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Lithium, but not Valproate, Reduces Impulsive Choice in the Delay-Discounting Task in Mice

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Both lithium and valproate are well-established treatments for bipolar disorder. Studies have also found that lithium is effective at reducing suicidal behaviors in patients with mood disorders. Impulsivity is a validated endophenotype of both bipolar disorder and suicidal behavior. We assessed effects of treatment with lithium or valproate on cognitive impulsivity in selectively bred mice previously shown to manifest relatively high levels of cognitive impulsivity. Mice were trained in the delay-discounting paradigm, a measure of cognitive impulsivity reflecting a behavioral bias towards immediacy, and then treated with lithium, valproate, or control chow. After 3 weeks of drug treatment, mice were tested at various delays to a large, delayed reward. Drug treatment continued during this time. Lithium reduced impulsivity, whereas valproate had no effect on choice behavior. Both drugs increased the number of choice trials and reinforcer intake, but effects on choice behavior did not depend on these motivational changes. To our knowledge, this is the first study demonstrating lithium's effects to reduce cognitive impulsivity. Future studies may focus on the ability of putative pharmacotherapies for patients at risk for bipolar disorder or suicide to modify the impulsive choice dimension of this diseases.
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INTRODUCTION

For over a century, clinicians treating patients suffering from a wide range of illnesses have prescribed various forms of lithium. Lithium has proven efficacy for the treatment of bipolar disorder (Geddes *et al*, 2004; Weisler *et al*, 2011). Extensive evidence also indicates that lithium is effective in reducing the risk of suicidal behaviors—both attempts and completions—in patients with mood disorders (Baldessarini *et al*, 2006; Cipriani *et al*, 2005; Guzzetta *et al*, 2007; Tondo *et al*, 1997). For example, Baldessarini *et al* (2006), in a pooled analysis of 31 studies, reported a highly statistically significant, 4.91-fold lower risk of suicidal acts during long-term treatment with *vs* without lithium, or an 80% sparing of risk associated with lithium treatment. This decreased risk remains highly significant when assessing only suicides or attempted suicides, or when only pooling results from randomized controlled trials (Baldessarini *et al*, 2006). Importantly, lithium is not only effective in reducing suicidal behavior in patients with bipolar disorder. A meta-analysis including eight studies of patients with major depressive disorder

found that the risk of suicidal behavior was nearly 90% lower with lithium treatment (Guzzetta *et al*, 2007).

The mechanism by which lithium effectively treats bipolar disorder and reduces the risk of suicidal behaviors is unknown. Important insight may arise from understanding the effects of lithium on endophenotypes associated with bipolar disorder and suicidal behaviors, which themselves may be more tractable to dissection in preclinical models or tests. Impulsivity is a prominent component of bipolar disorder and also has a strong correlation with suicidal behaviors (Courtet *et al*, 2011; Mann *et al*, 2009; Najt *et al*, 2007). Studies demonstrate that impulsivity is not only present during a bipolar disorder manic episode, which would indicate state dependence, but also during euthymic states indicating trait-like characteristic. For example, bipolar patients consistently have higher impulsivity ratings compared with healthy controls, regardless of whether they are in a manic or depressive episode (Etain *et al*, 2012; Lombardo *et al*, 2012; Peluso *et al*, 2007; Swann *et al*, 2001; Swann *et al*, 2003), supporting the conclusion that impulsivity is a potential endophenotype of bipolar disorder.

Similarly, impulsivity is a well-validated endophenotype associated with suicidal behavior. Data supporting this fact derives from case control, retrospective (psychological autopsy), prospective longitudinal, and family studies (Kovacsics *et al*, 2009; Melhem *et al*, 2007; Turecki, 2005). A number of studies have found that trait impulsivity meets criteria for an endophenotype such as being heritable,

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associated with suicide, state independent, and co-segregated with suicidal behavior in families (Grunebaum et al, 2006; Melhem et al, 2007; Oquendo et al, 2004). Lithium may exert its antisuicidal actions by modifying impulsive, as well as impulsive, aggressive behaviors (Kovacsics et al, 2010). Some clinical evidence suggests that lithium treatment reduces impulsivity in at-risk individuals. The results of randomized, placebo-controlled studies suggest that lithium decreases human impulsivity, although overall, the evidence for such an effect is complicated by concurrent diagnoses, such as pathological gambling, bipolar disorder, and ADHD (Dorrego et al, 2002; Hollander et al, 2005; Kovacsics et al, 2009).

