a piece of tape was placed across the forehead to serve as feedback for movement reduction.

Prior to the acquisition of anatomical scans, localizer scans were acquired. An echo-planar gradient-echo pulse sequence (TR=2000ms, TE=29, flip angle=75°) was acquired with an 8-channel head coil, and images were acquired parallel to the ventral surface of a participant's orbitofrontal cortex to reduce signal dropout and distortion in this region (Deichmann et al., 2003). Each volume acquired consisted of 33 axial slices (64×64 matrix, 3.75 × 3.75 mm², 3.5 mm thickness, 1 mm gap). In addition, a high resolution T1-weighted MP-RAGE anatomical image was acquired (TR=2530ms, TE=1.64ms, flip angle=7°, 192 sagittal slices, 256×256 matrix, slice thickness = 1mm, no gap) for each participant.

Image analysis

The first six volumes of each functional run were discarded to allow the magnet to reach steady state. MCFLIRT (Jenkinson et al., 2002) (FMRIB) was used to motion correct images within a run; each image within the run was aligned to the first volume within the run. Images were then deskulled using BET, spatially smoothed with a 5 mm full-width half-max Gaussian kernel, temporally filtered using a high-pass filter of 50 sec, and grand mean intensity normalized; all of these steps were performed using FEAT (FMRIB Expert Analysis Tool) (Smith et al., 2004).

All data was analyzed two different ways. In the first analysis, regressors were created based on participant responses for the following conditions: Easy now, Easy later, Hard now, Hard later. The primary contrast of interest was selection of the Later option vs. the Earlier option (Later vs. Now). In addition, in order to control for any differences that may have emerged in hemodynamic response fitting as a result of using reaction times as stimulus durations, we also used a model in which each trial type was modeled using a constant duration and included a regressor that modeled reaction times for each decision. Again, the contrast of interest was a comparison of Later vs. Now responses. Second, to examine the potential special role of immediately available rewards (i.e. those trials in which a reward was offered today), we used the analysis strategy proposed by McClure et al (2006) which models Beta and Delta trials separately. More specifically, Beta trials, those trials in which a reward is available today, were modeled as a function of participant response (Beta_now and Beta_later) as dummy coded regressors. Delta trials, or all intertemporal choice trials, were modeled according to participant responses (Delta_now and Delta_later) as dummy coded regressors. We then examined the contrasts of Beta_now vs. Beta_later and Delta_now vs. Delta_later at the group level.

For each participant, regressors were created based on participant responses and experimental condition as described above. In the analyses, regressors was set to a value of 1 for both the decision period (participant's RT) plus the 2-second portion during which the selected option was highlighted. As described above, we also analyzed the data using RT as a covariate, in order to account for any differences between trial types in RT that may have influenced the model's fit of the BOLD response. Statistical analyses were performed using the general linear model as implemented in FEAT. Customized square waveforms representing the condition of interest and the duration of stimulus presentation were convolved with a double gamma hemodynamic response function. In addition, movement parameters estimated by MCFLIRT were used as covariates within the multiple regression. Time series analyses were conducted using FILM (Woolrich et al., 2004) (FMRIB Improved Linear Model) with local autocorrelation estimation. This first level analysis generated parameter estimates for each condition of interest; contrast maps were then computed using these parameter estimates. An average EPI map was registered to the participant's high-resolution anatomical image and the MNI 152 brain template using FLIRT to determine normalization parameters and these parameters were subsequently used to register contrast maps to the MNI template (Jenkinson et al., 2002) (FMRIB Linear Image Registration Tool).

Individual runs were combined within subjects using a fixed effects model, which determines estimates of each participant's contrast map as well as variance map. These second level analyses were used in a third level analysis using FLAME (Woolrich et al., 2004) (FMRIB Local Analysis of Mixed Effects) stage 1 only. Before computing group level statistics, all second level images were registered to the MNI template. When examining group level maps at the whole brain level, we used minimum cluster sizes of $64 \times 2 \times 2 \text{ mm}^3$ voxels thresholded at $z=2.58$, $p<.005$. We used AlphaSim (Forman et al., 1995; Saad et al., 2006) to determine the minimum cluster size to reduce alpha to .01 when images were thresholded at $p=.005$.

