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Premonitory urges and tics in Tourette syndrome: computational mechanisms and neural correlates

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Tourette syndrome is characterized by open motor behaviors — tics — but another crucial aspect of the disorder is the presence of premonitory urges: uncomfortable sensations that typically precede tics and are temporarily alleviated by tics. We review the evidence implicating the somatosensory cortices and the insula in premonitory urges and the motor cortico-basal ganglia-thalamo-cortical loop in tics. We consider how these regions interact during tic execution, suggesting that the insula plays an important role as a nexus linking the sensory and emotional character of premonitory urges with their translation into tics. We also consider how these regions interact during tic learning, integrating the neural evidence with a computational perspective on how premonitory-urge alleviation reinforces tics.

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Introduction

Computational psychiatry aims at improving the comprehension, diagnostics, prognostics, and treatment of psychiatric disorders using mathematical and computational tools [1•,2,3]. Computational-psychiatry approaches can be broadly divided into data-driven and theory-driven [1•,4]. The former typically uses machine learning for classification, clustering, and prediction of patient data using high-dimensional, potentially multimodal, data [1•]. The latter allows, among other things, the *in silico* mechanistic study of the effects of specific biological disturbances or interventions, thereby allowing the development of new theories of pathophysiology and of the mechanisms of action of treatment under rigorous computational frameworks [1•,4,5]. Such mechanistic understanding is expected to ultimately provide better features for patient classification, clustering, and prediction than those that arise from theory-blind application of data-driven approaches [1•,4–6]. Here, we focus on a theory-driven approach to Tourette syndrome (TS).

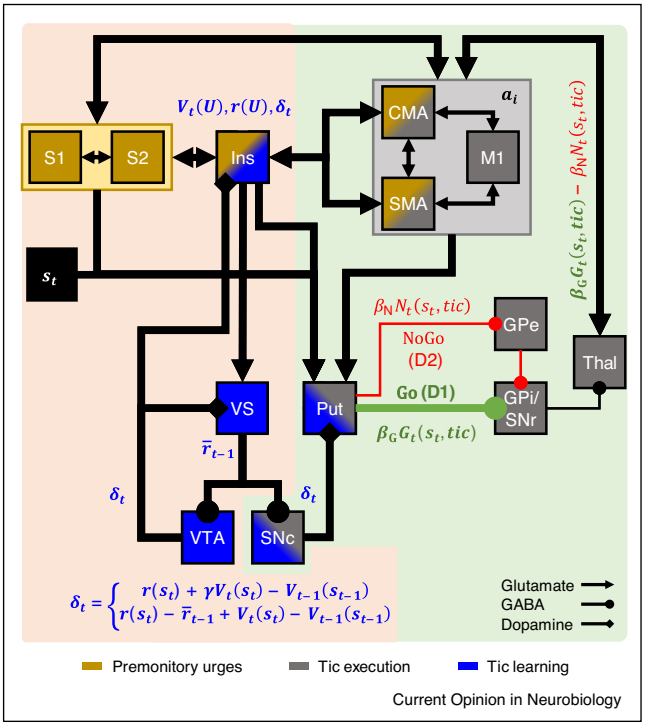
TS is characterized by motor and phonic tics, which are often preceded by premonitory urges: distressful sensations that build up prior to tic execution [7–9,10•]. Robust evidence implicates dopamine [5,11] (TV Maia, VA Conceição, unpublished review) and cortico-basal ganglia-thalamo-cortical (CBGTC) circuits [8,12] in tics, and we have recently proposed a computational account of the roles of dopamine and the motor CBGTC loop in tic learning and execution [13••]. Here, we extend that account by considering the computational mechanisms underlying the reinforcement of tics by premonitory-urge termination in light of recent evidence on the neural substrates of premonitory urges [14••].

The motor CBGTC loop and striatal dopamine in TS

Tic execution involves the motor CBGTC loop [12,15–20] and likely is modulated by striatal dopamine [5,13••]. Dopamine inhibits striatal D2 medium spiny neurons (MSNs) of the indirect (NoGo) pathway, decreasing their gain (β_N), and it facilitates the activation of striatal D1 MSNs of the direct (Go) pathway, increasing their gain (β_G) [21]. The likely striatal dopaminergic hyperinnervation in TS (TV Maia, VA Conceição, unpublished review) increases the probability of tic execution by increasing Go relative to NoGo activation [5,13••] (Figure 1; Box 1). Deficits in histamine biosynthesis [22] may promote tic execution by a similar mechanism, as histamine downregulates striatal dopamine levels [23]. Other disturbances that cause overactivation of Go relative to NoGo MSNs in the motor striatum may similarly promote tic execution. For example, reduced numbers of striatal GABAergic fast-spiking interneurons have been reported in TS [17]; given that these neurons preferentially target Go MSNs [24], such deficit may preferentially disinhibit the Go pathway.

The motor CBGTC loop and striatal dopamine are involved not only in tic execution but also in tic

