Interaction Between Family History of Alcoholism and Locus of Control in the Opioid Regulation of Impulsive Responding Under the Influence of Alcohol

Lee J. Altamirano, Howard L. Fields, Mark D’Esposito, and Charlotte A. Boettiger

Background: Naltrexone (NTX) is an opioid antagonist indicated for the treatment of alcoholism, which is not universally effective. Thus, identifying individual predictors of NTX’s behavioral effects is critical to optimizing its therapeutic use. Moreover, given the high rate of relapse during treatment for alcoholism, understanding NTX’s behavioral effects when combined with moderate ethanol intake is important. Our previous study of abstinent alcoholics and control subjects showed that a more internal Locus of Control score predicted increased impulsive choice on NTX (Mitchell et al., 2007, Neuropsychopharmacology 32:439–449). Here, we tested whether this predictive relationship remains in the context of moderate alcohol intake.

Methods: In this study, we tested the effect of acute NTX (50 mg) on impulsive choice, motor inhibition, and attentional bias after ingestion of moderate ethanol (0.3 g/kg, n = 30 subjects). Subjects included those recruited from a pool of ~1,200 UC Berkeley undergraduates on the basis of scores on the Barratt Impulsiveness Scale (BIS).

Results: Impulsive choice was positively correlated with breath alcohol concentration in placebo sessions. Locus of Control was again the sole predictor of NTX’s effect on decision making among subjects with a family history of alcoholism. We also found a weak interaction between BIS scores and NTX’s effect on impulsive choice.

Conclusions: Our results reinforce the predictive relationship between Locus of Control and NTX’s effect on decision making in those with a family history of alcoholism, suggesting a possible biological basis to this relationship.

Key Words: Decision Making, Delay Discounting, Ethanol, Impulsivity, Naltrexone.
to the variability in NTX's therapeutic efficacy. Here, we
deavored to test whether this personality factor, Locus of
Control, predicts NTX's effect on impulsive choice in a larger
sample in a clinically relevant context: after consumption of a
moderate dose of alcohol. When a patient samples alcohol
during NTX treatment, these "slips" less frequently precipi-
tate a full-blown relapse (Volpicelli et al., 1992). Although
several factors could underlie this therapeutic benefit, this
finding suggests that NTX effects on decision making may
persist in the context of moderate alcohol intake, helping to
favor the long-term benefits of stopping after just 1 or 2
drinks over the short-term benefits of subsequent drinking.

To determine whether the previously observed effect of
NTX on impulsive choice remains in humans under the influence
of a moderate alcohol dose, we used a modified delay-
discounting task, which allows for separate evaluation of
impulsive decision making and motor impulsiveness. In this
task, abstinent alcoholics select the smaller, sooner reward
option significantly more often than do moderate drinking
control subjects (Boettiger et al., 2007; Mitchell et al., 2005a,
2007). This tendency to choose impulsively was positively cor-
related with trait impulsivity as measured by the Barratt
Impulsiveness Scale (BIS) (Mitchell et al., 2005a). Using a
double-blind placebo-controlled randomized crossover
design, we tested whether impulsive choice was reduced in
healthy, young adults by a single acute dose of NTX (50 mg)
when subjects were under the influence of moderate alcohol.

Our earlier study also found that NTX reduced the "mismatch"
of choices in the dominant task condition and inferred choices in a control condition (Mitchell et al., 2007). Our
previous results supported the interpretation that this
effect was not caused by NTX effects on motor inhibition,
but rather on attentional bias toward large monetary rewards.
Thus, in this study, we included direct measures of motor con-
trol (Go–NoGo task) and attentional bias (dot-probe task).
This allowed us to determine whether a reduction in mis-
mismatch by NTX was attributable to improved motor inhibi-
tion or to reduced attentional bias toward large monetary
reward stimuli.