In order to examine correlations between discounting rates and the contrasts of Later>Now, we computed all discounting rates according to the method described below, and included $\ln(k)$ as a covariate in our group level analysis. $\ln(k)$ was used instead of k because k is not normally distributed. In addition to correlations with discounting rates, we also examined the relationship between AUDIT scores and contrasts of interest. In order to avoid the problem of non-independent tests (Kriegeskorte et al., 2009; Vul et al., 2009), we did not restrict our correlation analyses to our main effect masks, but rather examined correlations at the whole brain level.

Computation of discounting rate (k)

Because our task was designed to minimize differences in the number of immediate and delayed options selected by each group, we were unable to compute k according to standard procedures that involve using reversal points. Thus, to obtain estimates of the discounting parameter for trials that were completed during the fMRI session, we used a logistic regression model to compute k (Wileyto et al., 2004) instead of fitting reversal points to Equation 1. k was estimated by predicting responses (immediate vs. delayed) from a ratio of immediate to delayed rewards and the time difference between the immediate and delayed reward.

Thus, the model used to predict responses was:

$$\sum \beta X = \beta_1(1 - 1/R) + \beta_2(t), \quad (\text{Eq. 2})$$

where R is equal to:

$$\frac{1}{1+(\beta_2+\beta_1) * t}, \quad (\text{Eq. 3})$$

and k is then equal to β_2/β_1 . This method for computing k has been compared to the traditional nonlinear fitting method, and has been found to produce highly similar discounting rate estimates (Wileyto et al., 2004).

Results

Participants

There was a wide range of hazardous drinking (mean AUDIT total=17.90 (6.82)) within the sample, suggesting that our sample is representative of the range of drinking related problems in the larger population. Nine participants were dropped for motion exceeding 4 mm for a total usable sample of 151 participants. As seen in Table 1, the non-treatment seeking and treatment seeking participants were significantly different in the relative severity of alcohol use problems. However, combining the two samples is advantageous because doing so gives a wider range of drinking related problems, alcohol use, and discounting behavior.

Discounting parameter

Because k values are not normally distributed, a log transformation of k was used in all analyses. Overall, the mean discounting parameter was .027 (s.d.= .097, range=.001 – .963), meaning that a \$100 reward offered in 1 month would be equivalent to approximately \$55 offered immediately. In addition, we computed the median and 25th and 75th percentiles of k in order to more fully understand the distribution of this variable (k(25)=.012, k(50)=.029, k(75)=.086). These discounting rates are within the range of discounting rates reported in previous studies of alcohol use (Kollins, 2003; Mitchell et al., 2005; Petry, 2001), suggesting that our adaptation procedure did not influence the behavioral performance on the task. Also consistent with previous studies (Dom et al., 2006; Kollins, 2003; Mitchell et al., 2005; Petry, 2001; Petry et al., 2002), discounting rates correlated significantly with severity of drinking as measured by the AUDIT (Saunders et al., 1993) ($r(149) = .24, p = .003$).

Choice proportions

Because the delay discounting task used in this study was designed to minimize between subject differences in selection of the impulsive option, we expected that the number of choices of earlier and later options would be equivalent. However, participants did choose the earlier, more impulsive option more frequently (60.7%) than the more delayed option (39.2%; $t(150)=10.88, p<.001$).

Reaction times

Comparing decision times on now and later responses, we found that selection of the earlier option was faster (2213 (s.d.=381) milliseconds (ms)) than selection of the later option (2326 (s.d.=394) ms) ($F(1, 150)=39.56, p<.001$). Correlations between $\ln(k)$ and reaction times during the selection of the more immediate option ($r(149) = .36, p<.001$) and selection of the delayed option ($r(149) = .37, p<.001$) were significant (Fig. 2), such that more impulsive individuals were actually slower to make responses, suggesting that these intertemporal choices were more difficult for more impulsive individuals.

