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Dopamine Modulates Egalitarian Behavior In Humans

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SUMMARY

Egalitarian motives form a powerful force in promoting prosocial behavior and enabling large-scale cooperation in the human species [1]. At the neural level, there is substantial, albeit correlational, evidence suggesting a link between dopamine and such behavior [2, 3]. However, important questions remain about the specific role of dopamine in setting or modulating behavioral sensitivity to prosocial concerns. Here, using a combination of pharmacological tools and economic games, we provide critical evidence for a causal involvement of dopamine in human egalitarian tendencies. Specifically, using the brain-penetrant catechol-O-methyl transferase (COMT) inhibitor tolcapone [4, 5], we investigated the causal relationship between dopaminergic mechanisms and two prosocial concerns at the core of a number of widely used economic games: (i) the extent to which individuals directly value the material payoffs of others, i.e., generosity, and (ii) the extent to which they are averse to differences between their own payoffs and those of others, i.e., inequity. We found that dopaminergic augmentation via COMT inhibition increased egalitarian tendencies in participants who played an extended version of the dictator game [6]. Strikingly, computational modeling of choice behavior [7] revealed that tolcapone exerted selective effects on inequity aversion, and not on other computational components such as the extent to which individuals directly value the material payoffs of others. Together, these data shed light on the causal relationship between neurochemical systems and human prosocial behavior,

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AUTHOR CONTRIBUTIONS

Designed research: A.K. and M.H.

Performed research: A.K. and M.H.

Analyzed data: I.S., E.S., L.Z. and M.H.

Wrote paper: I.S., A.K. and M.H.

and have potential implications for our understanding of the complex array of social impairments accompanying neuropsychiatric disorders involving dopaminergic dysregulation.

RESULTS

The presence of other-regarding preferences, such as aversion to inequity and associated prosocial concerns, is widely thought to be instrumental to the development of large-scale cooperation in the human species [8, 9]. At the neural level, there is now substantial computational and neuroimaging evidence connecting such preferences to activity in brain regions known to receive abundant dopaminergic projections, particularly frontostriatal circuits [10, 11], in ways that are consistent with reward-encoding and reinforcement properties of dopaminergic neurons [12, 13]. However, despite these suggestions, as well as a wealth of evidence demonstrating dopamine's mechanistic involvement in regulating social behavior in model organisms, we still know little about the specific nature of dopamine's involvement in human prosocial behavior [14, 15].

Here we addressed these questions using pharmacological and computational tools to characterize dopaminergic contributions to an important class of prosocial behavior captured by economic games [6]. Specifically, we investigated the causal relationship between dopaminergic mechanisms and two prosocial concerns at the core of a number of widely used economic games, including the dictator, ultimatum, and trust games: (i) the extent to which individuals directly value the material payoffs of others, i.e., generosity, and (ii) the extent to which they are averse to differences between their own payoffs and those of others, i.e., inequity [6, 16].

To this end, we administered tolcapone to 35 healthy volunteers (Mean age 32.5; SD 9.0) using a within-subject, randomized, double-blind, placebo-controlled, crossover design (see Materials and Methods). Tolcapone is a brain-penetrant drug that enhances dopamine tone by acting as a competitive antagonist of catechol-O-methyl transferase (COMT), one of the main enzymes responsible for dopamine catabolism and signal termination [17]. *In vivo* microdialysis and voltammetry studies have shown that when administered alone, tolcapone selectively raises dopamine levels with little effect on norepinephrine and other monoaminergic systems [18]. In particular, tolcapone is thought to be differentially effective in augmenting dopamine tone in brain regions with low levels of dopamine transporter expression, especially the frontal cortex and hippocampus. In these areas, the catechol-O-methyltransferase (COMT) enzyme represents a significant pathway for dopamine signal termination by degradation [17, 19], in contrast to regions such as the striatum where the pre-synaptic dopamine transporter represents the dominant mode of dopamine regulation [20].

Following administration of either tolcapone or placebo, each subject participated in a continuous version of the Dictator game with an expanded choice space that allowed us to dissociate the behavioral effects of (1) inequity aversion and (2) the direct value placed on others' payoffs (i.e. generosity; see also Supplementary Methods) [21] (Fig. 1; Materials and Methods). As in the standard Dictator game [6], the participant in the position of the dictator received an endowment consisting of T tokens and could unilaterally choose to give some

portion T_o to an anonymous recipient while keeping the remaining T_s tokens (Fig. 1A). To dissociate the contributions of these two quantities to prosocial behavior, we manipulated the relative cost and benefit of giving on each trial by independently varying how much each token was worth to the dictator (r_s) and the recipient (r_o) (Fig. 1A). For example, under a 3:1 exchange rate, a token could be worth $3 if kept by the subject and $1 if given to the recipient. Under the 1:1 exchange rate, our task reduced to the standard Dictator game (Fig. 1B).

