Economic demand predicts addiction-like behavior and therapeutic efficacy of oxytocin in the rat

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Development of new treatments for drug addiction will depend on high-throughput screening in animal models. However, an addiction biomarker fit for rapid testing, and useful in both humans and animals, is not currently available. Economic models are promising candidates. They offer a structured quantitative approach to modeling behavior that is mathematically identical across species, and accruing evidence indicates economic-based descriptors of human behavior may be particularly useful biomarkers of addiction severity. However, economic demand has not yet been established as a biomarker of addiction-like behavior in animals, an essential final step in linking animal and human studies of addiction through economic models. We recently developed a mathematical approach for rapidly modeling economic demand in rats trained to self-administer cocaine. We show here that economic demand, as both a spontaneous trait and induced state, predicts addiction-like behavior, including relapse propensity, drug seeking in abstinence, and compulsive (punished) drug taking. These findings confirm economic demand as a biomarker of addiction-like behavior in rats. They also support the view that excessive motivation plays an important role in addiction while extending the idea that drug dependence represents a shift from initially recreational to compulsive drug use. Finally, we found that economic demand for cocaine predicted the efficacy of a promising pharmacotherapy (oxytocin) in attenuating cocaine-seeking behaviors across individuals, demonstrating that economic measures may be used to rapidly identify the clinical utility of prospective addiction treatments.

behavioral economics | reinstatement | extinction | long access | punished responding

There are currently no approved pharmacotherapies for the treatment of cocaine addiction, and timely development of future treatments will depend on animal models that predict the efficacy of treatment in human addicts. This requires a biomarker of addiction suitable for rapid testing in animals, and applicable in humans. However, animal models of neuropsychiatric diseases generally lack predictive validity (1, 2), and prevalent approaches that use drug self-administration in animals have not yet led to a successful clinical treatment for psychostimulant dependence (3, 4).

Economic models provide more promising approaches for this needed cross-species addiction biomarker (5, 6). They offer a structured quantitative method to model behavior that is mathematically identical across species (7–9), and accruing evidence indicates economic-based descriptors of human behavior may be particularly useful biomarkers of addiction severity (10–14). Notably, economic demand has been shown to correlate with lifetime years of cocaine, heroin, marijuana, and benzodiazepine use (15); severity of alcohol dependence (10, 11, 14) and craving (16); as well as severity of nicotine dependence (12, 13) and craving (17). However, economic demand has not yet been established as a biomarker of addiction-like behavior in animals, an essential final step in linking animal and human studies of addiction through economic demand.

We recently developed a mathematical approach for rapidly modeling economic demand in rats trained to self-administer cocaine within a single 110-min session (8). In our first set of studies here, we assess the degree to which this demand model can predict drug taking and drug seeking. We show that economic demand predicted a broad spectrum of these addiction-related behaviors, including relapse propensity, drug seeking in abstinence, and compulsive (punished) drug taking. We then used a long-access procedure to induce an addiction-like state, and we show that demand increased with this state and predicted increased compulsive (punished) drug taking. Our results support the view that excessive motivation plays an important role in addiction (18–20) and our results also provide a structured, graded continuum within which a shift from recreational to compulsive drug use (21, 22) can be quantified. Finally, we found that economic demand for cocaine predicted the ability of oxytocin, a promising new addiction pharmacotherapy, to attenuate cocaine-seeking behaviors across individuals. Our results demonstrate that economic measures may be used to rapidly identify the clinical utility of prospective addiction treatments in rats, and, consequently, can be used to accelerate the discovery of potential therapeutic approaches.

Results

Motivation for Cocaine Is Independent of Cocaine Intake. We trained rats to self-administer i.v. cocaine infusions paired with discrete light and tone cues by responding on a lever during daily, 2-h sessions for ∼1 wk (Fig. S1). Animals were then trained for ∼1 wk (*SI Materials and Methods*) on the within-session threshold procedure in which demand for cocaine (consumption) was measured in a 110-min session across increasing cocaine prices (responses per milligrams of cocaine) by successively decreasing cocaine doses in 10-min bins (23). An exponential demand equation (7) was then fit to each animal's results (8) to determine baseline economic demand for cocaine. Baseline demand parameters Q_0 and α were extracted from the resulting demand curves, and describe drug consumption at null cost (8) (Q_0; free consumption) and rate of consumption decline with increasing price (8) (α; demand

Significance

Cocaine addiction is a major public health problem with no current pharmacotherapy approved by the US Food and Drug Administration. To accelerate discovery of treatments, we developed an animal model based on economics. Economics allows mathematical alignment of animal and human behavior, permitting more confident predictions of efficacy in addicts. Although economic models are strongly associated with addiction severity in humans, they have not yet been shown to be a marker of addiction in rats. In this report, we confirm that economic demand is strongly associated with addiction-like behavior in rats, and can predict the efficacy of a promising addiction therapy. Our findings indicate that this economic approach can be used to accelerate the development of novel addiction therapies.

