Review

Biological Psychiatry

The Roles of Phasic and Tonic Dopamine in Tic Learning and Expression

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ABSTRACT

Tourette syndrome (TS) prominently involves dopaminergic disturbances, but the precise nature of those disturbances has remained elusive. A substantial body of empirical work and recent computational models have characterized the specific roles of phasic and tonic dopamine (DA) in action learning and selection, respectively. Using insights from this work and models, we suggest that TS involves increases in both phasic and tonic DA, which produce increased propensities for tic learning and expression, respectively. We review the evidence from reinforcement-learning and habit-learning studies in TS, which supports the idea that TS involves increased phasic DA responses; we also review the evidence that tics engage the habit-learning circuitry. On the basis of these findings, we suggest that tics are exaggerated, maladaptive, and persistent motor habits reinforced by aberrant, increased phasic DA responses. Increased tonic DA amplifies the tendency to execute learned tics and also provides a fertile ground of motor hyperactivity for tic learning. We review evidence suggesting that antipsychotics may counter both the increased propensity for tic expression, by increasing excitability in the indirect pathway, and the increased propensity for tic learning, by shifting plasticity in the indirect pathway toward long-term potentiation (and possibly also through more complex mechanisms). Finally, we review evidence suggesting that low doses of DA agonists that effectively treat TS decrease both phasic and tonic DA, thereby also reducing the propensity for both tic learning and tic expression, respectively.

Keywords: Basal ganglia, Computational psychiatry, Phasic dopamine, Tics, Tonic dopamine, Tourette syndrome

http://dx.doi.org/10.1016/j.biopsych.2017.05.025

Tourette syndrome (TS) has long been thought to involve dopaminergic disturbances (1,2). Despite substantial work investigating the dopaminergic system in TS (3,4), however, the nature of these disturbances has remained controversial. As we review in a recently submitted article (T.V. Maia, Ph.D., and V.A. Conceição, M.S., unpublished review, February 2017), existing hypotheses explain only restricted subsets of findings and, in some cases, are contradicted by substantial evidence. In that article, we show that the hypothesis that TS involves striatal dopaminergic hyperinnervation provides a parsimonious and integrated explanation for the various findings from studies of the dopaminergic system in TS. This dopaminergic hyperinnervation creates a hyperdopaminergic state, which explains why all medications that are effective for TS reduce dopamine (DA) neurotransmission (Maia and Conceição, unpublished review, February 2017). This hyperinnervation likely causes both phasic and tonic DA to be increased. Building on computational ideas about the roles of phasic and tonic DA in action learning and selection, respectively (5–7), in the present article we show computationally that increased phasic and tonic DA cause increased propensities to learn and express tics, respectively.

Phasic DA represents reinforcement prediction errors (PEs) (8,9), which support model-free, habit learning (10). We suggest that aberrant, exaggerated phasic DA signals abnormally reinforce motor behaviors, thereby causing tic learning. In other words, we suggest that tics are exaggerated, maladaptive, and persistent motor habits learned through aberrant phasic DA signals.

Tonic DA invigorates action (11–13) and increases the expression of previously learned behaviors (5). We suggest that increased tonic DA promotes tic expression by amplifying the tendency to execute learned tics; in addition, it increases the overall tendency for action, thereby creating a fertile ground for tic development.

COMPUTATIONAL ROLES OF PHASIC AND TONIC DA

Phasic DA bursts represent positive PEs (8,9) that drive action learning in the basal ganglia, strengthening corticostriatal synapses onto direct-pathway (Go) medium spiny neurons (MSNs), which represent the positive or Go value (*G*) of actions, and weakening corticostriatal synapses onto indirect-pathway (NoGo) MSNs, which represent the negative or NoGo value (*N*) of actions (5–7,14–16) (see Box 1). Exaggerated, and possibly abnormally timed, phasic DA signals therefore may cause exaggerated, aberrant learning of motor behaviors, thereby producing tics.

Whereas phasic DA bursts elicit transient DA concentrations ranging from 10 nM to more than 1 μM (17), tonic DA concentrations are in the low nanomolar range (18). In the striatum, most D_1 and D_2 receptors are in low- and high-affinity states, respectively (19), which are sensitive to micromolar and

ISSN: 0006-3223

Box 1. Computational Roles of Dopamine

Phasic Dopamine and Action Learning

Dopamine (DA) signals reinforcement prediction errors (PEs), which are the difference between the obtained and expected reinforcement (8,9). The reinforcement that a person expects to get in a given situation, s, is usually called the value of that situation and is represented by $V_t(s)$ (where the time subscript, t, indicates that this value can change over time). The PE, δ_t, is then given by

$$\delta_t = r_t - V_t(s_t),$$

where r_t and s_t are the reinforcement received and the state at time t, respectively.

PEs are useful because they can be used both to improve the estimate of the values of situations and to learn which actions to take in each situation. In the actor-critic model (143), these two processes are implemented in the critic and the actor, respectively, which map onto distinct neural substrates (8,144). The critic updates the values of the situation, s, using the following equation:

$$V_{t+1}(s_t) = V_t(s_t) + \alpha_C \delta_t,$$

where α_C is a parameter between 0 and 1 that represents the critic's learning rate. This equation ensures that the estimate of $V(s_t)$ is moved somewhat in the direction of r_t, making $V(s_t)$ an exponential recency-weighted average of past reinforcements (8). The actor similarly uses the PE to update its preference, $p(s_t, a_t)$, for taking the action that was executed, a_t, in situation s_t:

$$p_{t+1}(s_t, a_t) = p_t(s_t, a_t) + \alpha_A \delta_t,$$

where α_A is a parameter between 0 and 1 that represents the actor's learning rate. This equation ensures that actions that result in positive and negative PEs are strengthened and weakened, respectively.