Figure 1



Regions and computations involved in premonitory urges, tic execution, and tic learning. The figure depicts the main regions involved in premonitory urges (gold), tic execution (gray), and tic learning (blue), and the most important connections between them, according to the framework proposed in this article. This framework expands our previous computational account of the roles of dopamine and the motor cortico-basal ganglia-thalamo-cortical (CBGTC) loop in tic learning and execution [13••] (light-green shading; Box 1) by addressing the neural substrates and mechanistic roles of premonitory urges in tic execution and tic learning (light-orange shading). *Tic execution:* Cortical motor areas represent candidate actions (a_i), including tics, being considered for gating. Other cortical and noncortical areas represent the current state or situation (s_t). (The subscript t denotes time.) The putamen contains Go (direct-pathway, in green) and NoGo (indirect-pathway, in red) medium spiny neurons (MSNs). Striatal hyperdopaminergia in TS (TV Maia, VA Conceição, unpublished review) increases the activation of the Go relative to the NoGo pathway, by increasing the value of β_G relative to β_N, so it tends to increase the activations of actions. That increase, however, is disproportionately larger for strongly learned values (G and N) because the βs are multiplicative gain parameters. Consequently, as tics become strongly learned behaviors (see below and main text), striatal hyperdopaminergia will disproportionally increase the tendency for tic execution, making $\beta_G G_t(s_t, tic) \gg \beta_N N_t(s_t, tic)$ (compare the width of the green and red arrows leaving from the putamen; see Box 1) [13••]. As a consequence, there is strong inhibition of the globus pallidus internal segment (GPi) and substantia nigra *pars reticulata* (SNr) by the direct pathway [with a value of $-\beta_G G_t(s_t, tic)$, where the sign is flipped because of the inhibitory nature of the connection between the putamen and GPi/SNr], with weak disinhibition by the NoGo pathway [with a value of $\beta_N N_t(s_t, tic)$, where the sign remains the same due to the double inhibitory nature of this pathway: from putamen to globus pallidus external segment (GPe) and from the GPe to the GPi/SNr] [13••]. The GPi/SNr combines (sums) both inputs and sends the sum to the thalamus. Given the inhibitory nature of the projection from the GPi/SNr to the thalamus, the sign is flipped again, and the thalamus provides motor cortices with the weighted difference between the Go and NoGo values [$\beta_G G_t(s_t, tic) - \beta_N N_t(s_t, tic)$]. Given that $\beta_G G_t(s_t, tic) \gg \beta_N N_t(s_t, tic)$, tic execution is promoted [13••] (Box 1). *Tic learning*: The relevant variables for tic learning are $r(U)$ and δ_t (under both accounts), $V_t(U)$ (necessary for the account using standard reinforcement learning and optional for the account using average-reward reinforcement learning), and $\bar{r}_{t-1}$ (only for the account using average-reward reinforcement learning). These variables are depicted near the regions and/or connections that we hypothesize subserve them (see text). The prediction errors in the insula may be mostly aversive prediction errors (see text). *Additional figure details:* Some anatomical projections are omitted for simplicity. For clarity, both somatosensory cortical areas [primary (S1) and secondary (S2) somatosensory cortices] and cortical motor areas [cingulate motor area (CMA), supplementary motor area (SMA), and primary motor cortex (M1)] are grouped. The distinct ways of calculating δ_t according to each of the proposed computational accounts (see text) are grouped with curly braces: $\delta_t = r(s_t) + \gamma V_t(s_t) - V_{t-1}(s_{t-1})$ (standard reinforcement learning); $\delta_t = r(s_t) - \bar{r}_{t-1} + V_t(s_t) - V_{t-1}(s_{t-1})$ (average-reward reinforcement learning). Additional abbreviations: Ins: insula; Put: putamen; SNc: substantia nigra *pars compacta*; Thal: thalamus; VS: ventral striatum; VTA: ventral tegmental area.

learning. Indeed, tics are thought to result from aberrant habit learning and therefore to involve learning in the motor loop [13••,25••], like habits do [26,27]. Such learning likely is mediated by phasic dopamine [13••]. Phasic dopamine bursts signal positive prediction errors [5] that modulate long-term potentiation (LTP) and depression (LTD) of corticostriatal projections onto Go and NoGo MSNs, respectively [21,28], thereby inducing action learning (Box 1). Tics may therefore be learned via phasic dopamine responses that either occur at inappropriate times or, as discussed in more detail below, that are elicited by the termination of premonitory urges [13••].

Consistent with its likely role in TS, the motor loop presents structural and functional disturbances in TS that moreover often correlate with tic severity [17–19,29–31] (Figure 2a–c). In terms of structural disturbances, multiple, even if not all [18,32,33], studies have reported thinning of the sensorimotor and surrounding cortices [18,29,34,35,36••], with an association between greater thinning and more severe tics [18,34,35], and structural abnormalities in the putamen [18,30,32,37••,38]. Moreover, the sensorimotor cortex and supplementary motor area (SMA) exhibit increased structural connectivity with the striatum and thalamus in TS, and these increases correlate positively with tic severity [37••]; relatedly, increased structural connectivity between the SMA and putamen predicted tic severity in another study [25••]. Finally, TS patients have enhanced habit formation, which correlates positively with both tic severity and structural connectivity between the motor cortex and putamen [25••].

Functionally, tic-related activation has been reproducibly reported in the sensorimotor cortex [15,16,20,39,40], putamen [15,20,39,40], globus pallidus (GP) [16,20,39], thalamus [16,20,39,40], and substantia nigra (SN) [15,20]. At rest, hyperactivation of cortical motor areas has been

Box 1 Prior computational account

We recently proposed a computational account of the roles of dopamine and the motor cortico-basal ganglia-thalamo-cortical (CBGTC) loop in Tourette syndrome (TS) [13••]. In that account, we suggested that tics might be reinforced by positive prediction errors elicited by the termination of premonitory urges and signaled by phasic dopamine, but we did not delve into the computational or neural mechanisms underlying the calculation of those prediction errors. This box briefly reviews that prior framework, including the equations of the Opponent Actor Learning (OpAL) model [21] on which it is based, with some modifications that we introduced previously [13••].

The motor CBGTC loop mediates action selection, in a given state or situation (s_t), as a function of the difference between the action values coded in the direct (*G*) and indirect (*N*) basal-ganglia pathways [21]. Such values, moreover, are modulated by the total levels of dopamine in the striatum (tonic plus phasic) at the time of action selection [102] (Figure 1). Hence, the activation (Act_t) of a certain action (a) at time t is given by:

$$Act_t(s_t,a) = \beta_G G_t(s_t,a) - \beta_N N_t(s_t,a),$$

where s_t represents the state at time t, and β_G and β_N denote the gains of the direct (Go) and indirect (NoGo) motor basal-ganglia pathways, respectively.

Using the *softmax* equation, the probability of performing action a_i in state s_t at time t is then given by:

$$P_t(a_i|s_t) = \frac{\exp(Act_t(s_t,a_i))}{\sum_{a_j}\exp(Act_t(s_t,a_j))},$$

where the sum is over all actions available in state s_t. In TS, the likely striatal hyperdopaminergia (TV Maia, VA Conceição, unpublished review) inhibits the indirect pathway, by reducing β_N, thereby promoting tic execution [13••].

