Review

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Pharmacogenomics

Putative role of pharmacogenetics to elucidate the mechanism of tardive dyskinesia in schizophrenia

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Identifying biomarkers which can be used as a diagnostic tool is a major objective of pharmacogenetic studies. Most mental and many neurological disorders have a compiled multifaceted nature, which may be the reason why this endeavor has hitherto not been very successful. This is also true for tardive dyskinesia (TD), an involuntary movement complication of long-term treatment with antipsychotic drugs. The observed associations of specific gene variants with the prevalence and severity of a disorder can also be applied to try to elucidate the pathogenesis of the condition. In this paper, this strategy is used by combining pharmacogenetic knowledge with theories on the possible role of a dysfunction of specific cellular elements of neostriatal parts of the (dorsal) extrapyramidal circuits: various glutamatergic terminals, medium spiny neurons, striatal interneurons and ascending monoaminergic fibers. A peculiar finding is that genetic variants which would be expected to increase the neostriatal dopamine concentration are not associated with the prevalence and severity of TD. Moreover, modifying the sensitivity to glutamatergic long-term potentiation (and excitotoxicity) shows a relationship with levodopa-induced dyskinesia, but not with TD. Contrasting this, TD is associated with genetic variants that modify vulnerability to oxidative stress. Reducing the oxidative stress burden of medium spiny neurons may also be the mechanism behind the protective influence of 5-HT2 receptor antagonists. It is probably worthwhile to discriminate between neostriatal matrix and striosomal compartments when studying the mechanism of TD and between orofacial and limb-truncal components in epidemiological studies.

First draft submitted: 24 July 2019; Accepted for publication: 11 September 2019; Published online: 5 November 2019

Keywords: extrapyramidal • gene polymorphisms • pathogenetic hypothesis • pharmacological mechanism • tardive dyskinesia

The abnormal involuntary movement disorder tardive dyskinesia (TD) was first described by Schönecker [1], only 5 years after the introduction of antipsychotic treatment with phenothiazines [2,3]. The late appearance during phenothiazine treatment was first noted by Sigwald *et al.* [4] and the introduction of the term 'tardive dyskinesia' is attributed to Faurbye *et al.* [5]. Since then several thousands of articles have been published describing the epidemiology, genetics, clinical phenomenology, prevention, treatment and/or pathogenetic mechanism of this movement disorder, including at least three review articles in Pharmacogenomics [6–8].

The extrapyramidal disorders, also termed 'basal ganglia diseases,' comprise a set of movement disorders including Parkinson's disease (PD) and Huntington's disease (HD), but also mutual drug-induced movement disorders like akathisia, parkinsonism, dystonia and dyskinesia [9,10]. The clinical picture and course of TD is not unambiguously

defined. The involuntary repetitive movements are usually abrupt and irregular in nature. The movements may affect tongue, lips and jaw as well as the forehead, eyelids (blinking), lower face and throat (orofacial dyskinesia); the neck, trunk (rocking movements) and upper and lower limbs may also show rapid repetitive contractions (peripheral or limb-truncal dyskinesia). When the diaphragm and intercostal muscles are affected, dyskinetic movements result in making grumbling, snoring, groaning and/or sniffing noises (respiratory dyskinesia). Drug-induced dyskinesia can be acute, but more often is tardive that means appearing late during continuation of treatment. Several other drug-induced movement disorders may also have a tardive course and, moreover, TD is often accompanied by, for example, parkinsonism or akathisia [11,12]. This variation could make it hard to correctly diagnose a case with dyskinesia in epidemiological studies. Waln and Jankovic [11] have suggested reserving the name 'classic' TD for the form with the typical orofacial movements. Antipsychotic drugs can cause TD, but they can also suppress or mask this disorder [12]. In one of the first articles on TD, Uhrbrand and Faurbye [13] described that in some of their patients dyskinesia first appeared or worsened after drug withdrawal [3]. As most patients need long-term antipsychotic treatment, many TD cases will only become evident after a dosage reduction or a switch to a less potent dosage level of another drug [12]. In addition, since most patients use antipsychotics for many years and polypharmacy is not uncommon in daily practice, the neuroleptic load may show uncontrollable variation. The above considerations decrease the validity and reliability of studies dealing with the incidence, prevalence, risk factors and course of TD and may therefore darken the contribution of genetic factors, which could be used as a diagnostic marker to prevent the disorder.

Extrapyramidal disorders like TD are attributed to a dysfunction of the extrapyramidal system. Three different extrapyramidal divisions can be distinguished each of them having numerous parallel subdivisions: amygdaloid, ventral and dorsal [14–16]. In neurology, the last one in particular is considered; it consists of parallel cortico-striatal-[]-thalamo-cortical circuits including the dorsal striatum (caudate nucleus and putamen). This circuit contains a direct and indirect pathway (represented by -[]-), including globus pallidus, substantia nigra pars reticulata (SNr) and subthalamic nucleus (STh), as shown in Figure 1 [17,18]. The dorsal extrapyramidal circuit regulates the intensity of cognitive and motor programs. The ventral extrapyramidal circuit includes the accumbens nucleus and ventral pallidum and regulates the intensity of reward-seeking and distress-avoiding behavior [14–16]. The first division is often not considered to be an extrapyramidal circuit, although it can be considered to be the primary one [19,20]. The extrapyramidal circuit consists of serially connected glutamatergic and gamma (γ)-aminobutyric acid (GABA)-ergic neurons (Figure 1). The direct and indirect pathways start from the striatum via a different type of medium-sized spiny GABAergic projection neurons (MSNs). Direct pathway MSNs run to the internal section of the globus pallidus (GPi) and the SNr. These structures are also the final destiny of the indirect pathway, but then the striatal MSNs first project to the external section of the globus pallidus, which is connected with GPi/SNr via the STh. Activation of the indirect pathway MSNs finally results in limitation of the amplitude and velocity, while stimulation of the direct pathway enhances the movements. Direct pathway MSNs carry excitatory type 1 dopamine receptors (DRDs) and indirect pathway MSNs inhibitory type 2 DRDs. Hence, the activation of dopaminergic nigrostriatal fibers always results in augmentation of kinesis.

Pharmacogenetics and epigenetics can also be applied to elucidate the biochemical mechanisms behind a specific disorder. This strategy can be fruitful in TD as well as in several mental disorders, provided that one considers the multiple mechanisms behind these complex disorders. Theories-holding explanations for certain components of TD can be used to identify enzymes, transporters and receptors of which changes of activity may modulate the severity of the corresponding symptoms. Studying the influence of genetic variants with altered activity of the corresponding product may confirm or falsify a specific hypothesis derived from the theory. The theory itself may be derived from specific risk factors related to TD, but also from the pharmacological effects of certain TD treatments. They can be more accurate than the results of epidemiological studies and lead to support treatments that are believed to be ineffective when based on unreliable assessment in controlled clinical trials. This might lead, in turn, to the development of more effective therapies.

In the present article, we will deal systematically with the biochemical mechanisms which can be studied in order to elucidate the mechanism of TD. In addition, we will describe pharmacogenetic data we found in the literature confirming or falsifying hypothesis derived from this strategy. The essentials of the corresponding association studies are given in a supplementary table to this article.

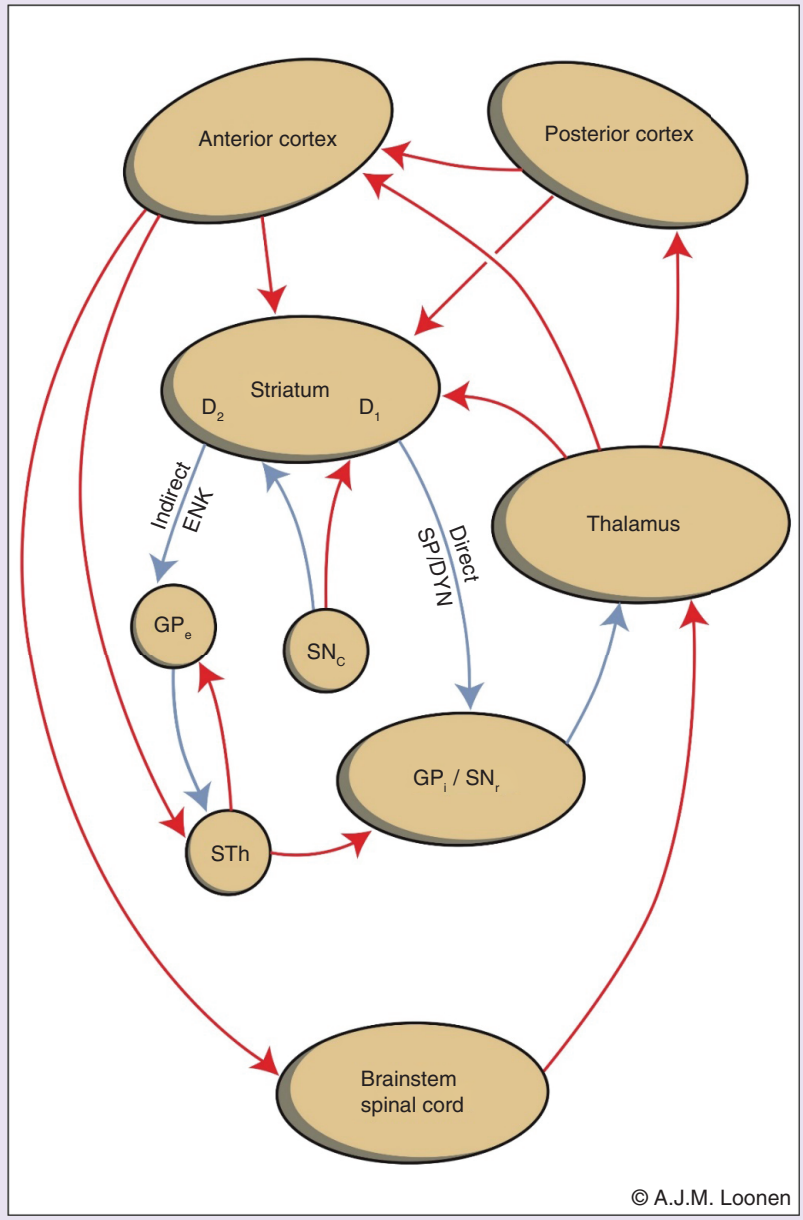

Figure 1. The cortico-striato-[]-thalamo-cortical circuits, including the indirect and direct pathways.
D1, D2: Medium spiny neurons with D1 or D2 receptors; ENK: Enkephalin; GPe: Globus pallidus, external segment; GPi: Globus pallidus, internal segment; SNc: Substantia nigra, pars compacta; SNr: Substantia nigra, pars reticulata; SP/DYN: Substance P/dynorphin; STh: Subthalamic nucleus.
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Role of separate striatal components

