Dopaminergic Disturbances in Tourette Syndrome: An Integrative Account

Supplemental Information

Table S1. Positron emission tomography (PET), single-photon emission computerized tomography (SPECT), and postmortem studies of the dopamine D_2 receptor in unmedicated patients with Tourette syndrome (TS) compared with healthy controls (HCs). ACC: anterior cingulate cortex; BA: Brodmann area; BP: binding potential; DA: dopamine; M1: primary motor cortex; MD: mediodorsal; mo: month; mos: months; MTG: middle temporal gyrus; OFC: orbitofrontal cortex; PCC: posterior cingulate cortex; STG: superior temporal gyrus; wks: weeks; yr: year; yrs: years; ↓: decreased in patients relative to controls; $\downarrow_{n.s.}$: scatterplots suggest a decrease in patients relative to controls, but such decrease was not significant (n.s.), possibly due to low power; =: patients and controls had largely overlapping values (and there were no significant differences between them); ↑: increased in patients relative to controls. The color-coding mimics the one used in Fig. 1 in the article. Specifically, studies are color-coded in dark green, yellow, or red depending on whether they reported increases, no significant differences, or decreases in patients relative to controls, respectively. Studies are color-coded in lime (light green) or orange if their findings are less clear (e.g., if the main analyses yielded no significant differences) but they still provide some evidence for increases or decreases in patients, respectively.

EFFECT	ARTICLE[a]	BRAIN REGION	NOTES	SAMPLE SIZE	PATIENT MEDICATION HISTORY[b]	AGE CONFOUND[c]	TECHNIQUE
PET AND SPECT STUDIES							
Basal Ganglia							
↑ binding in more severely affected twins	Wolf 1996 (1) [64]	Caudate	This study compared D_2 binding in the caudate and putamen between the more and less severely affected twins in 5 monozygotic twin pairs concordant for TS diagnosis but discordant for severity. The study did not report which patients had a history of neuroleptic use; it seems plausible that severity might have been confounded, at least in part, with neuroleptic exposure.	5 twin pairs	5 naïve; 3 neuroleptic-free > 3 yrs; 2 stopped neuroleptics 6 wks before		IBZM SPECT

EFFECT	ARTICLE[a]	BRAIN REGION	NOTES	SAMPLE SIZE	PATIENT MEDICATION HISTORY[b]	AGE CONFOUND[c]	TECHNIQUE
↑ density (B_{max}) in a subgroup of patients	Wong 1997 (2) [62]	Caudate	There were no overall differences in binding or B_{max} between patients and controls, but 4 patients had B_{max} values above the 95% prediction interval obtained using a regression of B_{max} on age in controls only. The study had two samples (which we refer to as Samples 1 and 2). Binding was analyzed in the two samples; density was analyzed only in Sample 2.	Sample 1: TS: 9; HC: 44 Sample 2: TS: 20; HC: 24	Sample 1: 4 neuroleptic-naïve; 5 neuroleptic-free > 6 mos Sample 2, subgroup of 4 patients with B_{max} values above the prediction interval: 2 medication-naïve; 1 neuroleptic-naïve; 1 neuroleptic-free > 6 mos Sample 2, remaining 16 patients: 13 neuroleptic-naïve; 3 neuroleptic-free > 6 mos		N-methyl-spiperone PET
= binding	Hwang 2008 (3) [44]	Striatum	The plots showed substantial overlap between patients and controls.	TS: 10; HC: 15	5 naïve; 5 on haloperidol > 3 mos before		IBZM SPECT
	Abi-Jaoude 2015 (4) [55]	Ventral, associative, and motor striatum	The plots showed substantial overlap between patients and controls.	TS: 11; HC: 11	4 medication-naïve; 2 DA-medication-naïve; 2 neuroleptic-naïve; 3 neuroleptic-free > 4 mos		Raclopride PET and PHNO PET
	Singer 2002 (5) [19]	Caudate and putamen	The mean difference between patients and controls was less than 1 SD.	TS: 7; HC: 5	2 medication-naïve; 2 neuroleptic-naïve; 3 unmedicated > 6 mos		Raclopride PET
	Turjanski 1994 (6) [54]	Caudate and putamen	The plots showed substantial overlap between patients and controls.	TS: 5; HC: 9; Age-matched HC: 5	3 naïve; 1 neuroleptic-free > 3 yrs; 1 neuroleptic-free > 3 mos		Raclopride PET