BOLD responses

We compared Now and Later responses across all participants using the contrasts of Now>Later and Later>Now. In addition, we examined the correlation between each contrast and 1) discounting rates ($\ln(k)$) to determine those brain regions that covaried with impulsivity and 2) scores on the AUDIT to determine how alcohol use severity covaried with activation differences.

Main effects—In order to determine which brain regions were involved in impulsive choice, we compared trials in which participants chose the smaller, more immediate option to trials in which the more delayed option was selected using a dependent samples t-test. This contrast showed activation differences primarily in right occipital cortex and cuneus, bilateral inferior frontal/orbitofrontal gyrus (IFG/OFG), and middle temporal gyrus (Fig 3 and Table 2). Conversely, brain regions that showed greater activation during the selection of the more delayed option compared to selection of the more immediate comprised a network including left postcentral gyrus, posterior insula, left lateral prefrontal cortex (middle frontal gyrus (MFG) and IFG), anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), caudate, and precuneus (Fig. 3 and Table 2). When controlling for reaction times on each trial, the main effect maps showed very similar effects as the analysis without an RT covariate. The Later > Now contrast contained a larger anterior cingulate cluster than the original analysis, which was the result of 2 separate cingulate clusters merging into the same cluster. In the Now > Later contrast, clusters in the precentral gyrus, right cerebellum, bilateral STG, and OFC were smaller in size, but continued to emerge at significant levels.

To determine whether decisions involving immediately available rewards were different from decisions that involved two delayed rewards, we examined the contrast of Now responses versus Later responses in Beta trials and Delta trials separately. The contrast of Later > Now and Now > Later for trials in which 2 delayed options (Delta) were presented revealed activation in similar areas as reported above and in Table 2, although slightly different cluster sizes were found. For trials in which an immediately available reward (Beta) was presented, we found some unique regions emerge in the comparison of Now and Later responses. In particular, we found that Now responses engaged SMA and cuneus/precuneus to a greater degree than Later responses.¹

To determine those brain regions that differ as a function of discounting rates, we examined the correlation between $\ln(k)$ and activation differences in the Later>Now contrast. This analysis allowed us to determine how impulsivity influenced brain activation differences between these trial types. When comparing selection of the delayed option to the immediate option, we found that greater impulsivity was associated with greater activation in left OFG/insula and angular gyrus (see Table 3).

Correlations with AUD severity—To examine the relationship between AUD severity and activation during intertemporal choice, we tested correlations between a measure of hazardous drinking (AUDIT total) and activation in the Later>Now contrast. In order to choose the more delayed response and avoid the impulsive choice, individuals with more severe alcohol problems recruited right cuneus, left anterior insula/OFG, inferior parietal lobe, left supplementary motor area (SMA), middle temporal gyrus, and right inferior frontal gyrus to a greater degree compared to individuals with fewer alcohol problems. In order to

¹We also modeled Now vs. Later decisions separately by each magnitude level, and examined the main effect of Now > Later and Later > Now collapsed across all conditions. However, in this analysis, 23 participants were dropped because they failed to make responses in at least one of the 6 conditions (now vs. later response at each of 3 levels of reward magnitude), making the contrast between now and later at a given level of magnitude unusable. Of note, when choices were modeled as a function of magnitude, the main effect of Now > Later resulted in significant clusters in both nucleus accumbens and amygdala.

confirm that the observed correlations were positive with the Later>Now contrast, we plotted mean percent signal change within each significant area against AUDIT scores (Fig. 4 and Table 4). In all cases, greater severity of alcohol use problems was associated with a greater difference in signal change between later and now responses. When we ran the same correlational analysis controlling for RT, we found that correlations between the AUDIT and Later>Now contrast showed similar activation patterns, with some minor differences. In the RT covariate analysis, SMA was no longer correlated with AUDIT scores, but we did find additional correlations in the rostral anterior cingulate.