Medium spiny neurons

MSNs are GABAergic projection neurons with a single long axon, medium-sized cell body and 5–10 extensively branched spiny dendrites; they account for 95% of the striatal neurons. The vast majority of these projection neurons express either met-enkephalin or dynorphin and substance P, which distinguishes them into indirect and direct pathway MSNs (Figure 1) [21]. The dorsal striatum consists of a cytologically homogenous matrix with embedded striosomes or patches, which decrease along the anterior–posterior and medial–lateral axis [22,23]. Matrix MSNs receive a more or less topographically arranged input from the cerebral cortex [24]. Striosomal MSNs are targeted

10.2217/pgs-2019-0100

by neurons of the medial prefrontal cortex [25]. The latter MSNs play an important role in reward-driven decision-making, which may be related to their addressing neurons within the globus pallidus, which in turn project to the lateral habenula [26,27]. Matrix MSNs are essential components of the converging cortico-striato-thalamo-cortical (CSTC) circuits that regulate the intensity of cognitive and motor programs [24].

Electrophysiological experiments have shown that MSN membrane potentials can be held in two preferential states: a more polarized level, called the 'down' state, of -61 to -94 mV; and a more depolarized level, called the 'up' state, varying among neurons from -71 to -40 mV [24,28]. Temporally and spatially focused glutamatergic corticostriatal input induces a localized down–up switch of MSNs and dramatically increase their vulnerability to independent glutamatergic input. This 'up' state can last hundreds of milliseconds, and it is then when MSNs spike. Activation of the dopamine receptors modulates the glutamatergic synapses responsible for the transition to the 'up' state. The qualitative features of the modulation depend upon which DA receptor is being stimulated: D_2 receptor signaling impedes the 'up' state transition and diminishes 'up' state spiking in indirect pathways MSNs, whereas D_1 receptor signaling does precisely the opposite in direct pathway MSNs [24,29]. In addition, indirect pathway MSNs are more excitable than direct pathway MSNs [29,30]. This would also make indirect pathway MSNs more vulnerable to long-term potentiation and glutamatergic excitotoxicity. In indirect pathway MSNs, the induction of long-term potentiation (LTP) requires activation of 2a adenosine receptors (ADORA2A or A2AR) [29,31]. The A2AR is a Gs-protein-coupled receptor that has been reported to bind to several other cellular proteins including the formation of a heteromeric complex with the dopamine D_2 receptor [32]. Growing evidence exists that tonic A2AR activation is an essential step in allowing neurotrophic factors to affect neuronal activity [33]. Ivanova *et al.* have shown that an *ADORA2A* variant, which is associated with the age of onset of HD, showed no relationship with the prevalence of TD [34]. The same is true for N-methyl-D-aspartate (NMDA) receptor, NR2A subunit (GRIN2A) variants associated with the age of onset of HD [35]. The glutamatergic NMDA receptor mediates LTP and corresponding excitotoxicity. Hence, an important consequence of the likelihood of an 'up' state of indirect pathway MSNs by decreasing dopamine D_2 receptors activation is an unlikely mechanism of TD. It may, however, be a component of the mechanism inducing degeneration of indirect pathway MSNs in HD and the mechanism of levodopa-induced dyskinesia (LID) in PD [35,36].

Dopamine-related neuroplastic changes of glutamatergic excitation of MSNs may also play a role in inducing dyskinetic movements. Modulation of the induction of striatal LTP and long-term depression by dopaminergic mechanism has been extensively studied, most often within the context of the mechanism of LID [37–39]. These dopamine-related changes of MSN excitability may also play an important role in procedural and motor learning as well as in the learning processes in reward-related behaviors [40]. An important limitation of the idea that changed excitability of MSNs might result in TD is that a second mechanism would be necessary to explain the late-onset and irreversible character.

A more fruitful line of research can be derived from taking the neuropathology of HD as a starting point. HD is an autosomal dominantly inherited multisystem neurodegenerative disorder characterized by progressive motor dysfunction including chorea ($\approx$ dyskinesia) and athetosis ($\approx$ dystonia). Neuropathologically, HD is characterized by bilateral symmetrical neuronal loss of the neostriatum next to many other neurodegenerative changes [41]. This neuronal loss can be attributed to glutamatergic cytotoxicity by the induction of oxidative stress [42–44]. The larger susceptibility of indirect relative to direct pathway MSNs to excitotoxic insults may be related to a higher vulnerability to glutamatergic excitation on the one hand, but also to being protected by different neurotrophic factors to the other hand [43]. It should be recognized that oxidation of dopamine to neuromelanin, exclusive of the presence of sufficient neuromelanin to prevent this, can result in the production of the neurotoxic substance aminochrome [45]. This is believed to be related to neurodegeneration of dopaminergic neurons in PD, but this mechanism might also be important in LID in PD and TD [18,36]. In reaction to dopamine D_2 receptor blockade by antipsychotic drugs, dopamine release from the corresponding terminals is probably increased (see below), which could result in increased uptake and oxidative metabolism by indirect pathway MSNs. A well-known theory to explain the pathophysiology of TD holds that increased oxidative stress causes neuronal damage [46–48]. This might be a related component of excess dopamine-associated damage to indirect pathway MSNs. Supportive evidence for this theory comes from the results of pharmacogenetic studies in which polymorphisms of genes related to antioxidant defense mechanisms were found to be associated with the prevalence of TD [8,48,49].

GABAergic interneurons

Aspiny GABAergic interneurons account for approximately 3–4% of the total number of striatal neurons. These medium-sized GABAergic interneurons were initially classified histochemically into: parvalbumin-positive; somatostatin-, neuropeptide Y- and nitric oxide synthase-positive; and calretinin-positive interneurons [22]. In addition, a newly discovered group of tyrosine hydroxylase (TH)-expressing interneurons was described [50]. Furthermore, several subtypes have been specified during the last decade, each with their own neurocytology, intrinsic electrophysiological properties and afferent/efferent connectivity and the end of this identification process is probably not yet in sight [51]. This complicates the identification of neurochemical interneuronal processes, which may contribute to pathogenesis of TD. GABAergic interneurons are organized within the context of striatal microcircuitry regulating the activity of projection neurons [52]. Altered functioning of this microcircuitry has been described in several movement disorders [53] and NO-producing interneurons may have a role in regulating LTP/long-term depression of glutamatergic synapses with GABAergic projection neurons [37,38]. Therefore, studying the association between the prevalence of TD and genes, which are specifically related to the functioning of specific interneurons may be very rewarding.

A special position appears to be taken by parvalbumin-expressing fast-spiking interneurons (FSI), which appear to function relatively independent from other GABAergic interneurons [52]. These cells contribute to feedback and feedforward inhibition in several CNS areas [22,52,54].

Cholinergic interneurons

Cholinergic interneurons account for only about 1–2% of all striatal nerve cells, but they nevertheless make the striatum to the most acetylcholine-enriched structure of the CNS. These giant, aspiny interneurons probably correspond to tonically active neurons identified by *in vivo* recordings in the putamen of primates [55,56]. This means that these neurons show spontaneous activity in which this basal activity can be modulated up and downward by synaptic input. Cholinergic interneurons ramify extensively and send projections widely throughout this ganglion [57,58]. Although both striosomes and matrix contain these neurons, they are unevenly distributed and may respond differently to specific input [23,59]. Acetylcholine stimulates both striatal nicotinic and muscarinic receptors. Muscarinic receptors are more widely spread and can be divided in excitatory M_1 class (M_1, M_3, M_5) and inhibitory M_2 class (M_2, M_4) receptors [57,60].

The majority of efferents of cholinergic interneurons run to MSNs [61]: their functioning is regulated through binding muscarinic receptors; evidence shows that MSNs express nicotinic receptors only to a very limited extent. There is evidence that direct and indirect pathway MSNs are mutually differently affected by cholinergic interneurons due to differences in their carrying excitatory M_1 and inhibitory M_4 receptors [62–64]. Both direct and indirect pathway MSNs carry both types of muscarinic receptors, but while M_1 receptors are equally distributed, inhibitory M4 receptors are far more abundant in direct pathway MSNs. M_2 receptors are predominantly muscarinic autoreceptors [65]. Also GABAergic interneurons are inhibited through M_2 receptors [57]. The same is true for thalamostriatal and corticostriatal glutamatergic terminals. However, these glutamatergic terminals may, similarly to dopaminergic terminals, also be stimulated by nicotinic receptors [57]. The same is true for several types of striatal GABAergic interneurons, which may, however, also receive cholinergic input from fibers originating in the brainstem [51].