We first examined the effects of exchange rate on baseline prosocial behavior in the placebo condition. On each trial, we operationalized generosity, the extent to which participants valued payoff of others, to be the total amount of money M_o given to the recipient, defined as the product of the number of tokens T_o given to the recipient and the value of each token to the recipient r_o, i.e. $M_o = T_o \cdot r_o$. We further operationalized inequity as the absolute difference between recipient and dictator payoffs, i.e., $|M_s - M_o| = |r_o \cdot T_o - r_s \cdot T_s|$. Consistent with previous studies [6, 21], we found that whereas amount given to the recipient increased monotonically as cost of giving decreased, inequity exhibited a U-shaped response (Fig. 2A). Specifically, mean amount given across all subjects was highest at the 1:3 exchange rate, for which the cost of giving was lowest and the benefit to the recipient was highest ($81.54±12.51 SEM). In contrast, mean inequity was lowest at the 1:1 exchange rate, when the cost of giving and the benefit to the recipient were equal ($46.44±9.21 SEM).

Importantly, how individuals respond to variation in the cost-benefit ratio provides key insights into the relative impact of generosity and inequity aversion on choice behavior [6, 21]. Because inequity-averse individuals give more to others when their own payoffs are greater (so-called advantageous inequity), but not when others' payoffs are greater (disadvantageous inequity), they will allocate tokens in a way that equalizes the payoffs between the two players across all exchange rates. In contrast, individuals who value payoff of others but are insensitive to inequity should increase giving when benefit to recipient is high, even in the presence of disadvantageous inequity. Overall, we found that the amount given to the recipient was not significantly associated with payoff inequity at both the subject level (R^2=0.059; Fig. 2B), and at the choice level (R^2=0.0006; Fig. S1).

We then used tolcapone to investigate how dopaminergic manipulation causally impacts prosocial behavior at the level of either inequity aversion or generosity. Current computational accounts of behavioral and neuroimaging findings suggest several possible mechanisms by which tolcapone might affect prosocial behavior [2, 3, 12]. First, the involvement of dopaminergic regions in representing both social rewards and self rewards [12, 16] suggests that tolcapone may impact the weight one places on others' payoffs (or conversely, one's own payoffs). Alternatively, the fact that some of these regions also appear to be sensitive to explicit measures of payoff inequity between participants suggests that tolcapone administration may result in selective changes in the weight participants attach to inequity [2, 3, 12]. Finally, it is possible that this manipulation would affect both or neither of these processes.

First, we found that tolcapone did not have a significant effect on the amount given to the recipient ($48.03±2.16 under placebo vs. $45.66±1.91 under tolcapone, with a paired

difference of $2.64±2.76, p=0.34, paired random effects t-test; Fig. 3A). This finding remained unchanged under a cost-based operationalization of generosity (30.52±3.28 tokens under placebo versus 30.04±3.32 tokens under tolcapone, with a paired difference of 0.48±1.51, p>0.5, paired random effects t-test; see Fig. S1). In contrast, tolcapone administration resulted in a highly significant mean reduction in overall inequity—from $87.08±3.45 in the placebo condition to $80.16±3.3 in the tolcapone condition—with a paired difference of $6.92±2.43 (paired random effects t-test, p<0.01, Fig. 3A). Similar results were obtained using nonparametric binomial tests, which are unaffected by variations in the size of endowments across trials. Specifically, change in inequity remained highly significant under the binomial test (p<0.001), and changes in the amount given to the recipient remained non-significant (p>0.1).

To more closely examine how tolcapone selectively affected inequity, we separately examined mean changes in advantageous and disadvantageous inequity. To do so, we examined potential changes in trials in which subjects incurred advantageous/disadvantageous inequity across conditions (Fig. 3B). If tolcapone administration resulted in a general increase in behavioral sensitivity to inequity, we should expect to see a decrease in both advantageous and disadvantageous inequity. Consistent with this hypothesis, we found that advantageous inequity decreased from $128.36±4.34 to $112.04±4.44 (p<0.01, two-tailed t-test), and disadvantageous inequity from $131±8.27 to $74.99±10.23 ($p<10^{-4}$, two-tailed t-test; Fig. 3B). Importantly, this concomitant reduction in both types of inequity, across all exchange rates (Fig. S1), further argues against the hypothesis that tolcapone directly increases the reward value attached to the payoff of others, which would instead predict a reduction in advantageous inequity and a corresponding increase in disadvantageous inequity.

To explore the possibility that tolcapone administration affected consistency of choices, we calculated a transitivity index to capture the degree to which participants' choices violated transitivity both on- and off-drug, where an index of 1 implies the absence of intransitivity (see SI Methods). We found that participants' choices were highly consistent in both conditions (Placebo: 0.97±0.014 SEM; Tolcapone: 0.98±0.009), indicative of well-behaved preferences. Additionally, there was no significant effect of tolcapone on choice consistency (p>0.1, paired t-test; Fig. S2).

Next, we examined how tolcapone effects in our task varied at the individual level. Because tolcapone reduced both advantageous and disadvantageous inequity, we compared mean inequity in individual subjects on tolcapone versus placebo. We found that mean inequity in both the tolcapone and placebo conditions was strongly correlated (R^2=0.94, $p<10^{-15}$), but that tolcapone administration resulted in a modest yet systematic increase in egalitarian behavior, reflected as a decrease in payoff inequity, in our participants (Fig. 3C, D; see Fig. S2 for analysis of trial-by-trial inequity changes).