MATERIALS AND METHODS

Subjects

Subjects (n = 30) were recruited from the community (n = 15)
and from a University of California, Berkeley (UCB; n = 15),
undergraduate population prescreened on the basis of scores on the
BIS (Barratt, 1994). Students in the middle, upper, and lower
20th percentiles of BIS scores were targeted for recruitment. Stu-
dents and community participants did not differ in terms of BIS
scores (t28 = 0.49, p = 0.63) and were equally distributed across
the high-impulsive and low-impulsive groups (χ2(1) = 0.13, p = 1).
All subjects were healthy individuals 21 to 35 years old with no
history of alcohol or opioid abuse, neurological disorders, current
treatment for any psychological disorders, or current psychoactive
drug use, excluding nicotine, caffeine, and moderate alcohol. Sub-
jects provided written, informed consent, as approved by the UCB
Committee for the Protection of Human Subjects. Subjects partici-
pated in 2 sessions 296 hours apart (mean session separation time:
13.9 days) to allow for elimination of NTX between sessions (Lee
et al., 1988; Verebey et al., 1976). Sessions spanned ~5 hours, and
subjects received monetary compensation for participating. In addi-
tion to the behavioral testing (see "Behavioral Tasks"), during ses-
sion 1, subjects completed a standard battery of questionnaires (see
"Behavioral Inventories"). Subjects were instructed to abstain from
alcohol and unnecessary medications for 24 hours prior to each
session, and to eat a low fat, light meal approximately 1 hour
before arriving. Upon arrival, subjects were screened for alcohol
use via breathalyzer (FC-10; Lifeloc Inc., Wheat Ridge, CO) and
for psychoactive drug use via urine screen (Biotechnostix Inc.,
Markham, ON). A nonzero breath alcohol concentration (BrAC)
was grounds for exclusion, as was a sample positive for cocaine,
amphetamine, methamphetamine/MDMA, or opiates. Because of the
long half-life of THC, urine samples positive for THC (n = 1)
were not considered grounds for exclusion.

Naltrexone Administration

Following screening for contraindications for NTX and ethanol,
including a urine pregnancy test for females, subjects were adminis-
tered either a 50-mg NTX capsule or an identical placebo capsule.
Capsule order was counterbalanced across subjects and double
blinded. During session 1, participants filled out a series of
questionnaires and then relaxed until the alcoholic drink was admin-
istered. Following the protocol of (Mitchell et al., 2007), administra-
tion of behavioral testing began approximately 3 hours following
capsule ingestion. This interval was selected to minimize acute physi-
ological effects of NTX during testing, while still achieving significant
opioid receptor blockade (Atkinson, 1984; King et al., 1997; Swift
et al., 1994).

Ethanol Administration

Two and a half hours following capsule ingestion, subjects com-
menced a 15-minute alcohol drinking interval. The alcohol drink was
prepared immediately prior to consumption and consisted of 190
proof U.S.P. ethyl alcohol (0.3 g/kg of body weight) diluted 1:5 in
fruit juice (Capri Sun; Kraft Foods, Northfield, IL). The drink was
consumed in 3 equal parts, and subjects were allowed 5 minutes to
consume each third, although in practice most took only 1 of the 5
allotted minutes. BrAC values were measured via breathalyzer
30 minutes after the onset of the drinking interval, and behavioral
testing commenced thereafter.

Behavioral Inventories

We administered a number of standard questionnaires to quantify
personal history and behavioral traits that could impact our results.
We quantified alcohol use behavior with the Alcohol Use and Disor-
ders Identification Test (AUDIT; Saunders et al., 1993) and drug
and alcohol use behavior with the Drug Use Screening Inventory,
Domain I (DUSI-I; Tarter, 1990). DUSI-I scores are reported in
terms of the percentage of affirmative answers from Domain I, part
B. We calculated density of familial alcohol abuse using the Family
Tree Questionnaire (FTQ; Mann et al., 1985). Gambling habits were
assessed with the South Oaks Gambling Screen (SOGS; Lesieur
and Blume, 1987). Neuropsychological questionnaires included the
BIS-11 (Barratt, 1994), the Beck Depression Inventory (BDI; Beck
and Steer, 1987), Rotter's Locus of Control Scale (LOC; Rotter, 1966),
the Future Time Perspective Inventory (FTPI; Wallace, 1956), the
State-Trait Anxiety Inventory (STAI; Spielberger, 1985), and the
Antisocial Practices Scale (APS) of the Minnesota Multiphasic Per-
sonality Inventory 2 (MMPI-2; Butcher et al., 1990). Education and
occupation were quantified with the Hollingshead Socioeconomic
Status (SES) score (Hollingshead, 1975). We estimated general intel-
lectual function with the Shipley Institute of Living Scale (SILS;
Behavioral Tasks

Delay-Discounting Task. The paradigm was based on a previously described task (Mitchell et al., 2005a, 2007). Briefly, in each session, subjects completed a short (~4 minutes) practice run and then 8 full runs of approximately 42 or 43 trials each (~7 minutes). There were 4 trial types or cues: WANT (W), DON'T WANT (DW), SOONER, and LARGER (together: CON for control conditions; see Fig. 1A). Trials were randomly ordered and weighted so that half of the trials were the W condition and the rest were evenly split between the other 3 conditions. Each trial began with an instruction cue, followed by 2 options (see Fig. 1B), each consisting of a monetary value and a time. Subjects were asked to evaluate the choices as if they would actually receive the specified amounts at the corresponding times. In each trial, one of the options consisted of 1 of 5 “full” amounts ($2, $5, $10, $20, or $100) and 1 of 5 future delays (1 week, 2 weeks, 1, 3, or 6 months). The other option included a discounted amount (70, 85, 90, or 95% of the “full” amount) always offered with no delay (“TODAY”).