Phasic firing of dopamine neurons signals positive prediction errors (δ) [5,21] that promote habit learning by inducing long-term potentiation (LTP) and long-term depression (LTD) of corticostriatal synapses onto medium spiny neurons of the Go and NoGo motor pathways, respectively [21,28]. Specifically, when the execution of an action, a, yields a positive prediction error ($\delta_t > 0$), the following learning equations apply [13••]:

$$G_t(s_t,a) = G_{t-1}(s_t,a) + \alpha_{G,LTP}\delta_t,$$
$$N_t(s_t,a) = N_{t-1}(s_t,a) - \alpha_{N,LTD}\delta_t,$$

where $\alpha_{G,LTP}$ and $\alpha_{N,LTD}$ are the learning rates associated with LTP and LTD in the Go and NoGo motor pathways, respectively. On the other hand, when the execution of an action, a, yields a negative prediction error ($\delta_t < 0$), the following equations apply [13••]:

$$G_t(s_t,a) = G_{t-1}(s_t,a) + \alpha_{G,LTD}\delta_t,$$
$$N_t(s_t,a) = N_{t-1}(s_t,a) - \alpha_{N,LTP}\delta_t,$$

where $\alpha_{G,LTD}$ and $\alpha_{N,LTP}$ are the learning rates associated with LTD and LTP in the Go and NoGo motor pathways, respectively. *G* and *N* reflect the strength of corticostriatal synapses, so they are constrained to always be greater than or equal to 0.

In addition to subserving action learning, prediction errors are also used to update the values of states, $V_t(s_t)$, in the critic component of the model, using the following equation:

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

where α_C is the learning rate of the critic. Details of the calculation of the prediction errors, δ_t, are provided in the main text.

reproducibly reported [17,18]. Other findings include increased resting-state activity in the putamen and thalamus, with the latter correlating positively with tic severity [41]; abnormalities in corticospinal excitability, which correlated with tic severity [42]; and positive correlations between tic severity and activation of motor and premotor regions during motor execution/imagination [43]. Moreover, functional coupling between the SMA and the primary motor cortex (M1) is increased in TS patients preceding and following tics [44] and during both preparation and execution of self-paced finger movements [45].

The clinical pharmacology of TS, as well as multiple studies using positron emission tomography and single-photon emission computerized tomography, strongly support a role for dopaminergic disturbances in TS [11] (TV Maia, VA Conceição, unpublished review). Structural and functional magnetic resonance imaging studies generally have not had sufficient resolution to ascertain if observed disturbances are specifically in dopaminergic regions. Nonetheless, gray matter has been reported to be increased in the midbrain [18,31], where dopaminergic nuclei are located, and, as mentioned above, tic-related activity has been reported in the SN, although with insufficient resolution to determine if it involved the SN *pars compacta* (SNc) [15,20].