To date, limited research has examined effects of lithium on impulsivity in laboratory animals. A recent study by Ohmura et al (2012) assessed the effects of a single i.p. injection of lithium, valproate, or carbamazepine on impulsivity as assessed by a 3-choice serial reaction time task (3-CSRTT). They reported that lithium significantly reduced premature responses in the task, whereas neither valproate nor carbamazepine had any significant effect. While the 3-CSRTT is considered as a measure of motor impulsivity (Winstanley et al, 2006), there has been little work assessing lithium's effects on a measure of cognitive impulsivity, such as delay discounting (DD). In the DD task, subjects are given a choice between a delayed, large reward and an immediate, smaller reward. Self-defeating choices of the immediate reward are thought to reflect impulsive choice (Rachlin and Green, 1972). Generally, choice of the immediate reward increases with increasing delays to the large reward. The delay-discounting paradigm has been successfully modeled in animals (Green and Snyderman, 1980; Oberlin and Grahame, 2009), and has shown sensitivity to pharmacological manipulation (Oberlin et al, 2010). These factors make DD a good candidate as a translational endophenotype, as it can be assessed in both humans and animals (Gould and Gottesman, 2006). We hypothesized that treatment with lithium would reduce cognitive impulsivity as assessed by the DD task in a strain of mouse previously characterized to manifest relatively high levels of impulsivity.

MATERIALS AND METHODS

Subjects

Experiments were conducted as two studies. Mice in both the studies were 24 female and 24 male High Alcohol-Preferring (HAP) line replicate II mice, aged between 45 and 51 days at the beginning of training. This line was selected because of their relatively high levels of impulsivity in the DD task relative to mice with lower alcohol intake (Oberlin and Grahame, 2009) and sensitivity to the anti-impulsive effects of d-amphetamine (Oberlin et al, 2010). In the lithium study, mice were from the 37th generation of selective breeding, and in the valproate study, the mice were from the 40th generation. Mice were balanced across sex, family, and birth date, and then counter-balanced across squad and run order. The mice were individually housed in polycarbonate cages ($27.9 \times 9.5 \times 12.7$ cm) with Cellsorb bedding starting 7 days prior to the study. They were kept on a reversed light–dark cycle with lights out from 0800 to 2000 hours, and were given ad libitum access to food and water, except that they were restricted to 2 h of access to water during the training phase and during the last phase of the DD testing in the lithium study to increase motivation.

Apparatus

The operant chambers, measuring $21.6 \times 19.7 \times 12.7$ cm inside, were contained within sound and light-attenuating cubicles fitted with electric fans to minimize ambient noise and light. Each apparatus contained an illuminated center nosepoke directly above the sipper tube opening. To the left and right of the nosepoke were LED signal lights positioned above response levers. Directly below the nosepoke was the opening for the sipper tube to descend into the chamber. The saccharin solution was dispensed from a 10 ml tube, and intakes were measured to an accuracy of 0.1 ml after each session. The chambers were operated through MED-PC IV software (Med Associates, St Albans, VT).
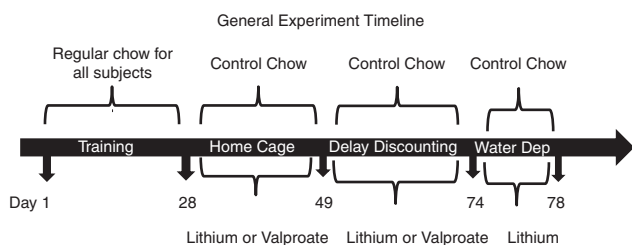
Procedures