Subjects were instructed to make a choice in each trial, according to the trial type. They were to select their preferred option on W trials, their nonpreferred option on the DW trials, and the side with the sooner time or larger amount of money for SOONER and LARGER, respectively. These control trials verified that subjects understood the task and maintained attention. The order of trial types was the same for all subjects; however, the delayed amount, delay time, and discount were selected from a randomly ordered list. Hypothetical rewards were used rather than actual money based on results from comparison studies (Critchfield and Kollins, 2001; Johnson and Bickel, 2002; Lagorio and Madden, 2005; Madden et al., 2003, 2004).

Go–NoGo Task. Subjects also completed a Go–NoGo task, which allowed direct measurement of the effect of NTX on motor inhibition. The “Go” stimulus was “$70,” in the same font and size as the stimuli used in the delay-discounting task. The “NoGo” stimulus was an identically formatted and positioned “$100.” On each trial, stimuli appeared on the screen for 700 milliseconds followed by a blank screen for 300 milliseconds. Subjects completed 2 runs of 80 trials each, with 15% NoGo trials, presented in pseudorandom order.

Dot-Probe Task. To measure NTX’s effect on attentional bias, subjects performed a dot-probe type task (MacLeod et al., 1986). The stimuli mimicked the option screen of the delay-discounting task (excluding the instruction cue). For each trial, the 2 stimuli appeared on either side of a fixation cross for 500 milliseconds. The stimuli then disappeared, and each was replaced by a target (2 dots) or non-target (1 dot). Subjects pressed a button to indicate the side of the target stimulus. To quantify attentional bias toward the larger amount, we calculated the following reaction time (RT) bias index from correct trials: $\text{RT}_{L} - \text{RT}_{S}$, where $\text{RT}_{S}$ indicates the mean RT for trials in which the target appears on the side with the smaller amount, and $\text{RT}_{L}$ indicates the mean RT for trials in which the target appeared on the side with the larger amount. Using this measure, positive values indicate faster responses to targets cued by the larger amounts, which reflects attentional bias to the larger amounts. During each session, subjects completed 1 run of 80 trials. For all but 4 subjects, the delay-discounting task preceded the dot-probe task.

Data Analysis

Our index of temporal discounting was the proportion of earlier choices, which we have termed the impulsive choice ratio (ICR). This value was calculated across all W trials, as well as separated according to delay time and delayed amount. On DW trials, inferred ICR (ICR) was calculated based on the nonselected value for each delay time. As a gross index of motor control, “motor mismatch” (MM) was calculated as the absolute difference between ICR and ICR for each delay time, averaged across all delay times.

To test the significance of across-group comparisons, we used unpaired 2-tailed $t$-tests for continuous measures and chi-square tests for categorical measures. For multifactorial comparisons, mixed repeated measures analyses of variance (ANOVAs) in SPSS were used, with group as a between-subject factor. When necessary, a Greenhouse–Geisser nonsphericity correction was applied. Post hoc paired comparisons were performed where indicated using 2-tailed $t$-tests. When data were not normally distributed, appropriate arcsine-root transformations were applied in Excel prior to making statistical comparisons to ensure the validity of parametric statistical tests. Simple regression analysis and analyses of covariance were performed in SPSS (SPSS Inc., Chicago, IL). To estimate which continuous variables had the greatest predictive value for the NTX effects on ICR,