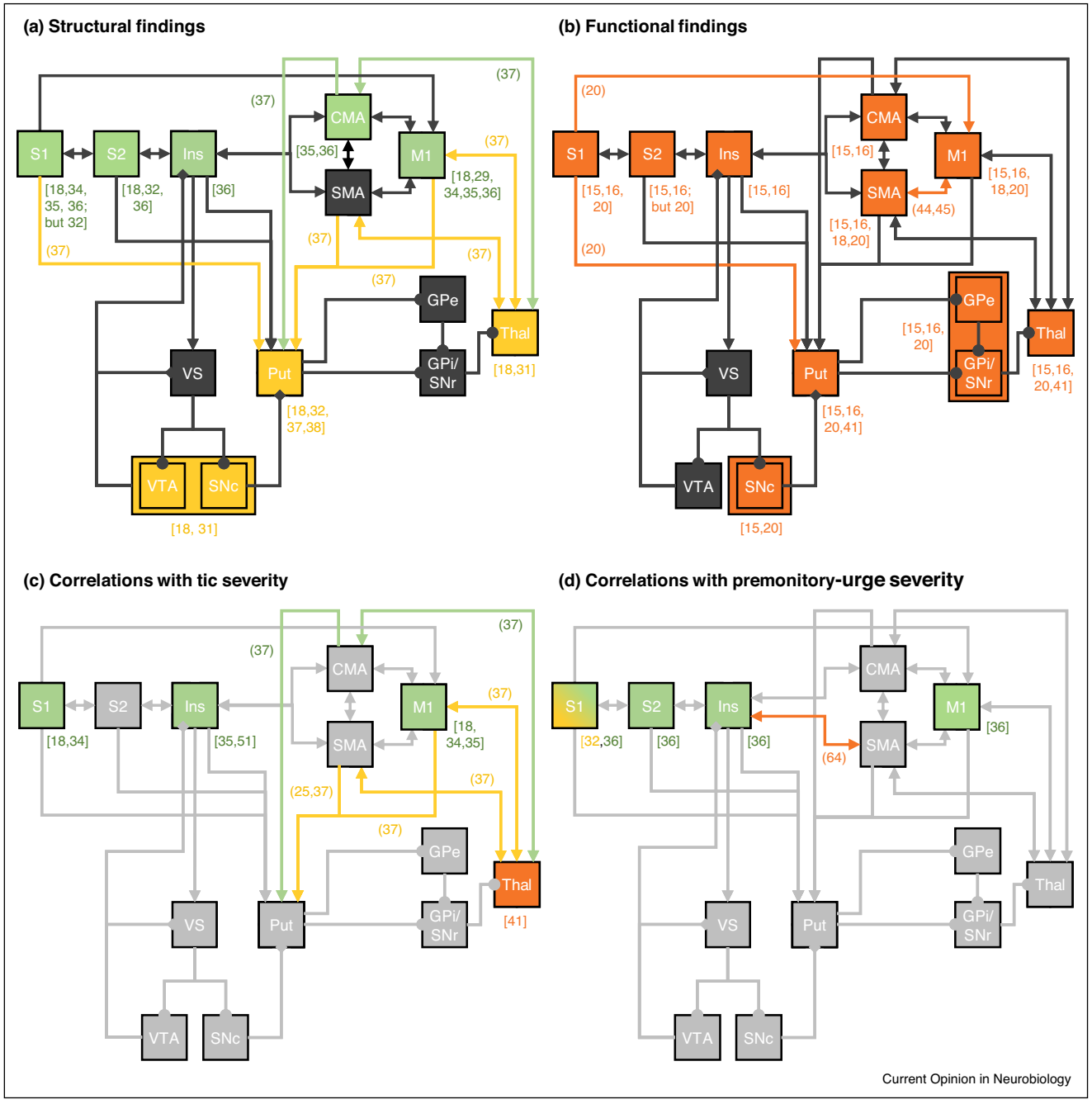
Premonitory urges in TS

Neural correlates

Consistent with the sensory character of premonitory urges, the primary and secondary somatosensory cortices (S1 and S2, respectively) have been implicated in such urges [8,14••,36••]. These areas activate prior to tics [15,16], when premonitory urges are felt, and they exhibit cortical thinning in TS [18,32,34,35,36••], with increased thinning correlating with increased premonitory-urge severity [36••] (and, in the case of S1, also with increased tic severity [18,34]) (Figure 2). These findings are consistent with the idea that premonitory urges arise from a disruption in sensory processes [46]. Further support for that idea comes from the finding that premonitory urges are reduced by intramuscular injections of botulinum toxin [47], which, in addition to their better-known effect of reducing neuromuscular transmission, also reduce afferent sensory neurotransmission [48]. Moreover, TS patients have heightened sensitivity to exteroceptive stimulation and possibly to interoceptive sensations [46], although one study found a positive correlation between premonitory urges and interoceptive awareness but lower interoceptive awareness in patients with TS relative to healthy controls [49].

S1 and S2 strongly project to the insula [50], which has also been implicated in premonitory urges. Like S1 and S2, the insula activates prior to tics [15,16] and is thinner

Figure 2



Structural and functional disturbances in the brain circuits implicated in premonitory urges and tics in Tourette syndrome (TS). **(a)** Structural findings: Green squares depict regions in which TS patients have decreased gray-matter volume or cortical thickness; yellow squares depict regions in which TS patients have increased gray-matter volume. Similarly, green and yellow arrows depict structural connections that are decreased and increased, respectively, in TS patients. The techniques used in the studies depicted did not allow determination of the directionality of projections, so the directionality of the arrows in the figure is based on known neuroanatomy. In the case of bidirectional projections, the directionality of the structural changes shown is not known. The enlargement of the thalamus includes its lateral portion [18], which contains nuclei associated with the motor cortico-basal ganglia-thalamo-cortical loop [31,103]. Studies reporting findings concerning the midbrain did not distinguish between the ventral tegmental area (VTA) and substantia nigra *pars compacta* (SNc), so we represent these regions together (indicated by a rectangle surrounding them). **(b)** Functional findings: Orange squares depict regions that activate shortly before and/or at tic onset. The supplementary motor area (SMA) and primary motor cortex (M1) [17,18], the putamen [41], and the thalamus [41] have additionally been shown to be hyperactive at rest (see text). Unidirectional orange arrows depict increased causal influence between regions (assessed with Granger causality) in TS patients during tics. The bidirectional orange arrow depicts increased functional connectivity between the SMA and M1, with directionality unspecified, during tics. Note that the findings concerning the globus pallidus and the substantia nigra did not distinguish

in TS patients relative to controls [36••], with thinning correlating positively with premonitory urges [36••] and tic severity [35,51] (Figure 2). Furthermore, one study reported a trend towards increased functional connectivity between the sensorimotor cortex and the right anterior insula in TS patients [52]. Premonitory urges are somatosensory and/or visceral sensations [14••] that are accompanied by emotional discomfort [20,53]. The insula is a nexus of convergence and integration of somatosensory, visceral, and emotional information [54], so it may play a role in providing premonitory urges their integrated sensory and emotional character (particularly their aversiveness, as discussed in more detail below). Indeed, insula stimulation can induce unpleasant somatosensory or visceral sensations [55,56]. Consistent with a role in premonitory urges, the insula is also implicated in a variety of natural urges [57] and in urges in addiction [58].

Role in tic execution

The insula is well positioned to translate the premonitory-urge-related complex of sensory and emotional content possibly represented therein into tics. Indeed, the insula projects strongly to both the SMA and the cingulate motor area (CMA) [50], which, in turn, project strongly to each other [59,60], to M1 [59,60], and directly to descending motor pathways [61] (Figure 1). The CMA and SMA activate shortly before tics [15,16], and the SMA and M1 activate during tics [15,16,20], so motor cortices likely play a key role in eliciting tics. Several lines of evidence suggest that the CMA and SMA may also play a role in premonitory urges: they have been implicated in a variety of natural urges [57]; their intraoperative stimulation in non-TS patients elicits both movements and urges to move [62,63]; and functional connectivity at rest between the insula and the SMA correlates positively with premonitory-urge severity in TS patients [64•]. Notably, in healthy participants, electrical stimulation of the hand or foot elicits activity in S1, S2, insula, CMA, and SMA [65], which illustrates how activity can propagate throughout all the regions that we have associated with premonitory urges and their ultimate translation to action.

Although the insula might be an important gateway linking the sensory and emotional character of premonitory urges to tics, such links do not necessarily have to go through the insula. For example, the causal influence of S1 over M1 is increased in TS patients during tics [20], possibly reflecting a direct link between simple sensations and simple tics. Such a link, in fact, might explain why patients with only simple motor tics have cortical thinning more restricted to M1 [34].

Tic execution, of course, is unlikely to be driven only by corticocortical projections. As reviewed above, subcortical components of the motor CBGTC loop activate during and shortly before tics [15,16]. Given the role of these regions in action selection [5], they likely play a role in tic selection — as is indeed predicted by our prior computational accounts [5,13••] (and therefore by the account herein). Consistent with this idea, the causal influence of the GP over the SMA, via the thalamus, is increased in TS during tics and correlates positively with tic severity, and the causal influence of the GP over M1, via the thalamus, also correlates positively with tic severity [20]. The finding that structural connectivity between S1 and the striatum is increased in TS [37••] suggests that the motor CBGTC loop may also play a role in translating premonitory urges to tics.

Cues that predict aversive outcomes promote the release of phasic dopamine into the core of the nucleus accumbens [66], which is implicated in action invigoration [67]. Such release during premonitory urges — which may act as aversive cues (see below) — might therefore promote tic execution.