DD task. The mice were trained according to the procedure described in Richards et al, 1997. Briefly, each trial begins with illumination of the center nosepoke light. A nosepoke response results in illumination of the lights above the levers, indicating that the levers are active. A response on the lever designated as the delay lever always results in 2 s of access to reward (0.032 or 0.32% saccharin in tap water) after the predetermined delay. A response on the immediate lever results in 1 s of access at the start of the session, but the duration of access is either increased or decreased by 0.2 s after each response to a ceiling of 2 s and a floor of 0 s. A choice of the delay lever increases the duration of access on the subsequent immediate choice, whereas a response on the immediate lever decreases it by the same amount, thus titrating the value of the immediate reward to the subjective value of the delayed reward at a given delay. There is a maximum of 60 trials per session. The average of this adjusting amount (over the last 18 trials of the session) represents the subjective value of the delayed reward. Higher adjusted amounts indicate lower levels of impulsivity (Richards et al, 1997). During initial training at a 0 s delay to the 'delayed' lever, mice were required to show magnitude discrimination (preference for the large reward), with criteria for advancement to the testing phase being a minimum of 18 trials completed per 60 min session and a minimum mean adjusted amount of 1.6 s for three out of four consecutive days. These mean adjusted amounts were later used in all analyses to demonstrate magnitude discrimination prior to onset of delayed rewards, and are represented on the graphs as the 0 s time point. These criteria ensured that the subject had acquired the task and was able to correctly choose the larger reinforcer at a 0 s delay. Thereafter, delayed reward trials ensued, with mice being tested for 5 days each at 1, 2, 4, and 8 s delays to the large reward in ascending order. Only sessions in which mice achieved at least 18 trials were counted to the mean adjusted amount at that delay, and mice had to achieve at least 18 trials on at least 2 of the 5 days at each delay. Both experiments in this study used identical training procedures; however, the concentration of the reward in the

valproate study was 0.32% saccharin in tap water due to low levels of responding in the absence of water deprivation.

Lithium administration and testing. After completion of training, mice were assigned to either control or lithium groups, balanced across sex, family, date of birth, and mean adjusted amount, and were then returned to their home cages. Their regular chow was replaced with either 4 g/kg LiCl chow or control chow (Custom Animal Diets, Bangor, PA). This dose was used because it results in circulating levels of lithium within the human therapeutic range (0.6–1.3 mM) and consistent behavioral actions of lithium in other mouse behavioral tests (Gould *et al*, 2008; Kovasics *et al*, 2010; Can *et al*, 2011). Mice were given *ad libitum* access to food and water, and a NaCl solution (9 g/l tap water) while in the home cage and weighed three times weekly. There was no testing at this time. After 3 weeks, the mice were returned to the magnitude discrimination task and run at a 0 s delay for 5 days. DD assessment followed. Because of higher fluid intake in the lithium condition, mice were tested for an additional 5 days at 8 s delay during which time mice in both treatment groups were restricted to 2 h of water access per day (given after daily DD sessions) to increase the fluid intake in both lithium and control groups. Drug treatment continued throughout the delay testing (see Figure 1 for a Timeline). After the conclusion of testing, brains were removed and analyzed for lithium levels. Entire brains were homogenized with a polytron homogenizer (Kinematica AG, Model PT-MR 2100, Littau, Switzerland) in three volumes of 0.5 N trichloroacetic acid, followed by centrifugation as described (Gould *et al*, 2007; Gould *et al*, 2008; Hamburger-Bar *et al*, 1986). Brain lithium levels (mmol/kg, wet weight) were measured with a flame photometer (Cole-Palmer Model 2655-00, Chicago, IL, USA).

Valproate administration and testing. The testing procedure for the valproate study was identical to the lithium study with the exception of drug and the reinforcer saccharin concentration. During training, many of the mice reduced responding once they were no longer being water deprived. In an effort to increase performance and maintain consistency with the lack of water deprivation in the lithium study, the saccharin concentration was increased. Mice in the valproate study received either sodium valproate (20 g/kg) or control chow (both from Custom Animal Diets, Bangor, PA) as previously described (Gould *et al*, 2004a; Hao *et al*, 2004). Drug exposure continued throughout the delay testing (Figure 1). After the conclusion of testing, mice

were decapitated, and to obtain sufficient serum for testing, blood from two like-treated mice were combined to yield sufficient serum for assessment of valproate levels. Serum was run at Indiana University Hospital Pathology Laboratory using standard procedures for clinical samples.