To assess the robustness of our results to potential confounding variables such as order of drug and placebo administration, gender, and body mass index (BMI), we performed a repeated-measures ANOVA including these measures, as well as their interactions with the drug condition, as covariates of no interest. We found that none of these factors exerted a

significant influence on behavior ($p > 0.1$ for all tests), and that the drug effect on inequity is robust to their inclusion ($p > 0.01$, see Table S1). In addition, we explored the extent to which observed individual differences related to other moderating variables. In particular, previous studies have suggested that the effects of dopaminergic drugs may be related to baseline behavioral state, such that differential effects might be observed depending on baseline inequity aversion or on COMT genotype [22]. However, we did not find a significant relationship between the mean inequity under placebo and tolcapone-induced changes in inequity (Fig. S2), and these effects did not covary with COMT genotype (Fig. S3 and Table S1).

Finally, we undertook a computational characterization of choice behavior, and formally connected tolcapone effects to mathematical models that relate brain activity to putative internal values underlying prosocial actions [2, 3, 12]. At the heart of these models is the idea that humans perceive certain actions as more or less rewarding depending upon their effects not only on one's own economic interests, but also on those of others [6, 7, 12]. That is, prosocial preferences serve to modify the value of a subject's own actions to account for his or her effect on other people. Specifically, following widely-used models of inequity aversion [6, 7], we defined the subjective value function as:

$$U(M_s, M_o) = M_s - p \cdot \alpha \cdot (M_s - M_o) - q \cdot \beta \cdot (M_o - M_s),$$

where M_s and M_o refer to self and other payoff, respectively, and p and q are indicator functions: $p=1$ if $M_s \geq M_o$ (advantageous inequity), and 0 otherwise; and $q=1$, if $M_s < M_o$ (disadvantageous inequity), and 0 otherwise. Thus, α and β quantify concern for inequity under advantageous and disadvantageous conditions, respectively. Given choice behavior, the model was then calibrated using a softmax specification with inverse temperature parameter λ using maximum likelihood (see Materials and Methods).

Using this model, we first assessed the extent to which there was an overall effect of tolcapone on preferences. Specifically, we compared, at the individual level, the pair-wise difference in Akaike Information Criterion (AIC) between a model where α and β were allowed to vary across tolcapone and placebo, versus the null model where α and β did not vary. Consistent with our results above, we found that there was a significant reduction in AIC (mean = −5.99, paired Wilcoxon test $p<0.05$; permutation test $p<0.001$; see Fig. S3), indicating that allowing α and β to vary across conditions provided a significantly better fit to the data.

Having assessed model fit, we next examined the extent to which inequity preferences were affected by tolcapone administration. Given our experimental design, a concomitant increase or decrease in sensitivity to advantageous (α) and disadvantageous (β) inequity would be consistent with an overall increase or decrease in inequity aversion, respectively. Conversely, changes in α and β of different signs would indicate an effect on generosity. For example, an increase in sensitivity to advantageous inequity but a decrease in sensitivity to disadvantageous inequity would capture individuals who value others' payoffs more under tolcapone, while the opposite would characterize individuals who value others' payoffs less. Consistent with the model-free results above, we found that tolcapone significantly

increased α by 0.097 (from $\alpha_{placebo}$ = 0.39 to $\alpha_{tolcapone}$= 0.49; bootstrap 95% C.I. = (0.01, 0.21)), and β by 0.17 (from $\beta_{placebo}$ = 0.20 to $\beta_{tolcapone}$= 0.37; bootstrap 95% C.I. = (0.02, 0.34)). That is, subjects in the tolcapone condition exhibited greater aversion to both advantageous and disadvantageous inequity (Fig. 4). Moreover, tolcapone did not appear to exert a significantly greater effect on disadvantageous inequity than on advantageous inequity ($p > 0.1$, paired t-test). In contrast, we did not find evidence for a change in the inverse temperature parameter λ under tolcapone ($\lambda_{placebo}$ = 0.025, $\lambda_{tolcapone}$ = 0.027, paired t-test p>0.5).

DISCUSSION

The mechanistic involvement of dopaminergic systems in regulating social behavior has been extensively studied in model organisms [23, 24]. Mesocorticolimbic dopamine, for example, has been shown to be necessary in the establishment and maintenance of social bonds in a number of species, and is thought to be an important biological pathway through which sex steroid and neuropeptide hormones, including oxytocin, exert their effects on social behavior [25]. However, in contrast to more basic perceptual, cognitive, and behavioral processes, a much greater gap exists between animal studies built on molecular and cellular approaches on the one hand and human neuroimaging studies on the other [12, 25, 26]. These differences relate not only to ones involving neural scale, but also to the complexities of the behaviors. For example, unlike other species, human practices detail division of labor and cooperation between genetically unrelated individuals in large groups [1, 27], and individuals regularly engage in costly rewarding and punishing of other individuals even in cases in which there is no individual economic benefit [6, 16].