Role in tic learning

Computational mechanisms

In our recent computational account of TS, we suggested that termination of premonitory urges might elicit positive prediction errors, signaled by phasic dopamine

(Figure 2 Legend Continued) between their subcomponents [globus pallidus external (GPe) versus internal (GPi) segments [16,20], and substantia nigra *pars reticulata* (SNr) versus SNc [15,20]]. **(c)** Correlations of structural and functional disturbances with tic severity: Green squares depict regions where gray-matter volume and/or cortical thickness correlate negatively with tic severity. Yellow and green arrows depict positive and negative correlations between structural connectivity and tic severity, respectively. The orange square depicts a positive correlation between resting-state activity and tic severity. Correlations with tic-related functional abnormalities are not depicted, although some have been reported [20]. **(d)** Correlations of structural and functional disturbances with premonitory-urge severity: Green squares depict regions where cortical thickness correlates negatively with premonitory-urge severity. The primary somatosensory cortex (S1) is shown in a yellow-green gradient to depict the existence of contradictory findings concerning the sign of the correlation between its thickness and premonitory-urge severity. The orange arrow depicts a positive correlation between functional connectivity, at rest, and premonitory-urge severity. *Additional figure details:* Numbers next to squares and arrows refer to the empirical studies and reviews that show the corresponding findings. Numbers within square brackets refer to the findings depicted in the closest square; numbers within parentheses refer to the findings depicted in the closest arrow. The color of the numbers matches the color of the depiction of the corresponding findings. For simplicity, not all connections between regions are depicted. Areas and connections where no, or only isolated, findings have been reported are depicted in gray (dark gray in Panels a,b and light gray in Panels c,d). Additional abbreviations: CMA: cingulate motor area; Ins: insula; Put: putamen; S2: secondary somatosensory cortex; Thal: thalamus; VS: ventral striatum.

release, which reinforce tics [13••]. Indeed, as we noted, negative reinforcement — that is, reinforcement due to escape from, or termination or avoidance of, an aversive stimulus — likely relies on positive prediction errors [68–70]. Furthermore, there is direct evidence that termination of aversive stimuli induces phasic dopamine release [69–71]. Here, we elaborate on the computational mechanisms that may produce such phasic dopamine release. We consider two possible accounts: one based on standard reinforcement learning and another based on average-reward reinforcement learning [72]. Both accounts start from the observation that premonitory urges are inherently aversive, so their primary reinforcement value is negative [$r(U) < 0$, in which U represents a state in which a premonitory urge is present]. The two accounts differ slightly, however, in the mechanisms that cause premonitory-urge termination to elicit positive prediction errors.

The account based on standard reinforcement learning is based on the simple idea that premonitory-urge termination causes a transition from a state with negative value [the urge, with $V(U) < 0$] to a neutral state S [with neutral value, $V(S) = 0$, and no primary aversive reinforcement, $r(S) = 0$] (Figure 3a). In standard reinforcement learning, prediction errors are calculated as:

$$\delta_t = r(s_t) + \gamma V_t(s_t) - V_{t-1}(s_{t-1}),$$

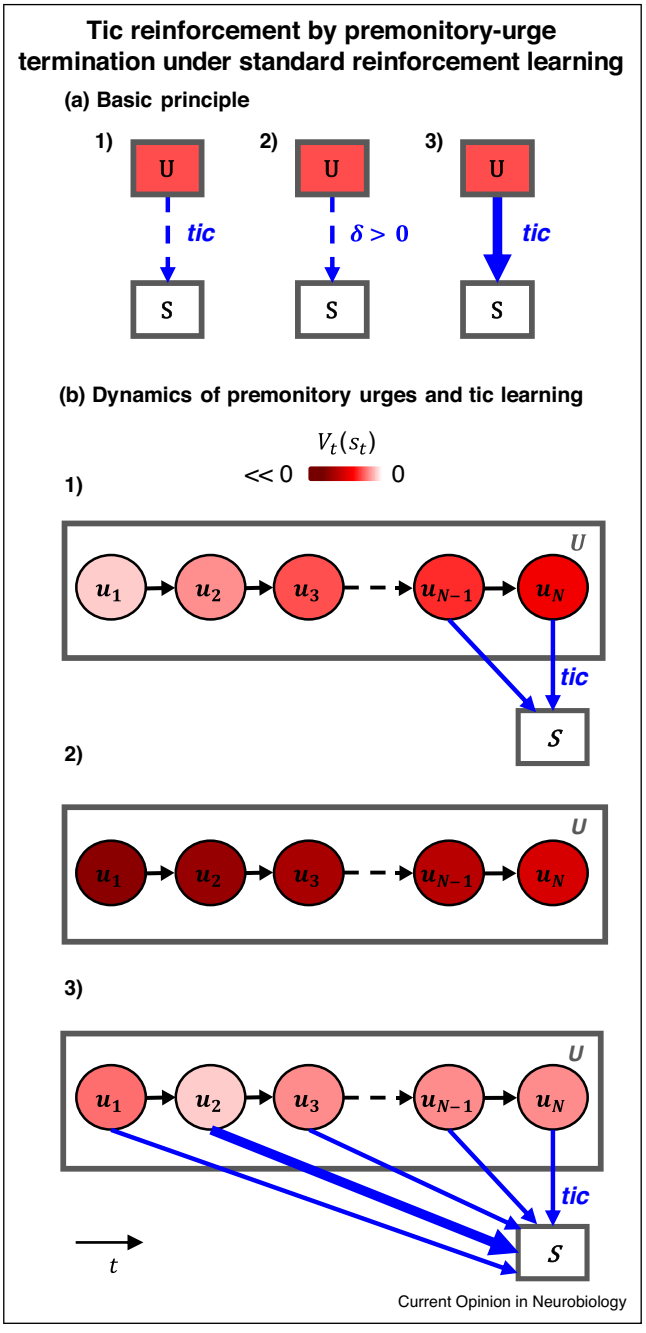
where $r(s_t)$ and $V_t(s_t)$ are, respectively, the primary reinforcement and value of state s_t, $V_{t-1}(s_{t-1})$ is the value of the preceding state, and γ is a future-discount factor. When a tic terminates a premonitory urge at a given time τ, there is a transition from a sub-state with negative value $[V_{\tau-1}(u_{\tau-1}) < 0]$ to state S [with $V_\tau(S) = 0$ and $r(S) = 0$]. This transition elicits a positive prediction error:

$$\begin{aligned}\delta_\tau &= r(s_\tau) + \gamma V_\tau(s_\tau) - V_{\tau-1}(s_{\tau-1}) \\ &= r(S) + \gamma V_\tau(S) - V_{\tau-1}(u_{\tau-1}) = |V_{\tau-1}(u_{\tau-1})| > 0,\end{aligned}$$

which then reinforces the tic. A more elaborate version of this framework provides additional insights into the dynamics of the relation between premonitory urges and tics (Figure 3b).