Statistics

Data were analyzed in SPSS software (SPSS, Version 18, Chicago, IL) and Prism software (Graphpad Prism, v. 5.0 La Jolla, CA). Group X Delay repeated measures ANOVAs were run on mean ± SEMs for adjusted amounts, number of trials completed, and volumes consumed during operant sessions. For analysis of stability of adjusted amounts within each delay, we assessed Group X Delay X Day analyses separately, including only days in which at least 70% of the subjects in each group achieved the trials criterion. Number of days used per delay were as follows: 3 days at 1 s delay, 5 days at 2 s delay, 3 days at 4 s delay and 5 days at 8 s delay, with data from a minimum of 16 mice per group per day. An α-value of 0.05 was set to test for significance.

Single values representing the impulsivity level for each mouse, integrating choices over all delays, were calculated according to the formula: mean adjusted amount = delayed reinforcer magnitude/(1 + k*delay). Larger values of *k* indicate steeper discounting. Mice with higher levels of impulsivity will generate steeper discounting curves. The resulting *k*-values showed a left skew, so they were log-10-transformed values prior to a *t*-test analysis.

RESULTS

Lithium

In the lithium study, 9 out of 48 (18.75%) mice were removed for failure to meet initial training criteria prior to lithium or control treatment. Lithium and control mice showed the same adjusted amounts at 0 s delay prior to diet introduction, both averaging (± SEM) 1.95 ± 0.20 s. A mixed ANOVA revealed that treatment with lithium resulted in higher adjusted amounts (ie, lower impulsivity) across all delays (Figure 2). There was an interaction of group X delay, $F(4, 148) = 2.77$, $P = 0.03$, as well as main effects of group,

Figure 1 Timeline showing the experimental procedure used in both studies.
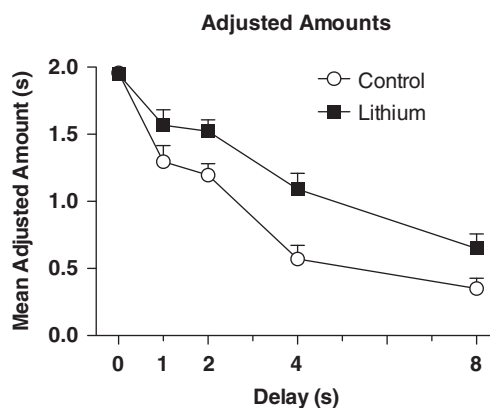
Figure 2 Group mean adjusted amounts ± SEM as a function of delay (0, 1, 2, 4 and 8 s). The lithium group (n = 18) had higher adjusted amounts than the control group (n = 20), $P < .001$ at all delays.

F(1, 37) = 11.25, $P = 0.002$, and delay F(4, 148) = 97.45, $P < 0.001$. Follow-up t-tests indicated that the interaction probably resulted from no difference at 0 s or the 1 s delay, ts(37) ⩽ 1.62, Ps ⩾ 0.11, whereas at longer delays, lithium increased adjusted amounts, ts(37) ⩾ 2.68, Ps ⩽ 0.05 The mean (± SEM) k-value for the lithium group was 0.301 ± 0.058 and for controls was 0.576 ± 0.094. A t-test on log-10-transformed values indicated a significant difference, $t(37) = 3.03$, $P = 0.005$, which is consistent with lithium-reducing impulsivity.

Indices of motivation were increased by lithium, consistent with its known polydipsic effect. A repeated measures ANOVA found a main effect of group on number of trials completed in a session, F(1, 37) = 11.97, $P < 0.001$. Lithium also increased fluid intake during the sessions, as indicated by a main effect of group on the volume of reward consumed during each session, F(1, 37) = 14.59, $P < 0.001$. Increasing delays were associated with decreasing trials completed and intakes, Fs (4, 148) ⩾ 3.8, Ps ⩽ 0.001, Figure 3.

