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Dysfunction of the corticostriatal pathway in autism spectrum disorders

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Abstract

The corticostriatal pathway that carries sensory, motor, and limbic information to the striatum plays a critical role in motor control, action selection, and reward. Dysfunction of this pathway is associated with many neurological and psychiatric disorders. Corticostriatal synapses have unique features in their cortical origins and striatal targets. In this review, we first describe axonal growth and synaptogenesis in the corticostriatal pathway during development, and then summarize the current understanding of the molecular bases of synaptic transmission and plasticity at mature corticostriatal synapses. Genes associated with autism spectrum disorder (ASD) have been implicated in axonal growth abnormalities, imbalance of the synaptic excitation/inhibition ratio, and altered long-term synaptic plasticity in the corticostriatal pathway. Here, we review a number of ASD-associated high-confidence genes, including *FMR1, KMT2A, GRIN2B, SCN2A, NLGN1, NLGN3, MET, CNTNAP2, FOXP2, TSHZ3, SHANK3, PTEN, CHD8, MECP2, DYRK1A, RELN, FOXP1, SYNGAP1,* and *NRXN,* and discuss their relevance to proper corticostriatal function.

Keywords

Corticostriatal pathway; long-term potentiation; long-term depression; autism spectrum disorders

1 | INTRODUCTION

The majority of cortical areas, including sensory, motor, and limbic cortices, send monosynaptic excitatory projections to the striatum (Hintiryan et al., 2016), which contribute to diverse sensorimotor and cognitive processing tasks (Graybiel, 2005, 2008; Haber, 2016; Yin & Knowlton, 2006). This glutamatergic corticostriatal pathway is strongly modulated by dopaminergic, cholinergic, GABAergic, and purinergic innervations, which underscores the complexity of this long-range circuit (Abudukeyoumu et al., 2019; Assous & Tepper, 2019; Gerfen & Surmeier, 2011; Mathur & Lovinger, 2012). Corticostriatal dysfunction has been involved in many neurological and psychiatric disorders, such as

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CONFLICT OF INTEREST

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amyotrophic lateral sclerosis, Huntington's and Parkinson's diseases, obsessive-compulsive disorder, attention-deficit hyperactivity disorder, and schizophrenia (Del Campo et al., 2011; Kuo & Liu, 2019; Rebec, 2018; Shepherd, 2013). This review aims to discuss current understanding of corticostriatal connectivity and describe its role in the context of autism spectrum disorder (ASD).

2 | STRUCTURE AND FUNCTION OF THE CORTICOSTRIATAL PATHWAY

The corticostriatal pathway has several unique features with regard to its cortical origin and striatal target. First, excitatory cortical projection neurons are classified into two distinct pyramidal cell types: intratelencephalic (IT) neurons and pyramidal tract (PT) neurons (Reiner et al., 2010; Shepherd, 2013). IT neurons project bilaterally to the striatum, whereas PT neurons project ipsilaterally to it. Second, the striatum is composed of the matrix and striosomal compartments, which receive axonal projections from the neocortex (including motor, somatosensory, and visual cortices) and the limbic cortex, respectively (Deng et al., 2015; Donoghue & Herkenham, 1986; Gerfen, 1984; Kincaid & Wilson, 1996; Ragsdale & Graybiel, 1990). Third, the main targets of cortical inputs in the matrix compartment are the spiny projection neurons (SPNs), which are also classified into two groups: SPNs of the direct pathway (dSPNs) that express D1 dopamine receptors (D1Rs) and project to the internal pallidal segment (GPi) and the substantia nigra pars reticulate (SNr), and SPNs of the indirect pathway (iSPNs) that express D2 dopamine receptor (D2Rs) and project to the external pallidal segment (GPe) (Gerfen 1989; Surmeier, Song, & Yan, 1996). A number of studies show that IT neurons primarily innervate dSPNs, whereas PT neurons target iSPNs (Lei et al., 2004; Reiner et al., 2010; but see Ballion et al., 2008; Kress et al., 2013). Furthermore, sensory cortex and limbic structures preferentially innervate dSPNs, while the motor cortex targets iSPNs (Wall et al., 2013; but see Guo et al., 2015). Such dichotomous properties of the corticostriatal pathway are also reflected in its distinctive development and the molecular composition of its synapses, as well as the properties of synaptic transmission and long-term plasticity.