The basal ganglia contain partly opposing direct (Go) and indirect (NoGo) pathways (6,145) that can be conceptualized as implementing two opponent actors: one, the direct (Go) pathway, that stores the positive values of actions, and another, the indirect (NoGo) pathway, that stores the negative values of actions (5,7). DA affects plasticity in corticostriatal projections to D_1 and D_2 medium spiny neurons (MSNs) of the direct and indirect pathways, respectively, in opposite ways: broadly speaking, DA stimulation of D_1 and D_2 receptors promotes long-term potentiation (LTP) and long-term depression (LTD) in D_1 and D_2 MSNs, respectively, and lack of DA stimulation promotes LTD and LTP in D_1 and D_2 MSNs, respectively (14,15). Therefore, PEs affect learning in Go and NoGo pathways in opposite ways:

$$G_{t+1}(s_t, a_t) = \begin{cases} G_t(s_t, a_t) + \alpha_{G,LTP}\delta_t, & \text{if } \delta_t \geq 0 \\ G_t(s_t, a_t) + \alpha_{G,LTD}\delta_t, & \text{if } \delta_t < 0 \end{cases}$$

and

$$N_{t+1}(s_t, a_t) = \begin{cases} N_t(s_t, a_t) - \alpha_{N,LTD}\delta_t, & \text{if } \delta_t \geq 0 \\ N_t(s_t, a_t) - \alpha_{N,LTP}\delta_t, & \text{if } \delta_t < 0 \end{cases},$$

where $G(s_t,a_t)$ and $N(s_t,a_t)$ represent the striatal Go and NoGo values, respectively, of the association between state s_t and action a_t (which are stored in corticostriatal synapses onto D_1 and D_2 MSNs, respectively) and are constrained to be greater than or equal to 0. The parameters $\alpha_{G,LTP}$, $\alpha_{G,LTD}$, $\alpha_{N,LTP}$, and $\alpha_{N,LTD}$ are learning rates between 0 and 1, with the subscripts G and N indexing plasticity in Go and NoGo MSNs, respectively, and the subscripts LTP and LTD representing LTP and LTD plasticity, respectively.

Tonic Dopamine and Action Selection

Actions are selected on the basis of the difference between their Go (G) and NoGo (N) values (5,6). A common function for such selection is the softmax (146), which in this case relates the difference between G and N for each action to the probability, $P_t(a|s_t)$, of selecting that action in current situation s_t:

$$P_t(a|s_t) = \frac{e^{\beta[G_t(s_t,a) - N_t(s_t,a)]}}{\sum_{a_i} e^{\beta[G_t(s_t,a_i) - N_t(s_t,a_i)]}},$$

where β is a gain parameter that controls the degree of randomness in action selection, and a_i ranges over all available actions in situation s_t.

DA at the time of action selection modulates the gain (i.e., the excitability) of Go and NoGo MSNs in opposite directions: broadly speaking, DA increases the gain of Go MSNs (i.e., it makes Go MSNs more excitable) through its stimulatory action on D_1 receptors, and it decreases the gain of NoGo MSNs (i.e., it makes NoGo MSNs less excitable) through its inhibitory action on D_2 receptors (5,147). Thus, instead of a single gain, β, that applies to both pathways, there are two gains, β_G and β_N, that apply to the Go and NoGo pathways, respectively:

$$P_t(a|s_t) = \frac{e^{\beta_G G_t(s_t,a) - \beta_N N_t(s_t,a)}}{\sum_{a_i} e^{\beta_G G_t(s_t,a_i) - \beta_N N_t(s_t,a_i)}}.$$

These two gains are modulated by DA in opposite directions (5) and depend on the total amount of DA, ρ, present during action selection, which consists of the sum of tonic DA, γ, and phasic DA signals due to any PEs, δ, that occur shortly before action selection (7):

$$\rho = \gamma + \delta.$$

A convenient mathematical formulation to capture the opposite modulation of β_G and β_N by ρ is

$$\beta_G = \beta(1+\rho)$$

and

$$\beta_N = \beta(1-\rho),$$

with ρ scaled to vary between −1 and 1 (5). The fact that ρ includes not only tonic DA but also phasic DA due to PEs (7) helps to explain why tics can get worse in exciting contexts with positive valence, such as going to Disney World for the first time or during birthdays or holidays, especially when these include presents (148). In this article, however, we focus on the simpler, more routine case in which DA at the time of action selection is determined by tonic DA levels. In that case, it is biologically more realistic to assume that tonic DA affects mostly β_N rather than β_G because of the

Box 1. Continued

high and low affinity of striatal D_2 and D_1 receptors, respectively (see main text). The equation capturing the effect of tonic DA, γ, on action selection therefore can be simplified to

$$P_t(a|s_t) = \frac{e^{\beta G_t(s_t,a)-\beta(1-\gamma)N_t(s_t,a)}}{\sum_{a_i} e^{\beta G_t(s_t,a_i)-\beta(1-\gamma)N_t(s_t,a_i)}},$$

with $\gamma \leq 1$. The basal ganglia have exactly the right anatomy to implement this selection mechanism (Figure 1).

nanomolar DA concentrations, respectively (19–21). Overall, the affinity of striatal D_2 receptors has been estimated to be 67 times higher than that of D_1 receptors (20). Therefore, tonic DA may act predominantly on NoGo (D_2-expressing) MSNs rather than on Go (D_1-expressing) MSNs (22,23). DA reduces the excitability (or gain) of NoGo MSNs (16,24), β_N, thereby suppressing the influence of NoGo values (N) on action selection and thus facilitating action execution (Box 1 and Figure 1). Increased tonic DA therefore invigorates action and amplifies the expression of learned tics (Figure 2A). The evidence for the roles of phasic and tonic DA on action learning and selection, respectively, has been reviewed elsewhere (5–7).

INCREASED PHASIC DA AND ENHANCED REWARD, HABIT, AND TIC LEARNING

Reinforcement Learning

If unmedicated patients with TS have increased phasic DA, they should have enhanced reward learning. Indeed, in an instrumental-learning task with subliminal cues, unmedicated patients with TS learned from gains but not from losses, and antipsychotics reversed those biases, with medicated patients learning from losses but not from gains (25). Patients with Parkinson's disease (PD) exhibited the opposite double dissociation: unmedicated patients learned from losses but not from gains, and patients on levodopa and DA agonists learned from gains but not from losses (25). Better learning from gains and losses in medicated and unmedicated patients with PD, respectively, has also been found with several nonsubliminal tasks (26). The opposite effects in TS and PD provide further evidence for hyperdopaminergia in TS; in addition, they suggest that tics might result from excessive, inappropriate reward learning. Indeed, reward-based motor-skill learning is increased in unmedicated patients with TS and is decreased in patients with TS on antipsychotics (27). Model-based analyses suggested that the increased reward-based learning in unmedicated patients with TS might be due to an increase in the reward representation (r), but the learning rates for the critic and actor were also increased, albeit nonsignificantly (27). Distinguishing between r and learning rates is often difficult (Figure 3). Furthermore, both parameters could capture increased positive-PE signaling, as would be expected with increased phasic DA.