In order to address whether higher adjusted amounts in the lithium group resulted from increased motivation due to thirst, the experiment was extended by 5 days at the 8 s delay. During this time, all mice were restricted to 2 h of water access per day to increase motivation and fluid intake in both groups to an equivalent level. Results from this phase (Figure 4) indicated that there was still a main effect of group on adjusted amount, $t(37) = 2.40$, $P = 0.02$. Importantly, during this period, there was no significant difference in either number of trials completed or volume of reward consumed during each session, ts(37) ⩽ 0.62, Ps ⩾ 0.54. These findings indicate that lithium continued to reduce impulsivity when motivation was equivalently high in both lithium and chow groups. We additionally used a paired t-test to compare adjusted amounts prior to and after water deprivation. Neither the control nor the lithium group was affected by water deprivation, Ps > 0.55, consistent with the idea that motivational differences did not drive drug-induced differences in adjusted amounts.

The analyses for the stability of responding across delays found no main effect of day or group by day interactions (Ps > 0.05). This demonstrates that mice showed relatively stable behavior within the days at each delay.
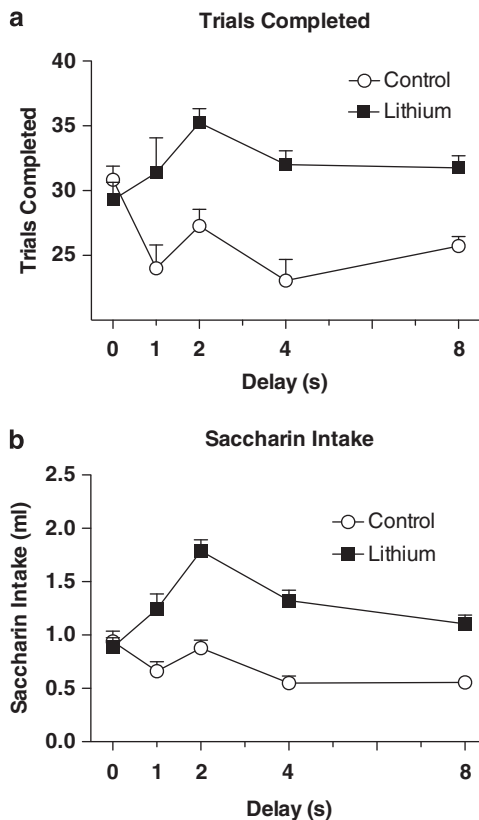
Figure 3 (a) Group mean number of trials completed per session ± SEM as a function of delay (0, 1, 2, 4, and 8 s). Mice in the lithium group completed a greater number of trials per session than the control group, $P < 0.001$. (b) Volume of saccharin solution consumed per session as a function of delay (0, 1, 2, 4 and 8 s) was also higher in the lithium group, $P < 0.001$.
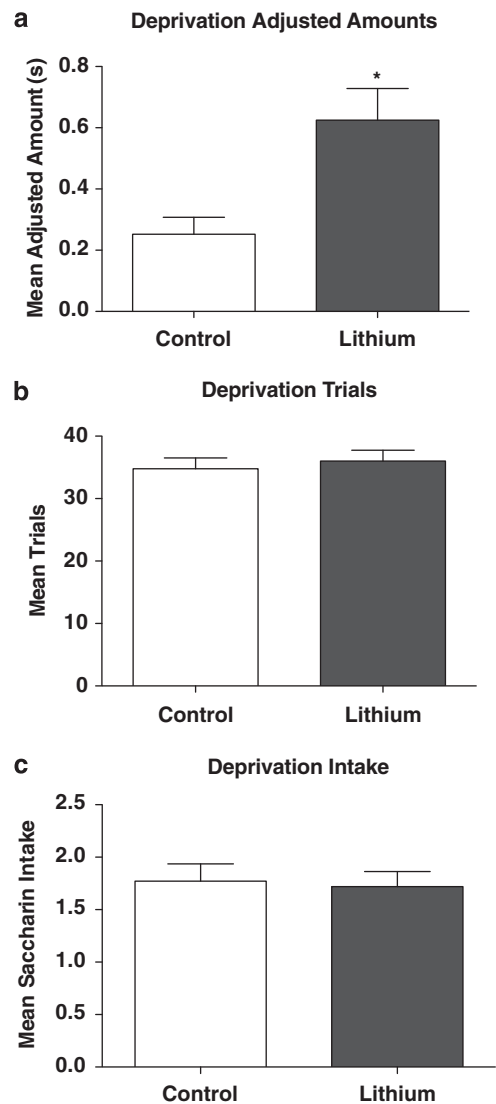
Figure 4 Mean (± SEM) adjusted amounts (a), trials (b), and intake (c) during the 8 s delay, when both lithium and control mice were water deprived. Adjusted amounts continued to be significantly higher with lithium treatment, (*$P < 0.005$), whereas trials completed and intake did not, demonstrating that the anti-impulsive effects of lithium were not secondary to its effects on thirst motivation during this task.
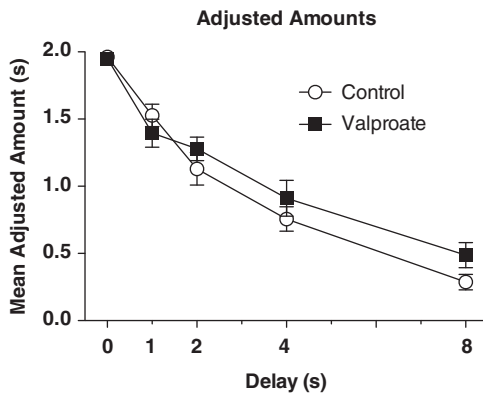
Adjusted Amounts

