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Likelihood of mechanistic roles for dopaminergic, serotonergic and glutamatergic receptors in tardive dyskinesia: A comparison of genetic variants in two independent patient populations

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Abstract

Objectives: An established theory for the pathogenesis of tardive dyskinesia is disturbed dopaminergic receptor sensitivity and/or dopaminergic intracellular signaling. We examined associations between genetic variants of neurotransmitter receptors and tardive dyskinesia.

Methods: We assessed tardive dyskinesia in Caucasian psychiatric inpatients from Siberia (N=431) and a long-stay population from the Netherlands (N=168). These patients were genotyped for 43 tag single nucleotide polymorphisms in five neurotransmitter receptor genes, and the results for the two populations were compared.

Results: Several significant associations with tardive dyskinesia were identified, but only *GRIN2A* (rs1345423) was found in both patient populations. This lack of agreement was probably due to the small effect size of the associations, the multiple testing and the small sample size of the Dutch patient population. After reviewing the literature, we propose that the constitutive stimulatory activity of serotonergic type 2 receptors may be relevant.

Conclusions: Inactivity of the serotonergic, type 2C receptor or blockade of these receptors by atypical antipsychotic drugs may decrease the vulnerability to develop tardive dyskinesia.

Keywords

Tardive dyskinesia mechanism, dopaminergic receptor, serotonergic receptor, glutamatergic receptor, NMDA receptor, genetic variants

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Introduction

Dyskinesia is a movement disorder characterized by involuntary, repetitive, and irregular motions that affect the mouth and face and/or the limbs and trunk.¹ Tardive dyskinesia (TD) is a well-known complication of long-term treatment with dopamine (DA) blocking agents, predominantly antipsychotic drugs.² The prevalence of TD can vary, because it depends on the influence of several risk factors like, for example, age, type, dose, and duration of antipsychotic drug usage, diagnosis, non-therapeutic risk factors, and plasma level related pharmacogenetic risk factors.³ For over six decades, antipsychotic drugs have remained the mainstay of schizophrenia treatment. Schizophrenia is a heterogeneous psychiatric disorder, with a lifetime prevalence of about 1%. TD in schizophrenic patients is associated with poor outcome and TD patients may suffer from more physical or psychological problems.³ The pathophysiological mechanism of psychotic symptoms in schizophrenia is partly explained by an increased effect of dopaminergic neurotransmission.^{4,5} This theory is based on the therapeutic effects of antipsychotic drugs, which are all DA receptor antagonists.⁶ The development of TD is also associated with dysregulation within the dopaminergic system, and is thought to be based on a structural change induced by the long-term blockade of DA receptors.^{7,8} These findings may explain why dopaminergic dysregulation in patients with schizophrenia is related to psychotic symptoms as well as spontaneous dyskinesia, for example, drug-naïve first-episode patients experience spontaneous dyskinesia more frequently than healthy controls.³

It is thought that TD is primarily related to DA dysregulation. Antipsychotic treatment with both serotonergic 5-HT_{2A} (*HTR2A*) and 5-HT_{2C} (*HTR2C*) antagonists resulted in a lower annual incidence of TD.^{9,10} This finding led to the hypothesis that *HTR2A* and *HTR2C* activate gamma-aminobutyric acid (GABA)ergic interneurons,¹¹ within the cerebral cortex, basal ganglia, and mesencephalic areas, resulting in decreased dopaminergic activity. Hence, *HTR2A* and *HTR2C* antagonism increases DA release.¹² Schizophrenia has substantial hereditary components and is associated with dopaminergic dysfunction; therefore, genes related to the dopaminergic neurotransmitter system are attractive candidates for studying its genetic basis.^{4,13} To a lesser extent, this is also true for the pathogenesis of dyskinesia.^{3,14} Therefore, numerous investigations have examined the association between genetic variants of DA enzymes and receptors when symptoms of dyskinesia are present. However, the results are inconsistent and even meta-analyses are not conclusive (see discussion).

In this report, we present new data on the association between genetic variants of neurotransmitter receptors and TD. We compared the results of genotyping for 43 tag single nucleotide polymorphisms (SNPs) in five receptors in two independent patient populations and related the findings

with the prevalence of TD. Our results do not differ much from those found in relevant meta-analyses, which led us to propose that genetically determined variations of DA type 2 receptors and/or DA type 2 receptor signaling are unlikely to affect the sensitivity to TD. We suggest that a mechanism other than *HTR2*-induced augmentation of DA release is responsible for explaining the lower incidence of TD after treatment with atypical antipsychotics.