In the aforementioned studies, learning did not appear to be driven by explicit knowledge (25,27). In tasks that rely on explicit knowledge, patients with TS generally do not differ from control subjects. In a deterministic reversal-learning task, patients with TS, with relatively light medication, performed like healthy control subjects, unless they had comorbid attention-deficit/hyperactivity disorder (ADHD), in which case they performed like patients with ADHD without comorbid TS (28). Nonetheless, patients with TS without comorbid ADHD had an abnormal P2 event-related potential for positive feedback. Patients with TS, mostly unmedicated, also performed like control subjects in the Iowa gambling task (29), in which explicit knowledge also likely plays an important role (30).

Habit Learning

Although the dichotomies between explicit and implicit learning and between goal-directed and habit learning do not entirely overlap, they relate: goal-directed actions are thought to rely on explicit processes, whereas habits are thought to rely on previously acquired, largely implicit stimulus–response associations (31,32). Consistent with the finding that unmedicated patients with TS have increased implicit reward-based learning (25,27), they also have an increased tendency to rely on habit learning relative to goal-directed actions in a reward-based learning context (33). This increased reliance on habits is consistent with the idea that tics are exaggerated motor habits learned by reinforcement learning (RL). Indeed, in unmedicated patients, both tic severity and the tendency to rely on habits correlated with structural connectivity between motor cortices and the posterior putamen (33), which are critical nodes of the motor habit-learning circuit (34–36). An overconnected, overactive habit system therefore might cause increased tendencies for both habits and tics, with tics being a type of motor habit. Indeed, in unmedicated patients, tic severity correlated positively with the tendency to rely on habits (33).

One limitation of this habit-learning study is that patients with TS exhibited a trend for impaired explicit learning of task contingencies (33). The increased reliance on habits therefore could have been caused by difficulties explicitly learning the contingencies to support goal-directed action, as was found in obsessive-compulsive disorder using the same task (37). This concern, however, is partly mitigated by the correlations with connectivity in the habit-learning circuit and by the preserved performance of patients with TS in other tasks involving explicit learning (28,29).

Two studies reported impaired performance in the weather prediction task in patients with TS, which was unlikely to be due to medication or comorbid ADHD (38,39). This task is hypothesized to probe habit learning (40), but it does not include the tests that support confident classification of behaviors as habits (34). These studies also did not disentangle learning from positive versus negative feedback; the impaired

