ORIGINAL ARTICLE

Reinforcement Learning and Gilles de la Tourette Syndrome

Dissociation of Clinical Phenotypes and Pharmacological Treatments

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Context: Gilles de la Tourette syndrome (GTS) is a hyperkinetic movement disorder with heterogeneous phenotypic expression ranging from simple motor and vocal tics to more complex tics associated with psychiatric comorbidities. The heterogeneity of clinical phenotypes may relate to the dysfunction of distinct frontal cortex–basal ganglia circuits.

Objectives: To assess the hypothesis that simple motor tics and comorbid obsessive-compulsive disorders are associated with dysfunction of motor and reward circuits, respectively, and to assess the effects of various antipsychotic medications because they are known to reduce motor tics and interact with dopamine-related reward processing.

Design: Sixty patients with GTS were divided into different subgroups depending on their clinical phenotypes and pharmacological treatments. The GTS patients and healthy control subjects underwent functional magnetic resonance imaging while they performed an instrumental learning task that involved adjusting choices between 2 responses (left- or right-hand movements) based on outcomes (reward or no reward).

Setting: Reference center for GTS, Centre de NeuroImagerie de recherche (CENIR) Paris, France.

Patients: Sixty GTS patients and 50 controls.

Results: Movement-related activation in motor circuits was diminished in GTS patients with simple tics only. Reward-related activation in limbic circuits was independently reduced by the following 2 factors: the presence of associated obsessive-compulsive symptoms (mostly compulsions) and the presence of medication with typical antipsychotics (dopamine receptor antagonists). Computational modeling with standard reinforcement learning algorithms indicated that, for both factors, the diminished reward-related activation could account for the impaired choice performance. Reinforcement learning was not affected by aripiprazole, a recent medication that acts as a partial dopamine agonist.

Conclusions: These results support the hypothesized correspondence between clinical phenotypes and frontal cortex–basal ganglia circuits. Antipsychotic treatment effects comply with formal conceptions that dopamine serves as a teaching signal for reinforcement learning. Furthermore, we suggest that, unlike typical antipsychotics, aripiprazole may preserve reward sensitivity and hence avoid blunting motivational drives.

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Gilles de la Tourette syndrome (GTS) is a childhood-onset hyperkinetic movement disorder characterized by the presence of multiple motor tics and at least 1 vocal tic.[1] The phenotypic expression of GTS ranges from simple tics to more complex associations of tics with psychiatric comorbidities, mostly attention-deficit/hyperactivity and obsessive-compulsive (OCD) disorders.[2-5] The heterogeneity of GTS clinical phenotypes may result from the disturbance of functionally distinct frontal cortex–basal ganglia (FC-BG) circuits.[6-8] Precisely, the dysfunction of sensorimotor circuits would lead to motor tics, whereas the dysfunction of limbic circuits would lead to the associated behavioral disorders.[9-11] This hypothesis is supported by findings in monkeys that perturbation of sensorimotor BG induces simple motor tics, whereas dysfunction of limbic BG can lead to more complex stereotypic behaviors.[12-14] A recent morphometric study also showed that cortical thinning was restricted to motor and premotor regions in patients with simple tics but extended to the prefrontal and parietal regions in patients with complex tics and to limbic regions in patients with associated OCD.[15] The first aim of the present study was to test the hypothetical relation-

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ship between clinical phenotypes and functional FC-BG circuits in GTS patients.

Other lines of evidence suggest that GTS is related to abnormal dopaminergic transmission. Notably, symptoms are markedly improved by typical antipsychotics (dopamine receptor antagonists), which remain the drugs of choice for the treatment of tics. A new generation of antipsychotics that have partial dopamine receptor agonist activity also seem to improve tics in GTS patients.[16] Moreover, abnormal ligand binding to dopamine receptors and transporters in the FC-BG circuits has been suggested by several positron emission tomography studies.[17-20] Postmortem studies have also found increased concentration of dopamine receptors and transporters in the FC and BG of GTS patients.[21,22] A possible mechanism relating dopaminergic activity to tic generation is reinforcement of BG circuits.[23,24] This mechanism normally occurs after unexpected reward receipt, which has been reported to elicit phasic dopamine release in monkeys and humans.[25-27] Phasic dopamine release is sufficient to condition behavior,[28] possibly via modulating the efficacy of corticostriatal synapses.[29-31] Thus, after unexpected rewards, phasic dopamine may reinforce the active BG circuits, and the same action would be facilitated in the future. Antipsychotic medications would interfere with this mechanism and hence reduce reinforcement learning abilities. A second aim of our study was to assess the impact of the different dopaminergic medications used in clinics on the activity of FC-BG circuits.

To address our 2 questions, we needed a functional neuroimaging paradigm that would (1) activate the motor and limbic FC-BG circuits with orthogonal contrasts and (2) implement dopamine-dependent reinforcement learning processes. We chose a probabilistic instrumental learning task that was used previously to investigate brain representations of action values.[32] Behavioral performance was well accounted for with a standard reinforcement learning model that updates action values in proportion to reward prediction errors (actual minus expected rewards). To test our first hypothesis, we recruited GTS patients with different clinical phenotypes, including simple tics, complex tics, and tics with associated OCD. Among psychiatric comorbidities, we focused on OCD because it is frequently associated with GTS[3-5] and because patients with OCD exhibit repetitive behaviors that have been linked to dysfunction of the limbic FC-BG circuits.[33-35] The group with complex tics was included as a control for the hypothesized motor dysfunction in the group with simple tics and the limbic dysfunction in the group with associated OCD.