Striatal cholinergic interneurons receive afferent input with a wide variety of neurotransmitters [57,61], including glutamatergic input from the intralaminar thalamic nuclei [52] and nigrostriatal dopaminergic input [57]. With respect to the latter type of input are dopaminergic projections, by far the most abundant in projecting to MSNs [66]. In addition, the majority of the cholinergic interneurons express inhibitory dopamine D_2 receptors and only about 20% of the neurons low levels of D_1 receptors [57]. Nigrostriatal projections, therefore, largely enhance the activity of more specific CSTC circuits and inhibit the more widespread activity of cholinergic interneurons. Via thalamostriatal projections from, in particular, the intralaminar thalamic nuclei [67–69], cholinergic interneurons play an essential role in integrating cortical and cerebellar neuronal networks by gating CSTC processing [67,70,71]. This is probably mediated by enhancing muscarinic M_1 and M_4 receptor activation that interrupts cortical signaling to striatal MSNs [67,72].

Affecting the signaling of the nicotinic cholinergic receptor (CHRN) is a well-known mechanism in showing how cholinergic interneurons may modify drug-induced movement disorders [73]. To our knowledge, the possible association between *CHRN* gene variants and the prevalence of movement disorders has not yet been studied. Our group has recently published the first study in 472 patients with schizophrenia dealing with *CHRM* gene variants

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and TD [74]. This study identified associations between an *CHRM2* variant and TD, but these were likely to be secondary to other concomitant factors.

Corticostriatal & thalamostriatal glutamatergic neurons

Cortical glutamatergic neurons projecting to the striatum originate within all cerebral lobes, but within the striatum their terminals are not evenly distributed [24]. While the striatal matrix is targeted by all cortical lobes, including the limbic cortical areas [75], striatal striosomes receive highly selectively input from limbic medial prefrontal cortical areas [76]. Also, the dorsal striatal targets of corticoid parts of the amygdaloid complex are largely confined to striosomes [77]. The striosomal compartment regulates – partly directly [78] and partly via the lateral habenula [27,79] – the activity of ascending dopaminergic neurons, which is important for neuroplastic changes of glutamatergic synapses with MSNs [37]. Corticostriatal neurons to matrix MSNs are part of the cortico-striatal-[]-thalamo-cortical circuits [24]. These are, however, not as parallel as previously believed because separate cortico-striatal converging processing units can be distinguished, forming the start of these circuits [see 24]. The synapses formed by cortical pyramidal neurons are exclusively on the dendritic spines of MSNs [29]. MSNs are also targeted by thalamostriatal glutamatergic neurons [68,80]. Two anatomically and functionally distinct thalamostriatal neuronal systems can be distinguished projecting from caudal intralaminar or nonlaminar (midline and specific relay) nuclei [80]. Caudal and rostral intralaminar nuclei can be considered to represent the thalamic component of the ascending reticular activating system [81,82]. Thalamostriatal neurons of intralaminar nuclei project preferentially to the striatum with collaterals to the cerebral cortex [80,83]. These neurons preferentially innervate MSNs and (in particular cholinergic) interneurons of striatal matrix in an focal, convergent manner. They form synapses with the dendritic shafts of MSNs and show no spatial relationship with dopaminergic terminals [80,83]. Thalamastriatal projections of the other neuronal group are mainly collaterals of thalamocortical neurons. They have a diffuse pattern of innervation of the striatum without preference for striosomes of matrix. They contact mostly MSNs and, similar to corticostriatal neurons, primarily target dendritic spines, making them vulnerable for dopaminergic activity [80,83]. The intralaminar thalamostriatal neurons are believed to play a role in basal ganglia-mediated learning and are known to degenerate in PD [80]. Part of these thalamostriatal fibers correspond to the disynaptic connectivity between cerebellar output nuclei and striatum [84–86]. These neurons belong to a striatal-subthalamic-cerebellar-thalamic-striatal network that links the two subcortical regulatory systems: basal ganglia and cerebellar [87–89]. This cerebellar network is believed to be involved in PD and dystonia [89].

Both corticostriatal and thalamostriatal fibers target MSNs as well as interneurons, but the strength of the input to striatal neurons differs [52]. Interactions between the interneurons have an essential modulating influence on the final activity of the GABAergic projection neurons [52]. Glutamatergic and dopaminergic terminals are, together with astroglial processes, part of 'striatal spine modules', which operate as an independent integrative unit [90]. GABAergic innervation from collaterals of MSNs, and predominately from interneurons, inhibits the further processing of activation of these units. Acetylcholine, mainly released from varicosities, activates perisynaptically localized metabotropic muscarinic receptors and presynaptic nicotinic receptors on dopaminergic and glutamatergic terminals where they stimulate neurotransmitter release. Adenosine also modulates the activity of striatal spine modules largely by affecting heteromers of adenosine, glutamate, dopamine and acetylcholine receptors [90]. Such heteromers were also shown to exist between cannabinoid CB_1 and adenosine A2A and/or dopamine D_2 receptors [91,92] as well as between cannabinoid CB_1 and μ-opioid receptors. Opioid μ receptors are particularly expressed in the dendritic spines of dynorphinergic GABAergic MSNs as well as in glutamatergic and GABAergic nerve terminals within the striosomes compartment. They appear to be targeted by collaterals of (indirect pathway) GABAergic enkephalinergic MSNs [91].

Glutamate released from glutamatergic synapses and astrocytes stimulates inhibitory metabotropic glutamate receptor 2 (mGlu2) autoreceptors on corticostriatal and thalamostriatal glutamatergic synapses [93]. In contrast to this, mGlu4 autoreceptors are exclusively expressed on corticostriatal terminals that preferentially target indirect pathway MSNs [94]. In addition, presynaptic NMDA receptors have been identified on glutamatergic corticostriatal terminals [95]. Adenosine inhibits glutamate release by interacting with presynaptically localized adenosine A_1 receptors [96]. Most studies agree that CB_1 receptors are localized presynaptically predominantly in the GABAergic neurons, and also in the glutamatergic terminals [91,97]. Nicotinic α7 acetylcholine receptors facilitate neurotransmitter release from striatal glutamatergic terminals [98].

Whether the functioning of the above 'striatal spine modules' are an important target to be addressed in pharmacogenetic studies of the pathophysiology of TD is uncertain. Turčin *et al.* [99] studied the effects of

18 polymorphisms of adenosine receptor genes *ADORA1*, *ADORA2A* and *ADORA3* in 127 outpatients with schizophrenia without finding a significant association with TD scores. This is well in line with the previously described findings that rs35060421 variant of *ADORA2A* was also not significantly associated [34]. However, several variants of *ADORA2A* are associated with the age of onset of HD [34,100]. This may correspond to our previous finding that *NMDA* receptor variants that are also associated with the age of onset of HD did not show any association with TD [35]. A similar association with the age of onset in HD was found for variations in the *CNR1* gene [101], but using 20 tagSNPs, which captured all variations of this gene, Tiwari *et al.* [102] found only a weak association with TD. The only association (rs806374) was marginal after correcting for multiple testing. In our opinion, dysfunction of striatal spine modules as a possible cause of TD should probably be abandoned.

Dopaminergic neurons

Dopaminergic terminals originating from cell bodies in the midbrain (Figure 2) are traditionally considered to be the predominant regulators of the activity of cortico-striatal-[]-thalamic-cortical circuits. They originate from the substantia nigra, pars compacta (SNc) and a small number of other areas, which form a continuous band within the midbrain, jointly corresponding to the areas A8, A9 and A10 [103]. Apart from the dopaminergic neurons of this so-called 'dorsal tier', which contain the calcium-binding protein calbindin, a 'ventral tier' can be distinguished [103]. Dopaminergic nigrostriatal neurons of the ventral tier do not contain calbindin and are more vulnerable to degeneration in PD. They also have cell bodies localized within the underlying SNr.

Dopaminergic neurons from the midbrain project over a wide area of the forebrain [17,104,105] and regulate a wide variety of motivational, emotional and cognitive processes [106–108]. Neurons of the nigrostriatal pathway also have a complex pattern of axonal arborization reaching several extrastriatal basal ganglia as well as other forebrain structures like thalamus and basal forebrain nuclei [103,109,110].

Another difference between dopaminergic neurons of dorsal and ventral tiers is their distribution within the striatum [22,103,109,110]. Innervation by nigrostriatal dopaminergic neurons of the dorsal tier is largely restricted to striatal matrix, while neurons of the ventral tier target both striosomes and matrix.

Both dorsal (caudate, putamen) and ventral (accumbens) striatum are densely innervated by dopaminergic fibers originating in the midbrain. Both types of GABAergic projection neurons as well as all GABAergic and cholinergic interneurons express dopamine receptors [22]. High-affinity dopamine D_2-type receptors (DRD2, DRD4) in particular are believed to be tonically activated by the spontaneously active dopaminergic neurons projecting from the midbrain, while behaviorally relevant stimuli result in elevation of the dopamine release, which results in also activating lower affinity D1-type receptors (DRD1, DRD5) [22]. Direct and indirect MSNs express DRD1 and DRD2, respectively, with about 10–20% overlap [22,111]. In both types of MSNs, dopaminergic terminals end on the shaft of the spines (in the direct vicinity of corticostriatal and thalamostriatal synapses) as well as on dendrites themselves [91,112,113]. However, most dopamine receptors are localized extrasynaptically and are probably stimulated by spillover away from release sites [22]. In the core of the striosomes, dopamine is released from varicosities of ventral tier fibers passing through to the matrix [103]. Fast spiking, parvalbumin-positive, GABAergic interneurons (FSI) have a prominent role in regulating the activity of MSNs [22]. Dopamine may excite these interneurons by activating DRD5 expressed by these interneurons, but also by activating DRD2-mediated inhibition of GABAergic input from other interneurons. Moreover, these FSI are heavily targeted by globus pallidus neurons, which express D2 receptors [29]. Low-threshold spiking, somatostatin-, neuropeptide Y- and nitric oxide synthase-positive striatal GABAergic interneurons (LTS) also express DRD5 receptors [22]. Cholinergic interneurons express both D_2 and D_5 receptors [22,29]. Dopaminergic terminals express DRD2-class autoreceptors [29]. Via activation of the presynaptic nicotinic receptors on dopamine terminals, cholinergic interneurons may activate dopamine release [22,114]. Extrasynaptic dopamine receptors are also found presynaptically at glutamatergic and dopaminergic terminals on enkephalin MSNs [90]. mGlu1R are localized presynaptically in dopaminergic synapses; the same is true for the localization of adenosine A_1 receptor that inhibit dopamine release [90]. Multiple lines of evidence indicate that a4b2 nAChRs on dopamine terminals in the striatum potently modulate dopamine release [98].