Materials and methods

Patients

The work described in this article was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki 1975, revised in Fortaleza, Brazil, 2013) for experiments involving humans. The majority of the patients in this study were retrieved from three psychiatric hospitals: Tomsk Clinical Psychiatric Hospital, Kemerovo Regional Clinical Psychiatric Hospital, and Chita Regional Psychiatric Hospital in Siberia. Written informed consent was obtained from each subject after obtaining approval of the study protocol from the institutional bioethics committee. None of the participants had a compromised capacity/ability to consent; hence, consent from the next of kin was not necessary and not recommended by the local ethics committee. The inclusion criterion was a clinical diagnosis of schizophrenia or schizotypal disorder (according to International Classification of Diseases (ICD)-10: F20 and F21, respectively). Exclusion criteria were as follows: non-Caucasian physical appearance (e.g. Mongoloid, Buryats, or Khakassians), use of clozapine with no TD (clozapine may ameliorate TD), relevant pharmacological withdrawal symptoms, and organic brain diseases. Details on the diagnosis and clinical features for the Russian and Dutch populations were previously published.^{15,16} To compare antipsychotic medications, all dosages were converted into chlorpromazine (CPZ) equivalents.¹⁷ The Abnormal Involuntary Movement Scale (AIMS) was used to assess TD.^{1,18} The AIMS scores were transformed into a binary variable (presence or absence of dyskinesia) according to the criteria of Schooler and Kane.¹⁹ In addition, a blood sample was obtained for DNA isolation and genotyping. All genotyping was performed without knowledge of the patient's clinical status.

DNA analysis

The DNA extraction and Veracode Assay were conducted according to standard protocols.¹⁵ We selected a subset of 43 informative SNPs, or tag SNPs, that would accurately represent the majority of SNPs for five neurotransmitter genes: the *glutamate receptor, ionotropic, N-methyl D-aspartate 2A* (*GRIN2A*) gene, *glutamate receptor, ionotropic, N-methyl D-aspartate 2B* (*GRIN2B*) gene, *DRD3* gene, *HTR2C* gene,

and *DRD4* gene. The selection method was previously described by Xu and Taylor (freely available at <http://snpinfo.niehs.nih.gov>). The following criteria have been applied for the selection of the tag SNPs: localization in the gene including 1000 bp upstream and downstream (5' and 3' flanking regions), linkage disequilibrium (LD) threshold=0.8, minor allele frequency (MAF) ≥ 0.1 , maximal distance between SNPs for calculation of LD=250,000 bp, Genotype data="European" (dbSNP). We selected only tag SNPs that captured at least 10 SNPs.

Statistical analysis

Different strategies were developed to account for missing data and interactions between different SNPs. Classical logistic regression and a log-linear regression approach were used to analyze the data. The Hardy-Weinberg equilibrium (HWE) of genotypic frequencies was checked by the chi-square test. For the SNPs in the X-chromosomal *HTR2C* gene, deviation from HWE was not calculated. The genotype prevalence of all polymorphisms was in agreement with HWE in the patient groups except for rs11866328 and rs7196095 in the *GRIN2A* gene and rs963468 and rs9817063 in the *DRD3* gene. All calculations were performed in the R statistical environment with the SNPAssoc package and basic R functions.²⁰ The allele prevalence was first calculated separately in patients with and without dyskinesia to define the percentage of missing genotypes. The HWE test was applied with Fisher's exact test to groups. This showed that one SNP, rs12858300, was monomorphic; therefore, it was removed from further analysis. To analyze associations between the SNPs and the phenotypes, we used logistic regression for binary response traits and log-linear regression for continuous traits. The following genetic models were tested:

1. *Co-dominant*. Both alleles of a SNP influenced the phenotype.
2. *Dominant*. Rare allele homo- and heterozygotes were tested against common allele homozygotes.
3. *Recessive*. Common allele homo- and heterozygotes were tested against rare allele homozygotes.
4. *Over-dominant*. Heterozygotes were tested against both homozygote alleles.
5. *Log-additive*. A trend test for the genotypes, similar to the allele model, but comparisons were among subjects (N) instead of chromosomes (2N). The test and estimates were based on a logistic regression model that coded the genotypes as 0, 1, or 2 to reflect the number of minor alleles.