To test our second hypothesis, we recruited patients who used no medications and patients using various medications. In a previous study, Palminteri et al[36] reported that dopamine receptor antagonists impaired instrumental learning in a small homogeneous group of GTS patients. Herein we intended to extend that result by testing a larger group, including various clinical phenotypes and both antagonists and partial agonists of dopamine receptors. We used functional magnetic resonance imaging to assess the integrity of motor and limbic FC-BG circuits in patients from the different GTS groups compared with control subjects.

METHODS

SUBJECTS

The study was approved by the Hôpital Pitié-Salpêtrière ethics committee. All patients and controls gave written informed consent before participation. Sixty adult GTS patients and 50 controls were enrolled in the study. There was no significant difference between patients and controls in age (mean [SEM] age, 30.1 [1.4] years for patients and 27.1 [1.3] years for controls [$P=.18$, 2-tailed t test]), sex (male to female ratio, 41:19 for patients and 27:23 for controls [$P=.08$, χ^2 test]), and educational level (mean [SEM], 2.3 [0.3] for patients and 3.2 [0.5] for controls [$P=.17$, 2-tailed t test]). (Level 2 corresponds to 14 years of study; level 3, to 16 years.) All these demographic variables were also matched between GTS subgroups (eTable 1 and eTable 2; available at http://www.archgenpsychiatry.com). We did not find any significant effect of these variables on our behavioral and neuroimaging measures in healthy controls. Moreover, we verified that our results were still significant when we regressed out the demographic variables.

The inclusion criteria for GTS patients were being older than 18 years and having a confirmed diagnosis of GTS. The exclusion criteria were the presence of any psychiatric disorder other than OCD established by the Mini International Neuropsychiatric Interview–French version,[37] including associated major depression, a history and a current diagnosis of psychosis, autistic spectrum disorders, substance abuse aside from tobacco smoking, the presence of other neurologic or movement disorders aside from tics, and a contraindication to magnetic resonance imaging. Inclusion criteria for controls were being older than 18 years and having no history of neurologic or psychiatric disorders. The exclusion criteria were the same as for patients with the addition of having a history of tics (childhood tics).

Patients were recruited from the reference center for GTS in Paris and were examined by at least 2 neurologists experienced in GTS (Y.W. and A.H.). Tic severity was assessed using the Yale Global Tic Severity Scale (YGTSS).[38] The presence and severity of associated OCD were evaluated during the psychiatric consultation using the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS).[39,40] Further clinical and demographic details are given in eTables 1 and 2.

To address our first question, all GTS patients were divided into 3 distinct clinical subgroups according to the symptoms they expressed: G1 for patients with simple motor and vocal tics (YGTSS complexity score of motor and vocal tics ≤ 2; 21 patients), G2 for patients with simple and complex motor and vocal tics (YGTSS complexity score of motor and vocal tics ≥ 3; 22 patients), and G3 for patients with associated OCD (who also had simple and/or complex motor and vocal tics; 17 patients). Simple tics included brief, recurrent, and nonrhythmic motor or vocal actions, such as eyes blinking or throat noises. Complex tics included more elaborated motor and vocal sequences, such as touching behavior, coprophenomena, echophenomena, and palilalia. Patients who had obsessive-compulsive symptoms that did not fulfill *DSM-IV-TR* criteria for OCD and had no history of OCD were included in the G1 (2 patients) or the G2 (3 patients) group.

To address our second question, GTS patients were divided into 5 groups according to their treatment: UM for those receiving no medication (n=28), AA for patients receiving dopamine antagonists only (haloperidol lactate, risperidone, or pimozide) (n=9), PA for patients receiving the dopamine partial agonist aripiprazole (n=10), AA+ for patients receiving a combination of dopamine antagonists and partial agonists (n=4), and other for patients receiving benzodiazepines and/or sero-

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tonin reuptake inhibitors (n=9). The last 2 groups were excluded from the analysis of treatment effects because medications were mixed. The composition of the different subgroups is summarized in eTable 3. Pharmacological therapy was stable in all patients receiving treatment for at least 2 months.

BEHAVIORAL DATA

Subjects performed a probabilistic instrumental learning task described previously[32] (**Figure 1** and eAppendix). Briefly, the task involved choosing between 2 cues that were associated with stationary reward probability (25% or 75%). The reward was a €0.50 coin; the alternative outcome was getting nothing. Subjects made their choice by pressing left or right response buttons with their left or right hand. There were 4 pairs of cues, randomly constituted and assigned to the 4 possible combinations of probabilities (25%/25%, 25%/75%, 75%/25%, and 75%/75%). Regarding payoff, learning mattered only for pairs with unequal probabilities (75%/25% and 25%/75%). Subjects were encouraged to accumulate as much money as possible and were informed that some cues would result in a win more often than others. They were given no explicit information regarding reward probabilities, which they had to learn through trial and error. They were told that part of their payoff would depend on the money actually won during the task; to avoid discrimination, all subjects received a fixed amount of €80 at the end of the experiment.

To generate learning curves, we averaged across subjects the proportion of correct responses (left response for the 75%/25% pair and right response in the 25%/75% pair). We checked that learning curves were not different between the 2 response sides ($P=.95$, 2-tailed paired t test). Raw learning curves were smoothed using a 5-trial moving window average. Starting response bias was removed by subtracting the performance observed in the first trial. Learning was assessed by comparing the average performance (percentage of correct responses) for all trials to a chance level (50% correct) using 1-sample 1-tailed t tests. Learning deficits were searched with comparison between patients and controls, using 2-sample 2-tailed t tests. For small groups in which the normality of data distribution could not be assumed, we verified the statistical significance using 1-sided Wilcoxon rank sum tests.