Fig. 1. Illustration of delay-discounting paradigm. (A) Depiction of the 4 trial types. The 4 trial types included WANT (W), DON'T WANT, and 2 controls: SOONER and LARGER. Trial ratio was 1/2 for the W condition and 1/6 each for the other 3 trial types. (B) The temporal sequence of events is shown for 1 example W trial. Illumination of a fixation cross (“Ready”) indicated the start of each trial. The instruction cue was then displayed for 2 seconds, informing the subject of the upcoming trial type. The 2 options were then presented while the instruction cue remained on the screen. The choices remained on the screen for 2 seconds; however, subjects had a total of 6 seconds to indicate their choice following the appearance of the 2 options. ITI, intertrial interval.
and MM, linear multiple regression analyses were carried out using SPSS. For each multiple regression analysis, we entered variables stepwise, divided into 5 blocks. The blocks were as follows: block 1—age, gender, ethnic group, years of education, HH-SES-self, HH-SES-parent, IQ, body mass index; block 2—AUDIT, FTQ density, DUSI; block 3—BIS, BDI, SOGS, LOC, APS, FTPI-I-mean extension, FTPI-I-max extension, FTPI-II-mean extension, STAI-State, STAI-Trait; block 4—peak BrAC or change in peak BrAC; ethanol (EtOH) metabolism rate or change in EtOH metabolism rate; block 5—WANT (or DW) trial RT or RT change, Go–NoGo false alarms (FA) or FA change, dot-probe RT difference or RT difference change.

RESULTS

Demographic and Psychometric Data

We previously found that BIS scores positively correlate with ICR (Mitchell et al., 2005a) and that abstinent alcoholics score significantly higher on the BIS relative to controls (Mitchell et al., 2005a, 2007). Here, we tested whether BIS scores predicted ICR differences in a sample with high variance in BIS scores, but no history of substance use disorders. We divided subjects into 2 groups based on a median split of BIS scores. There were no significant differences between the 2 groups in terms of age, education, SES, gender, ethnicity, family history of alcohol abuse (FTQ density), orientation toward the future (FTPI), LOC, or gambling history (SOGS; see Table 1). The more impulsive group (High Imp) did, however, report slightly greater depression (BDI), trait anxiety (STAI-T), alcohol use (AUDIT), and endorsed more positive answers on the DUSI-IB, than did the low-impulsive group (Low Imp).

Factors Predicting Impulsive Choice Tendency in the Presence of Alcohol

In the placebo session, the High Imp group tended to select the smaller, sooner reward more frequently (ICR: 0.40 ± 0.33) than did the Low Imp group (0.39 ± 0.38); however, this difference did not reach statistical significance (p = 0.79). A simple regression analysis also failed to find a significant relationship between BIS scores and ICR (p = 0.63). To identify factors that did predict ICR in the context of moderate alcohol consumption, we performed a multiple regression analysis of placebo session ICR data that identified 2 factors that predicted impulsive choice tendencies: future orientation (as measured by FTPI part I max) and peak BrAC (Table 2; Fig. 2A,B). ICR was negatively correlated with future orientation and positively associated with BrAC. This latter correlation indicates that moderate EtOH intake increases impulsive choices, although the mean placebo ICR we observed here (0.39) was similar to that observed in other samples with no history of substance use disorders and not under the influence of EtOH (0.3 to 0.4) (Boettiger et al., 2007; Mitchell et al., 2005a, 2007).

Acute Effects of NTX After Moderate Alcohol Intake

In the delay-discounting task, a mixed-model ANOVA revealed a significant main effect of trial type on RT, but no significant main effects of trait impulsiveness group or drug condition, nor any significant interaction between these factors (Table 3). These data are consistent with those found previously (Mitchell et al., 2005a, 2007) and indicate that NTX effects on RT are not altered by the presence of moderate alcohol. We found no main effect of NTX on ICR; however, there was a significant drug × group interaction.

<table>
<thead>
<tr>
<th>Table 1. Demographic and Psychometric Data</th>
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<tr>
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<tr>
<td><strong>Low imp</strong> <em>(n = 15)</em></td>
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<tr>
<td><strong>High imp</strong> <em>(n = 15)</em></td>
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<tr>
<td><strong>t(28)</strong></td>
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<tr>
<td><strong>p-value</strong></td>
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<tr>
<td><strong>General</strong></td>
</tr>
<tr>
<td>Age (years) 23 ± 4 23 ± 3 0.55 ns</td>
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<tr>
<td>Education (years) 16 ± 2 16 ± 2 0.00 ns</td>
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<tr>
<td>Hollingshead SES 41 ± 9 41 ± 9 0.12 ns</td>
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<tr>
<td>Gender (no. female) 10 10 ns*</td>
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<tr>
<td>Ethnicity 8 10 ns*</td>
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<tr>
<td>Alcohol related</td>
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<tr>
<td>AUDIT 4 ± 3 7 ± 4 2.22 0.034</td>
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<tr>
<td>DUSI-I (B) 1 ± 1 3 ± 2 2.98 0.006</td>
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<tr>
<td>FTQ density (%) 15 ± 16 15 ± 16 0.25 ns</td>
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<tr>
<td>Psychometric</td>
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<tr>
<td>Depression (BDI) 3 ± 4 7 ± 5 2.39 0.024</td>
</tr>
<tr>
<td>Impulsivity (BIS) 55 ± 7 74 ± 8 7.19 &lt;0.001</td>
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<tr>
<td>Future 33 ± 22 38 ± 17 0.72 ns</td>
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<tr>
<td>orientation (FTPI)</td>
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<tr>
<td>STAI—state anxiety 29 ± 4 32 ± 8 1.33 ns</td>
</tr>
<tr>
<td>STAI—trait anxiety 34 ± 7 43 ± 8 3.08 0.005</td>
</tr>
<tr>
<td>Internal–external control (LOC)</td>
</tr>
<tr>
<td>Antisocial practices (APS)</td>
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<tr>
<td>Gambling (SOGS) 0.2 ± 0.6 0.2 ± 0.4 0.00 ns</td>
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</table>