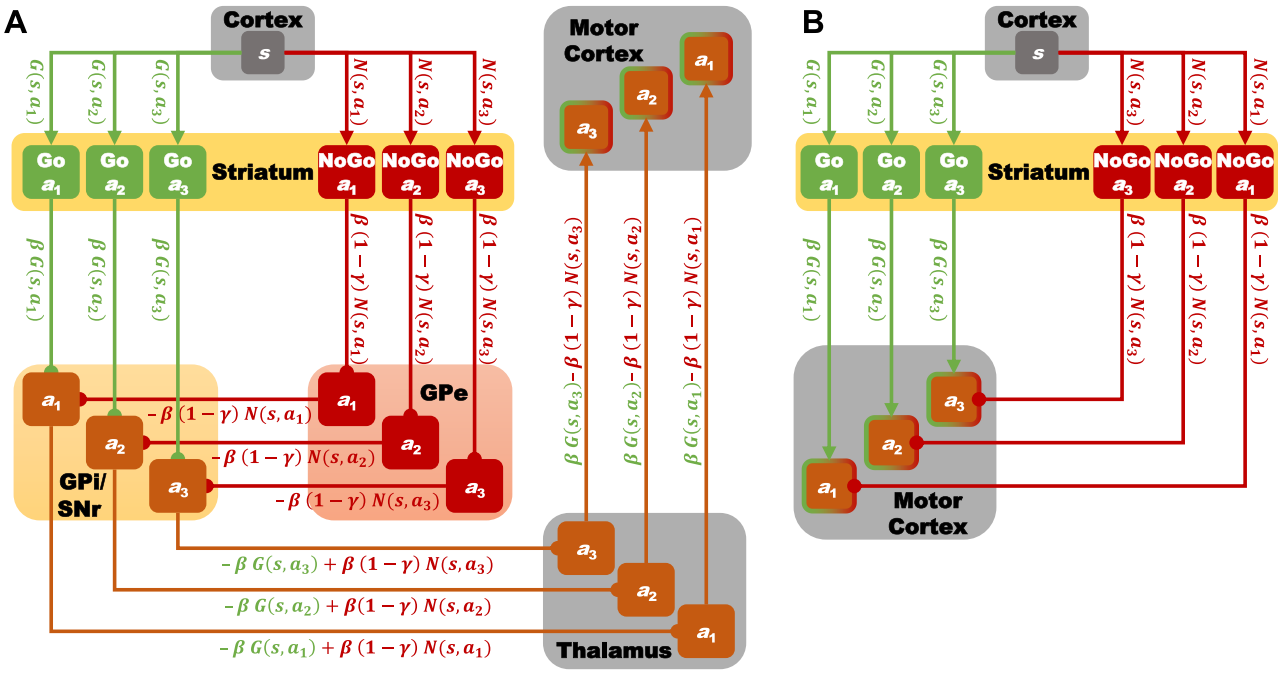

Figure 1. Computational perspectives on action selection by the basal ganglia. **(A)** Reinforcement-learning perspective on the roles of the direct (Go) and indirect (NoGo) basal-ganglia pathways in action selection. The current situation or state, s, is represented in cortex. Three possible actions (a_1, a_2, and a_3) are represented; their representation is kept separate in each anatomical region. Striatum contains two populations of neurons: D_1-expressing (Go) and D_2-expressing (NoGo) medium spiny neurons (MSNs), represented in green and red, respectively. Each of these populations contains a representation of the three actions. Go (G) and NoGo (N) values that represent the learned associations between state s and each of the actions are represented in corticostriatal synapses onto Go and NoGo MSNs, respectively. The gain of NoGo MSNs is negatively modulated by tonic dopamine, γ; the gain of Go MSNs is not modulated by tonic dopamine because of D_1 receptors' lower affinity for DA (see Box 1). The activation of Go and NoGo MSNs therefore is given by $\beta G(s,a_i)$ and $\beta(1-\gamma)N(s,a_i)$, respectively. Mathematically, inhibitory projections (represented by circles) flip the sign of the information (provided that there is intrinsic activity in the target structures, as is the case here). The anatomy of the basal ganglia therefore seems precisely suited to represent the difference between Go and NoGo activations, $\beta G(s,a_i) - \beta(1-\gamma)N(s,a_i)$, in thalamus. Internal variables, structures, and projections related to the direct and indirect pathways are coded in green and red, respectively. Excitatory projections are represented by arrowheads. **(B)** Simplified version of the circuit in **(A)** used in Figure 2. For simplicity and compactness, globus pallidus and thalamus are omitted, so Go and NoGo MSNs are shown directly stimulating and inhibiting motor cortex, respectively. Note from **(A)** that ultimately this is their functional effect. The excitatory and inhibitory connections from Go and NoGo MSNs to motor cortex represent the fact that action values ultimately correspond to a subtraction of the outputs of the Go and NoGo pathways. GPe, globus pallidus external segment; GPi, globus pallidus internal segment; SNr, substantia nigra pars reticulata.

performance in unmedicated patients with TS therefore might have been due to their impairment in learning from negative feedback (25).

Positive Versus Negative Reinforcement

The studies reviewed above suggest that patients with TS exhibit increased learning from rewards (i.e., positive reinforcement). Behavioral models of TS, however, suggest that tics are learned by negative reinforcement, not positive reinforcement, by temporarily decreasing the discomfort associated with premonitory urges (41,42). These ideas can be reconciled because negative reinforcement—reinforcement due to termination or avoidance of aversive stimuli—also relies on positive PEs (6,43,44). Indeed, both termination and avoidance of aversive stimuli elicit phasic DA responses (45–48) that reinforce the action that terminated or avoided the aversive stimulus (47,49). The termination of premonitory urges may similarly elicit phasic DA responses that reinforce tics. If phasic DA, which represents positive PEs, is increased in TS, both positive and negative reinforcement should be increased.

OVERLAPPING NEURAL SUBSTRATES FOR TICS AND HABIT LEARNING AND THEIR RELATION TO HYPERDOPAMINERGIA IN TS

Consistent with the idea that tics are motor habits, the neural substrates of tics prominently include the neural substrates of habit learning. Habit learning relies on the motor cortico–basal ganglia–thalamo–cortical loop, which involves sensorimotor cortices and the putamen (34–36). Much evidence implicates this loop in TS (50–52). Indeed, tic-related activation has been found in all structures of this loop: supplementary motor area (53–56), premotor cortex (53,56,57), sensorimotor cortex (53–57), putamen (53–55,57,58), globus pallidus (54,56), and thalamus (53–56).

Consistent with a hyperdopaminergic account of TS, most findings regarding the motor loop in TS are the opposite of those in PD: 1) several studies (59–63), even if not all (64,65), found increased putamen volumes or gray matter density in TS, whereas putamen volumes are decreased in PD (66); 2) structural connectivity within the motor loop is increased in TS (63) and is decreased in PD (67); 3) resting-state functional connectivity in motor networks is increased in TS (68) and is decreased in PD (69);