Here, by combining pharmacological tools with computational modeling of an important class of social behavior captured by economic games, we extend suggestions from previous studies [13, 28] and demonstrate a key functional link between dopamine and prosocial concerns that guide instrumental social actions in humans. In particular, we found that enhancing dopaminergic tone via COMT inhibition is sufficient to increase inequity-averse behavior. That this effect occurred in the absence of feedback about participants' actions also supports the idea that dopamine can influence valuation signals attached to prosocial actions, independent of its role in mediating the reinforcing effects of social rewards, and more specifically highlights the role of dopamine in setting or modulating prosocial preferences. Notably, we found that tolcapone appeared to exert similar effects on individuals regardless of their initial attitude toward inequity. The systematic changes under tolcapone observed in our data suggest that inequity aversion appears to be a robust trait-like phenotype, which likely reflects complex developmental and genetic contributions, whose state can nonetheless be causally affected via dopamine manipulation – further underscoring the importance of using a within-subject design in controlling for individual variation in baseline behavior.

At the computational level, our results support current models of prosocial behavior in which inequity is explicitly represented at the neural level and separable from computations of reward value for self and others [2, 3, 12]. Moreover, they are consistent with two broad accounts previously proposed for the role of dopamine in reward processing and goal-

directed behavior [29–32]. The first involves the possibility that different components of dopamine responses carry distinct, behaviorally relevant signals at multiple timescales. For example, in conditioning tasks, substantial neurophysiological evidence indicates that, in addition to fast phasic dopamine response to expected reward on the order of tens of milliseconds, there exists a slower tonic response to reward risk, defined as the expected variance of reward, that can last up to several seconds [33].

This independent coding of risk is particularly interesting in our case given the deep theoretical connection between decision-making under uncertainty and the measurement of inequity [34], based on the fact that both risk and inequity computations require an estimate of the relevant distributions over outcome probabilities or variation in earnings, respectively [2]. If tonic dopamine firing responses to inequity behave in a similar manner as those under risk, their influence on behavior could also be explained via the same mechanisms that have previously been hypothesized for risk. Most directly, a tonic inequity signal could be combined with phasic signals capturing the valuation for self and other to drive inequity-averse behavior, analogous to the combination of expected reward and reward variance to capture behavior in risk sensitive individuals [33, 35].

Under this view, inequity reduction under tolcapone derives from the known effects of COMT inhibition on tonic dopamine levels and, consequently, the balance between phasic and tonic dopamine. Specifically, a tolcapone-mediated increase in (cortical) tonic dopamine has been shown to increase corticostriatal signaling via glutamatergic projections [36]. The resulting increased stimulation of glutamate receptors located in presynaptic dopaminergic terminals is in turn known to concomitantly increase tonic dopamine release in striatum [37] and at the same time reduce phasic dopamine transmission through activation of presynaptic D2 autoreceptors [36]. Under such a mechanism, the blunting of phasic dopamine release in striatum, combined with the increase in tonic dopaminergic signaling, could allow the inequity signal encoded by the latter to come to the forefront and drive inequity-averse behavior.

Alternatively, it is possible that the observed effects do not involve a direct role of dopamine in the encoding of inequity per se, but rather reflect its modulatory effects on brain structures involved in the assessment of inequity. In keeping with this idea, previous neuroimaging studies have suggested that inequity, as opposed to reward to either self or other, is correlated with activity in cortical regions including the anterior insula [38], which has been hypothesized to play a role in social norm processing [39] and contains a high density of dopamine receptors [40]. In contrast, primary and secondary rewards to self and others are known to strongly activate midbrain and ventral striatal regions [41]. Consequently, if tolcapone selectively enhances dopamine tone in the cortex [5], selective change in inequity might be a product of strengthened cortical representations of inequity or social norms [39].

Interestingly, both accounts are able to reconcile differences between our findings and those of a previous study involving L-DOPA administration, where it was suggested that L-DOPA increased selfish behavior in a version of the dictator game [15]. In particular, L-DOPA is known to enhance both phasic and tonic dopaminergic components by increasing the

presynaptic availability of dopamine [42], and this increase in phasic dopamine signaling could exacerbate the relative importance of self-payoffs. In contrast, a cortically-driven tolcapone-induced increase in tonic signaling and decrease in phasic signaling [36] could lead to very different patterns of activity in striatum and cortex [36, 37], and potentially to different weightings of self versus other preferences [14, 15].

Discriminating between the above accounts will require additional experiments that contrast the behavioral effects of tolcapone with those of pharmacological compounds that, unlike L-DOPA, are known to exert dissociable effects on tonic and phasic dopamine release. For example, the dopamine reuptake inhibitor methylphenidate, like tolcapone, is thought to result in an increase in tonic dopamine signaling but reduction in phasic responses [43]. Unlike tolcapone, however, whose direct effects are thought to be in cortical areas [19], methylphenidate is thought to act primarily in the striatum, where the dopamine transporter is abundant [20]. Thus, methylphenidate should increase inequity aversion in a similar manner as tolcapone if tonic dopamine is responsible for carrying an “inequity signal”, but should not if the effect of tolcapone on inequity is primarily mediated by modulation of cortical activity. Future experiments using a combination of pharmacological and neuroimaging studies will also be helpful in defining regional differences in brain activity under these drugs. In complementary fashion, novel techniques that directly measure sub-second dopamine concentrations in the human brain could shed light onto the relative contribution of tonic and phasic aspects of dopaminergic signaling to behavior [44].