Values are reported as mean ± SD. Reported p-values reflect the results of unpaired 2-tailed comparison between groups. Exact p-values reported unless p < 0.001.

<table>
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<tr>
<th>Table 2. Results from Multiple Linear Regression Analysis of Predictors of ICR After Consuming a Moderate Dose of EtOH (Placebo Sessions)</th>
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<tbody>
<tr>
<td>Step 1</td>
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<tr>
<td>Constant 1.00 1.67</td>
</tr>
<tr>
<td>FTPI-MAX −0.01 0.004</td>
</tr>
<tr>
<td>β −0.44*</td>
</tr>
<tr>
<td>Step 2</td>
</tr>
<tr>
<td>Constant 0.44 0.24</td>
</tr>
<tr>
<td>FTPI-MAX −0.01 0.004</td>
</tr>
<tr>
<td>Peak BrAC 18.55 6.19</td>
</tr>
<tr>
<td>β 0.46*</td>
</tr>
</tbody>
</table>

B, beta value; SE B, beta value standard error; β, standardized beta; FTPI-MAX, future time perspective inventory (part I), maximum extension; BrAC, breath alcohol concentration; ICR, impulsive choice ratio; EtOH, ethanol.

*p < 0.01.
Post hoc tests suggest that this effect was driven by a trend for less impulsive decisions in the Low Imp group on NTX ($t_{14} = 1.93$, $p = 0.07$). These results indicate that NTX does not have uniform effects on decision-making behavior in the context of moderate alcohol intake.

In our previous laboratory study, we found NTX to significantly reduce MM in our task (Mitchell et al., 2007). Contrary to our expectation, we found that under the influence of moderate alcohol, NTX failed to reduce MM, $F(1, 28) = 0.05$, $p = 0.82$. We also found no significant drug × impulsivity group interaction, $F(1, 28) = 0.22$, $p = 0.64$. Thus, moderate alcohol appears to occlude NTX’s effect on MM. The Go–NoGo and dot-probe tasks were included as a means to dissociate expected NTX effects on MM into motor control and attentional bias factors. Given that we did not detect a significant reduction in MM on NTX, this need was eliminated. We also found that NTX had no effect on motor inhibition in the Go–NoGo task or attentional bias in the dot-probe task (maximum $F = 2.12$).

Factors Predicting NTX Effect on Impulsive Choice in the Presence of Alcohol

In our previous laboratory study of the effects of NTX on delay discounting, we found that a single factor held significant predictive value: Rotter’s LOC scores; this relationship was particularly strong in subjects with a history of alcohol use disorder (Mitchell et al., 2007). Here, we again used multiple linear regression to identify any demographic or psychological measures that had significant predictive value in terms of the NTX effect on ICR. No variable held significant predictive value in the whole sample. However, our previous
finding was derived from a sample in which 83% of participants reported a positive family history of alcohol abuse (FHP; Mitchell et al., 2007). Thus, we repeated the multiple linear regression procedure including only data from FHP subjects \((n = 15)\). Within the FHP group, we found that a single variable, LOC score, again significantly predicted NTX effects on ICR \((p = 0.001, \text{Fig. 4}; \text{see Table 4 for complete model})\). Lower LOC scores, which reflect a more internal attribution style, again predicted an increase in ICR on NTX, whereas a more external attribution style predicted reduced ICR on NTX.