Dopamine plays an essential role in regulating neuroplastic changes within striatal spine modules [29,37,38]. However, modulation of the vulnerability of MSNs to glutamatergic stimulation is more likely to be involved in the inducing of LID and HD, and not of TD, as has been explained in the above. Partly extrasynaptically localized dopamine receptors on dendrites and cell bodies of MSNs could also be involved. Early pharmacogenetic studies have revealed associations between *DRD2* and *DRD3* variants and TD [8,115,116]. Pharmacogenetic studies of a

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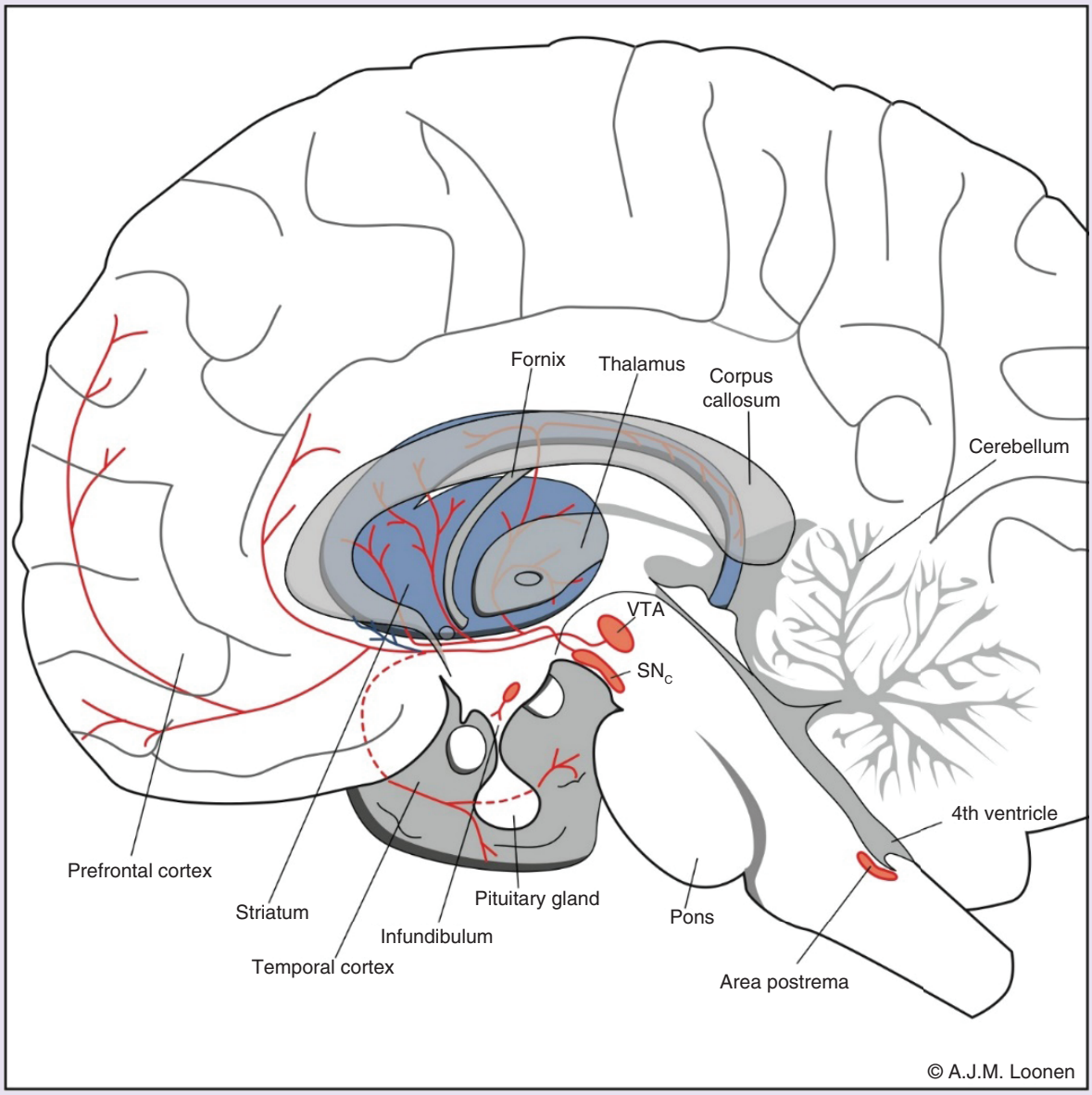

Figure 2. Principle dopaminergic neuropathways. Cell bodies are in the nuclei (red-filled shapes) positioned within the brainstem. Nerve fibers (red lines) terminate in the dorsal and ventral striata, amygdala and frontotemporal cortex [105].
SNc: *Substantia nigra* pars compacta; VTA: Ventral tegmental area.
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possible association with *DRD1* variant are relatively scarce and do not convincingly demonstrate an effect [117,118]. The latter is also true for *DRD4* variants [119–121]. We are not aware of studies of a possible association between *DRD5* and TD, but some evidence supports the involvement of the *DRD5* gene in idiopathic dystonia [122]. Studying the relationship between functional *DRD5* variants and TD could give important clue about the possible involvement of striatal interneurons.

Another thought explaining the relationship between dopamine and TD would be that TD is related to increased activation of dopaminergic nigrostriatal terminals. Striosomal GABAergic projection neurons inhibit the activity of dopaminergic nigrostriatal pathways [123,124]. This is probably mediated via straight striatonigral connectivity [78], but may also include a pathway via the lateral habenula [27]. Striosomes are not homogenous structures [23]. Although most striatal MSNs and their distant afferents tend to respect the striosomes-matrix borders, cholinergic and some

GABAergic interneurons occupy the peristriosomal/boundary region crossing these borders. Within striosomes, more DRD1 than DRD2-expressing MSNs are observed, while in the matrix the situation is opposite to this [23]. However, prefrontal corticostriatal neurons target the periphery of striosomes more heavily than their cores; this periphery contains more enkephalin-expressing indirect pathway MSNs than the corresponding cores [103]. Blocking DRD2 of these peripheral indirect pathway MSNs would result in increased activity of nigrostriatal neurons and an augmented release of dopamine within the core, activating DRD1 of direct pathway MSNs, but would also increase the oxidative stress burden of both striatal matrix and striosomes. Activation of striosomal direct pathway MSNs would prevent further augmentation of the dopamine release, but the final dopaminergic activity within the matrix would be higher. This could also promote degeneration of preferentially indirect pathway MSNs [18]. However, mutual findings complicate this theory. Genotypes that affect the activity of enzymes and transporters, which are expected to increase striatal dopamine concentration, should modify the incidence of TD. Concerning several dopamine degradation enzymes and synaptic dopamine uptake transporter, this is less obvious than to be desired. The rate-limiting step in the synthesis of dopamine is the hydroxylation of the amino acid tyrosine to levodopa via tyrosine hydroxylase (TH) [125]. The supposedly functional *TH Val81Met* polymorphism showed no association at all with TD in Korean patients with schizophrenia [126]. Although an association between certain variants of the dopamine catalyzing enzyme *COMT* gene has been described [115,127,128], meta-analysis have shown that the most important functional *COMT* Val158Met (rs4680) variant shows very little association with TD [115,128,129]. The *COMT* Val158Met variant is known to be associated with neuropsychiatric disorders such as Attention-Deficit/Hyperactivity Disorder [130], but not with LID in PD patients [131]. This could be related to the difference in expression of DA-transporters in different brain regions [131,132]. We identified only one study of a possible association of variants of the *MAOA* or *MAOB* genes with TD [133]. The relationship between MAO and the incidence of TD is theoretically complex as low activity would increase dopamine levels, but would decrease the oxidative stress burden of oxidative dopamine metabolism. VMAT2 transports and concentrates monoamines (catecholamines, serotonin, histamine) from the cytoplasm into synaptic vesicles in order to allow their concentrated release from synapses and varicosities after stimulation. Several variants of the *SLC18A2* gene which encode for VMAT2 were shown to be associated with TD [134,135]. The VMAT2 inhibitors reserpine, tetrabenazine, valbenazine and deutetrabenzine have at least some efficacy when treating TD [136]. The low-expression AA genotype of *SCL18A2* rs363224 variant appeared to be protective against TD and this variant interacted with the putative functional *DRD2* variant rs6277 [134]. The therapeutic activity of VMAT2 inhibitors, however, has an acute effect. Of note, we cannot be sure that the activity of VMAT2 is related to the pathogenesis of TD, since this treatment effect may only prevent dyskinesia from becoming symptomatic; classical antipsychotic drugs have similar dyskinesia-decreasing activity. The synaptic dopamine transporter (DAT) transports dopamine from the extracellular space into neurons [132]. Güzey *et al.* [137] studied *DAT1* VNTR polymorphism and found that the nine repeat alleles were more common in 119 patients with schizophrenia suffering from acute dystonia, parkinsonism and/or TD. The same polymorphism did not influence the prevalence of rigidity in 61 patients with schizophrenia in the study of Lafuente *et al.* [138]. Indirect evidence comes from the existence of a rare *SLC6A3*-related DAT-deficiency syndrome characterized by a hyperkinetic movement disorder [139]. Nevertheless, a possible relationship between DAT hypoactivity and TD has not (yet) been established.