An alternative (or complementary) account builds on the use of average-reward reinforcement learning [72], an alternative to standard reinforcement learning that aims to maximize the average reward per action and is an alternative to discounting in the case of infinite (or long-term) horizons [72]. This framework has previously been used to capture longstanding ideas about the opponency between appetitive and aversive processes [69,73]. Mechanistically, the key difference from standard reinforcement learning is that there is an ongoing computation of a recency-weighted average of past

Figure 3



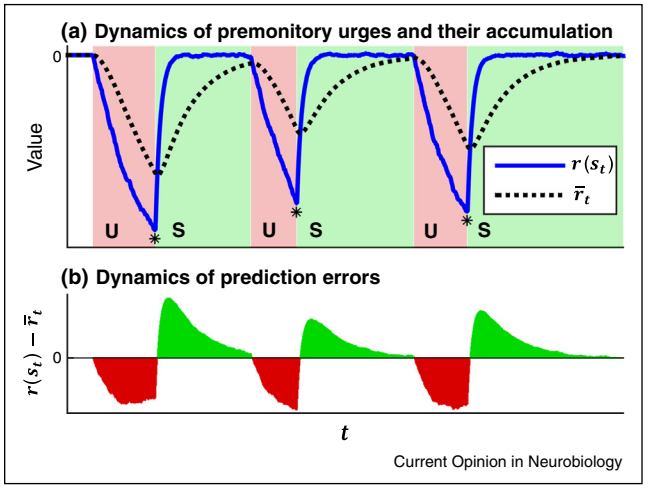
Tic reinforcement by premonitory-urge termination under standard reinforcement learning. **(a)** Basic principle: Premonitory urges (U) are intrinsically aversive, so they have a negative value [$V(U) < 0$, in red]. (1) Tic execution (dashed blue arrow) terminates the premonitory urge, thereby causing a transition to a state, S, in which no premonitory urge is present [$r(S) = 0$] or predicted, and which therefore has a neutral value [$V(S) = 0$, in white]. (2) This transition elicits a positive prediction error [$\delta = |V(U)|$; see text]. (3) The positive prediction error strengthens the tic (solid blue arrow) by causing long-term potentiation and depression of corticostriatal synapses onto the direct (Go) and indirect (NoGo) pathways, respectively [13••]. The elicitation of a positive prediction error by the transition from an aversive state to a neutral state has previously been suggested to underlie the learning of

reinforcements, $\overline{r}_{t-1}$, and primary reinforcements, $r(s_t)$, are evaluated relative to this average $[r(s_t) - \overline{r}_{t-1}]$ prior to being used to calculate prediction errors. The equation for the prediction error then becomes:

$$\delta_t = r(s_t) - \overline{r}_{t-1} + V_t(s_t) - V_{t-1}(s_{t-1}),$$

(Figure 3 Legend Continued) escape responses: responses that, like a tic, terminate ongoing aversive stimulation [68]. **(b)** Dynamics of premonitory urges and tic learning: Although the simple principle enunciated in Panel a provides a good and reasonably accurate intuition of the computational mechanisms involved, formally it suffers from a contradiction: positive prediction errors increase the value of the preceding state (Box 1), so each time a tic would be performed, the value of the urge [$V(U)$] would become less negative, eventually converging to 0. Premonitory urges, however, never lose their aversiveness. The simple principle in Panel a also cannot account for possibly clinically relevant issues related to the timing of tics relative to premonitory urges. Both problems can be solved by adding a representation of the passage of time during premonitory urges, which is done here using a tapped delay line: a sequence of sub-states (u_1, . . . , u_N, circles) within the larger U state (rectangle). Each sub-state has its own value, $V(u_t)$, color-coded in red, with darker red representing more negative values (where t represents the passage of time within an urge). (1) When a premonitory urge first starts, the values of the sub-states reflect mostly the aversiveness of the premonitory urge occurring at around that time [more precisely, $V(u_{t-1}) \propto r(u_t)$]. We represent negative value as increasing in magnitude from left (light red) to right (dark red) because urge intensity generally increases in time [10•]. At this point, tic reinforcement is substantially larger if the tic occurs in a later sub-state than in an earlier sub-state. Tics may therefore start by occurring at longer latencies following the onset of the premonitory urge. (2) Through classical conditioning, earlier sub-states gradually acquire a more negative value, as they begin to predict the aversive primary reinforcement of all subsequent states. In essence, a premonitory urge starts acting as a cue that predicts its own continuation. Formally, such learning occurs because the transition from a given sub-state, u_{t-1}, to the subsequent sub-state, u_t, elicits a negative prediction error ($\delta_t < 0$) that causes the value of the 'origin' sub-state, $V(u_{t-1})$, to become more negative [$V(u_{t-1}) \leftarrow V(u_{t-1}) + \alpha_C \delta_t$, where α_C is the critic learning rate] [68]. Repetition of this process would ultimately cause the value of each sub-state, $V(u)$, to converge to the (discounted) sum of the aversive primary reinforcements of all of its subsequent states, although such convergence is unlikely to occur because of tic learning (next point). (3) Tic execution causes a transition from a sub-state with negative value [$V(u_{t-1}) < 0$] to a state with neutral value [$V(S) = 0$], thereby producing a positive prediction error. This positive prediction error reinforces the tic. Note that because of the classical conditioning process (previous panel), tics are now strongly reinforced even if they occur earlier. Tics may therefore tend to occur sooner after the onset of the premonitory urge with learning (see Ref. [68] for a similar process in avoidance learning). In addition to reinforcing tics, positive prediction errors also cause progressive extinction of the negative value of the sub-states that precede tic execution (as indicated by the lighter colors, relative to Panel b, of the sub-states preceding the sub-states with high likelihood of tic execution). In essence, sub-states that occur before the typical latency time for tic execution no longer predict as much subsequent aversiveness because the tic cuts the premonitory urge short. If the tic starts to be executed increasingly earlier, conceivably almost immediately after urge onset, the value of the corresponding urge sub-state may tend to 0, so there may be little or no prediction error upon tic execution: $\delta = |V(u)|$, so if $V(u) \approx 0$, then $\delta \approx 0$. In that case, the tic would not be reinforced further, but it would nonetheless persist, as a prediction error of 0 implies no change in action strength. A similar mechanism, in fact, explains the remarkable persistence of avoidance responses [68].