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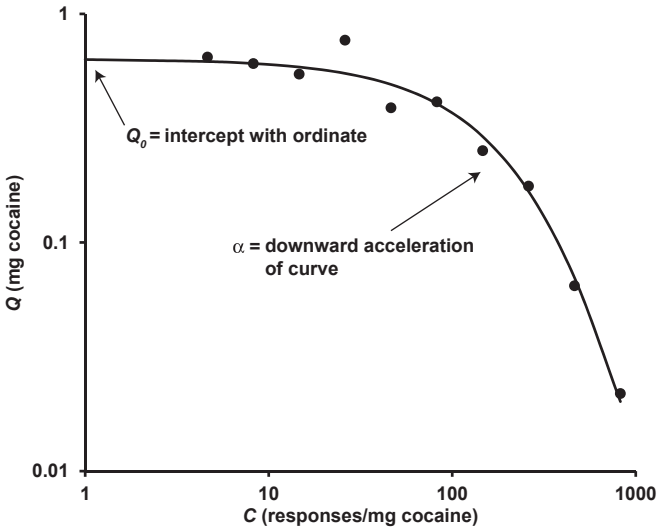

Fig. 1. Example of a demand curve. Data points indicate cocaine consumption during the within-session threshold procedure from a single animal during a single session; the best-fit exponential demand curve has been added. Q_0 is the theoretical demand (Q) at null cost, and α is a measure of how quickly consumption falls with increasing price.

elasticity), respectively (Fig. 1). Importantly, α (also referred to as "essential value") scales inversely with motivation for drug and represents an intrinsic property of the drug's motivational efficacy, independent of the animal's preferred drug consumption at null cost, Q_0 (7). Indeed, Q_0 and α were found to be unrelated ($r = -0.11$, $P > 0.05$) (Fig. S2). Addiction-like behavior, and the effectiveness of oxytocin in reducing such behavior, was evaluated in five independent groups of animals after baseline demand was established (Fig. S3).

Baseline Demand Predicts Drug Seeking During Abstinence. The inability to maintain abstinence is a trademark of addiction (24), and this is measured in animals as persistence in drug seeking during periods of drug unavailability (20). Twenty-four hours following baseline economic demand assessment, animals were run on daily extinction sessions, during which lever responses no longer resulted in drug or cue delivery (Fig. S3, groups 1–3, $n = 28$). The demand parameter α, but not Q_0, from the baseline session predicted the number of active lever responses during the first extinction session (Q_0: $\beta = -0.24$, $P > 0.05$; α: $\beta = -0.80$, $P < 1E\text{-}5$) (Fig. 2*A*), the maximum number of active lever responses during any extinction session (Q_0: $\beta = -0.26$, $P > 0.05$; α: $\beta = -0.77$, $P < 1E\text{-}5$) (Fig. S4*A*), and the number of days required for responding to taper to extinction criteria (Q_0: $\beta = -0.20$, $P > 0.05$; α: $\beta = -0.58$, $P < 0.01$) (Fig. S4*B*). Note that lower values of α indicate greater motivation for cocaine, so negative correlations show that motivation by this measure (obtained before abstinence or extinction) predicted greater drug seeking during abstinence.

Demand Predicts Reinstatement of Extinguished Drug Seeking. Addiction is a chronic disease in which drug-associated stimuli, or reexposure to drug itself, cause individuals to relapse to drug use after periods of abstinence (25); thus, after extinction criteria were met, we tested the ability of baseline economic demand to predict reinstatement (26) of drug seeking evoked by cocaine-associated light and tone cues (Fig. S3, groups 1–3, $n = 26$) or by a priming injection of cocaine (10 mg/kg i.p.; Fig. S3, groups 1–3, $n = 24$). We found that α, but not Q_0, predicted the number of responses during both cue-induced (Q_0: $\beta = 0.04$, $P > 0.05$; α: $\beta = -0.53$, $P < 0.01$) (Fig. 2*B*) and cocaine-primed (Q_0: $\beta = 0.20$, $P > 0.05$; α: $\beta = -0.75$, $P < 1E\text{-}4$) (Fig. 2*C*) reinstatement to drug seeking. Negative correlations with α indicate that greater motivation for cocaine by this measure (again, obtained before abstinence or extinction) predicted greater reinstatement of drug seeking.

Demand Predicts Compulsive (Punished) Drug Taking. A particularly striking feature of addiction is compulsive drug use in the face of aversive consequences (27). Compulsive drug use is often modeled in rats as the number of footshock-paired responses for drug that the animal will self-administer in a session (28). However, as typically implemented this method does not account for interindividual variability in preferred drug consumption at null cost (Q_0); hence, we developed an economic shock paradigm with price defined as the magnitude of footshock punishment [millicoulombs (mC)] paid per milligrams of cocaine infused (millicoulombs shock per milligrams of cocaine). The cocaine dose elicited by a lever response remained static throughout the session (26.1 responses per milligrams cocaine), whereas the footshock current successively increased in 10-min bins from 0 to 0.79 milliamps (mA). Using this paradigm, consumption changes are due entirely to the presence of shock (Fig. S5). Results were normalized for individual variation in Q_0 by defining punishment resistance as the maximum electrical charge an animal is willing to endure in a bin to defend its shock-free preferred cocaine intake, i.e., the product of number of infusions and charge per infusion. Thus, we asked what maximum punishment animals self-administered within any bin to maintain their particular Q_0. We found that the demand parameters α ($\beta = -0.83$, $P < 1E\text{-}3$) and Q_0 ($\beta = 0.35$, $P < 0.05$) independently predicted the maximum charge animals self-administered, and together they accounted for 95% of variance (Fig. 2*D* and Fig. S3, group 3, $n = 8$).

Demand Is Not Confounded by Time. The within-session threshold procedure used above presents prices in the same ascending order in every session, a necessary facet to assess animals' motivation to maintain Q_0 (8). However, this procedure also confounds time and price, and obscures whether results reflect a valid measure of drug demand or simply time in session. Thus, we developed an intermittent threshold procedure that imposes 20-min timeouts between 10-min periods of drug access. Timeouts force the animal's brain cocaine levels to decrease (29), and the animal must then work to regenerate its brain cocaine level at various prices. Because motivation to generate, not maintain, brain cocaine levels is assessed with this procedure, the order of price presentation may be reversed. Demand parameters were measured in animals with the threshold procedure, and then again on both ascending and descending price scales on the intermittent threshold procedure (Fig. S3, groups 1 and 2, $n = 16$). Threshold procedure demand parameters strongly predicted those from the intermittent procedure (Q_0: $r = 0.87$, $P < 10E\text{-}4$; α: $r = 0.76$, $P < 10E\text{-}3$) (Fig. S6), thereby indicating that economic parameters from the threshold procedure measured demand and not an epiphenomenon of the procedure itself.