IMAGING DATA

Acquisition and preprocessing parameters were previously described[32] (see also the eAppendix). The echo planar images were analyzed in an event-related manner, using statistical parametric mapping software (SPM5; Wellcome Department of Imaging Neuroscience, London, England). All statistical parametric maps were generated with a single general linear model. Each trial was modeled as having 2 time points corresponding to cue and outcome display onsets. Trials were sorted into 4 types depending on the response given (right or left) and the outcome obtained (€0.50 or nothing) by the subject. Two regressors were built with stick functions for left and right response events (at the time of cue display). Two other regressors contained stick functions for reward and no reward events (at the time of outcome display). These 4 regressors of interest were convolved with a canonical hemodynamic response function. The general linear model also included the 6 realignment parameters to account for motion artifacts. To limit movement artifacts on the images, GTS patients were asked to suppress their tics.

Linear contrasts of regression coefficients (β coefficients) were computed at the subject level and then taken to a group-level random effect analysis (1-sample t test). Neural activity related to movement execution and reward receipt was identified by contrasting the 2 response sides and the 2 outcomes, respectively. All subjects were included in the group-level analysis that served to localize the regions of interest (ROIs). All activations reported in the text survived a threshold of $P<.05$ after familywise error correction for multiple comparisons across the entire brain and contained a minimum of 33 contiguous voxels.

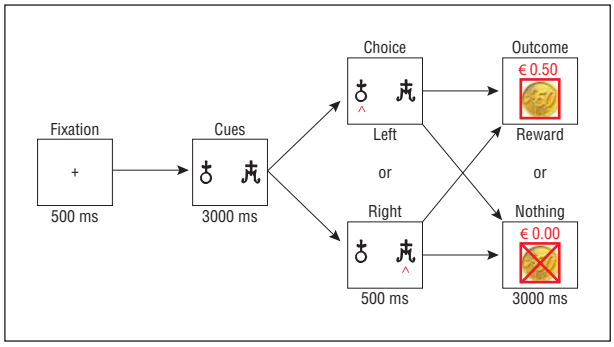

Figure 1. Successive screens of the behavioral task displayed during a trial. Subjects selected between left- and right-hand responses, corresponding to the 2 symbols displayed on screen, and subsequently observed the outcome of their choice (€0.50 reward or nothing).

We defined ROIs as 8-mm spheres centered on the maxima of activation found in the second-level analysis for the movement and reward contrasts. For movement-related activity, we analyzed 3 ROIs situated in the primary motor cortex, supplementary motor area, and cerebellum. For the reward-related activity, we analyzed 3 ROIs situated in the ventromedial prefrontal cortex (vmPFC), ventral striatum (VS), and posterior cingulate cortex (PCC). We extracted from each ROI the β coefficients obtained in each subject for the relevant contrasts. Bilateral activations were pooled into a same ROI. Differences between the GTS and control groups were assessed by comparing β coefficients with 2-sample 2-tailed t tests and confirmed with a 1-sided Wilcoxon rank sum test for small groups in which the distribution normality could not be assumed.

COMPUTATIONAL MODELING

To provide a statistical link between reward-related neural activity and instrumental learning performance, we also conducted a model-based analysis. We used a standard Q-learning algorithm that has been shown to give a good account of instrumental performance in humans.[41-43] For each pair of cues, the model estimates the expected values of the 2 options, Q_A and Q_B, on the basis of individual sequences of choices and outcomes. After every trial t, the value of the chosen option (eg, A) was updated according to the Rescorla and Wagner rule in which $Q_A(t+1)=Q_A(t)+[\alpha\times\delta(t)]$. In this equation, δt was the prediction error, calculated as $\delta(t)=R(t)-Q_A(t)$, with $R(t)$ being the outcome of choosing A at trial t. The learning rate, α, is a first free parameter that adjusts the amplitude of value changes from one trial to the next. Given the Q values, the associated probability of selecting each option was estimated by implementing the softmax rule, which is for choosing A, $P_A(t)=\exp[Q_A(t)/\beta]/\{\exp[Q_A(t)/\beta]+\exp[Q_B(t)/\beta]\}$. The temperature, β, is a second free parameter that adjusts the stochasticity of choices. Herein we considered R as another free parameter, adjusting the reinforcing effect of winning the coin.

Using this model, we ran 2 computational analyses. In the psychometric analysis, we fitted the individual learning curves by adjusting the free parameters so as to minimize the square distance between the actual curves and the curves generated with the model. From this we obtained a triplet of optimal parameters (learning