It can be concluded that the results of genotyping genes that encode for enzymes and transporters affecting dopamine processing within the striatum do not offer much support for a dominant role of excess dopamine concentrations in the pathogenesis of TD. This could be related to the functioning of dopamine within striosomes where it stimulates DRD1 carrying direct pathway MSNs, which results in inhibition of the activity of dopaminergic nigrostriatal neurons. Hence, increased extracellular concentration automatically decreases the activity of dopaminergic neurons projecting to the matrix. The neurochemical characteristics of striosomes appear to be rather complex and full of surprises [23]. Therefore, this mechanism of TD remains still strongly possible and should be considered in the light of future discoveries.

Serotonergic neurons

Cell bodies of neurons containing 5-hydroxytryptamine (5-HT, serotonin) are predominantly localized near the midline (raphe) of the brainstem (Figure 3). These serotonergic nuclei are divided into a group of upper and lower raphe nuclei [17,104,105,140]. The upper raphe nuclei are connected with the SNc and ventral tegmental area and with both dorsal and ventral striatum.

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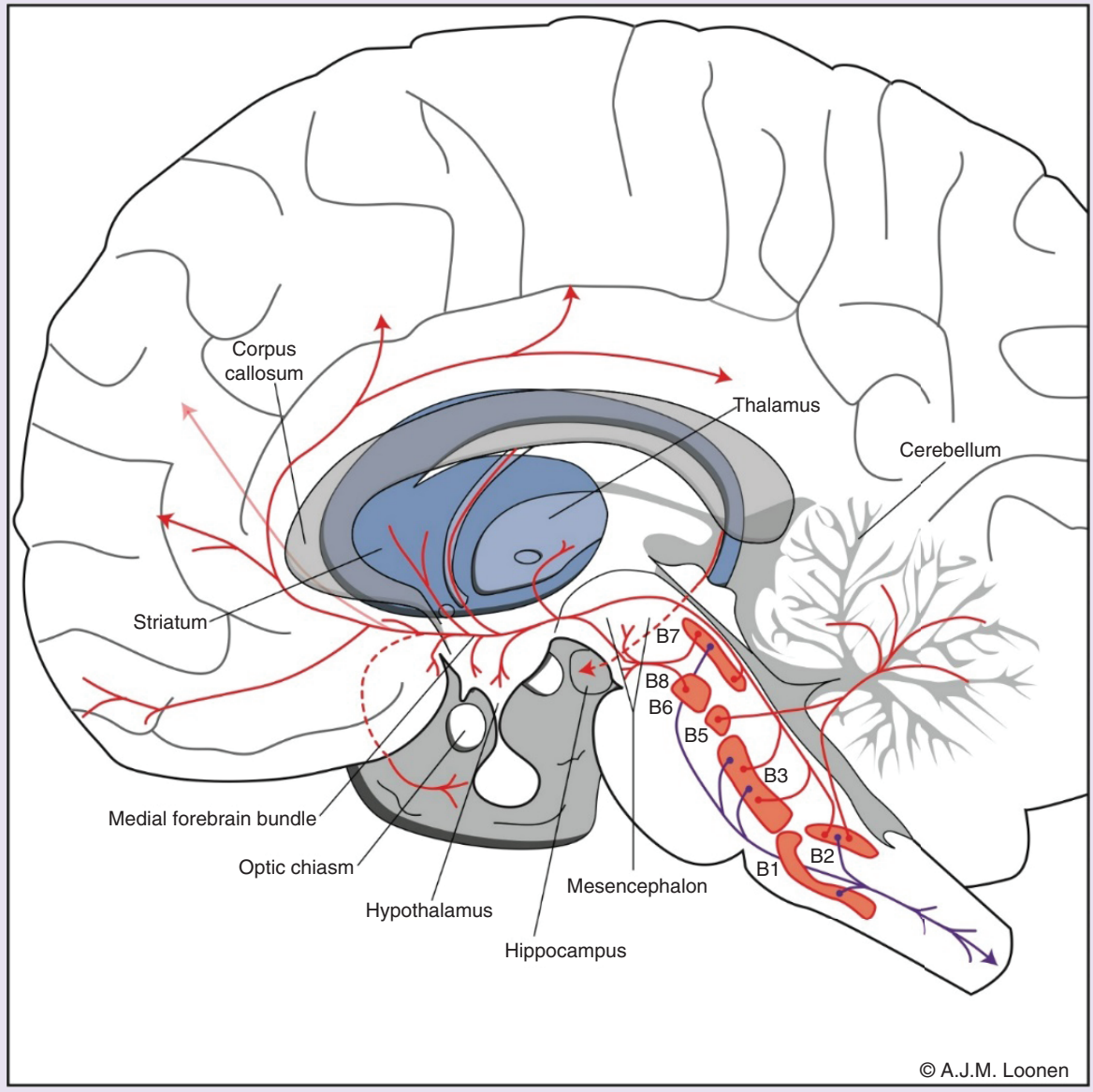

Figure 3. Serotonergic neurotransmitter system. Cell bodies are found in raphe nuclei (B1, B2, B3, B5, B7) near the midline within the brainstem. Fibers show widespread distribution within the CNS [105,140].
B7: Nucleus raphe dorsalis.
Reproduced with permission from [140].

A complicating factor may be that seven types of 5-HT receptors (HTRs) can be distinguished, most of them having several subtypes. All but one (HTR_3) are g-protein-coupled receptors [17]. For their role in dyskinesia, HTR_{1A}, HTR_{2A} and HTR_{2C} have been most extensively studied [141,142]. A peculiarity of HTR_2 is that this receptor is spontaneously active, which enables clozapine, for example, to have inverse agonistic activity, which means that it has a pharmacological effect opposite to 5-HT itself [143]. In order to understand how HTR_2 modify TD (and parkinsonism), the exact localization of HTR_{2A} and HTR_{2C} receptors in the midbrain, striatum and cerebral cortex should be considered [140]: HTR_2 are expressed by projection neurons, presynaptically on the fibers targeting these and on parvalbumin-expressing, GABAergic and FSI, but the ratio between HTR_{2A} and HTR_{2C} affecting these structures differs per area (Figures 4–6). We have concluded that, concerning the dorsal striatum, HTR_{2C} are predominantly involved. HTR_{2C} decrease dopamine release within the dorsal striatum by stimulating

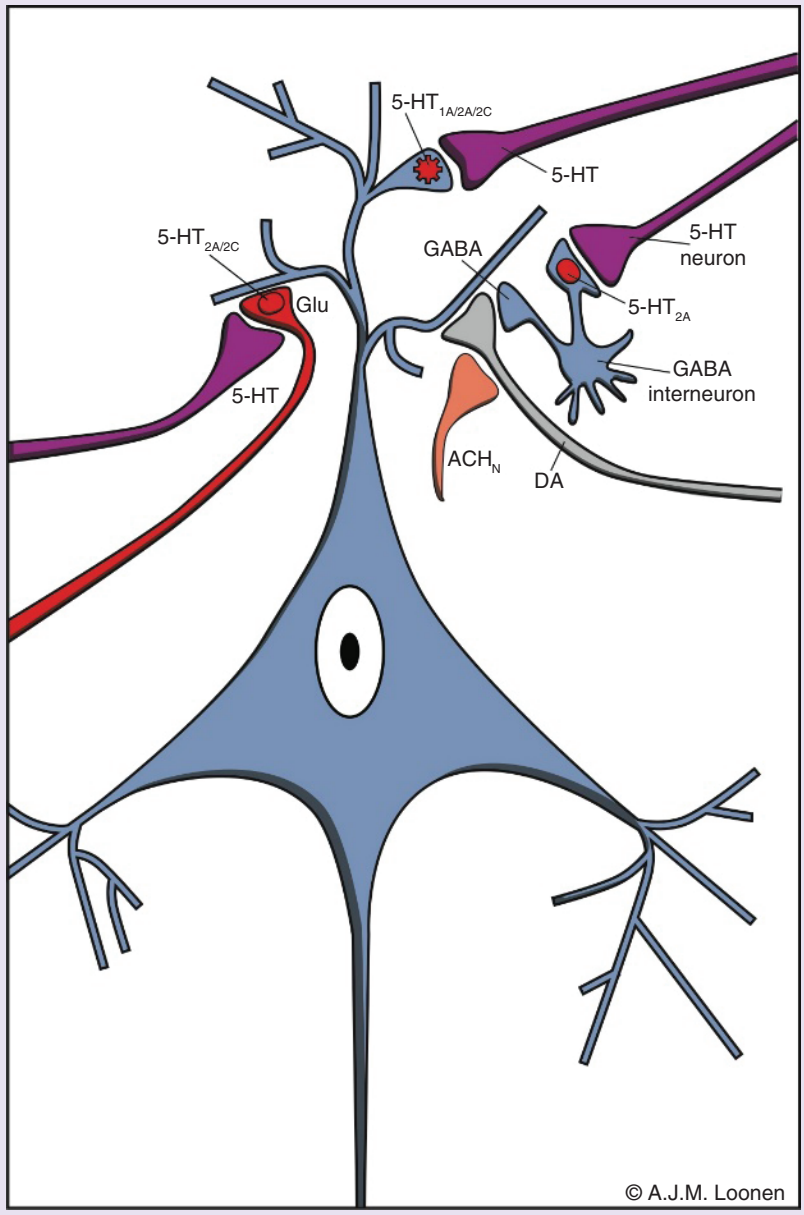

Figure 4. Distribution of 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors within the prefrontal cortex.
Reproduced with permission from [140].