Demand Is Elevated Following Long-Access Self-Administration. Addiction is a culmination of trait (predisposition) and state (exposure) variables (30). The results above only consider the predictive capacity of cocaine demand assessed early after acquisition of drug self-administration behavior, i.e., trait-dependent demand. We also asked how the state of cocaine demand was altered with extended self-administration history, as a function of the baseline demand trait. The addiction state can be reliably altered by allowing animals to self-administer drug during daily, extended-length sessions over several weeks (31). Extended-access procedures have been shown to elevate compulsive drug taking (32), cocaine consumption (31), and cocaine demand (33). For a separate group of subjects (Fig. S3, group 4, $n = 12$), baseline demand was assessed as above and then animals self-administered cocaine for 14 daily long-access sessions (LgA; 6-h duration). Mean cocaine consumption increased during LgA from 55.7 to 62.7 mg/kg per session (repeated ANOVA, $F_{13,143} = 2.54$, $P < 0.01$) and demand for cocaine on the first day following LgA termination was significantly greater than baseline demand (repeated ANOVA,

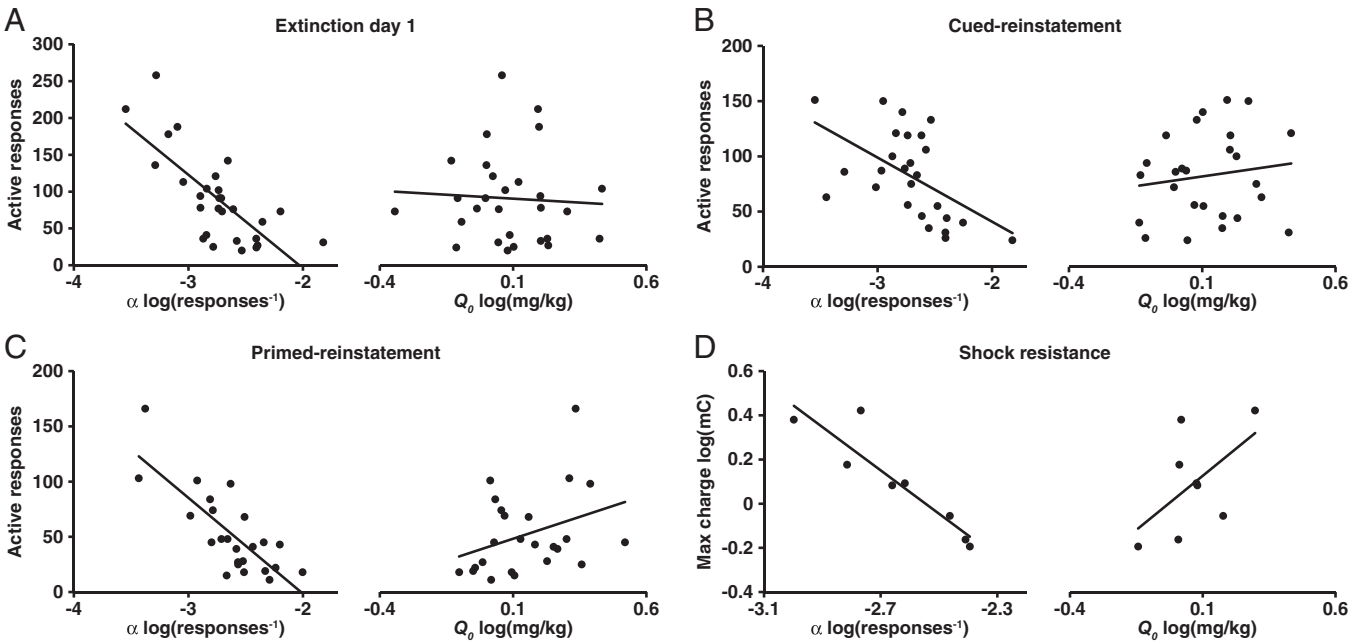

Fig. 2. Economic demand predicts addiction-like behavior. (*A*) α, but not Q_0, predicted drug seeking during abstinence on extinction day 1 [($n = 28$) (Q_0: $\beta = -0.24$, $P > 0.05$; α: $\beta = -0.80$, $P < 1E\text{-}5$)]. (*B*) After active responding was extinguished, α, but not Q_0, predicted cued reinstatement of drug seeking [($n = 26$) (Q_0: $\beta = 0.04$, $P > 0.05$; α: $\beta = -0.53$, $P < 0.01$)], as well as (*C*) cocaine-primed reinstatement of drug seeking [($n = 24$) (Q_0: $\beta = 0.20$, $P > 0.05$; α: $\beta = -0.75$, $P < 1E\text{-}4$)]. (*D*) α and Q_0 independently predicted compulsive drug taking, measured as the maximum electrical charge an animal would self-administer in a bin to defend initial, shock-free drug consumption [($n = 8$) (Q_0: $\beta = 0.35$, $P < 0.05$; α: $\beta = -0.83$, $P < 1E\text{-}3$)].