Figure 4



Computational mechanisms underlying tic reinforcement by termination of premonitory urges using average-reward reinforcement learning. This abstract simulation illustrates, qualitatively, the dynamics of premonitory urges and the positive prediction errors elicited by their termination, according to the average-reward account, but using the more realistic setting of continuous (rather than discrete) time. **(a)** Dynamics of premonitory urges and their accumulation: Premonitory urges (U; present during periods shaded in red) are inherently aversive [$r(U) < 0$; blue line during periods shaded in red] and tend to increase over time until a tic is executed [10•]. Tics (asterisks) provide temporary relief from these urges, causing a transition to a state (S; periods shaded in green) in which premonitory urges are not present [$r(S) \approx 0$; blue line during green-shaded periods]. Average-reward reinforcement learning [69,73] involves calculating a recency-weighted average of past reinforcements, $\overline{r}$ (dashed black line). During periods with premonitory urges (red shading), $\overline{r}$ becomes increasingly negative due to the accumulation of negative values of $r(U)$ (which, moreover, themselves get increasingly negative). During urge-free periods (green shading), in contrast, $\overline{r}$ decays back to 0 (assuming, for simplicity, that the aversive consequences of tic execution are negligible). However, whereas, following a tic, $r(s_t)$ very quickly returns to 0, reflecting the elimination of the premonitory urge, $\overline{r}$ is much slower to return to 0 because it reflects a recency-weighted average of $r(s_t)$ (compare the blue and dashed black lines at the beginning of periods shaded in green). **(b)** Dynamics of prediction errors: In average-reward reinforcement learning, prediction errors are defined as: $\delta_t = r(s_t) - \overline{r}_{t-1} + V_t(s_t) - V_{t-1}(s_{t-1})$, where the subscript t denotes time. This equation implies that, unlike in standard reinforcement learning, the termination of premonitory urges elicits positive prediction errors even without considering changes in state value. To illustrate this point, this panel shows the value of $r(s_t) - \overline{r}_t$ [which, in the continuous case used here, is similar to $r(s_t) - \overline{r}_{t-1}$ in the discrete case]. Corresponding periods in the two panels are aligned vertically. Following tics, $r(s_t) - \overline{r}_t > 0$ (green area in Panel b), which by itself will induce a positive prediction error (unless the changes in state value override this positive difference). This positive prediction error, in turn, will reinforce the tic. *Methods:* We simulated the increase in premonitory urges over time using bounded exponential growth and their decrease following a tic using exponential decay (with a much shorter time constant, to reflect the virtually immediate termination of the premonitory urge following a tic). We added Gaussian noise to both equations to depict the stochasticity of the corresponding processes. We calculated $\overline{r}$ using exponential smoothing of $r(s_t)$. Note that this simulation is intended to illustrate only how premonitory-urge termination produces positive prediction errors; it is not intended to capture more complex phenomena such as tic bouts [10•].

where a discount factor is not necessary. An ongoing premonitory urge causes accumulation of a negative average reward value ($\overline{r} < 0$) due to its aversive character [$r(u_t) < 0$]; when the premonitory urge is terminated by a tic at time τ, $r(S) = 0$ and $\overline{r}_{\tau-1} < 0$, so $r(S) - \overline{r}_{\tau-1} > 0$ (Figure 4). In this framework, therefore, the difference $r(S) - \overline{r}_{\tau-1}$ is sufficient to elicit a positive prediction error at premonitory-urge termination, so accounting for those positive prediction errors does not require postulating a change in values, V. The average-reward framework therefore obviates the need to assume that, in addition to having an inherently aversive character, $r(U) < 0$, premonitory urges also act as states with negative value, $V(U) < 0$. Even though the average-reward framework does not *require* differences in state values to explain positive prediction errors upon premonitory-urge termination, it certainly *allows* such differences to play a role.

Relation to neural substrates

Identifying the neural substrates of the aforementioned computational mechanisms amounts to identifying the neural substrates of the model variables: δ, $V(U)$, $r(U)$, and, to the extent that the average-reward account is correct, $\overline{r}$. We have already noted that the positive δs that are elicited by premonitory-urge termination likely are signaled by phasic dopamine. A region that represents $V(U)$, $r(U)$, and, indeed, the negative δs that occur at premonitory-urge onset or during the transition between premonitory-urge sub-states (Figure 3b) should be activated during premonitory urges. Among the regions associated with premonitory urges — as reviewed above, S1, S2, insula, and, to a lesser extent, CMA and SMA — the insula seems to stand out as a particularly plausible candidate to represent $V(U)$, $r(U)$, and the aforementioned negative δs. Indeed, the insula has been implicated both in premonitory urges and in the coding of aversive state values [$V(s) < 0$] [74,75], aversive prediction errors ($\delta < 0$) [69,75–77], and aversive outcomes, even when they are fully predicted [78–80], which suggests coding of primary aversive reinforcers ($r < 0$). The convergence of aversive values [$V(s) < 0$] and aversive prediction errors ($\delta < 0$) in the same region is, in fact, to be expected, given that the latter are necessary to update the former [$V_t(s_t) = V_{t-1}(s_t) + \alpha^- \delta_t$, where α^- is a learning rate]. As is thought to be the case in the ventral striatum [81], the prediction-error signals in the insula may, in fact, represent an incoming signal that is used to update locally represented state values.

If indeed the insula represents $V(U)$, $r(U)$, and negative δs (or, especially for the latter, receives that information in its inputs), and if phasic dopamine represents positive δs, the only other model variable remaining is $\overline{r}$ — assuming that the average-reward framework is correct. One theory, cast within that framework, suggests that tonic dopamine in the nucleus accumbens integrates phasic dopamine responses over time to represent $\overline{r}$ [82]. Some evidence supports such a role for dopamine in the shell: the shell receives projections from the ventral tegmental area (VTA) [83], so it receives information about prediction errors (δ), and appetitive and aversive stimuli induce phasic increases and decreases of dopamine in the shell, respectively [84,85]. To the extent that tonic dopamine in the shell reflects the accumulation of phasic responses over time — possibly due to the low density of dopamine transporters in the shell [83], which allows phasic responses to exert their influence well beyond release sites — these phasic responses may provide the necessary substrate for tonic dopamine to represent $\overline{r}$.