Examination of the correlation between AUDIT scores and the Beta_now vs. Beta_later and Delta_now vs. Delta_later mostly confirmed the findings from the main analysis. The Beta_later > Beta_now contrast showed significant positive correlations with AUDIT in early visual processing regions including the occipital pole and lateral occipital cortex. In contrast the Delta_later > Delta_now contrast showed significant correlations with left OFC/insula, right IFG, anterior cingulate, thalamus/dorsal striatum, middle temporal gyrus, and the cuneus.

Discussion

We provide evidence that sheds light on behavioral and neural mechanisms that underlie impulsive choice in individuals with AUDs. We found that whereas impulsive choices strongly activated visual processing regions as well as inferior frontal regions, selection of the delayed response engaged regions involved in behavioral control (e.g. IFG) and perception of emotional states (e.g. insula). In addition, greater discounting of future rewards was associated with greater activation of the insula/OFG in the Later>Now contrast. Greater discounting was also correlated with reaction time, suggesting that impulsive choice is deliberate rather than rash. Finally, we found that individuals with greater hazardous drinking showed increased discounting of future rewards as well as increased activation in several areas during the selection of the more delayed option compared to the more immediate option. As with the correlations between discounting rates and activation, the correlations with AUD severity suggest that individuals with greater alcohol problems require more effort and resources to delay gratification.

The current study contributes to knowledge regarding the neural mechanisms of intertemporal choice. For example, we found several regions that differed during the selection of the immediate and delayed options. Selection of the earlier option engaged lateral occipital cortex as well as bilateral IFG and right OFG and extensive activation throughout the temporal lobe, whereas selection of the later option resulted in activation primarily in pre/postcentral gyrus, left IFG, left MFG, and posterior insula. In addition, when trials including immediately available awards (Beta) were analyzed separately, we found that Now responses engaged SMA and cuneus to a greater degree than Later responses. The finding that bilateral IFG and left MFG are involved in impulsive choices is surprising given that these areas are known to contribute to inhibition/interference resolution and cognitive control (Aron, 2007; Wager and Smith, 2003). However, previous delay discounting findings have shown similar executive function regions during impulsive choice. For example, two previous studies found that activation in lateral PFC was positively associated with impulsive choice (Bickel et al., 2009; Boettiger et al., 2007). Increased response in SMA and cuneus during trials in which an immediate reward was available suggests enhanced saliency and value of the more immediate reward (Litt et al., *in press*), possibly acting in concert with lateral prefrontal regions to bias actions towards immediate rewards. Together with the current results, these data suggest that at least within the context of the delay discounting task, “control” may be implemented in order to obtain the immediate reward. Future studies are necessary to fully determine the role of control in

impulsive behavior and whether control is implemented effectively depending on the context. It is unlikely that choosing the immediate reward is as cognitively demanding as choosing to delay gratification, as evidenced by the increased reaction times for choosing the later option, but this does not preclude a role for control in impulsive decisions.

The results of the Later > Now contrast were similar to that observed in Wittman et al. (2007) who also showed posterior insula activation during the selection of the more delayed option. In addition, the finding of differential activation of the ACC in later and now responses suggests that choosing the more delayed option introduces conflict into the decision making process (Monterosso et al., 2007). Thus, one potential mechanism responsible for increased discounting is a reduced ability to overcome conflict associated with choosing the more delayed option when immediate options are present. Also of interest was the fact that more impulsive subjects (i.e. higher discounting rates) took longer to make decisions, suggesting potential differences in conflict resolution mechanisms. Increased RT accompanying greater impulsive choice has been reported previously, where adolescents with substance and conduct problems took longer to decide to pump air into a balloon despite more risky choices (Crowley et al., 2006). In summary, increased conflict may underlie impulsive decisions, but in more impulsive individuals the conflict resolution mechanism does not bias responses towards less impulsive decisions.