The statistical significance of a SNP was established with a likelihood-ratio test that compared the effect of a polymorphism with the null model (only including the intercept). The Akaike information criterion was applied to identify the model that best fits the data. The SNP effects were quantified

using the odds ratio (OR) and 95% confidence intervals (CIs). In the result tables, an OR for a log-additive model corresponds to an association between a rare allele and the presence of dyskinesia. The ORs for other models correspond to associations between the presence of dyskinesia and rare allele homo- and heterozygotes (dominant), common allele homo- or heterozygotes (recessive) or heterozygotes (over-dominant).

Dyskinesia was considered a qualitative trait (yes/no), but the degree of dyskinesia expression was analyzed as a quantitative trait. To avoid 0 values, 1 was added to the dyskinesia expression values, and then they were log2-transformed to obtain a log-normal distribution. There were many confounding factors in patients with schizophrenia, including gender, age, duration of disease, use of anticholinergic medicine, dose of anticholinergic medicine, and total CPZ equivalents on the day of assessment. Only gender and total CPZ equivalents were determined to be insignificant. The genetic models were adjusted for all the significant confounding factors.

The statistical power was estimated based on the prevalence of the tested phenotypes in the Siberian sample and assumptions of complete penetrance and disease allele prevalence of 0.2–0.3. For orofacial dyskinesia, the power estimates to detect associations with p-value <0.05 varied between 14%–50% for models assuming OR of 1.5; 44%–94% for models assuming OR of 2.0; and 78%–99% for models assuming OR of 2.5. For limb-truncal dyskinesia, the power estimates varied between 10%–31%, 27%–75%, and 53%–95% for these three OR values, respectively. For either type of dyskinesia, the power estimates varied between 18%–65%, 58%–99%, and 91%–99%. Overall, our study was reasonably powered to detect clinically relevant associations with an OR as little as 2.0.

Comparisons

For comparisons, we used the population described by Bakker et al.¹⁶ They included a group of 168 Caucasian patients (M/F ratio: 96/72) who were representative of a population with the most severe chronic mental illness, requiring long-stay care at a psychiatric institution. The DNA of these patients was analyzed in parallel with our patients' samples and the results were provided to Bakker and colleagues. Genotype and allele frequency comparisons were performed using a multilevel random regression method with three measurement occasions (baseline and two follow-ups) for continuous TD and other movement disorders.

Results

Of the 431 Siberian patients (269 males/162 females) included, 401 (95.1%) had schizophrenia. The mean age was 41.5 ± 15.3 years and the average duration of illness was 16.4 ± 13.5 years. The average antipsychotic dosage

Table 1. Associations between specific SNPs and orofacial TD in the Dutch and Siberian schizophrenic populations.

Receptor	SNP	Dutch population	Siberian schizophrenic population	
		TDof (B, P value)	TDof (OR (95% CI), P value)	TD expression level: sum of scores for 1–4 signs (P value ^a)
<i>GRIN2B</i>	rs220599	X	X	P=0.04451
<i>GRIN2A</i>	rs7192557	B=0.22, P=0.0291	X	X
	rs1650420	B=0.16, P=0.0336	X	X
	rs11646587	X	OR=0.62 (0.38–1.00), P=0.04652	X
	rs7206256	X	OR=1.73 (1.02–2.91), P=0.03570	X
	rs1345423	X	OR=0.35 (0.14–0.86), P=0.01043	P=0.027865
<i>DRD3</i>	rs167770	X	P=0.01751	X
<i>HTR2C</i>	rs4911871	B=-0.18, P=0.0131	X	X

TDof: orofacial tardive dyskinesia; OR: odds ratio; 95% CI: 95% confidence interval.

B=regression coefficient, P=chance, sum of scores=scores of AIMS scale.

^aOriginal value + 1, followed by log₂-transformation.

Table 2. Associations between specific SNPs and TDlt in the Dutch and Siberian schizophrenic populations.

Receptor	SNP	Dutch population	Siberian schizophrenic population	
		TDlt (B, P value)	TDlt (OR (95% CI), P value)	TD expression level: sum of scores for 5–7 signs (P value ^a)
<i>GRIN2A</i>	<i>rs1345423</i>	<i>B=-0.18, P=0.0190</i>	<i>X</i>	<i>P=0.02504</i>
	rs7192557	B=0.22, P=0.0430	X	X
	rs1650420	B=0.16, P=0.0471	X	X
	rs11866328	B=0.16, P=0.0330	X	X
	rs7190619	X	OR=0.44[0.19–1.03], P=0.04292	P=0.02510
	rs9788936	X	OR=0.51[0.27–1.00], P=0.04020	X
	rs11644461	X	X	P=0.03875
<i>DRD3</i>	rs963468	X	X	P=0.01533
	rs167770	X	X	P=0.012236

TDlt: limb-truncal tardive dyskinesia; OR=odds ratio; 95% CI=95% confidence interval.