Q_0: $F_{2,22} = 10.85$, $P < 0.001$; α: $F_{2,22} = 7.64$, $P < 0.01$) (Fig. 3). Animals were tested daily with the threshold procedure until their α value was stable across 3 d (*Materials and Methods*). We found that the rise in Q_0 persisted, and animals stabilized at a greater value of Q_0 (Bonferroni, $P < 0.05$) (Fig. 3*A*); the increase in motivation (reduced α) was largest on the first post-LgA session and tended to endure, although not significantly, when measured across the entire cohort (Bonferroni, $P > 0.05$) (Fig. 3*B*).

Baseline Demand Predicts Changes in Demand with LgA. Notably, we found that alteration in demand produced by LgA differed according to animals' baseline cocaine demand before LgA exposure. For example, persistent increases in motivation (significantly increased throughout the test period after LgA) were observed in animals with low, but not those with high, baseline demand. The cohort was split into high and low baseline demand groups based on the median α from the entire population of rats trained under the same criteria in our laboratory ($n = 131$, median $\alpha = 0.00216$). Demand groups were defined by α because that parameter, and not Q_0, reliably predicts addiction-like behavior (as described above). We found that LgA produced persistent reductions in α (increases in demand) in animals with low baseline demand, whereas LgA exposure did not alter α in high baseline demand animals (mixed model, demand group × time, $F_{2,20} = 11.06$, $P < 1E\text{-}3$) (Fig. 3*C*). Further, the increase in demand in response to LgA was predicted by baseline demand such that lower baseline demand animals showed greater increases in demand. Specifically, animals with the lowest baseline Q_0 showed the greatest proportional increase in Q_0 (Pearson, $r = -0.89$, $P < 1E\text{-}4$) (Fig. S7*A*), and animals with the highest baseline α showed the greatest proportional decrease in α (Pearson, $r = -0.87$, $P < 1E\text{-}3$) (Fig. S7*B*). Similarly, proportional escalation in cocaine consumption during LgA was also predicted by demand, with low Q_0 animals escalating the most ($\beta = -0.65$, $P < 0.05$); however, escalation was not related to baseline α ($\beta = -0.00$, $P > 0.05$) (Fig. S8). Thus, animals either displayed spontaneously high demand after acquiring cocaine self-administration behavior, or they were reliably made into high-demand rats by LgA exposure.

Demand Predicts Compulsive (Punished) Drug Taking Within a Mixed-State Group. The cause of addiction at an individual level is often unclear; hence, it is necessary that an addiction biomarker function regardless of etiology. We asked if the state-dependent, increased demand we observed following LgA was predictive of increased compulsive (shock-resistant) drug seeking within a mixed-state group (Fig. S3, groups 3 and 4, $n = 20$), i.e., containing both LgA-exposed rats and animals tested immediately following baseline measures of demand (non-LgA). LgA animals showed more compulsive drug taking than non-LgA rats (*t* test, $t_{18} = 2.55$, $P < 0.05$) (Fig. 3*D*), and demand predicted compulsive drug seeking (amount of shock self-administered) in all animals tested regardless of LgA exposure in both the Q_0 ($\beta = 0.57$, $P < 0.01$) and α measures ($\beta = -0.55$, $P < 0.01$) (Fig. 3*E*). The main effect of LgA was to reduce the variation in demand, such that LgA animals resembled high-demand rats not given LgA, both in the Q_0 and α measures.

Demand Predicts Oxytocin Treatment Efficacy. There is no current Food and Drug Administration-approved pharmacotherapy to evaluate the predictive validity of our economic demand procedures; however, oxytocin is a promising candidate (34, 35). In preclinical testing oxytocin attenuates self-administration of psychostimulants as well as reinstatement to drug seeking (36, 37), and early clinical testing confirmed that oxytocin attenuates drug craving (38, 39). We tested the effect of oxytocin pretreatment on cocaine demand and reinstatement of cocaine seeking to evaluate its potential as a cocaine addiction treatment as well as to demonstrate utility of this economic approach. A separate group of animals was trained to self-administer cocaine in 2-h, daily sessions for ∼2 wk (Fig. S3, group 5, $n = 14$). Baseline economic demand was determined, and animals were randomly administered oxytocin (1 mg/kg i.p.) or vehicle (saline) 30 min before session start in a within-subject cross-over design. Oxytocin treatment significantly reduced Q_0 (paired *t* test, $t_{13} = 3.20$, $P < 0.01$) (Fig. 4*A*) and increased α (paired *t* test, $t_{13} = 3.56$, $P < 0.01$) (Fig. 4*B*), indicating a reduction in both the amount of cocaine desired at null effort (free consumption) as well as