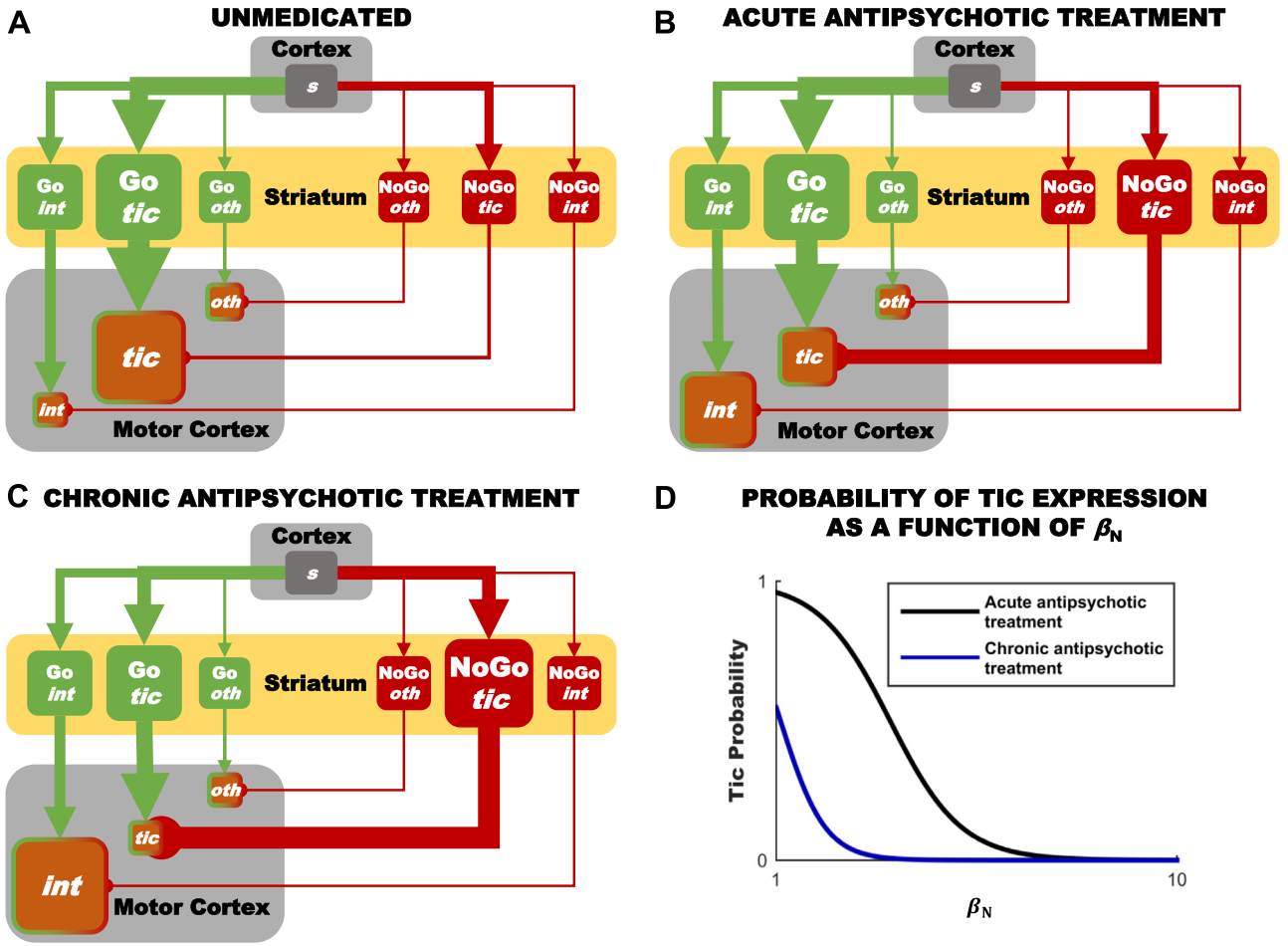

Figure 2. Effects of tonic dopamine (DA) and antipsychotic treatment on Tourette syndrome. Represented in each panel are three actions: an intended action (*int*), a tic (*tic*), and some other weakly supported action (*oth*). Panels **(A–C)** differ in terms of patient medication status. The figures in each panel follow the representation introduced in Figure 1B. The size of each square and the width of the arrow that departs from it represent the level of neuronal activity. **(A)** In unmedicated patients with Tourette syndrome, tics may have both 1) strong Go (*G*) values, learned through aberrant, exaggerated phasic DA responses or through negative reinforcement due to temporary relief of premonitory urges, and 2) strong NoGo (*N*) values, learned through aversive experiences with tics (e.g., social embarrassment, criticism). However, the high tonic DA suppresses the expression of *N* values (i.e., it makes β_N very small), so neural activation for the tic in motor cortex is high, making tic expression very likely. **(B)** Shortly after starting antipsychotic treatment (or reaching a sufficiently high dose), the antipsychotic markedly increases β_N, overweighting *N* values relative to *G* values, thereby making the tic less likely to be expressed. **(C)** Chronic antipsychotic treatment increases *N*, decreases *G*, or both; thus, with the same level of D_2 occupancy, and therefore the same increase in β_N, the tic becomes less likely to be expressed than it was shortly after starting antipsychotic treatment [compare with **(B)**]. For illustrative purposes, the figure shows the case of both increased *N* values and decreased *G* values, but the same effect would be obtained with changes in just one or the other. **(D)** Relation between medication dose and the probability of tic expression with acute treatment (black line) and after chronic treatment has increased *N* and decreased *G* (blue line). (Again, the same effect would be obtained by changing only *N* or *G*.) Tic suppression is more effective after learning (compare the two lines), which may allow a reduction in dose with no loss of efficacy. If, however, the medication is stopped, tics may return (see the intercept for the blue line): with continued or even reduced medication, β_N amplifies *N* values relative to *G* values sufficiently for tics not to be expressed, but when β_N becomes small following antipsychotic withdrawal and the return of high tonic stimulation of postsynaptic D_2 receptors, *G* values may become preponderant again, causing tics to return. Tic severity, however, may be reduced shortly after the end of treatment relative to before treatment (compare the intercepts for the two lines) because of the partial tic unlearning that occurs during treatment. These curves are intended to capture the phenomena qualitatively, not quantitatively. Details of these simulations are provided in the Supplement. These figures also shed light on why tics often are context dependent (149): tics, like habits, may depend on the situation (s). In fact, the defining characteristic of habits is that they consist of stimulus–response associations (36) (or, more generally, situation–response associations, where a situation can be a complex pattern of external and internal stimuli). Furthermore, the motor loop through the basal ganglia learns precisely those associations (35). Of course, tics may tend to generalize to multiple situations and contexts; (over)generalization, in fact, is a common characteristic of multiple disorders.

4) resting-state spatial covariance analyses showed hyperactivity in premotor and supplementary motor cortices and hypoactivity in thalamus and striatum in TS (70,71), whereas the same analyses showed hypoactivity in premotor and supplementary motor cortices and hyperactivity in thalamus and putamen in PD (72).

MECHANISMS OF ACTION OF ANTIPSYCHOTICS

Fast and Cumulative Effects of Antipsychotics

Antipsychotics have both a fast effect on tic reduction (73,74) and an additional cumulative effect that increases over weeks,