More broadly, our results highlight the potential of combining pharmacological probes with formal quantitative frameworks for social behavior to address questions at the molecular and genetic levels, the so-called “dark matter” of social neuroscience [25]. Clinically, such an approach has important implications, as the advancement of our understanding of the neurobiological basis of social behavior represents an important step toward the development of rational, mechanism-based treatments for disorders involving social dysfunction. For example, dopaminergic dysregulation, in particular affecting the prefrontal cortices, is frequently accompanied by social impairments in disorders such as schizophrenia and addiction [37]. However, whereas disruptions in motor, memory, or emotional functioning are readily recognized as symptoms of more serious underlying conditions, social deficits are frequently overlooked and poorly measured. Our results thus raise the possibility that assessing these deficits quantitatively through a formal framework combining computational modeling with game theoretic measures of behavior may continue to enable more focused hypotheses about their etiology [25, 45].

EXPERIMENTAL PROCEDURES

Participants

A total of 35 (18 female) healthy subjects (i.e. without a history of neurological or psychiatric illnesses) were eligible to participate. All subjects gave written informed consent in accordance with the Committee for the Protection of Human Subjects at the University of California, San Francisco and University of California, Berkeley. Mean age was 32.5±9.0 years; ethnicity was mixed, including 23 Caucasian, 5 African American, 4 Hispanic, and 2 Asian participants, and 1 subject of mixed descent.

Procedure

During their first visit, subjects underwent a medical history and physical exam, as well as blood testing for liver function to ensure that there were no medical contraindications to tolcapone use. Subsequently, subjects were randomized in double-blind, counterbalanced, placebo-controlled fashion to either placebo or a single 200mg dose of tolcapone on their second visit and the alternative treatment on their third visit. The pills were assigned a neutral label ('X' or 'Y'), so that neither the subject nor the experimenter was aware of the identity of the drug being administered. At least 90 minutes after pill ingestion, subjects received task instructions and underwent a brief practice session before performing the dictator task. Consistent with our other studies, subjects were unable to distinguish between tolcapone and placebo (χ^2 test = 1.458, $p > 0.2$), and tolcapone did not have noticeable side effects.

Behavioral Task

Subjects played a version of the Dictator Game (DG). In the DG, subjects are asked to unilaterally decide the allocation of a monetary endowment between themselves and a social partner who has no option to reciprocate. Payment was determined at the end of all sessions by randomly selecting one of the trials (see Appendix A). In our version of the DG, subjects received an endowment in the form of tokens, which were converted to dollars using separate multipliers for kept and sent tokens. On any given round, the self:other exchange rate was chosen from one of five values: 3:1, 2:1, 1:1, 1:2, 1:3. When the rate was 1:3, for example, a kept token was worth one dollar, but a sent token was worth three dollars. Behavioral results indicate that subjects were sensitive to the exchange rate (Fig. 2A). A linear regression suggested that difference between self and other payoffs would be zero at a 1:2.3 exchange rate; in other words, overall subjects valued equally $1 kept and $2.3 given. Instructions, quiz, and choice sheets are included in the Supplemental Information.

Computational Modeling

Denote T as the total number of tokens available, T_s and T_o as the number of tokens allocated to self and other respectively. Furthermore denote r_s and r_o as multiplier rates to self and other tokens, respectively, such that monetary payoffs to self and other are calculated as $M_s = r_s \cdot T_s$ and $M_o = r_o \cdot T_o$. We adopted a standard stochastic choice model in which choice probabilities are determined by the subjective value function:

$$U(M_s, M_o) = M_s - p \cdot \alpha \cdot (M_s - M_o) - q \cdot \beta \cdot (M_o - M_s),$$

where p and q are indicator functions, with p = 1 if $M_s \geq M_o$ (advantageous inequity), and p = 0 otherwise; and q = 1, if $M_s < M_o$ (disadvantageous inequity), and q = 0 otherwise. Thus, α and β quantify subjective aversion to inequity under advantageous and disadvantageous conditions respectively. Changes in these scale factors can represent a range of well-established social preferences that includes generosity and inequity aversion. For example, an increase in both α and β would mean that subjects became more sensitive to both advantageous and disadvantageous inequity, indicating an increase in inequity aversion; conversely, a decrease in both parameters would indicate a decrease in inequity aversion. If

α decreases but β increases, subjects became more sensitive to disadvantageous but not advantageous inequity, resulting in a decrease in generosity. Finally, if α increases but β decreases, the reverse is true, resulting in an increase in generosity. Given that participants could allocate only a discrete number of tokens, the value function can be rewritten as:

$$\mathrm{U(T_s, T_o)=r_s \cdot T_s - p \cdot \alpha \cdot (r_s \cdot T_s - r_o \cdot T_o) - q \cdot \beta \cdot (r_o \cdot T_o - r_s \cdot T_s),}$$

which was calibrated to choice behavior by using a softmax specification with inverse temperature parameter λ, such that on each trial, the probability of the participant choosing token allocation (T_s, T_o) is given by:

$$P(T_s, T_o)=\frac{e^{\lambda \cdot U(T_s, T_o)}}{\sum_{j \in J} e^{\lambda \cdot U(T_s^j, T_o^j)}},$$

where (T_s^j, T_o^j) denotes the possible number of tokens that could be allocated on the trial. We conducted maximal likelihood estimation by maximizing the log likelihood function over individual participant *i* and trial *t*.

