Supporting Information

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SI Materials and Methods

Subjects. A total of 85 subjects participated. All were native English speakers from South London and gave written informed consent in accordance with protocols approved by the Local Research Ethics Committee. Patients with schizophrenia ($n = 41$) were recruited from the South London and Maudsley National Health Service Trust and met DSM-IV criteria for the disorder. The diagnosis was made by an experienced psychiatrist using a structured diagnostic interview (SCAN, Schedules for Clinical Assessment in Neuropsychiatry; see ref. 1). When data from the SCAN was missing or incomplete, the diagnosis was determined by using OPCRIT (Operational Criteria Checklist; see ref. 2). The schedules for the assessment of positive (SAPS) and negative symptoms (SANS) were used to measure symptom severity at the time of scanning. All of the patients were in a stable clinical state and had previously been treated with antipsychotic medication. However, 5 of the patients were not taking antipsychotic medication at the time of scanning. The mean duration of antipsychotic treatment was 12 years. Healthy volunteers ($n = 44$) had no history of mental illness and no first-degree relatives with a psychotic disorder, as assessed using the Family Interview for Genetic Studies. Patients or volunteers who met DSM-IV criteria for a substance misuse disorder were excluded.

The 85 participants comprised the following groups: within controls, there were 18 9-repeat carriers (of which 5 were Met-158/Met-158, 8 Met-158-Val-158, and 6 Val-158/Val-158), and 26 10-repeat homozygotes (9 Met-158/Met-158, 11 Met-158-Val-158, and 6 Val-158/Val-158). Among the patient sample, there were 18 9-repeat carriers (6 Met-158/Met-158, 7 Met-158-Val-158, and 5 Val-158/Val-158) and 23 10-repeat homozygotes (6 Met-158/Met-158, 10 Met-158-Val-158, and 7 Val-158/Val-158).

There were no significant differences between the patient and control groups in age, ethnicity, or handedness, but patients had a lower mean IQ ($F = 41.02$; $P < 0.00001$), slightly fewer years of education ($F = 5.06$; $P = 0.03$), and a higher proportion of males ($\chi^2 = 12.24$; $P = 0.001$). Within each diagnostic group and within the total sample, there were no significant differences between the COMT genotype groups, nor between the DAT genotype groups, on any of the demographic variables, either within diagnostic categories or across the whole sample. Within the patient group, the genotype subgroups did not differ significantly in positive (total SAPS mean = 6.6; SD = 6.6) or negative (total SANS mean = 7.8; SD = 5.1) symptom scores, nor in the duration of illness (mean = 12.2 years; SD = 9.5), or the dose (chlorpromazine-equivalents = 598.8; SD = 452.3) or type (first or second generation) of antipsychotic medication.

IQ was assessed by using the Wechsler Adult Intelligence Scale-III (WAIS-III) (3), Wechsler Adult Intelligence Scale-Revised (WAIS-R) (4), the Wechsler Abbreviated Scale of Intelligence–Full Scale IQ (WASI-FSIQ-4) (5), or the Quick Test (6). The WAIS-III correlates highly both with WAIS-R (93.9%) (4) and with WASI-FSIQ (492%) (5). The Quick test has also been shown to yield comparable results to WAIS Quick Test, 78 ± 7 and WAIS, 83 ± 6 in schizophrenia) (7). The proportion of subjects assessed with each method was matched between genotype subgroups in patients and controls.

Genotyping. DNA was extracted from blood or cheek swabs by using standard methods. Ninety subjects, 90% of which Caucasian, were genotyped for the rs4680 SNP, which encodes the Val158Met polymorphism of COMT and for the variable number of tandem repeats (VNTR) in the 3′ UTR of the DAT gene as described (8). Three subjects carrying genotypes with alleles other than the 9-repeat and the 10-repeat allele (and 2 subjects for which genotype calling was unreliable) for the DAT 3′ UTR VNTR were not included in the 85-subject sample that was further analyzed, to reduce allelic heterogeneity.