2.1 | Development of corticostriatal synapses

2.1.1 | Axonal growth—Growth cones of corticofugal axon start to enter the developing striatum at embryonic day 12 (E12) (Sheth, Mckee, & Bhide, 1998). By E18, corticostriatal collaterals have been clearly observed to innervate the ipsilateral striatum, but callosal corticostriatal projections that could be clearly seen to innervate the contralateral striatum happen around postnatal day 3 (P3) (Sohur et al., 2014). At between P2–7, the corticostriatal arbors undergo a steady growth (Sheth, Mckee, & Bhide, 1998), and after P7 axonal growth declines, which coincides with the emergence of synapse formation (Dani, Armstrong, & Benowitz, 1991).

2.1.2 | Synaptogenesis—Corticostriatal synaptogenesis takes place after axons stopped growing. The number of dendritic spines is very few on SPNs at P6–7, and mature spines are first detected at P9–11 (Lee & Sawatari, 2011; Tepper et al., 1998). Then, dendritic spine density undergoes a marked increase until postnatal 3–4 weeks, when it stabilizes at levels comparable to those observed in the adult striatum (Sharpe & Tepper, 1998). In the

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dorsolateral striatum, dendritic spine pruning also occurs during this period (Uryu, Butler, & Chesselet, 1999). Morphological maturation of corticostriatal excitatory synapses is correlated with the maturation of their functional properties. Electrical stimulation of cortical afferents reliably evokes excitatory postsynaptic potentials (EPSPs) in SPNs at about P6, and at P21 the kinetics of EPSPs is similar to that in adult (Tepper et al., 1998). Similarly, optogenetic excitation of corticostriatal synapses evokes synaptic currents in SPNs at P6–7, and synaptic currents undergo a pronounced increase until they stabilize at P20–30 (Peixoto et al., 2016).

2.2 | Molecular bases of corticostriatal synapses

Corticostriatal excitatory synapses release glutamate from presynaptic terminals, which binds and open two main types of glutamate-gated ion channels: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) and N-methyl-D-aspartate receptors (NMDARs). In addition to this glutamatergic input, inhibitory GABAergic SPNs also receive feedback inputs from other SPNs, which constitute the majority of their GABAergic input. Apart from SPNs, the striatum contains a diverse population of GABAergic interneurons (Tepper, Wilson, & Koós, 2008). Early studies uncovered four classes of GABAergic interneurons: parvalbumin (PV)-expressing fast spiking (FS) interneurons, neuropeptide Y (NPY)/somatostatin (SOM)-expressing low-threshold spiking (LTS) interneurons, calretinin (CR)-expressing interneurons, and tyrosine hydroxylase (TH)-expressing interneurons (Tepper, et al., 2010). Recent investigations using 5HT3a-Cre mice in combination with electrophysiological and morphological approaches revealed three more GABAergic interneuron subtypes: neurogliaform (NGF) interneurons, fast-adapting (FA) interneurons, and spontaneously active bursty (SAB) interneurons (Tepper et al., 2018). It has been shown that among these GABAergic interneurons, FS and FA interneurons form strong inhibitory connections on SPNs whereas innervations of LTS and TH interneurons on SPNs are relatively weak. Furthermore, cholinergic interneurons generate robust tonic activity on SPNs (Abudukeyoumu et al., 2019), through their activation of nicotinic ACh receptors (nAChRs) and muscarinic ACh receptors (mAChRs). mAChRs are G protein-coupled receptors that are classified into group I (M1, M3, M5) and group II (M2, M4) receptors based on their intracellular signaling pathways. Group I mAChRs are coupled to $G_{q/11}$, which in turn activates protein kinase C (PKC) and phospholipase C (PLC), the latter producing inositol-tris-phosphate (IP3), resulting in an increase in intracellular Ca^{2+} caused by its release from intracellular Ca^{2+} stores with IP3 receptors. Group II mAChRs are coupled to $G_{i/o}$, which inhibits adenyl cyclase (AC) activity, thereby reducing cyclic adenosine monophosphate (cAMP) levels and closing voltage-gated Ca^{2+} channels (VGCCs). M1 receptors (M1Rs) are highly enriched in both dSPNs and iSPNs, while M4Rs are expressed predominantly in dSPNs. M2 and M3 receptors are present in corticorstriatal presynaptic terminals. As discussed above, corticostriatal synapses are subject to modulation by D1Rs and D2Rs. At the molecular level, D1Rs are coupled to $G_{s/olf}$, which stimulates AC and then activates protein kinase A (PKA), whereas D2Rs stimulate $G_{i/o}$, which targets VGCCs by inhibiting AC (Do et al., 2012; Gerfen & Surmeier, 2011).