FSI within the SNc and within the dorsal striatum itself [140]. Serotonin inhibits DA activity within the ventral striatum and frontal cortex mainly by affecting HTR$_{2A}$. By blocking HTR$_{2A}$, and to a lesser extent HTR$_{2C}$, atypical antipsychotics enhance dopaminergic activity within the prefrontal cortex and the striatum. Apart from promoting DA release from striatal DAergic fibers, HTRs may increase the activity of striatal GABAergic projection neurons (MSNs) directly (Figure 5). As HTR$_{2A}$, and more extensively HTR$_{2C}$, have constitutive activity, the blockade of these receptors by clozapine, for example, would result in decreased activity of MSNs. This is an attractive thought in explaining the low potential of clozapine to induce TD, because inhibition of the activity of indirect pathway MSNs would decrease their vulnerability for oxidative stress.

The complex effects of HTR$_{2A}$ and HTR$_{2C}$ on the functioning of the extrapyramidal system should also be considered when interpreting the results of pharmacogenetic studies of a possible association with TD. The

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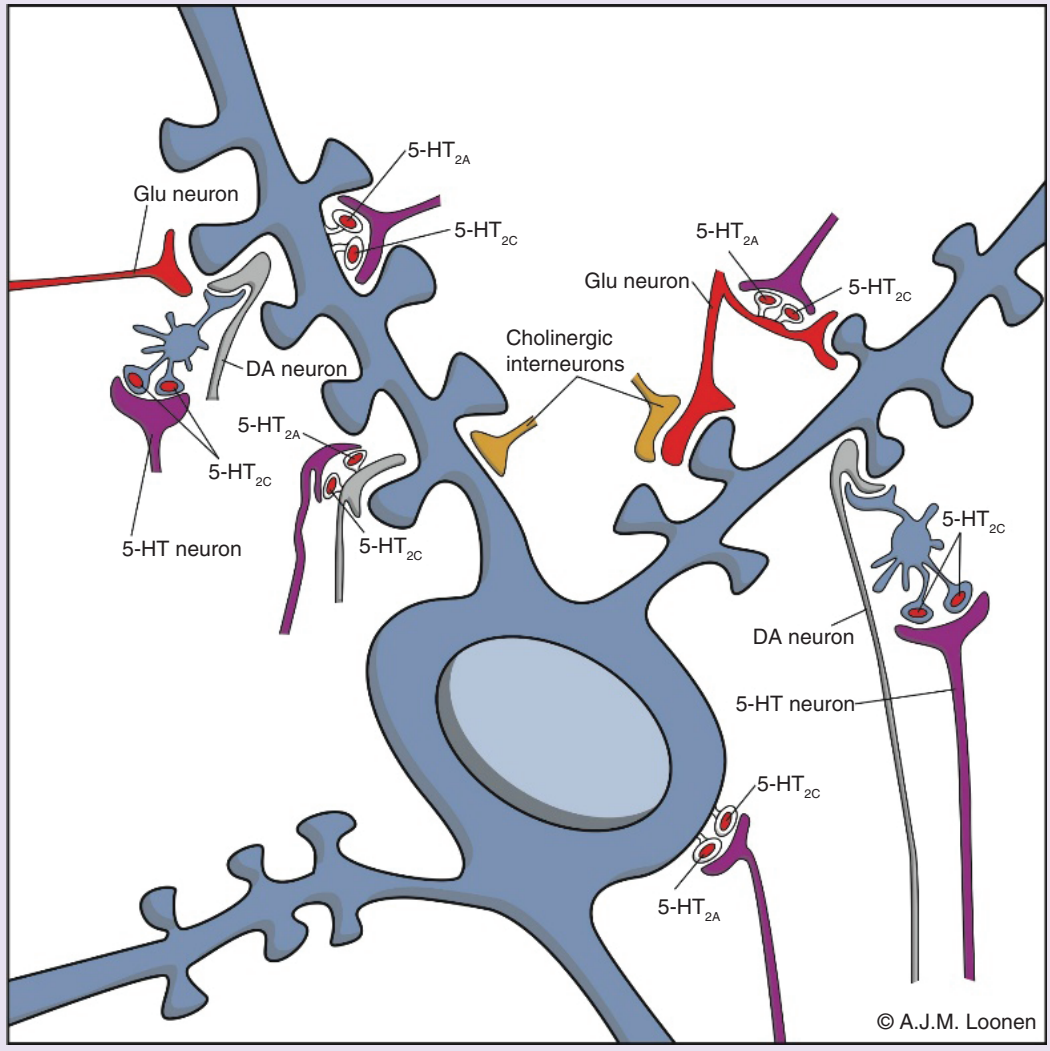

Figure 5. Distribution of 5-HT_{2A} and 5-HT_{2C} receptors within the striatum.
Reproduced with permission from [140].

HTR2C gene is X-bound and males are, therefore, hemizygotes, so always homozygous. Moreover, HTR_{2C} has more constitutive activity than HTR_{2A} and the influence of genetic variants on this constitutive activity has hitherto not been assessed. Atypical antipsychotics have variable affinity to HTR_{2A} and HTR_{2C}, and different drugs may have variable inverse agonistic activity. Some HTR_{2C} antagonists (e.g., agomelatine) are known to lack inverse agonistic activity [144]. This makes an *in vivo* or *ex vivo* test to estimate the functional consequence of HTR_{2C} variants essential, but until now we have failed to find one [145].

The authors have participated in studies addressing a possible association between HTR_2 and TD in four different patient populations (African–Caribbean, Dutch [2x], Siberian) [146–149]: the results are conflicting, which correspond to the results in other populations [135,150]. Due to their localization, HTR_{2C} deserves priority and the *HTR2C* Cys23Ser polymorphism (rs6318) has been studied most extensively. We believe that the differences between the results of these studies may be partly explained by the use of $HTR_{2A/2C}$ blocking agents (atypical antipsychotics), which apparently decrease the differences between carriers and noncarriers [149]. Other *HTR* genes studied are *HTR3A* [151] and *HTR6* [152], but the results for these C178T-HTR3A and C267T HRT6 polymorphisms were negative. The same is true for the *SLC6A4* gene of which the repeat polymorphism called

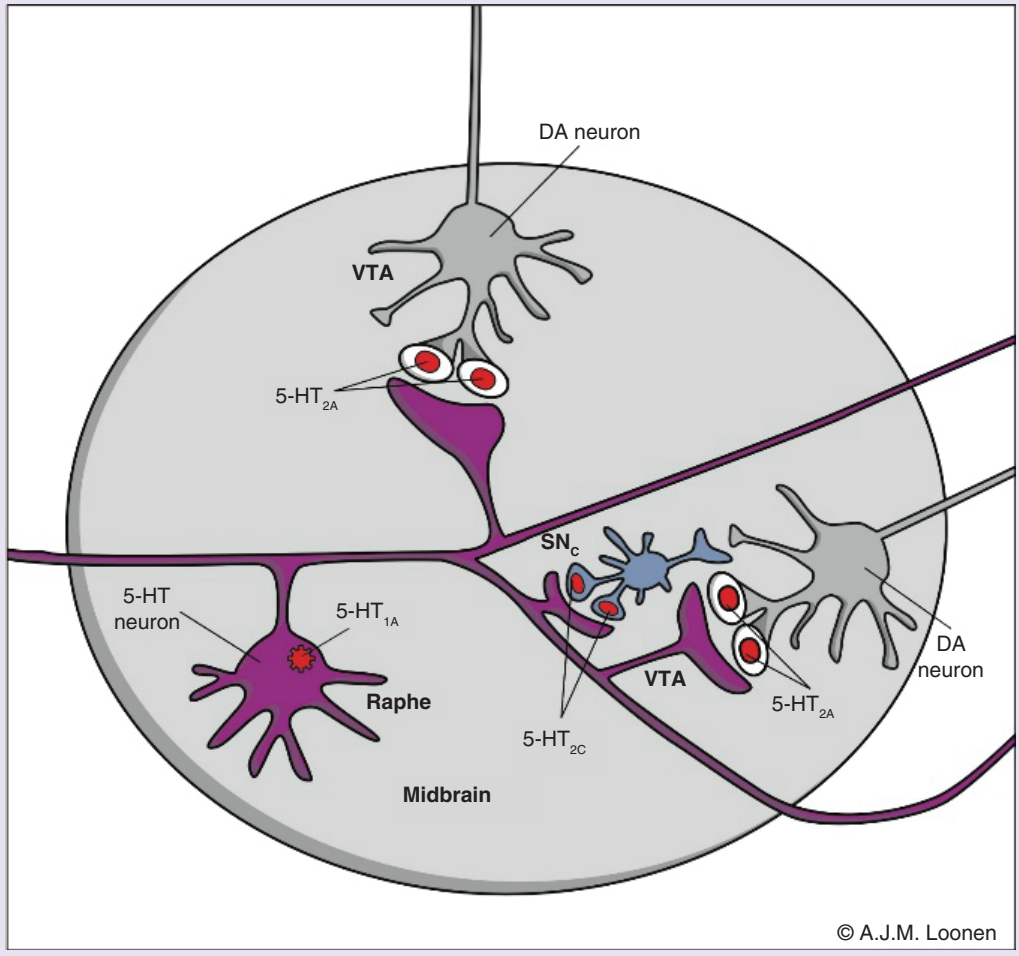

Figure 6. Distribution of 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors within the midbrain.
Reproduced with permission from [140].

HTTLPR has been sufficiently studied [137,153–156]. Changed activity of this transporter protein could modulate HTR stimulation. Also modulation of the enzyme involved in the biosynthesis of 5-HT: tryptophan hydroxylase (TPH) would have the same effect. The T366C variant of *TPH2* was found not to be significantly associated with the presence of TD [155]. Only a minor portion of tryptophan is metabolized to 5HT; the majority is metabolized via the kynurenine pathway [157,158]. The majority of the metabolites of this metabolic pathway are neuroactive, and imbalances of the pathway are assumed to contribute to complications of mental disorders [159,160]. Polymorphisms of genes of involved enzymes have been associated with schizophrenia and PD [157], but a possible association with TD has, as far as we know, not been studied.