Verbal Fluency Task. During a generation condition, subjects were visually presented with a series of letters and were required to overtly articulate a word beginning with each letter. This condition was contrasted with a repetition condition, in which subjects were presented with the word "rest" and were required to say rest out loud. A blocked design was used, with letter and rest cues presented in blocks of 7 events. The demands of the task were manipulated by presenting 2 different sets of letter cues, easy and hard (9). These sets of letter cues had previously been shown to be associated with a significant difference in behavioral performance in healthy volunteers (9). The easy condition involved the presentation of letters that are normally associated with relatively large numbers of correct responses and relatively few errors (e.g., T, B, and S), whereas the hard condition involved letters associated with the generation of fewer correct words and relatively more errors (e.g., N, E, and G). Five blocks of rest trials alternated with 5 blocks of easy letters or hard letters, resulting in a total of 70 generation and 70 repetition trials. The order of the easy and hard runs was counterbalanced across subjects. Verbal responses were recorded permitting the identification of incorrect trials, in which the subject did not generate any response, or generated repetitions, derivatives, or grammatical variations of a previous word.

Image Acquisition. T_2*-weighted gradient-echo single-shot echo-planar images were acquired on a 1.5-T, neuro-optimized IGE LX System (General Electric) at the Maudsley Hospital, London. Twelve noncontiguous axial planes (7-mm thickness, 1-mm slice skip, 3.75 × 3.75 mm voxel size in plane, and 64 × 64 mm matrix size in plane) parallel to the anterior commissure-posterior commissure line were collected over 1,100 ms in a "clustered" acquisition (TE = 40 ms, flip angle = 70°), which permitted articulatory responses to be made when images were not being acquired, minimizing the effects of head movement on the blood-oxygen-level-dependent signal (9). Immediately after each acquisition, a letter was presented (remaining visible for 750 ms, height: 7 cm, subtending a 0.4° field of view), and a single overt verbal response was made during the silent portion (duration = 2,900 ms) of each repetition (TR = 4,000 ms), with an image acquired over 1,100 ms. Head movement was minimized by a forehead strap. To ensure that subjects heard their responses clearly, their speech was amplified by a computer sound card and then relayed to the subject through an acoustic MRI sound system and noise-insulated stereo headphones.

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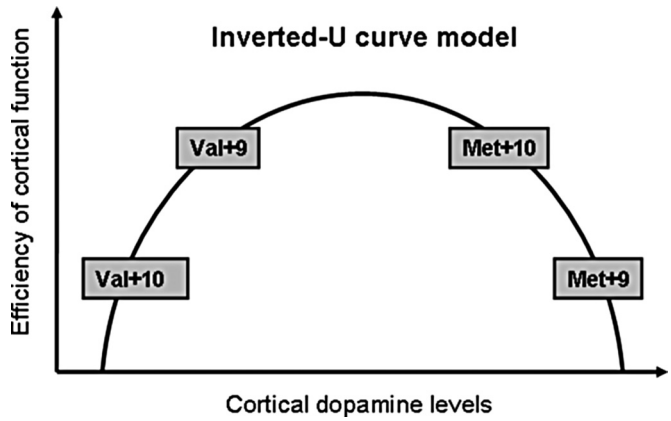

Fig. S1. Putative relationship between cortical afferent dopamine activity (*x* axis) and efficiency of left parietal cortical function (*y* axis), with respect to CT Val158Met and DAT 3′ UTR VNTR genotypes in healthy subjects. According to this model, combinations of the DAT-COMT alleles that together substantially increase (Val + 10) or reduce (Met + 9) dopamine levels are associated with less efficient activation than combinations whose net effect results in dopamine levels closer to the curve apex (Val + 9 or Met + 10).

Table S1. Demographic features comparing controls and patients

Variable	Controls	Patients
N	48	42
Age; mean (SD)	34.1 (10.7)	35.5 (11.4)
IQ; mean (SD)	118.2 (11.5)	97.2* (16.4)
Years of education; mean (SD)	15.1 (2.9)	13.5** (2.5)
Handedness (R/L)	46/2	37/5
Gender (M/F)	23/25	35/7***
Ethnicity (Caucasian/black-Caribbean/black-African/mixed)	46/0/1/1	35/5/1/1
Years on antipsychotics; mean (SD)	NA	12.3 (9.4)
Antipsychotic dose (CPZ equivalents); mean (SD)	NA	584.5 (456.2)
Total SAPS; mean (SD)	NA	6.5 (6.5)
Total SANS; mean (SD)	NA	7.8 (5.0)

NA, not applicable; CPZ, chlorpromazine; *, $F = 40.52$; $P < 0.00001$; **, $F = 5.35$; $P = 0.024$; ***, $\chi^2 = 12.26$; $P = 0.0005$; SD, standard deviation.