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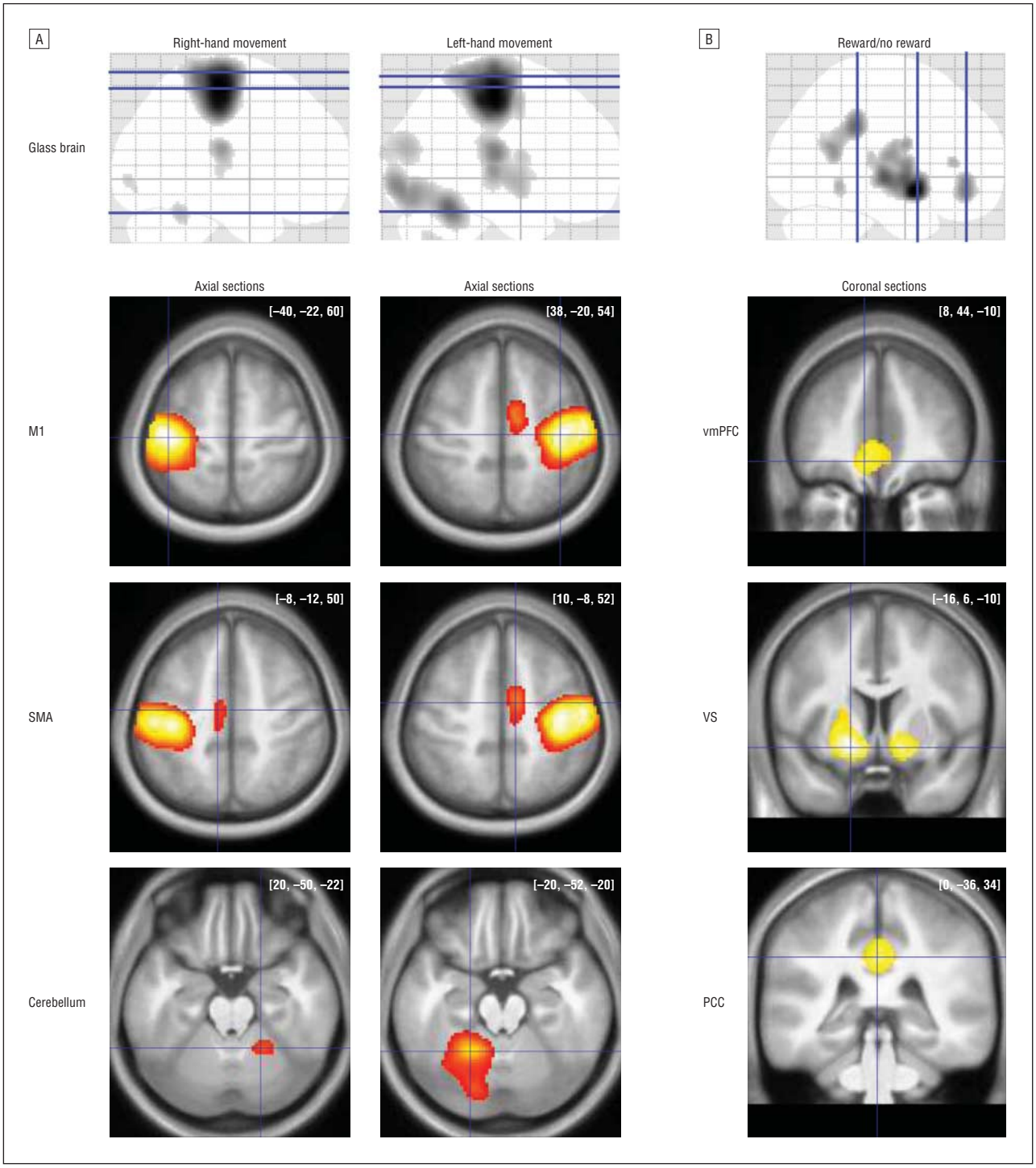

Figure 2. Whole-brain imaging results. A, Representation of hand movements at the time of cue onset. Axial sections (bottom) correspond to the blue lines on sagittal glass brains (top). B, Representation of reward receipt at the time of outcome onset. Coronal sections (bottom) correspond to the blue lines on sagittal glass brains (top). Areas colored in gray-to-black gradient on glass brains and in red-to-white gradient on sections demonstrated significant effects ($P<.05$, familywise error). The x, y, and z coordinates of maxima refer to the Montreal Neurological Institute. M1 indicates primary motor cortex; PCC, posterior cingulate cortex; SMA, supplementary motor area; vmPFC, ventromedial prefrontal cortex; and VS, ventral striatum.

rate, choice randomness, and reward magnitude) for each subject. In the neurometric analysis, reward magnitude was defined as the contrast extracted from imaging data (reward minus no reward at outcome onset). We then adjusted the learning rate and choice randomness to fit the individual learning curves, again using square distance minimization.

Only the cue pairs with unequal probabilities were taken into account, as for actual learning curves. For all cues, the Q values were initialized at €0.25, which corresponds to a 50% probability of winning €0.50. In the psychometric and neurometric fits, α and β were systematically explored in a range of 0:0.1:1, as previously reported.[32] The neurometric reward term was obtained for each subject by averaging the reward contrasts observed in all 3 reward-related ROIs (**Figure 2**). Occasional negative reward values were rounded up to 0, and these values were finally normalized for the mean to be €0.50 (the

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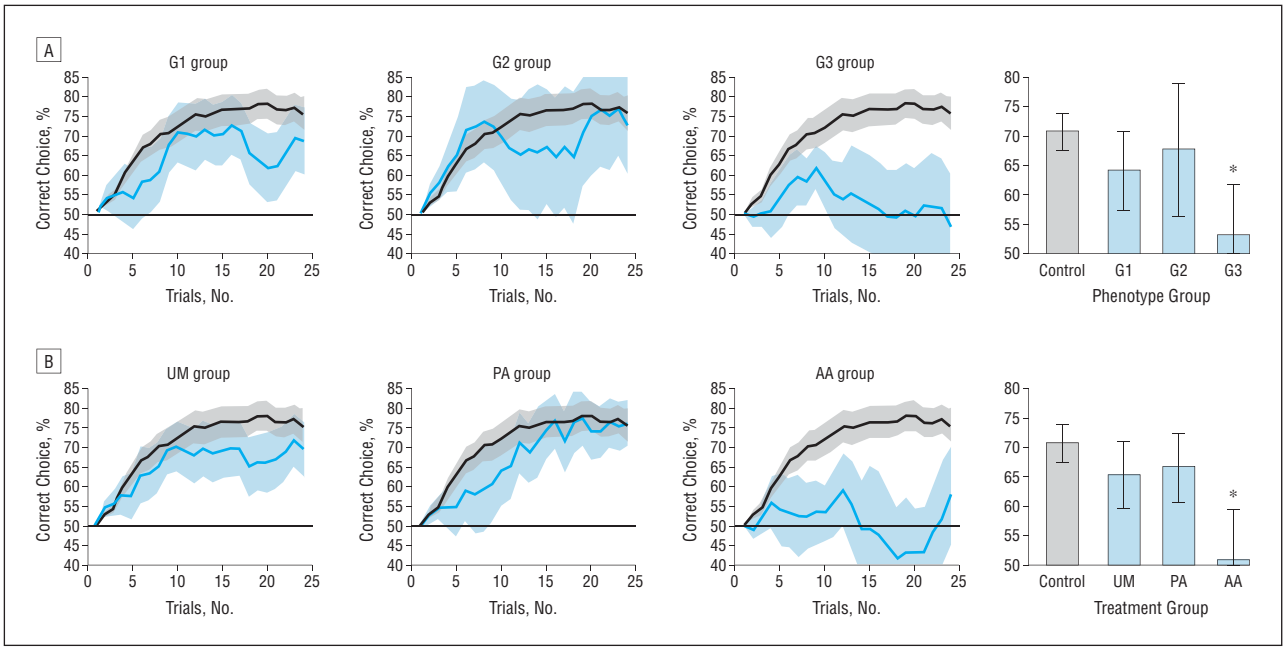