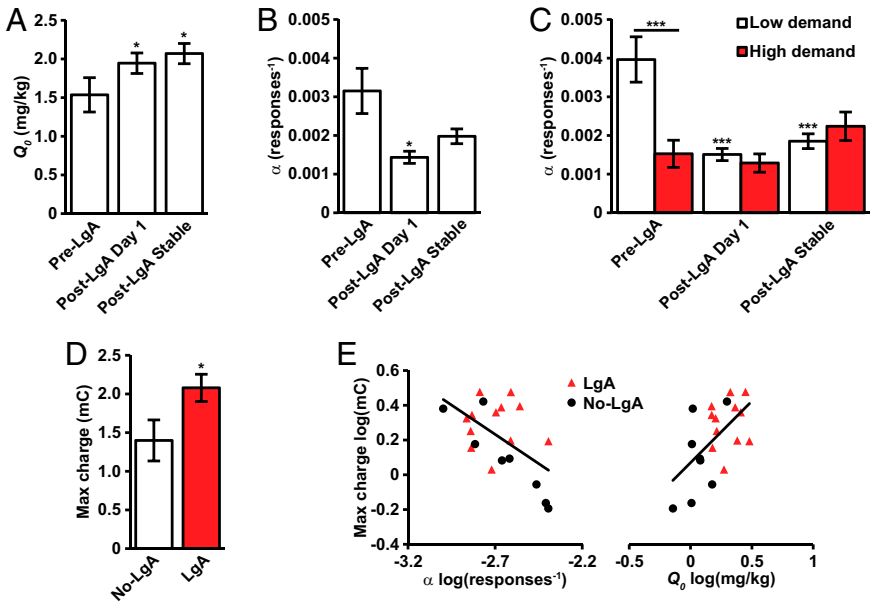

Fig. 3. LgA increases economic demand and compulsive drug taking. (*A*) Q_0 was significantly elevated the first day after LgA, and stabilized at a significantly greater value (*$P < 0.05$, Bonferroni). (*B*) α was significantly decreased the first day following LgA (*$P < 0.05$, Bonferroni); there also was a trend for the group to stabilize at a lower α (although not significant). (*C*) Low baseline demand animals had significantly greater baseline mean α (***$P < 0.001$, Bonferroni), and in contrast to high baseline demand animals, low-demand animals showed a significant decrease in α after LgA that persisted to stabilization (***$P < 0.001$, Bonferroni). (*D*) Animals exposed to LgA cocaine self-administration ($n = 12$) displayed significantly greater compulsive (punished) drug taking compared with a separate group of animals ($n = 8$) tested immediately after baseline demand was established (*$P < 0.05$, *t* test). (*E*) Regardless of LgA treatment, compulsivity remained associated with both Q_0 ($\beta = 0.57$, $P < 0.01$) and α ($\beta = -0.55$, $P < 0.01$). Error bars in *A*–*D* represent SEM.

motivation for cocaine (essential value). Moreover, the proportional change in α after oxytocin was predicted by individual animals' baseline α, with the largest effect observed in animals with high baseline demand (Pearson, $r = -0.62$, $P < 0.05$) (Fig. 4*C*). Apropos of the association between economic demand and relapse behavior, this attenuation of cocaine demand predicts oxytocin may also abrogate relapse to cocaine seeking. Indeed, we found that oxytocin pretreatment significantly reduced cue-induced reinstatement of cocaine seeking (paired *t* test, $t_{13} = 5.41$, $P < 0.001$) (Fig. 4*D*).

Discussion

We showed here that economic demand predicts an addiction-like behavioral phenotype and treatment efficacy in an animal model. This set of findings extends several lines of investigation and integrates them to provide a translationally significant tool for drug discovery; these are elaborated in the next paragraphs. Namely, in this report we extend behavioral–economic theory, provide relevance for within-session behavioral–economic methods, support a central role of motivation in addiction, provide a framework for interpreting the transition from recreational to compulsive drug use (21, 22), and provide a direct mathematical link between addiction-like behavior in rats and the behavior of human addicts.

This report extends behavioral–economic theory (7) by establishing a strong, predictive association between economic demand and addiction-like behavior. Previous reports have found that essential value (α) predicts cue-induced reinstatement of methamphetamine seeking (40), and that long-access self-administration of cocaine increases Q_0 while decreasing α (33). Our studies replicate these findings, and significantly extend them by also showing that essential value (α) predicts cocaine-primed reinstatement, drug seeking during abstinence, and compulsive (punished) drug taking. Further, we describe how trait-dependent cocaine demand—early in the animal's self-administration history—predicts changes in addiction state known to take place with exposure to LgA (31). Notably, we observed spontaneously high-demand rats (i.e., without LgA treatment) as well as low-demand rats that were transformed into high-demand rats with LgA, indicating that the addiction phenotype may occur anywhere along the etiological spectrum from trait to state dependence—a spectrum well known in human literature (30).

In contrast to the decreased interindividual variability in demand after LgA that we report here, and that others have also reported (33), prolonged access procedures tend to segregate animals, increasing interindividual variability (20, 28). In these prolonged access procedures animals self-administer drug in lower overall quantities per day than LgA procedures but for more than a month of daily sessions. Past reports have shown that animals segregate by reinstatement propensity with prolonged access (20), and because we found reinstatement propensity to be highly related to demand, we expect similar results would be produced if groups were initially defined by baseline cocaine demand. Thus, we hypothesize that with the prolonged access procedure demand groups will also segregate, with high-demand rats increasing in their cocaine demand and low-demand rats remaining low demand or marginally decreasing in their cocaine demand.

Our report uses a within-session behavioral–economic method (8, 23) and validates this approach for addiction behavior. Past reports have described how within-session measures of economic drug demand are affected by pharmacological intervention (23), various schedules of drug self-administration (29), and exposure to stress (41). Our analysis is unique in that we benchmarked the within-session threshold procedure against several well-established measures of addiction-like behavior in rats, including extinction, reinstatement, and punished responding. Furthermore, we used a normalized measure of demand elasticity (α), allowing independent assessment of changes in motivation for drug (α) versus changes in drug intake (Q_0) (7).