Adrenergic neurons

The adrenergic neuronal system of the brain consists of neurons that synthesize norepinephrine (NE, noradrenaline) with cell bodies in pontine and medullary brainstem [17,104,105]. About half of these are localized in the so-called locus coeruleus (LC) complex that is by far the most important adrenergic center of the brain (Figure 7). Although some non-LC neurons in particular may innervate the dorsal striatum [161], their number must be low as the NE content of the dorsal striatum is low in comparison to other forebrain regions [161,162]. LC neurons have been found not to innervate the caudate nucleus [163]. The ventral striatum, and particularly the shell part of the nucleus accumbens, is substantially innervated by adrenergic terminals, the core part appeared to virtually devoid

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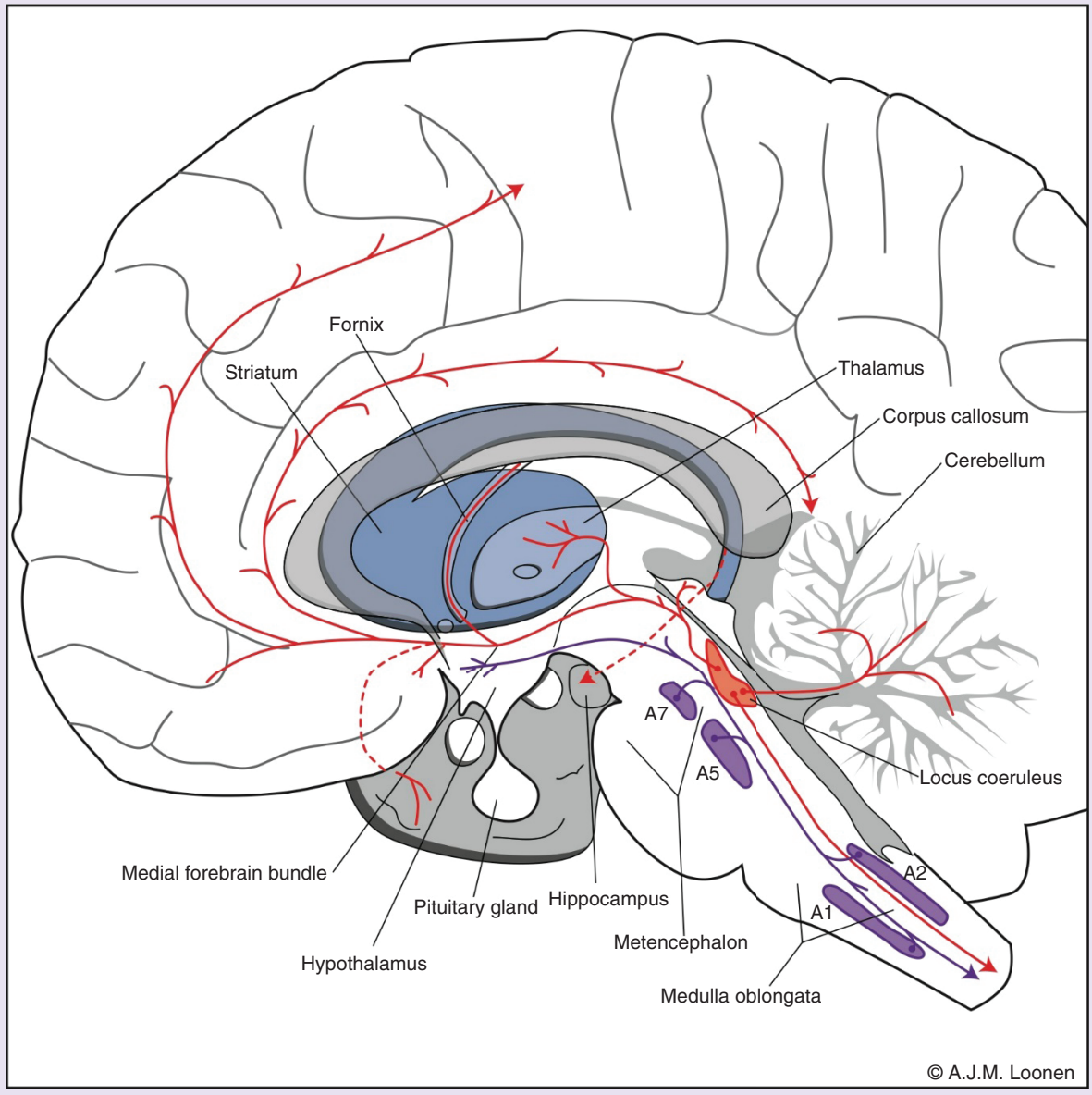

Figure 7. Adrenergic neurotransmitter system. Cell bodies within the locus coeruleus complex (red-filled shape) and a group of specific adrenergic cell groups (purple-filled shapes). Cell group A2 overlaps with nucleus solitarius and nucleus dorsalis nervi vagi. Reproduced with permission from [105].

of noradrenergic fibers [164]. We have previously described that these adrenergic fibers may play an important role in causing akathisia [165].

It will, therefore, not come as a big surprise that the results of pharmacogenetic studies did not support a possible role for the adrenergic system in causing TD. Several studies addressed polymorphisms of the *DBH* gene [166–169], but none of them showed an association with TD. To our knowledge, a possible relationship between variants of the *NET* gene and TD has not been studied. Similar to other catecholamines NE is catabolized by MAO and COMT.

It should be kept in mind that the above findings do not rule out a possible influence of the adrenergic system on the severity of TD symptoms. By temporally affecting the activity of corticostriatal, thalamostriatal and/or nigrostriatal neurons, the intensity of dyskinesias could be affected.

Some complicating factors

Spontaneous dyskinesia & dyskinesia related to schizophrenia

Dyskinesia is known to occur spontaneously, particularly in elderly persons [170,171], and also in drug-naïve persons with schizophrenia [172,173] as well as their direct relatives [174,175]. A systematic review of dyskinesia in drug-naïve patients with schizophrenia estimated a median rate of 9% [173]. The spontaneous occurrence of dyskinesia in the studied patient population can obscure the mechanism of drug-induced dyskinesia. This is not necessarily so as the pharmacological effect can also be the potentiation of a process linked to the schizophrenic disease. Still, this is a factor to consider when applying the results of pharmacogenetic studies when trying to explain the mechanism of drug-induced schizophrenia.

Orofacial versus limb-truncal dyskinesia

In the very first reports about this movement disorder, TD was described as a disorder characterized by involuntary orofacial movements [3]. Waln and Jankovic [11] suggest that this orofacial form should be termed 'classic' TD. We have observed that different gene variants are associated with orofacial versus limb-truncal dyskinesia [49,146]. We have also noticed that in LID, specific genetic associations exist with limb-truncal dyskinesia, but not with orofacial dyskinesia [35]. This may correspond with the observation that in HD and LID often large muscle groups are affected and in TD more subtle movements are present, most often in the orofacial area. Orofacial movements are related to a phylogenetically earlier developmental phase than limb movements [19,176]. This might indicate that orofacial dyskinesia is linked to the functioning of the so-called 'primary' brain, largely consisting of limbic cortical and ganglionic structures [14]. It is tempting to speculate that orofacial dyskinesia is more closely related to the functioning of striatal striosomes than peripheral dyskinesia; this hypothesis would necessitate the consideration of the intrastriatal distribution of, for example, HTR_{2C}. In an old autoradiographic study with [^{3}H]LSD and [^{125}I]DOI as ligands, Waeber and Palacios [177] have found that the localization of their binding sites in the human dorsal striatum is very similar to that of striosomes. More specific and *in vivo* studies are necessary to elucidate this matter in more detail.

Dopaminergic & serotonergic innervation of other cerebral structures

In this article, we have limited ourselves to possible modulation of the functioning of neostriatum, but the extrapyramidal system also includes extrastriatal basal ganglia, such as globus pallidus and STh. These structures are also innervated by dopaminergic, cholinergic and serotonergic neurons [103,178,179]. Moreover, the functioning cerebral cortex and corticoid amygdala possibly affects the occurrence and severity of TD by increasing the input to the neostriatum; the functioning of these cortical structures is also modulated by dopaminergic, cholinergic and serotonergic innervation [105,140]. This is especially true for connectivity within the pathways from the amygdala via the striatopallidum and habenula (or directly) to midbrain monoaminergic nuclei [19,20], which have, in this respect, barely been studied yet.

Conclusion

Many mental and neurological disorders are too complex to discover genes that are uniquely involved in their pathogenesis and therefore to offer the possibility for use as a biomarker to diagnose these disorders with sufficient validity and reliability. Therefore, the strategy applied in this paper could be a sensible alternative to make this type of research to a useful endeavor. Moreover, the atheoretical testing of variants associated with a specific disorder induces the need for correcting for multiple testing, which might obscure mutual relevant associations. This is not necessary when a specific hypothesis is confirmed or falsified by establishing a necessary association with a genetic variant known to be functional in another context. Several other variants of the same gene (functional and not functional) should be measured too in order to minimize the chance of establishing an accidental relationship.