Table S2. Demographic features of the sample, subdivided according to COMT Val158Met genotype within each group and independent of group

	Controls			Patients			Genotype independent of group		
Variable	M/M	M/V	V/V	M/M	M/V	V/V	M/M	M/V	V/V
N	15	20	13	13	17	12	28	37	25
Age; mean (SD)	32.0 (11.0)	32.5 (10.3)	38.9 (10.0)	38.5 (11.6)	35.6 (11.7)	31.9 (10.8)	35.1 (11.6)	34.0 (11.0)	35.6 (10.8)
IQ; mean (SD)	116.6 (10.0)	116.2 (12.0)	122.6 (12.1)	97.4 (15.0)	97.9 (19.1)	96.0 (15.3)	106.6 (15.9)	107.3 (18.1)	109.9 (19.1)
Years of education; mean (SD)	15.2 (3.2)	13.9 (2.4)	16.3 (2.5)	13.6 (2.8)	13.4 (2.7)	13.7 (2.2)	14.6 (3.1)	13.7 (2.5)	15.4 (2.7)
Handedness (R/L)	15/0	19/1	12/1	13/0	14/3	10/2	28/0	33/4	22/3
Gender (M/F)	6/9	12/8	5/8	12/1	12/5	11/1	18/10	24/13	16/9
Ethnicity (Caucasian/ black-Caribbean/ black-African/mixed)	14/0/0/1	20/0/0/0	12/0/1/0	11/0/1/1	16/1/ 0/0	8/4/ 0/0	25/0/1/2	36/1/0/0	20/4/1/0
Years on antipsychotics; mean (SD)	NA	NA	NA	16.1 (11.8)	10.4 (8.2)	11.0 7.5	NA	NA	NA
Antipsychotic dose (CPZ equivalents); mean (SD)	NA	NA	NA	465.4 (521)	700.0 (446)	550.0 (389)	NA	NA	NA
Total SAPS; mean (SD)	NA	NA	NA	7.3 (7.4)	6.88 (7.1)	5.0 (4.3)	NA	NA	NA
Total SANS; mean (SD)	NA	NA	NA	8.5 (4.8)	7.4 (5.2)	7.6 (5.4)	NA	NA	NA
Antipsychotics (none/first/second generation)	NA	NA	NA	3/4/6	2/0/15	1/3/8	NA	NA	NA

M, Met158; V, Val158.

Table S3. Demographic features of the sample, subdivided according to DAT 3′ UTR VNTR within each group and independent of group

	Controls		Patients		Genotype independent of group	
Variable	9-car.	10/10	9-car.	10/10	9-car.	10/10
N	18	26	18	23	36	49
COMT Val158Met (MM/MV/VV)	5/8/5	9/11/6	6/7/5	6/10/7	11/15/10	15/21/13
Age; mean (SD)	34.1 (9.7)	32.9 (10.6)	33.3 (10.9)	36.7 (11.9)	33.7 (10.2)	34.8 (11.3)
IQ; mean (SD)	116.4 (11.2)	119.2 (9.3)	101.1 (13.6)	93.2 (18.0)	108.8 (14.5)	105.8 (19.4)
Years of education; mean (SD)	15.1 (2.5)	15.2 (3.3)	13.5 (2.6)	13.7 (2.6)	14.4 (2.6)	14.5 (3.1)
Handedness (R/L)	18/0	24/2	17/1	19/4	35/1	43/6
Gender (M/F)	6/12	16/10	17/1	17/6	23/13	33/16
Ethnicity (cauc/black-carib/black-afric/mixed)	17/0/1/0	25/0/0/1	15/2/0/1	19/3/1/0	32/2/1/1	44/3/1/1
Years on antipsychotics; mean (SD)	NA	NA	9.4 (7.4)	14.4 (10.5)	NA	NA
Antipsychotic dose (CPZ equivalents); mean (SD)	NA	NA	563.9 (525.5)	526.1 (396.0)	NA	NA
Total SAPS; mean (SD)	NA	NA	7.6 (8.0)	5.9 (5.4)	NA	NA
Total SANS; mean (SD)	NA	NA	8.4 (5.1)	7.4 (5.2)	NA	NA
Antipsychotics (none/1st/2nd generation)	NA	NA	3/4/11	2/3/18	NA	NA

CPZ, chlorpromazine; M, Met158; SD, standard deviation; V, Val158.