In addition to determining the regions that code for the variables in a model, a full specification of the neural implementation of a model also requires a mechanistic understanding of how those regions interact to perform the necessary computations — that is, to implement the model equations. Our prior computational work already explains in detail the computational and neuronal mechanisms through which the phasic firing of dopamine neurons (elicited by premonitory-urge termination) reinforces tics [13••]. The key in the present context, therefore, is how the regions that implement $V(U)$ and $r(U)$ (possibly the insula) and, in the case of the average-reward framework, $\overline{r}$ (possibly tonic dopamine in the shell), may interact with dopaminergic neurons so that the latter can signal those positive prediction errors. The details of those mechanisms are unknown, but the brain's neural architecture seems to provide the machinery necessary for these regions to interact to perform those computations. Indeed, the insula projects to the VTA both directly [50] and indirectly through multiple regions, such as the anterior cingulate cortex [86] and the amygdala [83,86], that have also been implicated in TS [14••,53]. The VTA therefore has access to the representations in the insula [putatively, $V(U)$ and $r(U)$] necessary to calculate prediction errors.

Intriguingly, and admittedly speculatively, tonic dopamine in the shell might ultimately inhibit the VTA, as required to implement the subtraction of $\overline{r}$ in the prediction-error equation in average-reward reinforcement learning. Tonic dopamine acts predominantly on D2 receptors because of their higher affinity [13••], thereby inhibiting D2 MSNs. These neurons in the shell generally disinhibit dopamine neurons in the VTA by inhibiting GABAergic neurons in the ventral pallidum [87,88], which in turn tonically inhibit dopamine neurons in the VTA [89]. Inhibiting D2 MSNs in the shell may therefore increase tonic inhibition of the VTA, consistent with the representation of a slowly varying signal such as $\overline{r}$ that is subtracted in the prediction-error equation.

Prediction errors signaled by the VTA may then be propagated all the way to the putamen via the ascending

spirals that connect dopaminergic neurons and the striatum [83]. In the putamen, phasic dopamine promotes tic learning by inducing LTP and LTD in the corticostriatal synapses onto the MSNs of the Go and NoGo motor pathways, respectively [13••] (Box 1).

Some of these assignments of computational variables and calculations to regions are admittedly speculative and may be subject to change. Nonetheless, these hypotheses should help focus attention on the identification of these mechanisms. Note also that we focused on basal-ganglia-mediated tic learning, but learning in corticocortical connections may also play an important role [5]. Such learning might depend on VTA signals to the cortex.

The developmental course of TS

A common assumption in the field is that premonitory urges start around 3 years later than tics (8–10 compared to 4–7 years of age, respectively) [9]. Studies using the Premonitory Urge Tic Scale (PUTS) [90], however, show no difference in mean scores between younger and older children: only a difference in consistency [90,91]. These findings suggest that young children may also have premonitory urges but have less ability to consistently notice and report them. Young children, in fact, may even have difficulty reporting that they have tics [92]. Such difficulties with retrospective verbal reports do not imply that premonitory urges are absent (even if they might conceivably be more fleeting) or that their termination is not rewarding. Furthermore, dopamine-mediated reinforcement learning is increased in TS not only in conscious [93] but also in subliminal [94] conditions. Negative reinforcement of tics due to termination of premonitory urges might therefore occur throughout the entire developmental course of TS.

Clinical implications

If premonitory-urge termination indeed is a key driver of tic learning, treatments that directly target premonitory urges might act upstream of tic learning and execution and therefore better prevent relapse; treating tics without treating premonitory urges, on the other hand, might lead to tic relearning. Some studies have used repetitive transcranial magnetic stimulation (rTMS) of the SMA in TS, with open-label studies showing promising results [95,96] that, however, were not fully borne out under double-blind conditions [95]. Targeting upstream regions involved in premonitory urges — notably, S1, S2, and insula — could conceivably be more efficacious. Encouragingly, rTMS of S2 successfully reduced chronic orofacial pain [97], and rTMS of the insula and contiguous dorsolateral prefrontal cortex (DLPFC) substantially facilitated smoking cessation [98]. The latter effect could have been due to the DLPFC stimulation, but, intriguingly, rTMS of DLPFC reduces both cigarette cravings and resting-state activity in the insula [99,100]. A clinical trial of rTMS of just the insula for the treatment of alcohol addiction is currently underway [101]. We suggest that at least preliminary, exploratory studies of rTMS of S1, S2, and insula for the treatment of TS are well warranted and indeed overdue.

Conclusions

We recently proposed a computational account of the roles of dopamine and the motor CBGTC loop in tic learning and execution [13••]. In the present article, we extended our previous account by considering the neural substrates of premonitory urges and their roles in tic execution and tic learning. Premonitory urges have been associated with S1, S2, and the insula, and, to a lesser extent, with the CMA and SMA. In tic execution, activation may conceivably flow throughout this ensemble of regions, from purer sensory areas (S1 and S2), representing the sensory character of the premonitory urge, to the insula, where such sensory information is integrated with emotional and visceral information, and then to cortical motor areas, where tics are executed. This flow of information, however, likely is modulated by the motor CBGTC loop, including by the levels of striatal dopamine therein. Tic learning may be driven primarily by the termination of premonitory urges, which elicits a positive prediction error, signaled by phasic dopamine. This positive prediction error reinforces the tic in the motor CBGTC loop [13••] (Box 1). The insula may play a central role in representing the aversiveness associated with premonitory urges, potentially representing their primary aversive character [$r(U) < 0$] and their learned negative value [$V(U) < 0$], with the latter updated by negative prediction errors ($\delta < 0$). These representations may be conveyed by the insula to dopamine neurons, via either direct or indirect projections, for use in the calculation of the positive prediction errors that occur upon premonitory-urge termination. The calculation of those positive prediction errors may also make use of an average-reward signal that, speculatively, may be represented by tonic dopamine in the shell. Overall, this account provides a comprehensive, integrated perspective of the two key aspects of TS — tics and the premonitory urges that precede them — that encompasses their computational mechanisms, neural substrates, and the roles and interactions of those neural substrates in the implementation of the relevant computations. This account has immediate clinical implications, in the form of suggested new targets for rTMS; as a comprehensive, integrated account of the pathophysiology of TS, we hope that it also helps to conceptualize, and ideally further energize, research in this disorder.

Conflict of interest statement

Nothing declared.

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