$$\sum_i \sum_t \log(P_{i,t}(T_s, T_o; \alpha_{placebo}, \beta_{placebo}, \alpha_{tolcapone}, \beta_{tolcapone}, \lambda)$$

The standard errors of estimated parameters were obtained through a bootstrap procedure with 200 iterations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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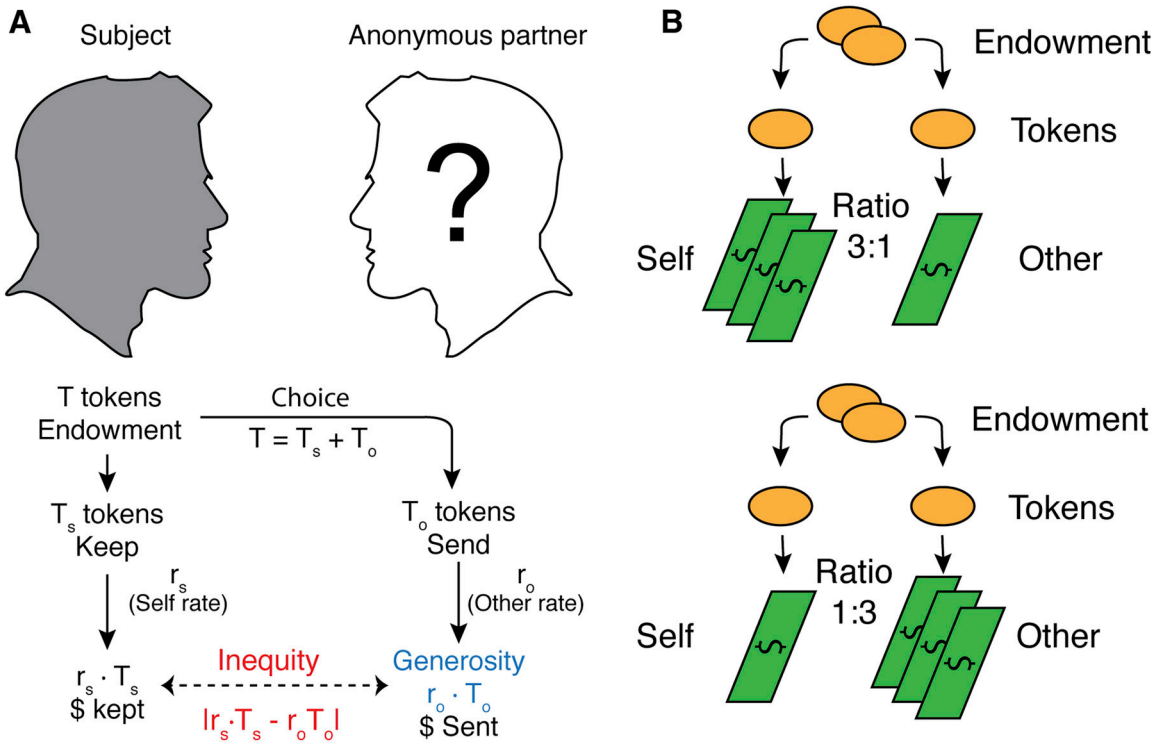

Fig. 1. Experimental Paradigm

(A) Following double-blind administration of tolcapone or placebo, the subject in the position of a Dictator received an endowment of tokens and unilaterally chose to give some portion to an anonymous recipient. On each trial, the relative cost and benefit of giving were manipulated by applying separate self and other multiplier rates (r_S, r_O) to convert tokens to payoffs for the subject and the recipient, respectively. Generosity (blue), the extent to which individuals directly value the material payoffs of others, is operationalized as the amount of money sent to the recipient, i.e., $M_O = r_O \cdot T_O$. Inequity (red) is operationalized as the absolute difference between self and other payoffs, i.e., $|M_S - M_O| = |r_S \cdot T_S - r_O \cdot T_O|$. **(B)** The relative value of kept/exchanged tokens varied trial by trial. For example, under a 3:1 exchange rate, a token was worth \$3 if kept by the subject and \$1 if given to the recipient (top). In contrast, under the 1:3 exchange rate, a token was worth only \$1 if kept by the subject and \$3 if given to the recipient (bottom). Note that whereas the inequity in both cases is \$2, the generosity is lower under the 3:1 exchange rate than the 1:3 exchange rate.