EFFECT	ARTICLE[a]	BRAIN REGION	NOTES	SAMPLE SIZE	PATIENT MEDICATION HISTORY[b]	AGE CONFOUND[c]	TECHNIQUE
↓ density (B_{max}) but ↑ affinity ($1/K_D$)	Wong 2008 (7) [40]	Anterior putamen	Binding potential did not differ between patients and controls.	TS: 13; HC: 3	In the overall TS sample (N_{TS}=14): 7 naïve; 4 unmedicated > 6 mos; 3 unmedicated. Medication not reported for the N_{TS}=13 subsample used in these analyses.	Older patients (TS: 31 ± 8.9; HC: 24 ± 2.5), but analyses used age as a covariate	Raclopride PET
$\downarrow_{n.s.}$ binding	Müller-Vahl 2000 (8) [56]	Striatum	Given that D_2 binding decreases throughout the life span (2, 9), the fact that controls were much older may have prevented the difference between groups from being significant.	TS: 10; HC: 7	6 naïve; 4 neuroleptic-free > 1yr	Younger patients (TS: 22 ± 8; HC: 40 ± 16)	IBZM SPECT
↓ binding in sub-analysis and $\downarrow_{n.s.}$ binding	George 1994 (10) [57]	Basal ganglia	Binding was significantly reduced in a sub-analysis with 3 patients but not in a different analysis with all patients. The plots with all patients, however, also suggest reduced binding in patients.	TS: 8; HC: 6	4 naïve; 4 unmedicated > 3 mos	Younger patients (TS: 23 ± 12.1; HC: 30, SD not reported)	IBZM SPECT
↓ binding	Denys 2013 (11) [51]	Putamen		TS: 12; HC: 12	9 naïve; 1 neuroleptic-free > 1 yr; 2 on α_{2A} agonists yrs before		Raclopride PET
Outside the Basal Ganglia							
↓ binding	Steeves 2010 (12) [52]	ACC, PCC, MTG, STG, cuneus, claustrum, insula, thalamus		TS: 8; HC: 8	All naïve		FLB457 PET
	Gilbert 2006 (13) [58]	ACC, OFC, MD thalamus, M1, hippocampus		TS: 6; HC: 6	All neuroleptic-free > 2 yrs, with maximum neuroleptic exposure < 1 mo; 1 on clonidine at the time of study		Fallypride PET

EFFECT	ARTICLE[a]	BRAIN REGION	NOTES	SAMPLE SIZE	PATIENT MEDICATION HISTORY[b]	AGE CONFOUND[c]	TECHNIQUE
POSTMORTEM STUDIES							
↑ density	Yoon 2007 (14) [16]	Several frontal cortex regions (BA 4, 6, 9, 10, 11)		TS: 3; HC: 3	2 long-term neuroleptics and other medications; 1 long-term neuroleptics and died of cocaine overdose		Semi-quantitative immuno-blotting
	Minzer 2004 (15) [17]	Prefrontal cortex (BA9)	One of the patients (a female) had adult-onset tic disorder not otherwise specified rather than TS. All patients had possible substance abuse and/or alcohol dependence.	TS: 3; HC: 3	1 haloperidol > 15 yrs prior to death; 1 long-term neuroleptics but neuroleptic-free > 2mos, and died of drug overdose; 1 long-term neuroleptics		Semi-quantitative immuno-blotting
↑ binding	Singer 1991 (16) [15]	Caudate and putamen	The increases were quite small.	TS: 3; HC: 7 for caudate, 13 for putamen	2 long-term haloperidol; 1 no information	Probably younger patients (TS: 51 ± 11; HC: 64, SD not reported). But HC ages for subsamples used in these analyses were not reported.	Spiperone binding

[a] Reference numbers in parentheses refer to the supplemental bibliography at the end of this document, per journal style. To facilitate comparison with Fig. 1 in the article and cross-referencing with the article's text, the corresponding reference numbers in the article's bibliography are shown in square brackets.

[b] Information about the medication history is provided in such a way that each patient is categorized according to the more specific information available for that patient. For example, in the entry for the study by Abi-Jaoude et al. (2015), the information "4 medication-naïve; 2 DA-medication-naïve; 2 neuroleptic-naïve; 3 neuroleptic-free > 4 mos" implies that there were a total of 8 neuroleptic-naïve patients: 4 who were entirely medication-naïve, plus 2 who were naïve to any DA medication, plus 2 who were neuroleptic-naïve but had been exposed to other DA medications. Presenting information in this way ensures that the sum of the numbers of patients in each cell is equal to the number of patients in the corresponding study (e.g., in the entry for the study by Abi-Jaoude et al., there were a total of 4 + 2 + 2 + 3 = 11 patients).

[c] D_2 binding and density decrease throughout the life span (2, 9), so age differences may confound study results. Empty cells in this column mean that the patient and control groups were well matched for age. In non-empty cells, values in parentheses represent mean ± standard deviation (SD) of ages in years.

Table S2. Efficacies (E_{max}), potencies (EC_{50}), and (inverse) affinities (K_i) for the dopamine (DA) D_2 short (D_{2S}), D_2 long (D_{2L}), and D_3 receptors, as well as comparison of those efficacies, potencies, and affinities for the D_3 vs. D_{2S} receptors and for the D_{2L} vs. D_{2S} receptors, for various DA agonists. The DA agonists shown are those that are approved for use in humans from amongst those whose E_{max} and EC_{50} values were reported in Ref. (17) and whose K_i values were reported in Ref. (18). The color-coding mimics the one used in Fig. 4 in the article: DA agonists that have been tested with success in clinical trials for Tourette syndrome (TS) are represented in green; DA agonists that have failed clinical trials for TS are represented in red; DA agonists that have not yet been tested in clinical trials in TS are represented in yellow.