Figure 5 Group mean adjusted amounts ± SEM as a function of delay (0, 1, 2, 4 and 8 s). Adjusted amounts did not differ between valproate (n = 17) and control treatments (n = 19), P = 0.358.

Mean brain lithium levels were 0.74 ± 0.082 mmol/kg wet weight. This is within the recommended human therapeutic range of 0.6–1.3 mM. We and others have reported previously that brain lithium levels in rodents following chronic treatment are similar to serum levels (Ghoshdastidar *et al*, 1989; Gould *et al* 2007; Gould *et al* 2008; Can *et al*, 2011). There were no significant weight differences between the lithium and control chow-treated groups throughout the duration of the study, $F(1, 38)$, $P = 0.967$.

Valproate

In the valproate study, 11 mice were removed for failure to meet criteria prior to drug treatment, and one mouse in the valproate group died from unknown causes during the study. There was no significant difference in adjusted amounts prior to drug exposure; the valproate group averaged 1.95 ± 0.02 and the control group averaged 1.96 ± 0.01. The repeated measures ANOVA found no effect of group on adjusted amounts, $F(1, 34) < 1$, $P = 0.393$ (Figure 5). Like lithium, though to a lesser degree, valproate significantly increased the number of trials completed during each session, $F(1, 34) = 5.92$ $P = 0.02$, as well as the amount of reward consumed, $F(1, 34) = 4.32$, $P = 0.045$ (Figures 6a,b). There was also a main effect of delay on adjusted amount, $F(4, 136) = 125.56$, $P < 0.001$, on number of trials completed, $F(4, 136) = 14.73$, $P < 0.001$ and on volume of reward consumed, $F(4, 136) = 22.26$, $P < 0.001$. The k-values derived for these groups were analyzed with an independent sample t-test and, consistent with the adjusted amounts, showed no difference, $t(34) = <1.0$, $P = 0.37$. The mean k-values for the valproate group and control groups were 0.425 ± 0.074 and 0.486 ± 0.06, respectively.

Blood serum was collected from 16 mice from the valproate group and tested for valproate levels. The mean blood serum level was 77.88 ± 11.47 mg/l, which is within the human therapeutic range of 50–100 mg/l. There were significant differences in weight between the valproate and control groups over the course of the study, $F(1, 36) = 106.0$, $P < 0.001$, with mice in the valproate group averaging 27.4 ± 0.01 g and the control group averaging 28.6 ± 0.14 g at completion of the study.