Figure 3. Behavioral results. Learning curves are shown for the different phenotype-based (A) and treatment-based (B) groups. Solid lines represent the mean performance and tinted areas represent the intersubject SEM. For comparison, each graph includes the performance of control subjects in gray. Bars on the right indicate the mean performance across all trials and error bars indicate the intersubject SEM. AA indicates patients receiving dopamine antagonists only; G1, patients with simple motor and vocal tics; G2, patients with simple and complex motor and vocal tics; G3, patients with associated obsessive-compulsive disorder; PA, patients receiving dopamine partial agonist aripiprazole; and UM, patients receiving no medication. *$P<.05$, 2-sample 2-tailed *t* test comparison with control subjects.

real reward at stake). The reward term of the psychometric analysis was systematically explored in a range of 0:0.1:1.4, corresponding to the minimum and maximum neurometric reward terms observed in the imaging data.

We used 2-sample 2-tailed *t* tests to compare the adjusted parameters between patients and controls and to assess whether the adjusted parameters would capture the observed learning deficits. We also used linear regression to test the correlation between the psychometric and neurometric reward magnitudes and to assess whether brain reward sensitivity could explain interindividual differences in learning abilities. Finally, we took the psychometric and neurometric reward magnitudes as proxies for behavioral and neural reward sensitivity. We then performed linear regressions to examine whether interindividual differences in reward sensitivity could be explained by clinical scores on the Y-BOCS and YGTSS. Unless otherwise indicated, data are expressed as mean (SEM).

RESULTS

BEHAVIORAL PERFORMANCE

As expected, control subjects efficiently learned to choose the most rewarding stimuli because their average percentage of correct responses was significantly above the chance level (70.5% [3.0%]; $t_{49}=6.536$ [$P<.001$]). In all GTS patients pooled together (eFigure 1A), we found a significant learning effect (57.5% [3.1%]; $t_{59}=2.363$ [$P=.01$]) that was blunted compared with healthy controls ($t_{108}=2.982$ [$P=.004$]). Among phenotype-based groups, we found a significant learning effect in the G1 (59.3% [5.3%]; $t_{20}=1.771$ [$P=.046$]) and G2 (60.0% [5.1%]; $t_{21}=1.960$ [$P=.03$]) groups but not in the G3 group (52.2% [6.6%]; $t_{16}=0.323$ [$P=.37$]), for whom performance was not different from chance level. The direct comparison between controls and patients in the G3 group also yielded significant results ($t_{65}=2.793$ [$P=.007$]). Among treatment-based groups, learning effects were significant in the UM group (61.7% [4.8%]; $t_{27}=2.426$ [$P=.01$]) and PA group (65.7% [5.2%]; $t_{9}=2.997$ [$P=.007$]) but not in the AA group (54.1% [7.7%]; $t_{8}=0.531$ [$P=.30$]). Performance was not different from random choices for patients in the AA group and was significantly deteriorated relative to controls ($t_{57}=2.042$ [$P=.046$]).

Because the G3 and AA groups shared some patients, there was a risk of confounding the 2 effects (association with OCD and medication with dopamine agonists). We therefore excluded patients receiving medication from phenotype-based groups and patients with OCD from treatment-based groups. The resulting composition of each group is shown in eTable 1. Among these deconfounded populations (**Figure 3**), we confirmed a selective learning deficit in the G3 group ($t_{56}=2.051$ [$P=.045$, *t* test]; rank sum=153 [$P=.03$, Wilcoxon test]) and AA group ($t_{54}=2.076$ [$P=.04$, *t* test]; rank sum=96 [$P=.02$, Wilcoxon test]). Because this classification allowed independent testing for the effects of comorbid OCD and dopamine antagonists, we kept it for the analysis of brain imaging data (**Figure 4**). The same analyses have also been conducted on the initial groups including all patients and reached the same conclusions (eTable 4).