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2.3 | Corticostriatal synaptic plasticity

Activity-dependent long-term alterations in the strength of corticostriatal synapses underlie striatal learning and habit formation (Koralek et al., 2012; Lerner & Kreitzer, 2011; Yin et al., 2009). Two forms of synaptic plasticity have been observed in the striatum: long-term potentiation (LTP) and long-term depression (LTD). However, the stimulation protocols that induce LTP and LTD at excitatory synapses in the hippocampus result in different outcomes at corticostriatal excitatory synapses. For example, the typical LTP-inducing high-frequency stimulation (HFS) of presynaptic afferents in the presence of normal extracellular Mg^{2+} results in the induction of LTD in the striatum (Kreitzer & Malenka, 2005; Lovinger, Tyler, & Merritt, 1993). Moreover, synaptic plasticity in the striatum is not homogenously expressed. For instance, LTP is primarily observed in the dorsomedial and rostral striatum, whereas LTD is more common in the dorsolateral and caudal striatum (Partridge, Tang, & Lovinger, 2000).

2.3.1 | Corticostriatal LTP—Several approaches have been used to induce LTP at corticostriatal synapses in *ex vivo* slices of the striatum. LTP can be reliably evoked by HFS in the absence of Mg^{2+}, which removes its block of the NMDAR ion channel pore (Calabresi et al., 1992; Kerr & Wickens, 2001). Stimulation of cortical afferents with a more physiologically relevant theta-burst stimulation (TBS) also induces LTP at corticostriatal synapses in Mg^{2+}-containing aCSF (Hawes, et al., 2013; Park, Popescu, & Poo, 2014). Furthermore, different protocols of spike-timing-dependent plasticity (STDP) have been shown to induce corticostriatal LTP (Perrin & Venance, 2019). LTP can be induced by pairing presynaptic stimulation and postsynaptic action potentials in a presynaptic->postsynaptic order, either with a TBS pattern or at lower rate (0.1Hz) (Pawlak & Kerr, 2008; Shen et al., 2008). On the other hand, pairing at 1Hz with a reversed order (postsynaptic spikes preceding presynaptic stimulation), induces LTP (Fino, Glowinski, & Venance, 2005; Cui et al., 2015, 2016), instead of the commonly observed LTD after low frequency stimulation. In addition to the difference in the rate of paired stimulation, this apparent inconsistency can be explained by differences in experimental conditions. Among them, the use of an antagonist of GABA receptors is critical, because it was later found to be able to reverse the direction of the plastic change (Fino et al., 2010; Paille et al., 2013; Valtcheva et al., 2017).

LTP at corticostriatal synapses requires proper expression levels and function of NMDARs, D1Rs, A2-type adenosine receptors (A2ARs), and mAChRs (Lovinger, 2010) (Figure 1). Pharmacological blockade or genetic deletion of NMDARs prevents different forms of LTP at corticostriatal synapses (Calabresi et al., 1992; Dang et al., 2006; Hawes et al., 2013; Kerr & Wichens, 2001; Jia et al., 2008). Selective deletion of the GluN1 subunit of NMDARs from cortical projecting neurons also abolishes LTP, indicating that presynaptic NMDARs are as important for LTP as postsynaptic NMDARs are (Park, Popescu, & Poo, 2014). D1Rs are involved in corticostriatal LTP (Calabresi et al., 2007), because an antagonist of D1R impairs LTP (Calabresi et al., 2000; Calabresi et al., 1992; Kerr & Wichens, 2001). Interestingly, selective blockade of D1Rs in dSPNs results in corticostriatal LTD when the LTP-eliciting STDP protocol is used (Shen et al., 2008). In D2R-expressing iSPNs, LTP requires A2ARs, which function similarly as D1Rs in dSPNs (Shen et al., 2008). Evidence

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also suggests that ACh also plays a significant role in corticostriatal LTP: selective inhibition of M1R activity prevents LTP induction (Calabresi et al., 1999). The function of M1 in LTP could be mediated through modulation of NMDARs (Calabresi et al., 1998a). In contrast, inhibition of M2R activity enhances LTP (Calabresi et al., 1998b). Furthermore, activation of M4Rs in dSPNs prevents D1R-dependent LTP, likely through decreasing NMDAR-mediated Ca^{2+} release from intracellular stores (Shen et al., 2015).