This independent analysis of drug intake and motivation provides insight into the central role of the motivation for drug in addiction behavior. Prevalent measures of drug motivation, such as progressive ratio breakpoint, depend on extrinsic factors such as the dose size chosen and drug pharmacokinetics, and lack a direct relationship with drug motivation (e.g., manipulations that reduce

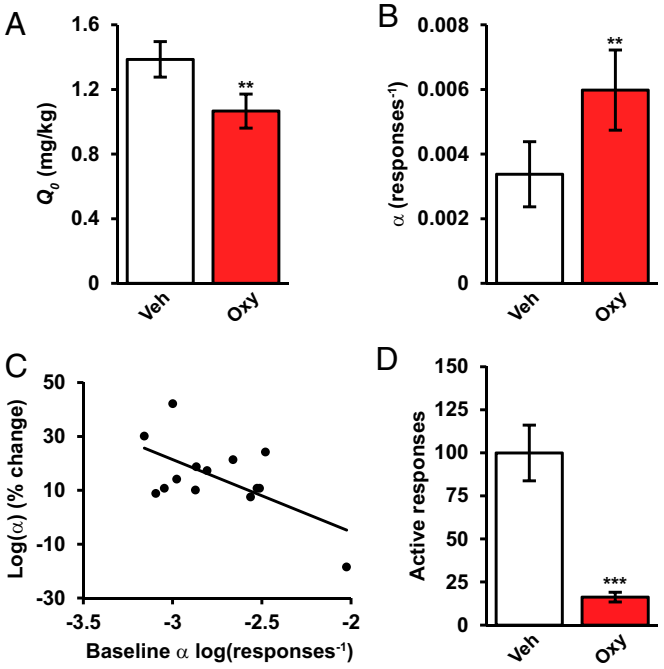

Fig. 4. Oxytocin pretreatment significantly decreases cocaine economic demand. (*A*) Animals ($n = 14$) pretreated with oxytocin (Oxy) displayed a significantly lower Q_0 than when pretreated with saline vehicle (Veh) (paired t test, $^{**}P < 0.01$), (*B*) as well as increased demand elasticity (α) (paired t test, $^{**}P < 0.01$). (*C*) Baseline demand (on the abscissa) predicted the treatment effect of oxytocin (percentage change in demand, on the ordinate; Pearson, $r = -0.62$, $P < 0.05$). (*D*) Oxytocin pretreatment ($n = 14$) significantly reduced active responding during cued reinstatement of cocaine seeking (paired t test, $^{***}P < 0.001$). Error bars in *A*, *B*, and *D* represent SEM.

cocaine reward can either increase or decrease the maximum number of times an animal will respond for a single drug delivery) (7, 42). Normalized measures of demand elasticity, such as the essential value parameter α, were developed specifically to overcome these limitations and report the subject's intrinsic motivation for a reinforcer (7). Hence, by showing that cocaine essential value (α) predicts a broad spectrum of addiction-like behavior, we confirm previous associations reported between measures of drug motivation and addiction-like behavior (20).

Although cocaine essential value (α) reliably predicted addiction-like behavior, free consumption of drug (Q_0) did not significantly predict any measures of drug seeking during abstinence, i.e., extinction responding or reinstatement. However, Q_0 significantly predicted punishment resistance of cocaine taking, independently of α, albeit to a lesser degree. Q_0 is a measure of preferred drug intake (7); thus, we hypothesize that Q_0 aids in predictions of variables that are related, in part, to drug intake. In our shock paradigm, animals self-administered drug at a relatively low effort-based price, and our measure of punishment resistance was both dependent on preferred intake and resistance to changes in that intake with associated shock devaluation, i.e., it was a product of both number of infusions and shock value at that infusion. Thus, in this case both punishment resistance and preferred level of drug intake are expected to contribute to the total shock self-administered. Of note, Q_0 has been reported to be associated with alcohol-related problems and misuse (10, 11, 14) and nicotine dependence (12, 13), and could be a clinically relevant measure of addiction severity. This is consistent with the view that Q_0 parameter is similar to hedonic set point (8), a concept thought to be important in addiction behavior (31, 43).

Although demand elasticity (α) is a measure of motivation when the price of drug is effort based (as it is with the threshold procedure used here), α can be more broadly interpreted as sensitivity to drug devaluation. Notably, the strong association we show between sensitivity to effort-based devaluation and punishment-based devaluation (shock resistance) indicates that individual variability in devaluation sensitivity is not specific to devaluation modality. This finding is consistent with a major theory that posits addiction is the end result of a progression of drug taking behavior from initial recreational use—during which the individual is sensitive to drug devaluation—to compulsive, devaluation-insensitive drug seeking (21, 22). In parallel with this hypothesis, we found that devaluation sensitivity (α), rather than preferred magnitude of drug consumption Q_0, predicted a broad spectrum of addiction-like behavior. Notably, our economic approach provides a high-resolution gradient within which devaluation sensitivity and associated neural substrates may be quantified across species. Moreover, our results indicate that the shift from recreational to compulsive drug use does not result in a complete loss of value-dependent behavior. Indeed, although the elasticity of demand decreased, and this decreased elasticity was associated with punishment resistance, we found that a degree of elasticity remained regardless of the severity of addiction-like behavior. Sensitivity to devaluation was reduced with LgA; yet, value-based decision-making never ceased to occur. Similarly, value-dependent demand for psychostimulants has been repeatedly observed in human addicts (9, 15, 44, 45), and from this observation some have inferred that even those with severe addiction will continue to make rational price-dependent choices concerning drug (44, 45). Thus, value-independent drug seeking is likely a theoretical limit of this transition rather than an observed behavior.

The economic framework in which we parameterize addiction behavior is also significant, because it provides a direct mathematical link between the addiction-like behavior in rats and humans. Economic demand is associated with measures of addiction in humans for several drugs, such as lifetime years of cocaine, heroin, marijuana, and benzodiazepine use (15); severity of alcohol dependence (10, 11, 14) and craving (16); as well as severity of nicotine dependence (12, 13) and craving (17). A model of economic demand was recently validated in cocaine-dependent participants (9), providing the means for ready, direct comparison of animal and human studies of addiction treatments.