Bold italics are statistically significant in both populations.

B=regression coefficient, P=chance, sum of scores=scores of AIMS scale.

^aOriginal value + 1, followed by log₂-transformation.

(± standard deviation (SD)) at assessment was 717±770.3 CPZ mg equivalents per day. The 168 Dutch patients were older (48.8±12.4 years) and were admitted to the hospital for an average of 23.4±12.9 years. In addition, this group was less homogenous with respect to disease characteristics and included, according to the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV) Axis I, patients with schizophrenia (N=112), psychosis (N=9), affective disorders (N=27), another Axis I diagnosis (N=11), and no Axis I diagnosis (N=9).

The associations between SNPs and orofacial TD (TDof) are shown in Table 1 for the Dutch and Siberian patient populations. Significant associations were found between eight SNPs encoding four receptors (*GRIN2B*, *GRIN2A*, *DRD3*,

and *HTR2C*) and TDof. However, these SNPs were not the same for the two groups. The associations between SNPs and limb-truncal TD (TDlt) are displayed in Table 2 for the Dutch and Siberian patients. Significant associations were found between nine SNPs of two receptors (*GRIN2A* and *DRD3*) and TDlt. Yet, only rs1345423 in *GRIN2A* was significantly associated with TDlt in both patient groups: Dutch patients (B=-0.18, P=0.0190) and Siberian patients (TD expression level, sum of scores for five to seven signs: P=0.02504). The associations between SNPs and overall TD are displayed in Table 3 for the Dutch and Siberian patient populations. Significant associations were found in seven specific SNPs encoding three receptors (*GRIN2B*, *GRIN2A*, and *DRD3*). Only rs1345423 in *GRIN2A* was significantly associated with overall TD in both studied groups.

Table 3. Associations between specific SNPs and either type of TD in the Dutch and Siberian schizophrenic populations.

Receptor	SNP	Dutch population	Siberian schizophrenic population	
		TD (B, P value)	TD (OR (95% CI), P value)	TD expression level: sum of scores for 1–7 signs (P value ^a)
<i>GRIN2B</i>	rs2192970	X	OR = 1.93 (1.22–3.06), P = 0.005411	X
<i>GRIN2A</i>	rs1345423	B = -0.13, P = 0.0421	OR = 0.42 (0.20–0.89), P = 0.015210	P = 0.014524
	rs7192557	B = 0.22, P = 0.0159	X	X
	rs1650420	B = 0.16, P = 0.0193	X	X
	rs11644461	B = -0.13, P = 0.0385	X	X
<i>DRD3</i>	rs324035	X	X	P = 0.03211
	rs167770	X	X	P = 0.02197

OR: odds ratio; 95% CI: 95% confidence interval.

Bold italics are statistically significant in both populations.

B = regression coefficient, P = chance, sum of scores = scores of AIMS scale.

^aOriginal value + 1, followed by log₂-transformation.

Discussion

The results were inconsistent between the two populations, except for rs1345423 in *GRIN2A* for limb-truncal and all types of TD. The following methodological problems may explain these differences: the limited sample size (particularly of the Dutch study already published in PLoS One), multiple testing of several SNPs, age differences between the patient groups, diagnostic heterogeneity, variable influence of other risk factors, and poor clinical diagnosis of TD with the use of the AIMS.^{1,18} Furthermore, our study was cross-sectional, while the Dutch study was prospective with two follow-ups. This may have resulted in different outcomes, considering that dyskinesia fluctuates over time in relation to stress, anxiety, or fatigue.¹ However, in our opinion, the main problem was that the magnitude of the association between the presence of a specific genetic receptor variant and the clinical phenomenon of TD was at the utmost very small and therefore irrelevant.