BRAIN IMAGING

Before testing our hypotheses with the ROI analyses, we verified that direct comparisons between controls and patients did not yield any significant activation in other brain

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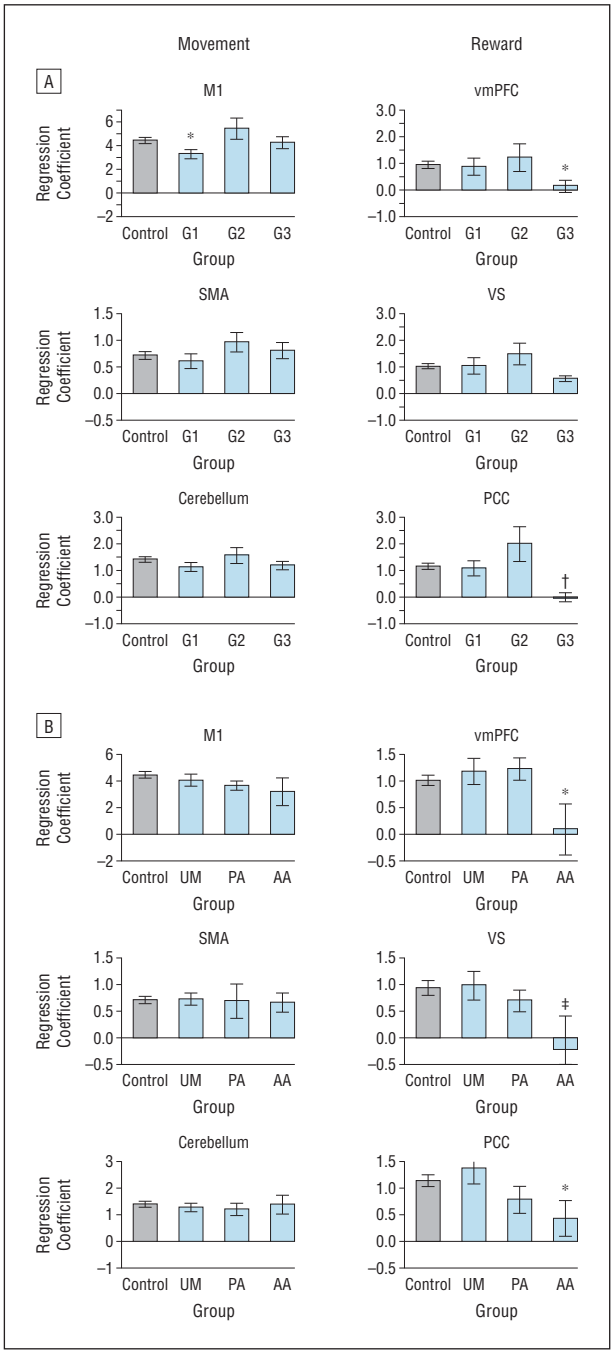

Figure 4. Regions of interest results. Bars represent the mean regression coefficients (β coefficients) for movement and reward representations for each phenotype-based (A) and treatment-based (B) group. Error bars represent intersubject SEM. Abbreviations are defined in the legends to Figures 2 and 3. *P* values were calculated as 2-sample 2-tailed *t* test compared with the control group. **P*<.05. †*P*<.001. ‡*P*<.01.

regions. We first identified movement-related areas by contrasting left and right responses at the time of cue onset with a group-level analysis including all subjects (n=110). For both response sides, we found large contralateral activations centered in the primary motor cortex, with extensions to the supplementary motor area and posterior insula, plus an ipsilateral activation in the cerebellum (Figure 2A). With left-hand movements, activations additionally extended to the contralateral putamen, thalamus, and occipital cortex. These activations were also present with right-hand movements at a lower statistical threshold (data not shown) but did not survive our highly conservative threshold ($P<.05$ after familywise error correction). We then identified reward-related areas by contrasting reward with no reward receipt at the time of outcome onset. We found significant bilateral activations (Figure 2B) in the vmPFC, VS, and PCC.

We first tested for deficits in GTS patients (pooling all subgroups) by comparing contrasts extracted from the main motor and limbic activation foci (eFigure 1B). The GTS patients exhibited significantly reduced activation in the vmPFC ($t_{108}=2.648$ [$P=.009$, *t* test]) and PCC ($t_{108}=2.681$ [$P=.008$, *t* test]) but not in the other regions of interest (all, $P>.1$). Because of the well-documented involvement of BG in GTS, we also analyzed data from the right putamen (eFigure 2), but the results are not discussed further because of the absence of a significant effect in this ROI for any subgroup of patients.

To examine which phenotypes and treatments were driving the reduced activations, the imaging contrasts were systematically compared between GTS subgroups and controls. Regarding movement processing in phenotype-based groups (Figure 4A, left), activation was significantly reduced only for the G1 group in the primary motor cortex ($t_{61}=2.146$ [$P=.04$, *t* test]). We found no treatment effect (**Figure 5**B, left) in any movement-related area (all, $P>.1$). Regarding reward processing in phenotype-based groups (Figure 4A, right), activation was significantly reduced for the G3 group in the vmPFC ($t_{56}=2.274$ [$P=.03$, *t* test]; rank sum=126 [$P=.007$, Wilcoxon test]) and PCC ($t_{56}=4.074$ [$P<.001$, *t* test]; rank sum=78 [$P<.001$, Wilcoxon test]). The same trend was found in the VS, bordering significance ($t_{56}=1.873$ [$P=.07$, *t* test]; rank sum=141 [$P=.02$, Wilcoxon test]). Among treatment-based groups (Figure 4B, right), reduced activation was observed only for AA group patients in the vmPFC ($t_{54}=-2.554$ [$P=.01$, *t* test]; rank sum=99 [$P=.02$, Wilcoxon test]), VS ($t_{54}=-2.807$ [$P=.007$, *t* test]; rank sum=101 [$P=.03$, Wilcoxon test]), and PCC ($t_{54}=-2.079$ [$P=.04$, *t* test]; rank sum=103 [$P=.04$, Wilcoxon test]).