We demonstrated use of our within-session economic method for predicting therapeutic benefit with a promising addiction treatment—oxytocin. There is strong preclinical evidence for oxytocin as a treatment for psychostimulant addiction (34, 35, 37), and early clinical studies have confirmed that oxytocin reduces craving for marijuana and alcohol (38, 39). We found that oxytocin dramatically reduced cocaine demand in animals with a standard self-administration history; this finding, in view of the relationship between demand and addiction-like behavior reported here, predicts that oxytocin may effectively treat psychostimulant dependence in the clinic. Consistent with this, reduced cocaine demand after oxytocin pretreatment was strongly associated with baseline demand. This finding parallels a human study, which also found that demand predicted treatment outcomes (46). Furthermore, it is clinically appealing because it indicates that oxytocin may have a preferential effect on patients with the most extreme addiction phenotype. Finally, we also found that demand reduction by oxytocin predicted attenuation of relapse behavior, supporting the value of demand as an addiction biomarker. This observation is consistent with a recent human study (47) that found a pharmacotherapy that reduced demand for cigarettes also increased the duration patients remained abstinent. Finally, although oxytocin is a peptide and therefore may not cross the blood–brain barrier, systemic administration nevertheless produces robust central activation of oxytocin neurons in supraoptic and paraventricular nuclei (48), indicating systemic oxytocin administration is a viable method of inducing central nervous system (CNS) release of oxytocin and altering CNS activity.

In summary, we showed that economic demand for cocaine predicts a broad spectrum of addiction-like behavior. Our findings

mirror clinical evidence for economic demand as an addiction biomarker, and support a central role of drug motivation as measured by demand elasticity in the addiction phenotype. The economic structure of these results provide a high-resolution, structured framework for quantifying the degree of devaluation insensitivity, indicating addiction severity and providing a context for investigating the transition from recreational to compulsive drug use. Moreover, the economic structure allows for ready comparison with clinical research (9), directly linking animal and human studies of addiction treatments, and the relative ease of this approach provides a means to rapidly test the potential of novel addiction therapies.

Materials and Methods

All materials and methods used in this study are detailed in *SI Materials and Methods*. This includes a detailed description of animal housing, drugs, cocaine self-administration training, threshold procedure testing, extinction training, the LgA procedure, reinstatement testing, footshock procedures, and oxytocin treatment. A detailed description of statistical tests can also be found therein.