Dopamine Agonist	D_{2S}			D_{2L}			D_3			D_3 vs. D_{2S}[a]			D_{2L} vs. D_{2S}[b]		
	E_{max}[c]	EC_{50}[d]	K_i[e]	E_{max}	EC_{50}	K_i	E_{max}	EC_{50}	K_i	$\frac{E_{max}\ D_3}{E_{max}\ D_{2S}}$	$\frac{EC_{50}\ D_{2S}}{EC_{50} D_3}$	$\frac{K_i\ D_{2S}}{K_i D_3}$	$\frac{E_{max}\ D_{2L}}{E_{max}\ D_{2S}}$	$\frac{EC_{50}\ D_{2S}}{EC_{50} D_{2L}}$	$\frac{K_i\ D_{2S}}{K_i D_{2L}}$
Pergolide	112	8.71	31.62	52	8.51	25.70	71	0.51	5.50	0.63	16.98	5.75	0.46	1.02	1.23
Ropinirole	108	660.69	676.08	52	416.87	933.25	59	27.54	37.15	0.55	23.99	18.20	0.48	1.58	0.72
Pramipexole	130	426.58	954.99	70	338.84	1698.24	70	2.24	10.47	0.54	190.55	91.20	0.54	1.26	0.56
Talipexole	89	371.54	616.60	71	331.13	977.24	88	20.42	67.61	0.99	18.20	9.12	0.80	1.12	0.63
Apomorphine	79	19.50	34.67	53	21.88	83.18	82	11.75	25.70	1.04	1.66	1.35	0.67	0.89	0.42
Bromocriptine	41	4.47	5.01	28	3.89	14.79	68	4.17	6.76	1.66	1.07	0.74	0.68	1.15	0.34
Cabergoline	102	0.54	0.62	75	0.41	0.95	86	0.78	0.79	0.84	0.69	0.78	0.74	1.32	0.65
Lisuride	55	0.29	0.34	21	0.72	0.66	49	0.58	0.28	0.89	0.50	1.20	0.38	0.40	0.51
Piribedil	42	194.98	131.83	21	275.42	173.78	34	123.03	234.42	0.81	1.58	0.56	0.50	0.71	0.76
Roxindole[f]	11	0.89	2.82	0	0.29	2.34	30	0.59	1.17	2.73	1.51	2.40	0.00	3.09	1.20
Terguride	39	0.46	0.81	0	0.24	1.15	36	0.66	1.00	0.92	0.69	0.81	0.00	1.91	0.71

[a] For ease of interpretation, the ratios comparing D_3 and D_{2S} receptors are calculated in such a way that greater values indicate greater efficacy, potency, and affinity for D_3 as compared to D_{2S} receptors. Given that greater efficacy is indicated by larger values of E_{max}, but greater potency and affinity are indicated by smaller values of EC_{50} and K_i, respectively, the efficacy ratios have the values of E_{max} for D_3 and D_{2S} in the numerator and denominator, respectively, but the

potency and affinity ratios have the values of EC_{50} and K_i for D_{2S} and D_3 in the numerator and denominator, respectively. As discussed in the article, the most promising DA agonists for the treatment of TS might be those with less action at D_3 relative to D_{2S} receptors. If that idea is correct, then smaller values of the ratios comparing D_3 and D_{2S} receptors should in principle be better.

[b] For ease of interpretation, the ratios comparing D_{2L} and D_{2S} receptors are also calculated in such a way that greater values indicate greater efficacy, potency, and affinity for D_{2L} as compared to D_{2S} receptors. As discussed in the article, low doses of DA agonists for the treatment of TS should act mostly on presynaptic (D_{2S}) rather than postsynaptic (D_{2L}) D_2 receptors. Thus, all else being equal, smaller values of the ratios comparing D_{2L} and D_{2S} receptors should in principle be better.

[c] E_{max} values were obtained from Ref. (17) and are expressed as a percentage relative to the stimulation obtained with a maximally efficacious DA concentration.

[d] EC_{50} values are expressed in nmol and were calculated from the pEC_{50} values in Ref. (17) using the following formula: $\mathrm{EC}_{50} = 10^{-\mathrm{pEC}_{50}} \times 10^9$ (where the multiplication by 10^9 converts the values from mol to nmol).

[e] K_i values are expressed in nmol and were calculated from the pK_i values reported in Ref. (18) using the following formula: $K_\mathrm{i} = 10^{-\mathrm{p}K_\mathrm{i}} \times 10^9$ (where the multiplication by 10^9 converts the values from mol to nmol).

[f] Roxindole is not included in Fig. 4 in the article because its E_{max} ratio for the D_3 vs. D_{2S} receptors is substantially larger than that for all of the other medications, so, if the idea that the most promising medications are those with less action on the D_3 relative to the D_{2S} is correct, it may be less likely to be helpful in TS. Excluding roxindole from Fig. 4 allowed the axis representing the E_{max} ratio for the D_3 vs. D_{2S} receptors to be adjusted in a way that improved visualization of the remaining, potentially more promising, medications. Roxindole does, however, have one factor potentially in its favor as a candidate treatment of TS: its E_{max} for the D_{2L} is 0, so it may have little or no postsynaptic effect.

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