Thus, comparison with controls suggested deficits in movement processing for G1 group patients and in reward processing for G3 and AA group patients. We confirmed these deficits by directly contrasting patient subgroups on *z*-scored β coefficients averaged over all movement- and reward-related areas. We first tested the interaction between clinical phenotype (G1 vs G3) and encoded dimension as movement (G1, –0.31 [0.16]; G3, 0.03 [0.21]) vs reward (G1, 0.07 [0.18]; G3, –0.59 [0.10]). The impact of clinical phenotype (G1 vs G3) was significantly different for movement- and reward-related activations ($t_{19}=2.789$ [$P=.01$, *t* test]; rank sum=52 [$P=.005$, Wilcoxon test]). The same comparison was significant if we kept all GTS patients (not just untreated patients) in the analysis ($t_{36}=2.247$ [$P=.03$, *t* test]). We then tested comparisons of reward-related activations between the AA and PA groups (AA, –0.47 [0.42]; PA, 0.32 [0.17]); the result bordered significance in small samples excluding G3 group patients ($t_{13}=-2.010$ [$P=.07$, *t* test]; rank sum=34 [$P=.06$, Wilcoxon test]) but reached signifi-

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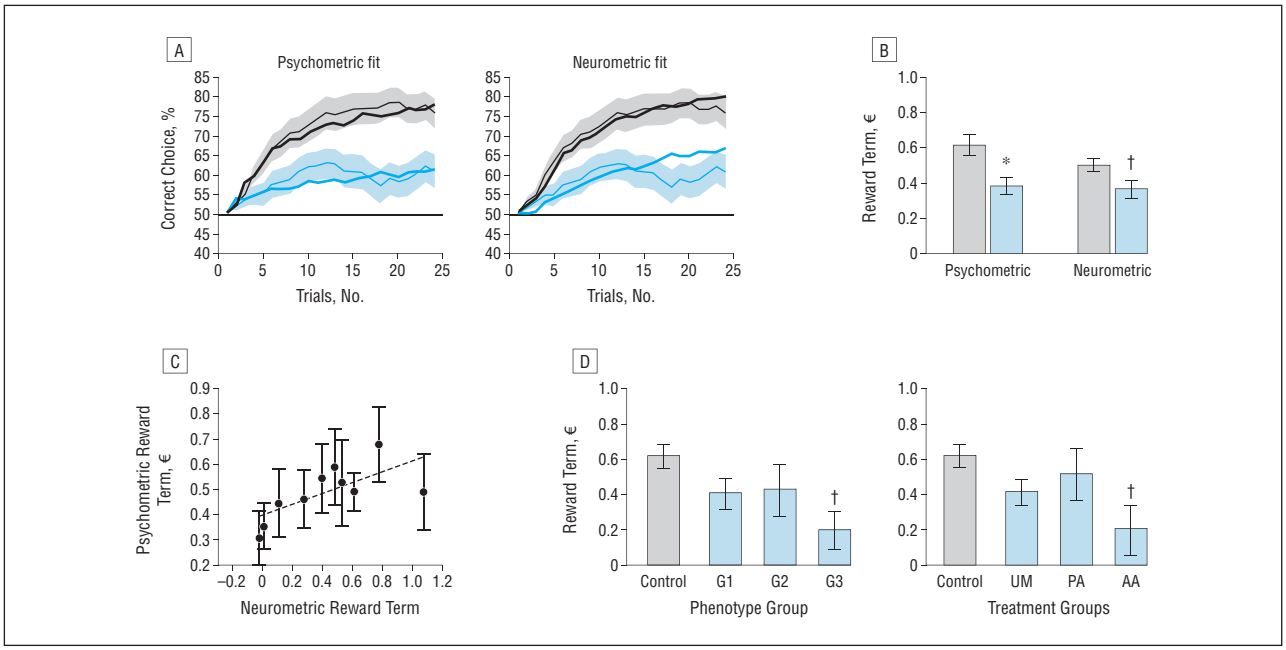

Figure 5. Computational modeling. A, Learning curves and model fit. Thin lines represent the mean performance, and tinted areas represent the intersubject SEM. Bold lines represent the performance estimated by the model. Control subjects are shown in gray and patients with Gilles de la Tourette syndrome (GTS) in blue. B, Mean reward magnitudes obtained with psychometric and neurometric fit. Error bars are intersubject SEM. Control subjects are shown in gray and patients with GTS in blue. C, Correlation between psychometric and neurometric reward magnitudes for all subjects. Each point represents a bin of 11 subjects. Error bars are intersubject SEM. D, Psychometric reward magnitude obtained in the different phenotype- and treatment-based groups. Abbreviations are defined in the legends to Figures 2 and 3. *P* values are calculated as 2-sample 2-tailed *t* test compared with the control group.*$P<.01$. †$P<.05$.

cance when including all GTS patients ($t_{17}=-2.494$ [$P=.02$, *t* test]; rank sum=64 [$P=.02$, Wilcoxon test]).

COMPUTATIONAL MODELING

Psychometric and neurometric analyses provided a similarly good fit of the data (Figure 5A). For both analyses, we systematically compared each free parameter between the GTS groups and controls. With the psychometric analysis, there was no significant difference in learning rate or choice temperature ($P>.10$ for both), but there was one in the reward term ($t_{108}=-2.917$ [$P=.004$]). The parameter that better captured the learning deficit observed in GTS patients was therefore the reward magnitude (Figure 5B). The neurometric analysis also pointed to the reduction in reward magnitude ($t_{108}=-2.175$ [$P=.03$]), without any significant difference in the learning rate or choice temperature ($P>.10$ for both). The correlation between the psychometric and neurometric reward terms (Figure 5C) was significant ($R^2=0.47$ [$P=.03$]). We last compared the reward magnitude obtained from psychometric fit between each GTS group and controls (Figure 5D). Significant reductions were found only for the G3 group ($t_{56}=-2.537$ [$P=.01$, *t* test]; rank sum=128 [$P=.01$, Wilcoxon test]) and AA group ($t_{54}=-2.176$ [$P=.03$, *t* test]; rank sum=97.5 [$P=.03$, Wilcoxon test]).