a

Trials Completed

b

Saccharin Intake
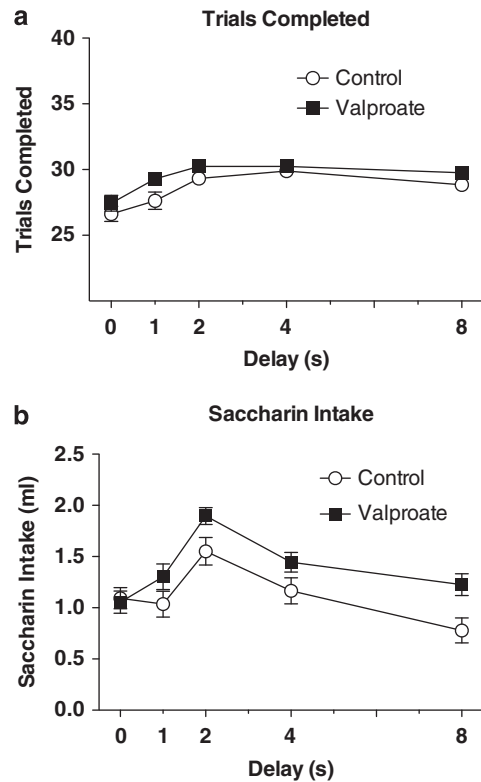
Figure 6 (a) Group mean number of trials completed per session ± SEM as a function of delay (0, 1, 2, 4 and 8 s). Valproate mice completed modestly more trials per session than the control mice, P = 0.02. (b) Valproate mice consumed more saccharin solution than control mice across all delays, P = 0.008.

DISCUSSION

To our knowledge, this is the first study to assess the effects of lithium on cognitive impulsivity in rodents. The DD task is representative of a cognitive choice that is affected in many psychopathologies, including bipolar disorder, suicidal behavior, and alcoholism. The main finding from this study is that lithium treatment reduced cognitive impulsivity, whereas another mood stabilizer, valproate, did not. A limitation of our study is that we only used a single dose of lithium or valproate. However, levels of both valproate and lithium were within the human therapeutic range, which is the outcome that guided our choice of drug levels. Similarly, we only addressed a single time point for the effects of lithium, and did not test whether the actions of lithium persisted following withdrawal. Subjects in the lithium group completed a greater numbers of trials per session and consumed more of the saccharin reinforcer, suggesting a possible difference in motivation. We addressed this by water depriving both groups. Water deprivation had no effect on discounting, which is consistent with a prior report (Richards *et al*, 1997), and lithium continued to exert its effect on mean adjusted amounts during this period, indicating that changes in subjective reward evaluation were not secondary to motivational differences between lithium and control groups. In addition, although valproate treatment also increased the number of trials and volume of reward

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consumed (albeit more modestly than did lithium treatment), it did not decrease impulsivity. These findings indicate that motivational differences are not primarily responsible for the lower levels of impulsive behavior in lithium-treated mice.

Overall, these findings support our *a priori* hypothesis that lithium, but not valproate treatment, would decrease impulsivity in relatively impulsive, HAP mice. Impulsivity is a state independent aspect of bipolar disorder, present in manic, depressive and euthymic states, as well as independently associated with suicidal behavior (Kovacsics *et al*, 2009; Lombardo *et al*, 2012; Swann *et al*, 2001; Swann *et al*, 2003). The ability of the DD task to illustrate changes in cognitive impulsivity due to pharmacological interventions makes it an ideal paradigm in which to test the efficacy of possible new treatments, for such disorders where impulsivity plays a role. Previous studies have shown that treatment with lithium decreases both suicide and suicide attempts in patients with bipolar disorder and major depressive disorder (Baldessarini *et al*, 2006; Guzzetta *et al*, 2007). In addition, other effective antidepressants and mood stabilizers may not have similar antisuicidal efficacy (Collins and McFarland, 2008; Goodwin *et al*, 2003). For example, Goodwin *et al* (2003) found that the risk of suicide was significantly (2.7 times) higher during the treatment with valproic acid (valproate) than with lithium. Collins and McFarland (2008) reported that suicide attempts were more common in bipolar patients taking valproate than in those taking lithium. In a meta-analysis, Cipriani *et al* (2005) reported that lithium is more effective in randomized controlled trials in reducing the risk of suicide, deliberate self-harm, and overall mortality than placebo, anticonvulsants, or antidepressants in subjects with mood disorders. However, there are equivocal findings (Oquendo *et al*, 2011). Both lithium and valproate have been shown to decrease impulsivity in clinical populations (Swann *et al*, 2002). The mechanism underlying these actions have not been established, but have been speculated to involve decreases in limbic hyper excitability in the case of valproate, and enhancing cortical inhibition in the case of lithium (Terao, 2008). How these putative mechanisms relate to drug action vis-à-vis clinical syndromes remains to be fully elicited.