**NTX May Retard Ethanol Metabolism**

A surprising finding in this study was a trend toward slower ethanol metabolism in NTX than in placebo sessions, \(F(1, 26) = 3.901, p = 0.059\). This effect has not been reported previously; however, NTX has been reported to alter the subjective effects of alcohol, decreasing the stimulating effects and increasing the sedating effects of alcohol compared to placebo (Swift et al., 1994). A slowing of ethanol metabolism by NTX could contribute to changes in perceived subjective effects of ethanol. Moreover, published reports have been based primarily on Caucasian subjects, while our subject pool was only 40% Caucasian.

**DISCUSSION**

**Trait Impulsivity, Impulsive Choice, and Moderate Alcohol**

Previous research has found a correlation between delay-discounting behavior and subjective measures of trait impul-

![Table 4. Results from Multiple Linear Regression Analysis of Predictors of NTX Effect on ICR (arcine-root transformed)](image)

<table>
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<tr>
<th></th>
<th>(B)</th>
<th>(SE\ B)</th>
<th>(\beta)</th>
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<tbody>
<tr>
<td><strong>FHP group only</strong></td>
<td></td>
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<td></td>
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<tr>
<td><strong>Step 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>0.89</td>
<td>0.22</td>
<td>-0.75*</td>
</tr>
<tr>
<td>LOC</td>
<td>-0.08</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

\(B\), beta value; \(SE\ B\), beta value standard error; \(\beta\), standardized beta; LOC, Rotter’s Locus of Control Scale; FHP, family history positive for alcohol abuse; NTX, naltrexone; ICR, impulsive choice ratio. \(^*p < 0.01.\)

sivity (Mitchell et al., 2005a; Swann et al., 2002), although this finding is not universal (Lane et al., 2003; Mitchell, 1999). This variability may have several causes. First, self-report measures are prone to numerous limitations (Nisbett and Wilson, 1977; Wilson and Dunn, 2004) such that these may not accurately reflect actual behavior. That said, the measure of trait impulsivity used here, BIS score, has shown substantial heritability (>40%) in twin studies (Seroczynski et al., 1999), supporting its validity as a phenotypic measure of at least certain aspects of the multifaceted construct of impulsivity (Congdon and Canli, 2005; Evenden, 1999). Second, different methods have been used to measure delay discounting. The one used here shows high test–retest reliability (Christopher Smith and Charlotte Boettiger, personal communication, September 2010) and demonstrated significant correlation with BIS scores in a previous study (Mitchell et al., 2005a). Thus, we expected to replicate that finding here. However, while BIS scores were collected when subjects were sober, delay discounting was measured following moderate alcohol intake. Although impulsiveness under the influence of moderate ethanol has not been extensively studied, some studies have found increased impulsive choice (Petry, 2001), while others have not (Ortner et al., 2003; Richards et al., 1999). Here, we found that the BrAC achieved by the single alcohol dose was positively correlated with impulsive choice, supporting the idea that ethanol concentration promotes the tendency to choose immediate over delayed rewards. This effect may have occluded the relationship between trait impulsivity and delay discounting observed under sober conditions.

**MM: Occlusion of NTX Effect by Moderate Ethanol**

Based on our earlier finding that NTX significantly reduced MM, we were surprised to find a lack of effect here. The average MM scores in placebo sessions (~0.1) were nearly identical to those seen in control subjects in 2 previous studies (Mitchell et al., 2005a, 2007), and the range of MM scores was also the same. The simplest explanation is that alcohol is occluding the effect of NTX on MM, but the question arises: Which system is mediating this effect? Two conditions must be met. First, the function of a candidate system must be altered by NTX. Second, alcohol intake must independently alter this same system. Although alcohol elicits endogenous opioid release (Gianoulakis, 1993), which would be the first
system to consider, NTX would block any effect of such release (Herz, 1997). Thus, MM is not likely to result from elevated endogenous opioid signaling. A second candidate system regulating MM is the dopamine (DA) system. NTX can indirectly reduce DA release in striatal targets (Fields et al., 2007; Herz, 1997; Herz and Spanagel, 1995; Spanagel et al., 1992), a possible mechanism underlying its ability to reduce MM. In contrast, acute ethanol potentely enhances DA release in the striatum (Herz, 1997). Thus, these 2 opposing actions on the DA system could underlie the lack of an effect of NTX on MM observed in the present study. One hypothesis generated by this interpretation is that high levels of baseline DA signaling should be associated with higher levels of MM. Support for this hypothesis comes from our previous data showing significantly less MM in people with a history of alcoholism (Mitchell et al., 2007), a group reported to exhibit depressed levels of striatal DA (Volkow et al., 2007). Future investigations using genetic methods to address this question may prove illuminating.