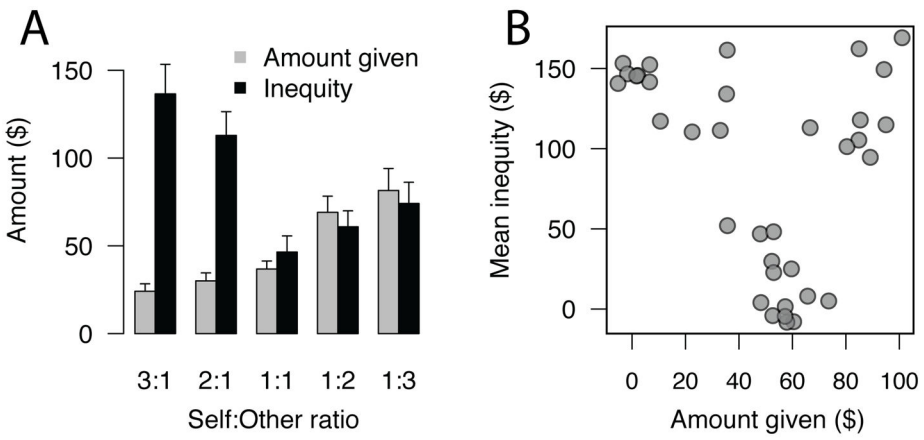

Fig. 2.

(A) Generosity, operationalized as amount of money given to the anonymous recipient, and inequity, operationalized as the absolute difference in self vs. other payment, had different dependencies on exchange rate. Amount given to the recipient (gray bars) exhibited a monotonic relationship with exchange rate, such that subjects increased monetary allocation to the recipient as the cost of sending money decreased. In contrast, inequity was minimal at the 1:1 exchange rate and exhibited a U-shaped relationship with respect to different exchange rates (black bars). **(B) Amount given and payoff inequity were dissociable at the individual level.** The scatterplot shows the lack of correlation (R^2 = 0.059, n.s.) between average amount given and inequity across all choices for every subject, under baseline (placebo) conditions.

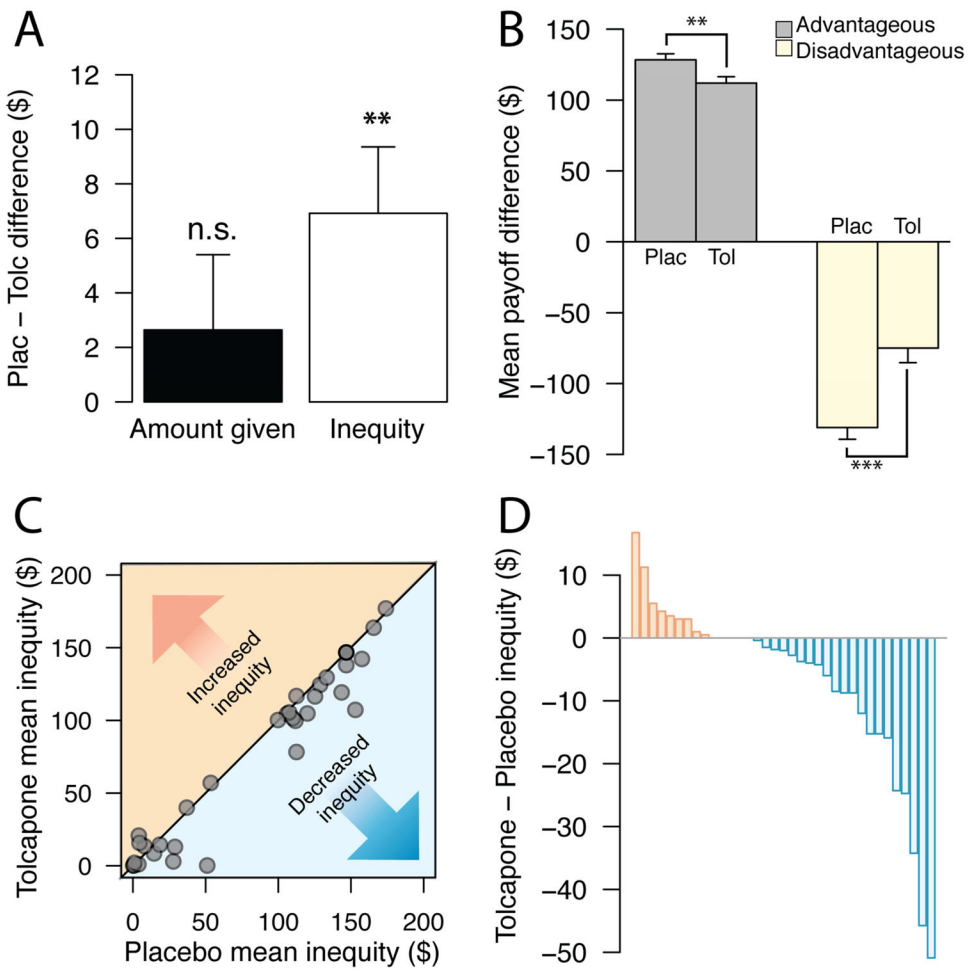

Fig. 3.