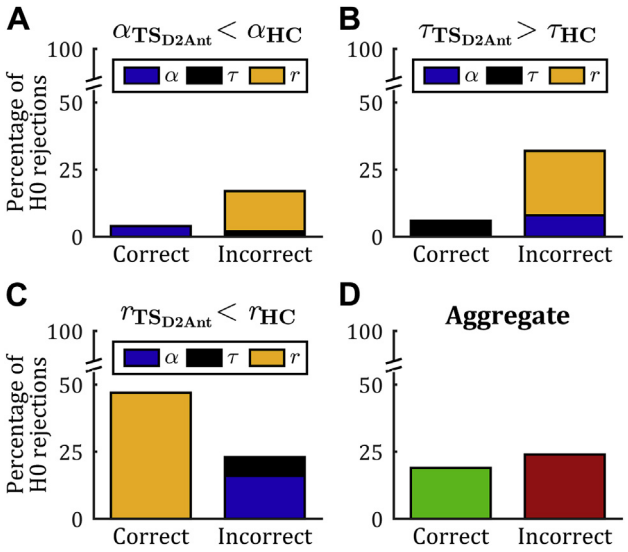

Figure 3. Using models with related parameters can produce misleading results. Many articles use models with parameters that are closely related mathematically—especially some combination of a learning rate, α, a gain, β (or its inverse, a temperature), and a representation of the primary reinforcer, r—without ensuring that the task and fitting procedure used can provide reasonably accurate parameter estimates. The conclusions of those studies can be misleading. To illustrate this point in the context of reinforcement-learning research in Tourette syndrome (TS), we created artificial (simulated) data for a published experiment (100) using, as the generative model, the model that was used in that study to analyze the data. We then applied to our simulated data the same model-fitting procedures and statistical analyses that were applied in the original study to subjects' data. Given that we knew the ground truth by having simulated the data, we could assess the accuracy of the conclusions reached by applying the original model-fitting and statistical procedures. Details about the simulations and analyses are provided in the Supplement. Briefly, the original study used a reinforcement-learning model with three parameters: a learning rate (α), a temperature (τ), and the value of the primary reward (r). [The temperature τ is the inverse of β, that is, $\tau = 1/\beta$. In the original study, the temperature was called β, but here we adopt the more common convention of using τ for the temperature (146).] No model-selection procedures were employed to compare this model with other models, including with reduced models with a subset of these parameters. The main reported result was that patients with TS on antipsychotics (TS_{D2Ant}) had smaller r values than healthy control subjects (HCs) did. In the model, however, α, τ, and r are closely intertwined. To test whether a statistically significant difference in r could be attributed with reasonable confidence to differences in r, rather than in α or τ, we ran three sets of simulations; in each set, the simulated TS_{D2Ant} and HC groups had a very large difference (Cohen's $d = 2.0$) in one of the parameters and did not differ in the other two parameters. The direction of the difference in each of the parameters was such that performance in the TS_{D2Ant} group would be expected to be worse, as was found in the original study. We ran 100 simulations in each set, as if replicating 100 times the original study. In each simulation, we used the model-fitting procedures from the original study and compared the parameters across the two groups using two-tailed unpaired Student's t tests (also as in the original study). We then determined the percentage of simulations in each set in which the null hypothesis (H0) of no difference between groups for each parameter was rejected: correctly, if the null hypothesis was rejected for the parameter that indeed was different in that set, or incorrectly, if the null hypothesis was rejected for a parameter that did not differ across the groups in that set. **(A)** Simulations in which the TS_{D2Ant} group had smaller values of α than the HC group, and τ and r did not differ between the groups. Applying the procedures used in the original study resulted in incorrect rejection of the null hypothesis of no differences between r more often than it resulted in correct rejection of the null hypothesis of no differences between α. **(B)** Simulations in which the TS_{D2Ant} group had greater values of τ than the HC group, and α and r did not differ between the groups. Applying the procedures used in the original study resulted in incorrect rejection of the null hypothesis of no differences between r more often than it resulted in correct rejection of the null hypothesis of no differences between τ. **(C)** Simulations in which the TS_{D2Ant} group had smaller values of r than the HC group, and α and τ did not differ between the groups. Applying the procedures used in the original study resulted in correct rejection of the null hypothesis of no differences between r more often than it resulted in incorrect rejections of the null hypotheses for the other parameters. In summary, in all three sets of simulations, the null hypothesis that was rejected most frequently was the one for no differences in r, independent of whether that was the true underlying difference or not. We also calculated the conditional probability of r truly being different given rejection of the null hypothesis for no differences in r; that probability was .55. Knowing that the original study rejected that null hypothesis therefore provides fairly weak evidence that indeed there was a difference between groups specifically in r because conditional on that rejection, the probability that there was a difference in r (.55) was not much larger than the probability that there was no difference in r (.45). **(D)** Aggregate percentages of correct and incorrect rejections of the null hypotheses combining the data from the three sets of simulations. The percentage of incorrect rejections was even larger than the percentage of correct rejections. The Supplement contains additional simulations and analyses demonstrating that the problem with the original study (100) was not with the fitting procedure as such but rather with the unsuitability of this task and experimental design to obtain accurate estimates of the highly interrelated parameters in the model. In particular, r strongly correlates negatively with α and positively with τ, which likely explains why differences in those parameters were often captured in r. Other simulations and analyses in the Supplement demonstrate other limitations with the original study and suggest alternative interpretations for its other findings. The Supplement also discusses how these types of problems can be prevented, diagnosed, and overcome.

months, and even years (75–79). The fast effect likely is due to blockade of postsynaptic D_2 receptors, which increases indirect-pathway activity, thereby suppressing tics. Computationally, antipsychotics increase the gain of NoGo MSNs, β_N, thereby amplifying NoGo values ($\beta_N \times N$; Box 1 and Figure 1). Therefore, the learned NoGo values (N) for tics, which result from prior negative experiences with tics—such as embarrassment, criticism, or physical discomfort—get amplified, suppressing tic execution (Figure 2B). The amplified negative (NoGo) values might also include cognitive beliefs (e.g., that tics are bad), which interact with RL processes (80).

The cumulative effects of antipsychotics might be due to gradual biological adaptations. Acute antipsychotic administration increases tonic and phasic DA because of autoreceptor blockade (81–83). Chronic antipsychotic administration, however, reduces tonic and phasic DA (84–86), possibly by inducing depolarization block in DA neurons (86,87). The cumulative effects of antipsychotics therefore might be due to the gradual development of depolarization block. In a hyperdopaminergic animal model, however, acute antipsychotic administration suffices to induce depolarization block (88). Whether that might also occur in TS is unclear; if it does, the gradual improvements with chronic administration might be due to other mechanisms.

An alternative, or additional, explanation for these gradual improvements draws on DA's role in learning. Antipsychotics may cause gradual tic unlearning through mechanisms discussed below that may increase NoGo values (N), decrease Go values (G), or both for tics. Such tic unlearning would explain the tic improvement with continued treatment (Figure 2C), why antipsychotic dose can often be reduced during treatment (75,89) (Figure 2D), and why tics do not always return with full

force—and in some cases may not return at all—following medication withdrawal (74–76) (Figure 2D). Of course, these effects are difficult to disentangle from the natural waxing and waning of tics and from the tic reduction that typically occurs during adolescence and young adulthood (90).

Antipsychotic discontinuation has been associated with a return of tics after a few days (74,89,91), when most of the antipsychotic has left the organism. In two crossover studies, tics increased at the end of the placebo period relative to the end of the preceding treatment period, reaching pretreatment levels in one study (92) but not the other (76). Thus, if tic unlearning occurs during antipsychotic treatment, such unlearning likely is only partial. Computationally, partial tic unlearning is exactly what would be expected: a given increase in *N*, decrease in *G*, or both may completely suppress tics during antipsychotic treatment, when β_N is increased, and yet be insufficient to suppress tics after antipsychotic discontinuation, when β_N is reduced because of the high stimulation of postsynaptic D_2 receptors by elevated tonic DA (Figure 2D). In fact, the successful suppression of tics after only partial tic unlearning during treatment, while β_N is elevated, may preclude further tic unlearning because *G* and *N* values change only when the action is executed.