**Individual Differences in NTX Effects on Impulsive Choice: Possible Explanations for the Interaction Between Family History of Alcoholism and LOC**

**Dopamine System.** In our previous study of subjects with or without a personal history of alcoholism, we found that LOC scores were the sole predictor of NTX’s effect on immediate reward bias (Mitchell et al., 2007). LOC is a personality measure reflecting one’s perception of control over life events (Rotter, 1966), and LOC scores show substantial heritability (Miller and Rose, 1982; Pedersen et al., 1989), suggesting a biological basis. Based on the evidence that LOC scores reflect tonic frontal DA transmission (Declerck et al., 2006) and that acute elevation of DA may reduce delay discounting (de Wit et al., 2002; Wade et al., 2000), we reasoned that NTX may alter impulsive choice by altering the level of tonic DA transmission in the frontal cortex (Herz and Spanagel, 1995; Margolis et al., 2006; Spanagel et al., 1992). It is important to point out that NTX is an antagonist at both \( \mu \)- and \( \kappa \)-opioid receptors, albeit with approximately 2.5-fold larger affinity for \( \mu \)-opioid receptors (Emmerson et al., 1994). A 50-mg oral dose of NTX will achieve nearly complete blockade of \( \mu \)-opioid binding sites in the human brain (Lee et al., 1988; Weerts et al., 2008). The current lack of suitable \( \kappa \)-opioid positron emission tomography (PET) ligands prevents us from knowing how completely this NTX dose blocks \( \kappa \) receptors in the human brain, but we do know that this dose blocks \( \approx 20\% \) of delta-opioid receptors in the human brain, for which NTX has approximately 25-fold lower affinity, relative to \( \kappa \) receptors (Emmerson et al., 1994). Thus, a 50-mg oral dose of NTX is certainly achieving very significant blockade of \( \kappa \)-opioid receptor sites, which are comparable in abundance to \( \mu \)-opioid receptors in the brain (Pfeiffer et al., 1982). Furthermore, there is evidence from rodent studies that whereas \( \mu \) agonists raise DA levels in prefrontal cortex, \( \kappa \) agonists have the opposite effect (Herz and Spanagel, 1995; Margolis et al., 2006; Spanagel et al., 1992). People with a personal or family history of alcoholism are reported to have relatively low levels of circulating endogenous \( \mu \)-opioid agonists (Dai et al., 2005; del Arbol et al., 1995; Gianoulakis et al., 1989; Govoni et al., 1983; Vescovi et al., 1992). Therefore, we previously speculated that such individuals would experience more of a DA-elevating effect of NTX, because of relatively enhanced \( \kappa \)-opioid blockade effects of NTX (Mitchell et al., 2007). That speculation was supported by our observation that the predictive relationship between LOC and NTX effects on impulsive choice was stronger among the abstinent alcoholic subjects in our previous study. This hypothesis is further supported by the present data showing that LOC most strongly predicts NTX’s effect on decision making among subjects with a family history of alcoholism. We now expand upon our previously hypothesized model for dopaminergically mediated effects of NTX on decision making. First, we propose that owing to opposing effects of \( \mu \) - and \( \kappa \)-opioid receptors on forebrain DA release, individuals with no personal or family history of alcoholism, NTX likely has mixed, opposing effects on frontal DA release (Fig. 5A), with some subjects experiencing DA increases, others, DA decreases, and still others, no net effects on DA signaling. In contrast, individuals with a family history of alcoholism would be expected to experience relatively greater effects of \( \kappa \)-opioid receptor blockade; thus, such individuals would tend to experience an elevation in frontal DA levels in response to NTX (Fig. 5B). Dopaminergic modulation of frontal functions often follows a U-shaped curve, where too little or too much of NTX would block any effect of such release (Herz, 1997). Thus, MM is not likely to result from elevated endogenous opioid signaling. A second candidate system regulating MM is the dopamine (DA) system. NTX can indirectly reduce DA release in striatal targets (Fields et al., 2007; Herz, 1997; Herz and Spanagel, 1995; Spanagel et al., 1992), a possible mechanism underlying its ability to reduce MM. In contrast, acute ethanol potentely enhances DA release in the striatum (Herz, 1997). Thus, these 2 opposing actions on the DA system could underlie the lack of an effect of NTX on MM observed in the present study. One hypothesis generated by this interpretation is that high levels of baseline DA signaling should be associated with higher levels of MM. Support for this hypothesis comes from our previous data showing significantly less MM in people with a history of alcoholism (Mitchell et al., 2007), a group reported to exhibit depressed levels of striatal DA (Volkow et al., 2007). Future investigations using genetic methods to address this question may prove illuminating.
much DA causes inefficiencies in frontal functioning (Arnsten, 1997; Williams and Castner, 2006; Zahrt et al., 1997). We propose a U-shaped relationship between impulsive choice and frontal DA levels (Fig. 5C). Such a model fits our experimental data (shown in Fig. 4) well, in that NTX’s effects on ICR are reliably predicted for FHP subjects, but not for FHN subjects. One prediction of this model is that the effects of direct elevation of frontal DA on impulsive decision making should depend on baseline frontal DA levels, and effects are not expected to interact with family history of alcoholism. Future studies will address this hypothesis.