To examine interindividual differences in reward sensitivity, neurometric and psychometric reward magnitudes were regressed against clinical scores (eFigure 3). In GTS patients with positive Y-BOCS scores (n=22), we found that the compulsion scores were a better predictor of reward sensitivity (psychometric analysis, $R^2=0.19$ [$P<.05$]; neurometric analysis, $R^2=0.13$ [$P<.1$]) compared with the obsession scores (psychometric analysis, $R^2=0.12$ [$P>.1$]; neurometric analysis, $R^2=0.001$ [$P>.9$]). We did not find any significant correlation between Y GTSS scores and neurometric ($R^2=0.006$ [$P>.5$]) or psychometric ($R^2=0.002$ [$P>.5$]) reward parameters, suggesting that GTS per se does not affect reward sensitivity.

COMMENT

We found that differences between GTS patients and healthy controls in brain reward sensitivity were driven by the following 2 factors: association with OCD (G3 group) and medication therapy consisting of typical antipsychotics (AA group). Behavioral deficits were also observed specifically in the G3 and AA groups, who were unable to learn and choose the most rewarded actions. In both cases, the link between the diminished brain responses to rewards and diminished learning abilities was established using computation modeling.

We replicate herein the basic results of a previous study in healthy controls.[32] The neuroimaging paradigm was successful in activating movement- and reward-related regions, and the computational model provided a good fit of learning curves. Executing simple movements commonly activates the contralateral primary motor cortex, supplementary motor area, posterior putamen, and ipsilateral cerebellum.[44,45] Receiving a reward commonly implicates the vmPFC, PCC, and VS.[46-48] Thus, the isolation of movement- and reward-related circuits matched the distinction between the FC-BG motor and limbic circuits established with axon tracing in monkeys[49,50] and reproduced with fiber tracking in humans.[51,52]

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Computational modeling suggested that the reduced sensitivity of reward-related regions observed in the G3 and AA groups can account for their deficit in reinforcement learning. Indeed, the psychometric fit pointed toward the reward magnitude (not the learning rate or choice temperature) as being the key free parameter that captured the learning deficit. Thus, G3 and AA group patients were not impaired in learning or decision making per se but rather in their sensitivity to reinforcements. Moreover, the reward magnitude estimated from learning curves (psychometric fit) could be replaced by the reward magnitude observed in brain imaging contrasts (neurometric fit). This suggests a direct link between the reward magnitude incorporated in the model and the reward magnitude encoded in limbic circuits. It accords well with previous studies that have also demonstrated a link between reinforcement variables and VS activity across various clinical and pharmacological conditions.[42,53,54]

Our first hypothesis was confirmed. When comparing phenotype-based groups, we found dissociation between GTS patients with simple motor and vocal tics only (G1 group), who exhibited reduced movement-related activations, and patients with tics plus OCD (G3 group), who exhibited reduced reward-related activations. Our results concerning movement-related activations corroborate previous studies describing structural and functional abnormalities of sensorimotor pathways in GTS patients that were linked to tic generation.[15,55-58] Electrophysiological studies in GTS patients also highlighted diminished motor cortex activation during voluntary movement preparation and execution.[59,60] Regarding reward-related activations, our results accord well with previous studies reporting structural abnormalities[61,62] and dysfunction of the vmPFC during cognitive flexibility and reversal learning tasks[63,64] in patients with OCD who do not have tics. Our results suggest that dysfunction of reward processing in GTS patients is linked to the presence of OCD. Moreover, the reduction of reward sensitivity was correlated with the severity of compulsions in our patients. One can speculate that a deficit in reinforcement learning leads to the maintenance of the maladaptive behaviors, such as compulsions in patients with OCD with and without tics.

Regarding our second hypothesis, comparison between treatment-based groups showed that reward processing was abolished by antagonists (AA group) but preserved by partial agonists (PA group) of dopamine receptors. The AA effects are in line with previous studies reporting impaired instrumental learning and reduced reward sensitivity in limbic brain regions during antipsychotic therapy.[42,65] This accords well with the widely assumed role of dopamine in reinforcement learning.[43,66] To our knowledge, this is the first study investigating the effects of aripiprazole in reward processing. Aripiprazole is a recently introduced medication used in schizophrenia as well as GTS.[16,67,68] Aripiprazole has a unique pharmacological profile characterized as partial D_2 receptor agonism.[69-72] Some clinical advantages for aripiprazole over typical antipsychotics have already been reported, such as improvement of working memory in schizophrenic patients.[73] Our data suggest that aripiprazole preserved reward sensitivity and may avoid certain adverse effects of typical antipsychotics, such as loss of motivational drives, which is a main factor for nonadherence to drug therapy.[74] However, the clinical benefit of changing typical antipsychotics for aripiprazole would need further investigation.

Although our study clearly outlines the necessity of carefully distinguishing between phenotypes and medications when assessing GTS patients, it has a number of limitations. A first potential confound is the higher male to female proportion in controls compared with patients. However, controls did not show any significant sex difference in reward sensitivity. Moreover, analysis of variance results with group and sex as between-subject factors replicated all the significant group effects without showing any significant sex effect. Another potential bias may be the presence of tic-induced artifacts in the imaging data. Although we asked patients to suppress their tics and subsequently checked for the presence of artifacts, we cannot exclude that some occasional movements might have affected the results. In an effort to regress out movement-induced variance, we included realignment parameters in the general linear model. We also verified that the variance of the realignment parameters was not significantly different among GTS subgroups. A final limitation is the small number of patients in each subgroup, particularly after excluding patients who would have confounded phenotype- and treatment-based categories. Although their significance could be shown using nonparametric statistical tests, our results need to be confirmed in larger samples.

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