Data on illness course after antipsychotic discontinuation are sparse, but tics may tend to gradually worsen (93). Periods of remission of up to 6 months followed by relapse have been reported (75). Again, disentangling these findings from the natural waxing and waning of tics is difficult; nonetheless, gradual worsening of tics following antipsychotic discontinuation could be due to tic learning, which might affect preferentially incompletely unlearned prior tics. Indeed, case reports tend to note the preferential return of prior tics (74,91).

Antipsychotics and Increased NoGo Learning

Long-term depression (LTD) and long-term potentiation (LTP) of corticostriatal synapses onto D_2 MSNs require D_2-receptor stimulation and lack of stimulation, respectively (14,15). Antipsychotics therefore prevent and facilitate indirect-pathway LTD and LTP, respectively, increasing NoGo learning. Consequently, the NoGo value (*N*) for tics might increase, making them less likely to occur. Chronic antipsychotic administration induces homeostatic adaptations that counteract the increased NoGo function elicited by D_2 blockade; such chronic administration, however, strengthens a subset of corticostriatal synapses onto D_2 MSNs (94). Which synapses onto D_2 MSNs get strengthened and which get weakened is unclear (94); understanding the biological mechanisms, or possibly the behavioral contingencies, that underlie these differential effects could facilitate better treatments for TS.

Consistent with the idea that antipsychotics may reduce tics in part by increasing NoGo learning, patients with TS on chronic antipsychotic treatment have increased NoGo learning relative to unmedicated patients (25). Increased NoGo learning is also found in unmedicated patients with PD (25,26), healthy subjects under DA depletion (95), and healthy subjects low on striatal tonic DA as assessed indirectly via spontaneous blink rate (96). Low DA therefore also causes increased NoGo learning, likely because of reduced stimulation of postsynaptic D_2 receptors (26).

Antipsychotics and Blunted Go Learning

Antipsychotics impair reward-based learning in animals (97), healthy humans (98,99), and patients with TS (25,100). One study claimed that this impairment is on action selection rather than on learning because 1) the antipsychotic seemed to affect only late, asymptotic behavior, not earlier learning, and 2) in model fits, the affected parameter was the gain for rewards, β_G, not the learning rates for rewards, α_G, or losses, α_N, nor indeed the gain for losses, β_N (99). Such a conclusion, however, seems highly debatable because 1) participants above a median split on serum antipsychotic levels were impaired right from the initial trials, and 2) α and β frequently are not identifiable simultaneously because of their strong mathematical interrelation (Figure 3). Furthermore, this study administered a single high dose of an antipsychotic; an effect on β_G with no effect on β_N seems implausible biologically because a high antipsychotic dose should affect mostly the indirect pathway, not the direct pathway. Finally, studies in animals show that antipsychotics impair reward-based learning over and above possible effects on action selection (97). Consistent with the idea that active-avoidance learning also relies on positive PEs (6,43), antipsychotics also impair active-avoidance learning in healthy humans (98) and animals (101).

Antipsychotic treatment in TS virtually abolishes reward-based learning (25,100) and the effects of rewards on motor-skill learning (27). Notably, antipsychotics do not simply normalize patients' biases: they flip those biases from enhanced reward and blunted punishment learning in unmedicated patients to blunted reward and enhanced punishment learning in medicated patients (25,27,100). This bias reversal may facilitate tic unlearning.

Model-based analyses suggested that antipsychotics have this effect in TS by blunting primary reward, *r* (not β) (27,100). However, estimating α, β, and *r* simultaneously in tasks such as the ones in these studies produces unreliable results (Figure 3). Nonetheless, one of these studies showed that antipsychotics blunted neural activation to rewards during learning, with the degree of such blunting explaining the behavioral impairment (100). Overall, these findings suggest that antipsychotics blunt reward-based learning in TS over and above possible effects on action selection; however, they do not license more fine-grained interpretations about the underlying mechanisms (e.g., whether the effect is on primary rewards, PE magnitude, postsynaptic effects of PEs, or another mechanism).

Antipsychotics go beyond blunting Go learning: they cause progressive extinction of previously learned responses (97). Therefore, they should cause gradual tic extinction. Notably, antipsychotics cause response extinction even if the response continues to be reinforced (97). Thus, tics may extinguish even if they continue to alleviate premonitory urges.

The mechanisms by which antipsychotics blunt Go learning are unclear. Chronic antipsychotic administration decreases DA-neuron firing (87,102) and reduces phasic and tonic DA (84–86), which should blunt Go learning and expression. However, acute antipsychotic administration, which increases DA-neuron firing (102) and phasic and tonic DA (81,82), also blunts Go learning (97,99,103). Presynaptic effects therefore are, at best, a partial explanation that applies only to chronic

administration. A postsynaptic explanation, however, seems counterintuitive: antipsychotics block receptors in NoGo MSNs; how can that affect Go learning? We envision three possibilities (that are not mutually exclusive).

First, antipsychotics might not affect the Go pathway: they might just increase NoGo learning and expression, as discussed above. Studies of the effects of antipsychotics on RL typically use probabilistic tasks, which involve Go and NoGo learning for the same stimulus–action pair; increased NoGo learning and expression therefore may counteract Go learning and expression, giving the impression of impaired Go learning. Although this explanation seems likely, it may be insufficient because, in some studies, antipsychotics blunted Go learning without affecting NoGo learning (99,103).

Second, antipsychotics may decrease LTD but not increase LTP in D_2 MSNs. LTD in D_2 MSNs requires both stimulation of D_2 receptors and lack of stimulation of adenosine A_{2A} receptors (14); therefore, antipsychotics are sufficient to block LTD. LTP in D_2 MSNs, however, requires A_{2A} stimulation and lack of D_2 stimulation (14); therefore, antipsychotics alone are insufficient to induce LTP because A_{2A} stimulation is also required. Indeed, antipsychotics abolish LTD but, by themselves, only weakly—if at all—induce LTP in D_2 MSNs (15). In probabilistic tasks, even good actions are occasionally followed by bad outcomes, causing some NoGo learning; impaired LTD in D_2 MSNs would preclude that learning from being "erased" by good outcomes, giving the impression of impaired Go learning. Given that antipsychotics might not increase LTP in D_2 MSNs, they would not improve NoGo learning for bad actions. The behavioral effects therefore would be impaired Go learning but no effect on NoGo learning, as indeed has been found (99,103).