Impulsivity is a multi-faceted construct, difficult to encapsulate with a single definition or behavioral task (Evenden, 1999). Ohmura *et al* (2012) recently reported data demonstrating that acute lithium administration, but not treatment with valproate or carbamazepine, decreased impulsivity as measured in a 3-CSRTT. Although this task is reliable for measuring motor impulsivity (Winstanley *et al*, 2006), it may not be adequate for encompassing all aspects of impulsivity. The DD paradigm is designed to evaluate behavioral choice involving cognitive mechanisms. This argues that converging effects of lithium and valproate in multiple domains of impulsivity may be important to how these pharmacotherapies influence this important endophenotype, as it is unclear which method for measuring impulsivity is more closely associated with suicidal behaviors. The present data add to those of Ohmura *et al* (2012) in confirming the anti-impulsive actions of lithium, but not valproate.

Our study did not examine molecular targets of lithium that may be responsible for the anti-impulsive effect. Lithium has well-documented effects to increase activity of the 5-HT system (Kovacsics *et al*, 2008; Shaw and Ratcliffe, 1976; Treiser *et al*, 1981). The 5-HT system has been implicated in both motor and cognitive impulsivity (Mobini *et al*, 2000; Winstanley *et al*, 2004; Wogar *et al*, 1993). In terms of molecular targets, lithium also has many known effects on intracellular signaling pathways (Gould *et al*, 2002; Gould *et al*, 2004b). Of particular importance may be the effects of lithium on the enzyme glycogen synthase kinase-3 (GSK-3) (Gould, 2006; Jope, 2003; Klein and Melton, 1996). Data support a role of GSK-3 in mediating many of the behavioral effects of lithium in rodents related to its antidepressant and antimanic efficacy, as well as modulating serotonin- and dopamine-mediated signaling (Beaulieu *et al*, 2004, 2008; Li *et al*, 2004; O'Brien *et al*, 2004; Gould *et al*, 2004b). It will be interesting for future studies to assess effects of known direct targets of lithium, such as GSK-3 inhibition, on impulsivity.

Overall, the selectively bred HAP mice used in this study may be useful for modeling aspects of bipolar disorder in addition to identification of novel pharmacotherapies. Approximately 45% of all bipolar patients have a comorbid alcohol addiction and display high levels of impulsivity (McElroy *et al*, 2001; Swann *et al*, 2003). HAP mice consistently consume excessive amounts of ethanol, reaching average blood ethanol levels of over 200 mg/dl on a daily basis (Matson and Grahame, 2011) and demonstrate higher levels of impulsivity than selectively bred Low-Alcohol-Preferring (LAP) mice and their outbred progenitor line (Oberlin and Grahame, 2009). In these ways, they parallel the patients with bipolar disorder more closely than LAP mice, which are less impulsive and do not drink alcohol. In addition, we had also previously reported that HAP mice manifest affect-related behavioral changes when compared with LAP mice (Can *et al*, 2012). In the present study, lithium decreased impulsivity in HAP mice, which suggests that use of this mouse line may be an effective way to test novel bipolar disorder treatments, especially those aimed at reducing comorbid substance abuse. We did not assess effects of either lithium or valproate on the less-impulsive LAP mice. Our rational for choosing HAP mice was due to their high trait impulsivity, and that anti-impulsive effects of *d*-amphetamine had previously been validated in this line, thus proving its predictive value as a model in which to test anti-impulsive drugs (Oberlin *et al*., 2010). As LAP mice manifest relatively low levels of impulsivity, there is the possibility of a floor effects in this line, and therefore limited sensitivity to the anti-impulsive effects of drugs. In addition, studying the effects of lithium and valproate on a less-impulsive line of mice would be less appealing from an external validity standpoint because these drugs are typically used in patients with bipolar disorder and the concomitant high trait impulsivity observed in such patients.

In conclusion, the results of this study demonstrate that chronic treatment with lithium reduces cognitive impulsivity in HAP mice. This same effect was not seen with chronic valproate treatment. These findings support the hypothesis that lithium may exert therapeutic action by decreasing impulsivity.

DISCLOSURE

The authors declare no conflict of interest.

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