(A) Overall effect of tolcapone. Amount given to the recipient was unchanged between tolcapone and placebo conditions ($48.03±2.16 under placebo vs. $45.66±1.91 under tolcapone; paired difference=2.64±2.76, p=0.34, paired random effects t-test), but there was a significant decrease in inequity between subjects and their counterparts ($87.08±3.45 under placebo to $80.16±3.3 under tolcapone; paired difference=$6.92±2.43, paired random effects t-test, $p<0.01$). **(B) Changes in inequity for trials in which subjects incurred advantageous (i.e. self>other payoff, grey) or disadvantageous (self<other payoff, yellow) inequity**. Reductions in both advantageous and disadvantageous inequity contributed to the overall decrease in inequity: advantageous inequity was reduced from $128.36±4.34 under placebo to $112.04±4.44 under tolcapone (two-tailed t-test, $p<0.01$), whereas disadvantageous inequity changed from $−131±8.27 to $−74.99±10.23 (two-tailed t-test, $p<10^{-4}$; all SEM). Neutral trials, defined as those in which no inequity were observed under either placebo or tolcapone, were excluded from this analysis. See Fig. S2 for similar results following inclusion of neutral trials. **(C) Comparison of individual-level inequity under tolcapone and placebo.** Each point corresponds to mean inequity of a single subject under placebo (*x*-axis) and tolcapone (*y*-axis). Points on the diagonal represent subjects whose mean inequity was identical between tolcapone and placebo conditions. Points below

(above) the diagonal colored in blue (orange) represent subjects for whom mean inequity decreased (increased) under tolcapone administration. Mean inequity was highly stable across conditions (R^2=0.94), suggesting that the behavioral trait under study is highly robust. Nonetheless, inequity declined for the majority of subjects in the tolcapone condition (blue area), suggesting that the behavioral state can be modified. **(D) Change in inequity across subjects**. Each bar represents the total change in inequity (tolcapone minus placebo) for each individual, averaged over all choices. Most subjects experienced a reduction in inequity (blue bars) on tolcapone compared to baseline (placebo) behavior.

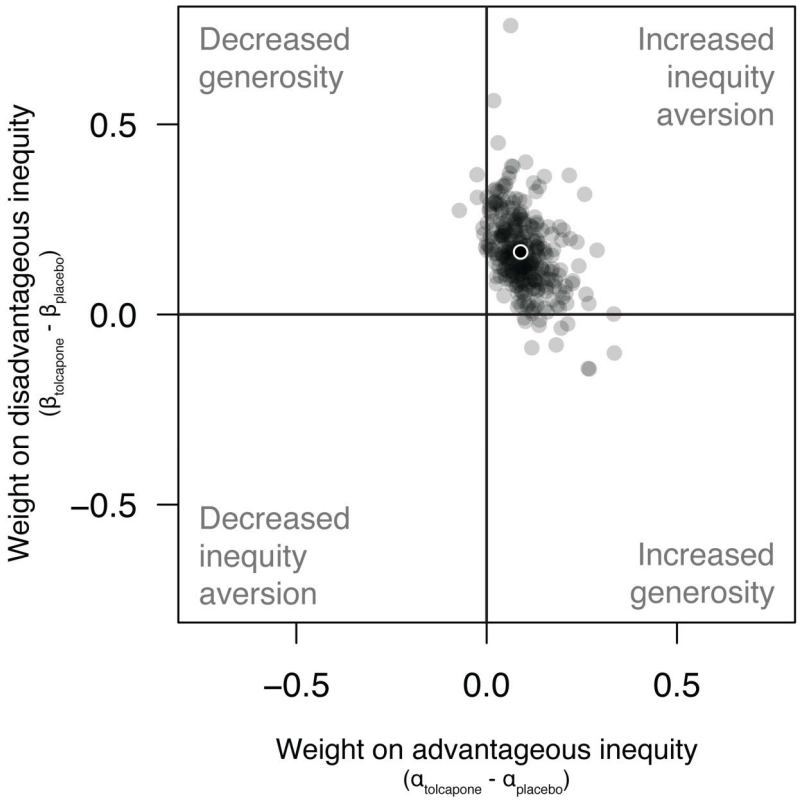

Fig. 4. Computational characterization of prosocial preferences

Tolcapone effects are captured by model parameter differences under tolcapone or placebo, where α (β) controls the sensitivity to advantageous (disadvantageous) inequity. Quadrants correspond to possible effects in terms of generosity and inequity: an increased (decreased) sensitivity to both advantageous and disadvantageous inequity, captured by positive (negative) changes in both α and β, reflects individuals with increased (decreased) inequity aversion under tolcapone. In contrast, an increased sensitivity to advantageous inequity but decreased sensitivity to disadvantageous inequity captures individuals who became more generous under tolcapone. Finally, the opposite indicates individuals who became less generous. Tolcapone significantly increased sensitivity to both advantageous ($\alpha_{tolcapone} - \alpha_{placebo}$=0.097, paired difference 95% C.I.=(0.01, 0.21)) and disadvantageous inequity ($\beta_{tolcapone} - \beta_{placebo}$=0.17, paired difference 95% C.I.=(0.02,0.34)). The white circle identifies the maximum likelihood estimate of the tolcapone effect, and smaller gray points represent bootstrap pseudo-sample estimates (Materials and Methods).