Third, antipsychotics might blunt phasic DA responses via striatal cholinergic tonically active neurons. These neurons pause firing for unpredicted salient positive events, at the same time that DA neurons burst fire (104). The resulting reduction in acetylcholine facilitates DA release during DA-neuron burst firing, when DA neurons are firing at high frequencies, through nicotinic receptors in dopaminergic terminals (104). D_2 blockade in tonically active neurons reduces their firing pauses (105), so it may blunt phasic DA release.

MECHANISMS OF ACTION OF DA AGONISTS

Low doses of some DA agonists, particularly pergolide (106,107), are effective treatments for TS. At low doses, pergolide acts mostly on D_2 autoreceptors, thereby decreasing DA-neuron firing (108,109) and DA levels (110). We are aware of only one RL study with pergolide, in which pergolide dose correlated with reversal errors in patients with PD (111). The doses, however, substantially exceeded those used for TS, so this finding likely is attributable to postsynaptic effects: postsynaptic D_2 agonism should impair learning from negative feedback by inhibiting the indirect pathway. Low doses of pergolide impair other forms of associative learning, probably by blunting phasic DA (112). Furthermore, low doses of cabergoline, another ergot-derived DA agonist with similar binding affinities to pergolide (113), impair reward-based learning (114). A limitation of these preclinical studies is that they used acute (108–110,114), or at best short-term (112), pergolide administration. Chronic low doses of pergolide may aggravate parkinsonism (115), however, so such chronic administration likely also inhibits DA neurotransmission.

Acute administration of a low dose of pramipexole, another DA agonist, also inhibits DA-neuron firing (116,117) and impairs reward-based learning (118,119). However, a clinical trial of low doses of pramipexole for TS failed (120). The likely reason for this failure is that whereas, acutely, pramipexole inhibits DA-neuron firing (116,117), with chronic administration, DA-neuron firing normalizes (116), and DA levels (121,122) and postsynaptic D_2 stimulation (123) increase. Indeed, the dose (0.5 mg) that impaired RL in control subjects when given acutely (118,119,124) is used, twice daily, to treat early-stage PD (125). Furthermore, in patients with PD with comorbid impulse control disorders using DA agonists chronically, most of whom were on 0.5 to 1 mg of pramipexole, the DA agonist increased reward-based learning (126). The contrasting effects of chronic low doses of pergolide and pramipexole, illustrated by their respective aggravation (115) and amelioration (125) of PD, may relate to their different affinities for the D3 receptor (Maia and Conceição, unpublished review, February 2017).

MECHANISMS OF ACTION OF OTHER MEDICATIONS

TS is often treated with α_2 agonists, which may decrease both tonic and phasic DA (Maia and Conceição, unpublished review, February 2017). Tetrabenazine, an inhibitor of the vesicular monoamine transporter 2 used to treat TS (127), also decreases both tonic DA (128,129)—possibly after a short-duration increase (128,130)—and phasic DA (130).

COMORBIDITY BETWEEN TS AND ADHD

More than half of patients with TS have comorbid ADHD (131), typically including hyperactivity–impulsivity (i.e., of the combined or hyperactive–impulsive subtypes) (132,133). Conversely, more than 20% of patients with the hyperactive–impulsive subtype of ADHD have comorbid TS, whereas only about half as many with the inattentive subtype do (134). In the general population, TS-like symptoms are also associated with hyperactivity–impulsivity but not with inattention (135). An association between TS and hyperactivity is predicted by our account because increased tonic DA amplifies both tics and the overall tendency for action.

DEVELOPMENTAL COURSE OF TS

Tics tend to increase until periadolescence (around 10 years of age) and then decrease throughout adolescence (136). In rodents, striatal D_1 and D_2 receptors follow exactly that pattern (137). Notably, only male rodents exhibit the peak around periadolescence (138), which might explain the increased prevalence of TS in male individuals. Data in humans are sparser, but striatal D_1 and D_2 receptors and tyrosine hydroxylase activity seem to decrease throughout adolescence (139–141). The course of TS therefore may parallel the course of functional activation of the DA system.

THE CLASSICAL THEORY OF TONIC–PHASIC DA DYSFUNCTION IN TS

A prominent theory suggests that the primary disturbance in TS is an overactive DA transporter, which reduces DA spillage beyond the synapse, thereby causing reduced tonic DA; reduced tonic DA, in turn, would reduce autoreceptor stimulation, which, together with the increased DA available in presynaptic terminals due to increased reuptake, would increase phasic DA (3,142). An obvious problem with that theory is that if the main disturbance in TS were an overactive dopamine transporter, then dopamine transporter inhibition—using, for example, psychostimulants or bupropion—should be an excellent treatment for TS, which is not the case. Multiple other lines of evidence, which we review in a recently submitted article, also make that theory unlikely (Maia and Conceição, unpublished review, February 2017).

CONCLUSIONS

Our suggestion that TS involves increased tonic and phasic DA is grounded in an extensively validated computational understanding of the roles of phasic and tonic DA in action learning and selection, respectively, and it provides a coherent, integrated explanation for a broad range of clinical, experimental, and pharmacological findings in TS. The distinction between the roles of increased phasic and tonic DA on tic learning and expression, respectively, also has practical implications for the rational development of new drugs for TS. For example, it suggests that drugs that reduce phasic DA but not tonic DA might be better at preventing learning of new tics than at suppressing existing tics, whereas drugs that reduce tonic DA but not phasic DA might suppress tic expression but not prevent the learning of new tics (which might remain latent for the duration of treatment because of the drug-induced suppression of tic expression).

ACKNOWLEDGMENTS AND DISCLOSURES

The authors acknowledge funding from the Tourette Association of America (to TVM) and from Fundação para a Ciência e a Tecnologia, Portugal (Ph.D. Fellowship PD/BD/105852/2014 to VAC).

The authors report no biomedical financial interests or potential conflicts of interest.

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Received Feb 16, 2017; revised May 8, 2017; accepted May 28, 2017.

Supplementary material cited in this article is available online at http://dx.doi.org/10.1016/j.biopsych.2017.05.025.

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