We found that individuals with more severe AUDs showed activation during the selection of the delayed response that was greater than that observed in individuals with fewer alcohol problems. Specifically, activation was correlated with alcohol problems in several areas, including left anterior insula/OFG, right IFG, SMA/rACC, cuneus, and inferior parietal lobe. The correlations with insula are interesting in light of several studies implicating the role of the insula in substance abuse (Naqvi and Bechara, 2009; Naqvi et al., 2007) and recent studies showing that the anterior insula is important for intertemporal choices when a delay condition is present (Luhmann et al., 2008). Increased activation differences between later and now responses in more severe users suggest that the insula may be necessary for individuals to delay gratification. The combination of activation in anterior insula in the Later>Now contrast suggests increased conflict, in terms of somatosensory representations (Critchley, 2005). Given the role of the anterior insula in the experience of negative events and bodily sensations (Paulus, 2007), consideration of delayed options may increase negative feelings and internal conflict, making these delayed gratification decision less appealing to individuals with more severe AUDs. Delaying gratification may be aversive to individuals with alcohol use problems, such that it is often worth choosing immediate rewards over delayed rewards. In addition to potential conflict of representations in insula, the finding of increased cingulate response during the selection of the later option compared to the earlier option in users with more severe alcohol problems also is suggestive of increased conflict. While our original analysis of Later vs. Now trials showed a correlation with SMA, controlling for RT in the image analysis resulted in significant correlations emerging in rACC rather than SMA. These results suggest that the SMA response was the result of slower reaction time in more impulsive participants. Moreover, the correlation between AUDIT and rACC response is consistent with increased response conflict. Several previous studies have implicated rACC in response conflict using tasks that require participants to overcome a strong prepotent response tendency (Fan et al., 2008; Milham and Banich, 2005; Orr and Weissman, 2009; Wittfoth et al., 2008). These results suggest that conflict resolution may be impaired in individuals with more severe AUDs, and this impairment may lead to impulsive decisions.

Correlations between the IFG activation in the later versus now contrast and severity of AUDs were also observed. The finding in IFG may represent increased difficulty withholding the immediate response or alternatively may result from increased selection

demands (Badre et al., 2005). Ballard and Knutson (2009) found that right IFG activated as a function of the interaction between magnitude and delay period, but the activation observed in their study was located more posterior to the cluster observed in the current study, suggesting that the activation was not the result of differences in delay period or magnitude perception. Overall, the current results suggest that brain activation underlying impulsive choice in AUDs is similar to that observed in healthy control subjects, given that others have noted similar activation patterns in healthy controls (Bickel et al., 2009; Monterosso et al., 2007; Wittmann et al., 2007). However, the findings within the anterior insula seem to be unique to impulsive choice in participants with AUD, suggesting that heavy alcohol use alters functioning of this region, possibly leading to greater levels of impulsive choice.

While this study has provided important information regarding the neural mechanisms that underlie impulsive choice in alcohol use disorders, one limitation that should be considered is the effect of reward magnitude on brain activation and choice (Estle et al., 2006). One potential limitation was the use of different magnitudes of rewards, given the well-known magnitude effect in delay discounting wherein larger rewards are discounted to a lesser degree than smaller rewards. As noted in the results section, when reward magnitude was included in the first level analysis, we found that selection of immediate rewards was associated with enhanced response in nucleus accumbens and amygdala, two regions that play an important role in impulsive decisions (Bechara, 2005). However, our correlations with AUDIT scores were not localized to regions known to be sensitive to magnitude (Ballard and Knutson, 2009). Thus, while the magnitude of a delayed reward affects brain activation, the correlations reported here are not likely to result from differences in magnitude representation. Future studies that allow for better control of subject responses across different reward magnitude levels will be important for better understanding the neural basis of the magnitude effect and its relationship to alcohol use disorders. Another potential limitation of the current study is the inability of discounting rates obtained during practice to accurately predict performance during the scanning portion of the protocol. Although our target response rate for immediate and delayed responses was 50%, on average participants chose the immediate option 60% of the time. Future studies may attempt to remedy this problem by providing a greater number of practice trials from which a better estimate of k would be obtained. The current study used only 4 reversal points to compute k , whereas several other studies have used at least 6 of these points. Even with more reversal points to estimate k , it is well known that the hyperbolic discounting function does not perfectly predict intertemporal choice, thus providing an upper limit in the predictability of choice behavior that is not 100%. An additional limitation of the current study is the lack of a non-drinking or light drinking control group. While the addition of a control group would bolster the interpretability of the current findings, the absence of a control group does not reduce the impact of the current study. First, examination of main effects across the contrasts of interest reveal similar patterns of activation that have been reported in previous studies of delay discounting, suggesting similar neural mechanisms underlie intertemporal choice in individuals at risk for developing alcohol dependence. Second, our primary aim in the present study was to determine the neural mechanisms responsible for increased impulsive choice in more severely dependent individuals. While a control group would have added more variability at the low end of AUDIT scores, it is unlikely that the relationship between hazardous drinking and choice-related activation would have been altered significantly. Finally, studies with “control” groups can be deceptive, since these “control” groups rarely control for all of the conditions that are comorbid with alcohol dependence (e.g., depression, anxiety, tobacco dependence, drug use, etc.) making the interpretation of these studies difficult.