Glutamatergic receptors

In our current study, only rs1345423 in *GRIN2A* showed a significant association with TD in the Dutch and Siberian patient populations. This [G/T]-SNP is an intron variant in *GRIN2A*, encoding one of the glutamatergic *N*-methyl-D-aspartate (NMDA) receptor subunits. It is a tag SNP, which is genetically independent from the *GRIN2A* variants rs7192557 (rs1969060) and rs8057394 that are associated with dyskinesia's age of onset in Huntington's disease, as well as with levodopa-induced dyskinesia.¹⁵ The OR for rs1345423 was smaller (0.42; 95% CI: 0.20–0.89, P = 0.0152) for “all locations” TD than for rs7192557 and levodopa-induced dyskinesia in 101 patients with Parkinson's disease (OR = 3.21; 95% CI: 1.37–7.51, P = 0.0062). The association was not found in the Siberian population when another statistical method was used.¹⁵ Therefore, this finding is not likely of significant clinical importance.

Dopaminergic receptors

The magnitude of the association between the presence of variants of the DA receptor and the presence of TD is very small. In a meta-analysis of 12 studies, Bakker et al.²¹ found a pooled OR (1.17, 95% CI: 1.01–1.37) for TD among carriers of the Ser9Gly allele (rs6280) in the *DRD3* gene that was smaller than the OR found by Lerer et al.²² (OR = 1.33, 95% CI: 1.04–1.70) in a meta-analysis of eight studies. Tsai et al.²³ found a non-significant OR after meta-analyzing 13 studies. Comparable results were found for *DRD2*^{24,25} and *DRD4*.^{26–30} The magnitude of the association between *DRD* polymorphisms and TD is too weak to have a pathophysiological meaning.

A pharmacological problem should also be discussed. The Ser9Gly *DRD3* variant (rs6280) has functional consequences.³¹ The Gly variant has a frequency of ~35% in non-African populations, and is actually the ancestral allele. The homogenous Gly variant has been associated with 4-fold greater DA binding affinity *in vitro*.³² However, the affinity of DA for its D₂-family receptors is in the micromolar range; while, the affinity of antipsychotic drugs (when clozapine and quetiapine are excluded) is in the nanomolar range.³³ Even when DA would have sufficient affinity to compete with antipsychotics for binding to the homogenous Ser9Gly variant of *DRD3*,³² it is difficult to understand how this activation could overcome the remaining blockade of *DRD2* and *DRD4* receptors within the dorsal striatum. The *DRD3* receptor is characterized by an extraordinary large binding affinity for DA.³⁴ It should be emphasized that *DRD3* receptors are largely confined to the ventral striatum;³⁴ while, the site of action of TD inducing mechanisms should be the putamen.²

It can be concluded that DA is unlikely to compete with antipsychotics for the DA type 2 receptor, even when it has far greater affinity than normal to a genetic variant of *DRD2*, *DRD3*, or *DRD4*. Moreover, most antipsychotics are full antagonists and dysfunctional variants of *DRD2*, *DRD3*, or *DRD4* do not modify the influence of these drugs. This probably explains