Considering the evidence presented in this paper, it can be concluded that the results of genotyping genes that encode for enzymes and transporters affecting dopamine processing within the striatum do not offer much support for a dominant role of excess dopamine concentrations in the pathogenesis of TD. This is also true for the dopamine induced switching of striatal indirect pathway MSNs into their excitability 'on' state, which would increase their vulnerability to glutamatergic excitotoxicity. This mechanism, which may have an important role in HD and LID, is probably prevented in TD by the blockade of type 2 DRDs by the obligatory usage of antipsychotic drugs. Furthermore, little evidence can be found for excess stimulation of type 1 DRDs as a mechanism of inducing TD by causing LTP at direct pathway MSNs. However, DRD5 has been insufficiently studied to be able to exclude a

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possible role of striatal GABAergic interneurons affecting the excitability of striatal GABAergic MSNs. A possible role of cholinergic interneurons in causing TD is rather unlikely. Serotonergic transmission may play a role in the pathogenesis of TD by stimulating HTR_2 of striatal MSNs directly. This would increase the vulnerability of indirect pathway MSNs for glutamatergic excitotoxicity. Clozapine and other atypical antipsychotics may prevent this due to causing HTR_2 inverse agonism. That excitotoxicity probably plays a role in the pathogenesis of TD is suggested by its relationship with oxidative stress factors.

When interpreting the results, possible artefacts should be thoroughly considered. The large variations between the results of different studies of a possible association between *HTR2* variants and TD may be related to not considering the usage of HTR_2 antagonizing compounds by the investigators. The acute effects of these drugs might minimize differences between the activities of genetic *HTR2* variants. Considering the observation that the dorsal striatum and core part of the ventral striatum is barely innervated with adrenergic fibers originating within the LC, it can hardly come as a surprise that the results of pharmacogenetic studies did not support a possible role for the adrenergic system in causing TD. It should be kept in mind, however, that the severity of TD symptoms is also influenced by the activity of the stress system. By affecting the activity of corticostriatal, thalamostriatal and/or nigrostriatal neurons, usage of stress reducing or inducing medication may modulate the intensity of TD. This might influence the findings of epidemiological pharmacogenetic studies of TD obscuring relevant pharmacological mechanisms of the disorder.

The limited relationship with factors which increase dopamine exposure on the one hand and the clear relationship with (possibly dopamine-related) oxidative stress on the other hand is a puzzling phenomenon. A possible explanation could be that TD is primarily related to a dysfunction of mechanisms within the striatal striosomal compartment. Excess dopamine levels within the striosomal compartment would automatically result in inhibition of the activity of dopaminergic neurons projecting to the matrix by stimulating DRD1-carrying direct pathway MSNs, which results in inhibition of the activity of dopaminergic nigrostriatal neurons. The mechanism of TD could be related to a dysfunction of striosomal indirect pathway MSNs, which is related to increased vulnerability to oxidative stress. The importance of the striatal striosomal-matrix diversity in causing TD is obviously worthwhile elucidating, but this is currently still outside the scope of pharmacogenetic research. What could help is, when pharmacogenetic studies discriminate between orofacial (primary in TD) and limb-truncal (primary in HD and LID) dyskinesia in order to address different components of these extrapyramidal disorders.

Future perspective

When considering the above conclusions, five subjects for important future research come to mind. Most important, in our opinion, may be the discrimination between orofacial (i.e., 'classical') TD from limb-truncal (i.e., 'peripheral') TD in association studies. Orofacial TD can be assessed with the first four items of the Abnormal Involuntary Movement Scale, which is incorporated in the Schedule for the Assessment of Drug-Induced Movement Disorders [9,10]. Limb-truncal TD is measured with the items 5–7 of the Abnormal Involuntary Movement Scale. It might be useful to reanalyze the data of older association studies in this respect as well as studying classical TD separately in future studies.

Respiratory TD has hardly been studied, which is probably an inadequacy of this type of research. It would be rational trying to find out whether respiratory TD is closer related to classical or more linked to peripheral TD.

The intensity of TD is well known to be connected to the patient's anxiety level. It might be sensible to measure this anxiety level (with a rating scale or psychophysiological method) and to include this measure as an independent variable when statistically analyzing association data.

When studying functional variants of the HTR_2 genes, a possible relationship with TD can be distorted by the TD intensity in patients using HTR_2 antagonists (several second generation antipsychotics) or inverse agonists (clozapine). The same is true when CHRM variants are studied in patients using CHRM antagonists. Prospective studies in a sufficiently large cohort of patients without such treatments are, in our opinion, obligatory.

The possible role of DRD5 in regulating the activity of several GABAergic striatal interneurons could make association studies of DRD5 variants with the prevalence and severity of TD a very useful endeavor. To our knowledge, such studies are still lacking. A limitation might be that DRD5 SNPs with functional consequences have not yet been identified [183], although some evidence supports the involvement of the *DRD5* gene in idiopathic dystonia [122].

Executive summary

Theoretical background

- Tardive dyskinesia (TD) is a motor complication of long-term treatment with antipsychotic drugs, characterized by involuntary repetitive movements of mouth and face (orofacial/classic TD), neck, torso and extremities (limb-truncal/peripheral TD) and/or diaphragm and intercostal muscles (respiratory TD).
- TD is attributed to a dysfunction of parallel cortico-striatal-[direct/indirect pathway]-thalamo-cortical (CSTC) circuits including the dorsal striatum of the extrapyramidal system.
- Possible neostriatal cellular components are GABAergic medium spiny projection neurons (MSNs), GABAergic interneurons, cholinergic interneurons, corticostriatal and thalamostriatal glutamatergic neurons, dopaminergic neurons, serotonergic neurons and adrenergic neurons.
- Pharmacogenetics and epigenetics can be applied here by showing how changed activity of certain enzymes, transporters and/or receptors can modulate the severity of symptoms of that disorder.

Medium spiny neurons

- MSNs account for about 95% of the striatal neurons and can be divided into motor activity-augmenting, DRD1-carrying, direct pathway, and activity-diminishing, DRD2-carrying, indirect pathway, GABAergic projection neurons.
- Indirect pathway MSNs are more vulnerable to excitotoxicity/oxidative stress than direct pathway MSNs.

GABAergic interneurons

- Medium-sized, aspiny GABAergic interneurons account for 3–4% of striatal neurons and are organized within the context of striatal microcircuitry regulating the activity of MSNs.
- Parvalbumin-expressing, fast-spiking interneurons regulate relatively independently from other GABAergic interneurons and contribute to the inhibition of dopaminergic and serotonergic input to MSNs.

Cholinergic interneurons

- Giant, aspiny cholinergic interneurons account for 1–2% of striatal neurons, they affect activity of MSNs via excitatory M1-class and inhibitory M2-class CHRM receptors and the activity of glutamatergic and dopaminergic terminals as well as GABAergic interneurons via excitatory CHRN receptors.
- An observed association between CHRM2 variants and TD was likely secondary to other contributing factors.

Corticostriatal & thalamostriatal glutamatergic neurons

- The spines of matrix MSNs are targeted by converging corticostriatal and collaterals of thalamocortical glutamatergic fibers as well as by dopaminergic nigrostriatal terminals, which together with astroglial processes form converging 'striatal spine modules'.
- Intralaminar thalamostriatal neurons mainly target striatal cholinergic interneurons, which have a more widespread influence on the activity of CSTC circuits.
- The results of various association studies oppose the hypothesis of a possible role of striatal spine module dysfunction in TD.

Dopaminergic neurons

- Early pharmacogenetic studies have revealed associations between DRD2 and DRD3 variants and TD. DRD1 and DRD4 variants do not convincingly show a relationship. DRD5 has not yet been studied.
- Apart from VMAT2 (which concentrates monoamines into their synaptic vesicles), addressing enzymes and transporters affecting dopamine levels within the striatum did not demonstrate an important contribution to the prevalence or severity of TD.

Serotonergic neurons

- Cell bodies of neurons containing 5-HT, which are localized within upper brainstem raphe nuclei, are connected with midbrain dopaminergic areas and with both dorsal and ventral striatum.
- The results of association studies of HTR2C variant rs6318 were conflicting which may be partly explained by the use of atypical antipsychotics (HTR2A/2C blocking agents) by patients.

Adrenergic neurons

- The dorsal striatum is hardly targeted by terminals of neurons that synthesize norepinephrine, but these neurons may affect the severity of TD by modifying the anxiety level.
- The results of pharmacogenetic studies do not support a possible role for the adrenergic system in causing TD.

Complicating factors

- Dyskinesia can occur spontaneously and in drug-naïve persons with schizophrenia and these perhaps unrelated adverse movements may modify measured TD.
- The genetic background of the orofacial form of TD (classic TD) is probably different from that of peripheral and possibly also respiratory TD.
- Dopaminergic, serotonergic and adrenergic activity can modulate the severity of TD by affecting the functioning of other forebrain structures.

Conclusion

- The results of pharmacogenetic studies do not support a dominant contribution to the pathogenesis of TD of excess dopamine concentrations within the neostriatum.

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- Increased probability of excitotoxicity due to dysfunction of striatal spine modules of indirect pathway MSNs is also unlikely.
- Genetically determined increased vulnerability to oxidative stress of indirect pathway MSNs may represent a more plausible mechanism.
- HTR2C-associated overstimulation of indirect pathway MSNs, which would also enhance neurotoxicity, is also worthwhile considering as a possible mechanism.

Future perspective

- In future pharmacogenetic studies classic (orofacial) TD is better distinguished from peripheral (limb-truncal) TD with the addition of respiratory TD as a separate entity.
- Other advances may come from considering the usage of drugs with affinity to the receptor or enzymes studied and the influence of psychic phenomena (e.g., anxiety) on the severity of TD symptoms.
- The possible association between variants of DRD5 and CHRN with the prevalence and severity of TD has not been studied until now.

Acknowledgments

The authors greatly appreciate the help of Mrs Kate Barker who has proofread the manuscript. This work resulted from a collaboration between the Mental Health Research Institute in Tomsk and the Groningen Research Institute of Pharmacy (GRIP) of the University of Groningen. The Russian part is carried out within the framework of Tomsk Polytechnic University Competitiveness Enhancement Program, which did not provide financial assistance for research.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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10.2217/pgs-2019-0100