In summary, this research investigated intertemporal choice in individuals with varying degrees of alcohol related problems and found several potential mechanisms that extend the previous literature on delay discounting as well as mechanisms that may underlie impulsive choice in addictive disorders. The present findings replicate previous reports in terms of the brain regions that are associated with impulsive choice. The findings also suggest, that in a large sample that spans low levels of abuse and severe dependence, the brain mechanisms that underlie impulsive choice are also associated with the severity of alcohol problems, which is consistent with the theory that deficits in impulse control are a cause rather than a consequence of alcohol use disorders. However, we also found different regions of activation that correlated with impulsive choice, suggesting that severe alcohol use may alter normal functioning and increase impulsive choice. Future longitudinal studies will be needed to fully address how these neural mechanisms of impulsive choice change over the course of an AUD.

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Figure 1.

Sample trial in delay discounting task. Participants were given two options, one smaller amount that was available sooner and one larger amount that was more delayed than the more immediate option. When a response was selected, the chosen option was highlighted for 2 seconds, and then a fixation cross was presented for a variable length intertrial interval (ITI).

Figure 2. Correlation between $\ln(k)$ and reaction times during the selection of the more immediate response (a) and the larger, more delayed option (b). More impulsive participants, as measured by $\ln(k)$, took longer to make a response during the delay discounting task, suggesting that impulsive choice is not necessarily a rash decision.

Figure 3.

Main effects of Now vs. Later contrast across all participants. In the Now>Later contrast (blue), impulsive choices activated regions of visual cortex and bilateral PFC. In contrast, selection of the more delayed option (yellow/orange) activated posterior insula, anterior and anterior cingulate cortex, and postcentral gyrus.

Figure 4.

Correlation between AUDIT scores and the contrast of Later > Now responses in the delay discounting task. Significant correlations were found in SMA, left insula, right IFG, and cuneus. In all cases, individuals with more severe alcohol problems showed a greater difference between Later and Now trials than individuals with fewer problems.

Table 1

Sample characterization

Measure	Non-treatment	Treatment
AUDIT*	14.82(5.54)	22.33 (6.00)
TLFB Average Drinks*	5.78 (2.19)	8.26(3.80)
Age*	25.93 (4.68)	39.67 (8.92)
%Male	71.43	70.00
% Smoker	50.55	45.00
% Marijuana Smokers (any use)*	49.45	31.67
% Marijuana Smokers (weekly use)*	27.47	15.00
BDI*	8.60 (7.58)	14.80 (9.14)

* significantly different at $p < .05$. AUDIT Alcohol Use Disorder Identification Test; TLFB Timeline Followback; BDI Beck Depression Inventory

Table 2

Main effects for the Now vs. Later contrast.