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1. Becker RE, Greig NH (2010) Lost in translation: Neuropsychiatric drug development. *Sci Transl Med* 2(61):61rv6.
2. Markou A, Chiamulera C, Geyer MA, Tricklebank M, Steckler T (2009) Removing obstacles in neuroscience drug discovery: The future path for animal models. *Neuropsychopharmacology* 34(1):74–89.
3. Haney M, Spealman R (2008) Controversies in translational research: Drug self-administration. *Psychopharmacology (Berl)* 199(3):403–419.
4. Pierce RC, O'Brien CP, Kenny PJ, Vanderschuren LJMJ (2012) Rational development of addiction pharmacotherapies: Successes, failures, and prospects. *Cold Spring Harb Perspect Med* 2(6):a012880.
5. Heinz AJ, Lilje TC, Kassel JD, de Wit H (2012) Quantifying reinforcement value and demand for psychoactive substances in humans. *Curr Drug Abuse Rev* 5(4):257–272.
6. Bickel WK, Johnson MW, Koffarnus MN, MacKillop J, Murphy JG (2014) The behavioral economics of substance use disorders: Reinforcement pathologies and their repair. *Annu Rev Clin Psychol* 10:641–677.
7. Hursh SR, Silberberg A (2008) Economic demand and essential value. *Psychol Rev* 115(1):186–198.
8. Bentzley BS, Fender KM, Aston-Jones G (2013) The behavioral economics of drug self-administration: A review and new analytical approach for within-session procedures. *Psychopharmacology (Berl)* 226(1):113–125.
9. Bruner NR, Johnson MW (2014) Demand curves for hypothetical cocaine in cocaine-dependent individuals. *Psychopharmacology (Berl)* 231(5):889–897.
10. Gray JC, MacKillop J (2014) Interrelationships among individual differences in alcohol demand, impulsivity, and alcohol misuse. *Psychol Addict Behav* 28(1):282–287.
11. Murphy JG, MacKillop J, Skidmore JR, Pederson AA (2009) Reliability and validity of a demand curve measure of alcohol reinforcement. *Exp Clin Psychopharmacol* 17(6): 396–404.
12. Murphy JG, MacKillop J, Tidey JW, Brazil LA, Colby SM (2011) Validity of a demand curve measure of nicotine reinforcement with adolescent smokers. *Drug Alcohol Depend* 113(2-3):207–214.
13. Chase HW, Mackillop J, Hogarth L (2013) Isolating behavioural economic indices of demand in relation to nicotine dependence. *Psychopharmacology (Berl)* 226(2): 371–380.
14. MacKillop J, et al. (2010) Alcohol demand, delayed reward discounting, and craving in relation to drinking and alcohol use disorders. *J Abnorm Psychol* 119(1):106–114.
15. Petry NM (2001) A behavioral economic analysis of polydrug abuse in alcoholics: Asymmetrical substitution of alcohol and cocaine. *Drug Alcohol Depend* 62(1):31–39.
16. MacKillop J, et al. (2010) Behavioral economic analysis of cue-elicited craving for alcohol. *Addiction* 105(9):1599–1607.
17. MacKillop J, et al. (2012) Behavioral economic analysis of withdrawal- and cue-elicited craving for tobacco: An initial investigation. *Nicotine Tob Res* 14(12):1426–1434.
18. Solomon RL (1980) The opponent-process theory of acquired motivation: The costs of pleasure and the benefits of pain. *Am Psychol* 35(8):691–712.
19. Kalivas PW, Volkow ND (2005) The neural basis of addiction: A pathology of motivation and choice. *Am J Psychiatry* 162(8):1403–1413.
20. Deroche-Gamonet V, Belin D, Piazza PV (2004) Evidence for addiction-like behavior in the rat. *Science* 305(5686):1014–1017.
21. Everitt BJ, Robbins TW (2005) Neural systems of reinforcement for drug addiction: From actions to habits to compulsion. *Nat Neurosci* 8(11):1481–1489.
22. Everitt BJ, Robbins TW (2013) From the ventral to the dorsal striatum: Devolving views of their roles in drug addiction. *Neurosci Biobehav Rev* 37(9 Pt A):1946–1954.
23. Oleson EB, Richardson JM, Roberts DCS (2011) A novel IV cocaine self-administration procedure in rats: Differential effects of dopamine, serotonin, and GABA drug pretreatments on cocaine consumption and maximal price paid. *Psychopharmacology (Berl)* 214(2):567–577.
24. American Psychiatric Association (2013) *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Publishing, Inc, Arlington, VA).
25. Kalivas PW, O'Brien C (2008) Drug addiction as a pathology of staged neuroplasticity. *Neuropsychopharmacology* 33(1):166–180.
26. Shaham Y, Shalev U, Lu L, De Wit H, Stewart J (2003) The reinstatement model of drug relapse: History, methodology and major findings. *Psychopharmacology (Berl)* 168(1-2):3–20.
27. Volkow ND, Baler RD, Goldstein RZ (2011) Addiction: Pulling at the neural threads of social behaviors. *Neuron* 69(4):599–602.
28. Chen BT, et al. (2013) Rescuing cocaine-induced prefrontal cortex hypoactivity prevents compulsive cocaine seeking. *Nature* 496(7445):359–362.
29. Zimmer BA, Oleson EB, Roberts DC (2012) The motivation to self-administer is increased after a history of spiking brain levels of cocaine. *Neuropsychopharmacology* 37(8):1901–1910.
30. O'Brien CP (2008) Review. Evidence-based treatments of addiction. *Philos Trans R Soc Lond B Biol Sci* 363(1507):3277–3286.
31. Ahmed SH, Koob GF (1998) Transition from moderate to excessive drug intake: Change in hedonic set point. *Science* 282(5387):298–300.
32. Vanderschuren LJMJ, Everitt BJ (2004) Drug seeking becomes compulsive after prolonged cocaine self-administration. *Science* 305(5686):1017–1019.
33. Christensen CJ, Silberberg A, Hursh SR, Roma PG, Riley AL (2008) Demand for cocaine and food over time. *Pharmacol Biochem Behav* 91(2):209–216.
34. Carson DS, Guastella AJ, Taylor ER, McGregor IS (2013) A brief history of oxytocin and its role in modulating psychostimulant effects. *J Psychopharmacol* 27(3):231–247.
35. Sarnyai Z, Kovács GL (2014) Oxytocin in learning and addiction: From early discoveries to the present. *Pharmacol Biochem Behav* 119:3–9.
36. Carson DS, Cornish JL, Guastella AJ, Hunt GE, McGregor IS (2010) Oxytocin decreases methamphetamine self-administration, methamphetamine hyperactivity, and relapse to methamphetamine-seeking behaviour in rats. *Neuropharmacology* 58(1):38–43.
37. Cox BM, Young AB, See RE, Reichel CM (2013) Sex differences in methamphetamine seeking in rats: Impact of oxytocin. *Psychoneuroendocrinology* 38(10):2343–2353.
38. McRae-Clark AL, Baker NL, Maria MM-S, Brady KT (2013) Effect of oxytocin on craving and stress response in marijuana-dependent individuals: A pilot study. *Psychopharmacology (Berl)* 228(4):623–631.
39. Pedersen CA, et al. (2013) Intranasal oxytocin blocks alcohol withdrawal in human subjects. *Alcohol Clin Exp Res* 37(3):484–489.
40. Galuska CM, Banna KM, Willse LV, Yahyavi-Firouz-Abadi N, See RE (2011) A comparison of economic demand and conditioned-cued reinstatement of methamphetamine-seeking or food-seeking in rats. *Behav Pharmacol* 22(4):312–323.
41. Groblewski PA, Zietz C, Willuhn I, Phillips PEM, Chavkin C (2014) Repeated stress exposure causes strain-dependent shifts in the behavioral economics of cocaine in rats. *Addict Biol*, 10.1111/adb.12123.
42. Stafford D, LeSage MG, Glowa JR (1998) Progressive-ratio schedules of drug delivery in the analysis of drug self-administration: A review. *Psychopharmacology (Berl)* 139(3):169–184.
43. Ahmed SH, Koob GF (1999) Long-lasting increase in the set point for cocaine self-administration after escalation in rats. *Psychopharmacology (Berl)* 146(3):303–312.
44. Hart CL, Haney M, Foltin RW, Fischman MW (2000) Alternative reinforcers differentially modify cocaine self-administration by humans. *Behav Pharmacol* 11(1):87–91.
45. Kirkpatrick MG, et al. (2012) Comparison of intranasal methamphetamine and d-amphetamine self-administration by humans. *Addiction* 107(4):783–791.
46. MacKillop J, Murphy JG (2007) A behavioral economic measure of demand for alcohol predicts brief intervention outcomes. *Drug Alcohol Depend* 89(2-3):227–233.
47. McClure EA, Vandrey RG, Johnson MW, Stitzer ML (2013) Effects of varenicline on abstinence and smoking reward following a programmed lapse. *Nicotine Tob Res* 15(1):139–148.
48. Carson DS, et al. (2010) Systemically administered oxytocin decreases methamphetamine activation of the subthalamic nucleus and accumbens core and stimulates oxytocinergic neurons in the hypothalamus. *Addict Biol* 15(4):448–463.