The differential effects of NTX on FHP versus FHN subjects is potentially clinically relevant in light of the fact that NTX appears to be more effective in reducing alcohol intake among FHP alcoholics relative to those that are FHN (Krishnan-Sarin et al., 2007; Monterosso et al., 2001). Here, we propose that the differential effects reflect a greater effect of κ-opioid receptor blockade by NTX in FHP subjects. In contrast, O’Malley and colleagues have made the opposite prediction, arguing that NTX effects on alcohol intake are primarily κ receptor mediated in FHN alcoholics (Krishnan-Sarin et al., 2007). In this regard, animal studies can either increase (Mitchell et al., 2005b) or decrease (Walker et al., 2011) alcohol consumption depending upon the behavioral state of the animal. Direct tests of these opposing hypotheses may be possible in the future via PET imaging of NTX’s actions on each receptor system. The availability of new, receptor-specific ligands would also allow us to directly probe the role of each receptor subtype.

Stress System. Individuals with a family history of alcoholism experience an elevated release of cortisol in response to acute NTX administration (King et al., 2002). Moreover, data suggest that the hypothalamic–pituitary–adrenocortical axis responds differently to stress based on LOC, with an external LOC predicting a more exaggerated cortisol release in response to stress (Bollini et al., 2004). Thus, cortisol is a hypothetical mediator of the observed interaction between LOC and family history of alcoholism in predicting NTX’s effects on impulsive decision-making. The hyper-release of cortisol in response to NTX of our FHP subjects would be expected to vary with LOC, such that in more internal individuals, cortisol goes up less than it does in external FHP individuals. Some data support the idea that high cortisol levels reduce delay discounting (Takahashi, 2004), which could possibly explain our observed results of reduced discounting on NTX in external FHP subjects and increased discounting on NTX in internal FHP subjects. It is worth noting that 1 primary mediator of the dysphoric effects of stress is the κ-opioid system (Bruchas et al., 2010). Thus, dysregulation of the stress system in FHP subjects may well be associated with dysregulation in the κ-opioid system as well. An up-regulation of κ-receptor signaling in FHP subjects could thus also contribute to the scenario we propose in Fig. 5B.

**Summary**

In conclusion, in a young, healthy control sample under the influence of moderate alcohol, we did not find a significant correlation between trait impulsivity and the tendency to choose impulsively. Rather, myopia for the future and peak BrAC levels best predicted increased frequency of impulsive choices. In addition, we extend the previous finding that LOC predicts NTX’s effect on impulsive choice, demonstrating that this relationship is also present after moderate ethanol consumption. Again, a lower LOC, reflecting a more internal attribution style, correlates with an increase in impulsive choice on NTX. Importantly, we have determined that this predictive relationship is found among individuals with an FHP. Trait impulsivity showed a weaker but significant interaction of NTX’s effect on impulsive choice, with NTX more effectively reducing impulsive choices in subjects with low trait impulsivity. Consistent with previous findings, moderate acute ethanol intake did not grossly increase impulsive choices (Ortner et al., 2003; Petry, 2001; Richards et al., 1999); however, peak BrAC positively correlated with impulsive choice tendency and bias toward smaller, immediate rewards. These data suggest that increasing ethanol intoxication impairs decision making by biasing decisions toward immediate gratification. We found that NTX fails to reduce mismatch of choices in the DON’T WANT condition in the presence of alcohol. Finally, we made the unexpected finding that NTX slowed ethanol metabolism. Together, the results reported here provide new insights into possible mechanisms for NTX’s ability to reduce total ethanol intake following moderate ethanol ingestion and suggest several novel lines of research in this area.

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