Contrast	Region	BA	Max Z	vox	x	y	z
Now>Later	Cuneus (R)	17	9.61	10387	14	-92	2
	Middle Temporal Gyrus (L)	22	5.49	1559	-52	-44	2
	Inferior Frontal Gyrus (L)	45	4.7	633	-52	22	4
	Precuneus (R)	7	4.92	320	26	-56	54
	Lingual Gyrus (L)	18	4.06	293	-16	-84	-12
	Inferior Frontal Gyrus (R)	45	4.3	245	54	26	10
	Cerebellum (L)		4.48	234	-18	-78	-38
	Precuneus (L)	7	4.95	210	-6	-56	46
	Precentral Gyrus (L)	4	3.94	197	-44	-12	44
	Middle Occipital Gyrus (L)	19	4.08	189	-30	-84	20
	Middle Temporal Gyrus (R)	21	3.8	156	50	-24	-12
	Cerebellum (R)		3.76	126	22	-74	-34
	Inferior Temporal Gyrus (R)	20	3.57	118	48	-6	-32
	Superior Temporal Gyrus (R)	38	3.67	111	32	10	-30
	Superior Temporal Gyrus (L)	38	3.31	105	-44	16	-32
	Cuneus (L)	18	3.93	102	-8	-76	10
	Inferior Occipital Gyrus (L)	18	3.33	97	-42	-80	-12
	Orbital Frontal Gyrus (R)	47/11	3.62	97	50	34	-12
Later>Now	Postcentral Gyrus (L)	3	5.58	2369	-38	-24	54
	Cuneus (L)	18	5.14	455	-6	-96	4
	Inferior Frontal Gyrus (L)	46	4.1	215	-40	36	10
	Insula (L)	13	4.58	177	-42	-6	8
	Superior Parietal Lobule (L)	7	3.56	171	-32	-76	44
	Cingulate Gyrus (L)	32	4.09	153	-4	28	36
	Parahippocampal Gyrus (R)	19	3.82	148	34	-40	-2
	Posterior Cingulate (L)	30	3.42	140	-22	-56	30
	Cerebellum (R)		4.07	140	20	-48	-26
	Transverse Temporal Gyrus (R)	41	3.61	116	50	-20	14

Contrast	Region	BA	Max Z	vox	x	y	z
	Middle Frontal Gyrus (L)	8	3.36	87	-24	26	40
	Cerebellum (R)		3.81	87	24	-52	-54
	Cingulate Gyrus (L)	31	3.42	77	0	-34	34
	Anterior Cingulate (L)	32	3.04	76	-6	36	20
	Caudate (L)		3.46	70	-14	14	8
	Cerebellum (R)		3.39	68	46	-70	-34
	Parahippocampal Gyrus (L)	30	3.5	65	-28	-40	2

BA=Brodman area, Max z = maximum z statistic within the cluster, vox=number of voxels in cluster. Coordinates are presented in MNI space.

Table 3

Correlations of discounting rates (ln(k)) and activation in the contrasts comparing Now and Later responses.

Contrast	Region	BA	Max Z	vox	x	y	z
Now>Later	Putamen (R)		3.25	145	26	-4	-6
Later>Now	Angular Gyrus (R)	40	3.36	244	56	-54	18
	Orbital Frontal/Insula (L) *	47/13	3.31	54	-28	26	0

BA=Brodmann area, Max z = maximum z statistic within the cluster, vox=number of voxels in cluster. Coordinates are presented in MNI space.

* Corrected for whole brain significance at alpha=.05.

Correlations between alcohol use severity as measured by the Alcohol Use Disorder Identification Test (AUDIT) and activation in the Later>Now contrast.

Table 4

Contrast	Region	BA	Max Z	vox	x	y	z
Later>Now	Cuneus (R)	18	3.95	496	12	-80	12
	Orbital Frontal Gyrus/Insula (L)	47/11	3.43	214	-38	24	-4
	Inferior Parietal Lobule (R)	40	3.67	170	50	-48	26
	Middle Temporal Gyrus (L)	21	3.55	161	-50	-34	-6
	Supplementary Motor Area (L)	6	3.31	101	0	6	64
	Inferior Frontal Gyrus (R)	47	3.51	95	50	28	0

BA=Brodmann area, Max z = maximum z statistic within the cluster, vox=number of voxels in cluster. Coordinates are presented in MNI space.