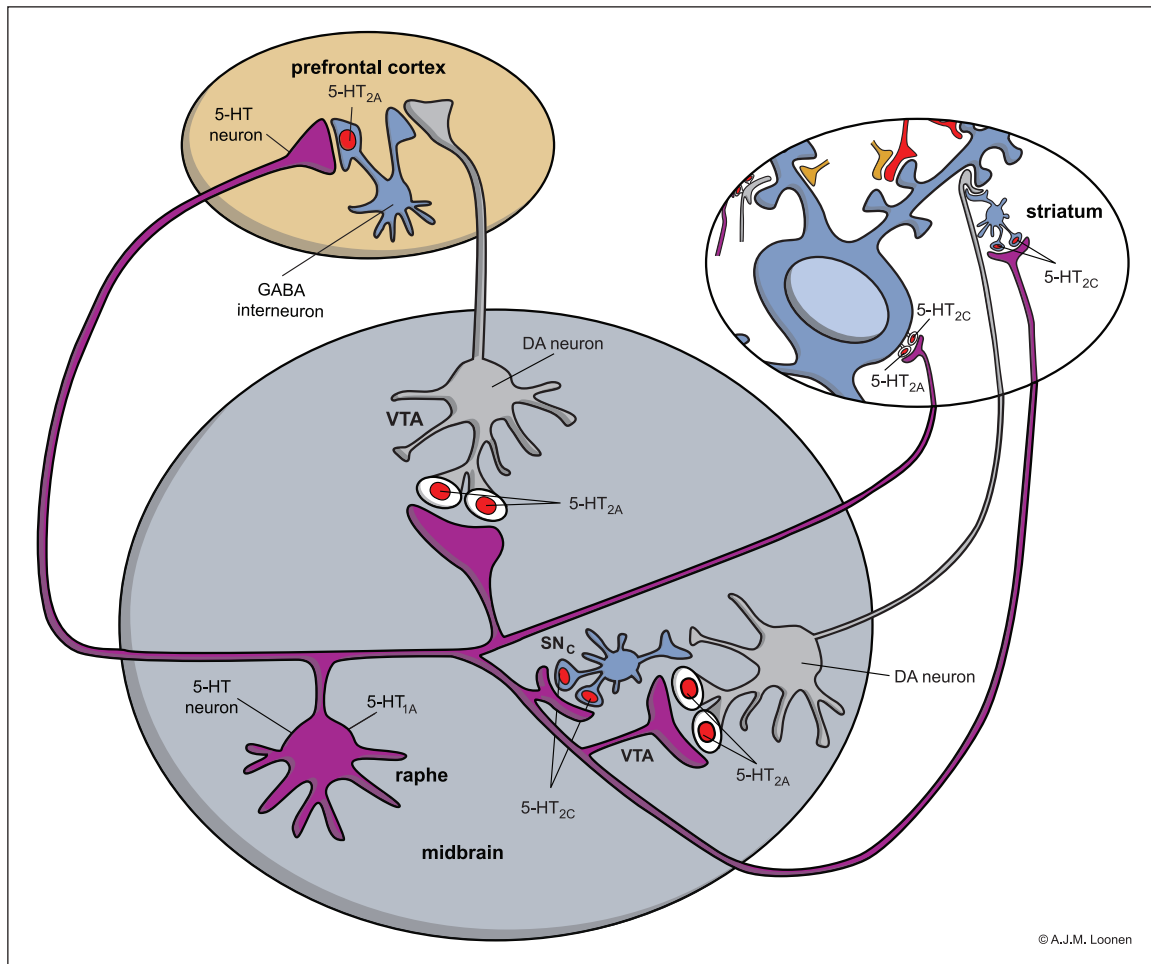


Figure 2. Model for the distribution of 5-HT_{2A} and 5-HT_{2C} receptors in the midbrain, striatum, and prefrontal cortex.

Note: Blue: GABAergic, MSNs or fast-spiking interneurons; grey: dopaminergic neuron; purple: serotonergic interneuron; red: glutamatergic cortico-striatal neuron; and tan: striatal cholinergic interneuron. The model explains the clinical differences when 5-HT_{2C} receptors show far more constitutive activity than 5-HT_{2A} receptors (colour figure in DOI: 10.1177/2050312116643673).

Therefore, the differences between the results of these studies may be partly explained by the use of *HTR2A/2C* blocking agents, which apparently decrease the differences between carriers and non-carriers. This also supports our idea that the inactive variant of *HTR2C* protects against developing TD.

To understand how blockade of 5-HT_{2A/2C} receptors results in less Parkinsonism and TD, the neuronal localization of these receptors should be considered (Figure 2).⁴⁹ The 5-HT_{2A/2C} receptors not only activate GABAergic interneurons within the midbrain, striatum, and prefrontal cortex, but also stimulate MSNs within the striatum.⁴⁹ Blockade in the midbrain results in DA release, but blocking the striatum directly inhibit MSNs.⁴⁹ This inhibition may protect these MSNs from neurotoxicity induced by oxidative stress caused by oxidative metabolism of the excess DA.²

Conclusion

Only rs1345423 in *GRIN2A* showed a significant association with TD in the Dutch and Siberian patient populations. It

may be concluded that a direct modulation of the DA type 2 receptors is unlikely to be responsible for the protective effects of atypical antipsychotic drugs on TD. The 5-HT_{2C} receptor may better explain this effect, particularly when its constitutive activity is considered.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics approval

Ethical approval for this study was obtained from: “Локальный этический комитет при ФГБУ «НИИПЗ» СО РАМН, Томск, Российская Федерация” (Local Ethics Committee at the Mental Health Research Institute of Siberian Branch of RAMSc, Tomsk, Russian Federation) [decision №21/2.2009 from 21.09.2009].

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Informed consent

Written informed consent was obtained from all subjects before the study. None of the participants had a compromised capacity/ability to consent; hence, consent obtained from the next of kin was not necessary and not recommended by the Local Ethics Committee.

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