2.3.2 | Corticostriatal LTD—Several protocols have been used to evoke LTD at corticostriatal synapses. HFS induces LTD in striatal slices in the presence extracellular Mg^{2+} (Calabresi et al., 1992; Lovinger, Tyler, & Merritt, 1993). Like for spike-timing-dependent LTP, several STDP protocols have been shown to induce LTD. For example, spike-timing-dependent LTD can be induced by the conventional "postsynaptic->presynaptic" protocol, in which the postsynaptic spike precedes the presynaptic spike (Pawlak & Kerr, 2008; Shen et al., 2008); however, it can also be induced by the "presynaptic->postsynaptic" paring under certain conditions (Fino, Glowinski, & Venance, 2005; Cui et al., 2015, 2016). Furthermore, LTD can be also induced by pharmacological activation of group I metabotropic glutamate receptors (mGluRs), mGluR1 and/or mGluR5, either by itself or in combination with a small postsynaptic depolarization (Gubellini et al., 2003; Kreitzer & Malenka, 2005; Sung, Choi, & Lovinger, 1997; Wu et al., 2015). Of note, there is also evidence showing that group I mGluRs may be involved in LTP in dorsal and ventral striatum (Gubellini et al., 2003; Schotanus & Chergui, 2008). LTD requires retrograde signaling by endocannabinoids (eCB) (Gerdeman, Ronesi, & Lovinger, 2002; Ronesi, Gerdeman, & Lovinger, 2004), which are generated by two distinct biosynthetic pathways: (1) phospholipase D (PLD) catalyzes anandamide (AEA) to eCB, and (2) PLCβ and diacylglycerol lipase α (DGLα) catalyze DAG to eCB. Consistently, PLCβ is activated by group I mGluRs and VGCC activity. Therefore, it is plausible that LTD induction results in the activation of postsynaptic L-type VGCCs and mGluR5, which triggers the synthesis of eCBs that diffuse retrogradely to activate presynaptic CB1 receptors (CB1Rs) that in turn reduce presynaptic glutamate release by acting on presynaptic VGCCs. In addition to this eCB-dependent presynaptic form of LTD, a postsynaptic form of LTD that depends on the synthesis and diffusion of nitric oxide (NO) has been reported at corticostriatal synapses. Inhibition of NO synthesis and its downstream target cGMP hinders LTD induction (Calabresi et al., 1999). This NO signal may originate from striatal interneurons because selectively activating guanylyl cyclase (GC) and protein kinase G (PKG) in SPNs induces LTD (Rafalovich et al., 2015).

Whether different striatal cell types exhibit specific forms of LTD has been interrogated for many years; however, no decisive conclusion has been reached. Some studies show that LTD induced by moderate frequency stimulation of cortical afferents is expressed in D2R-expressing iSPNs, but not in D1R-expressing dSPNs (Kreitzer & Malenka, 2005, 2007). However, in several other studies using HFS, LTD is induced in both cell types (Bagetta et al., 2011; Wang et al., 2006). Furthermore, by using an STDP protocol with electric stimulation, LTD can be induced in iSPNs, and also in dSPNs provided that D1R activity is abolished (Shen et al., 2008). Interestingly, LTD induced by pharmacological activation of mGluRs occurs in both dSPNs and iSPNs even in the absence of a D1R antagonist (Wu et

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al., 2015); this study also shows that LTD induced with an STDP protocol using optogenetic stimuli is observed not in iSPNs but rather in dSPNs. These discrepancies are thought to be caused by different stimulus patterns, *ex vivo* slices cut at different planes, and different neuromodulatory systems recruited during LTD induction.

D2Rs, mAChRs, serotonin (5-HT) receptors, and opioid receptors also play a significant neuromodulatory role in corticostriatal LTD. $G_{i/o}$-associated D2Rs are negatively coupled to AC5, an intracellular enzyme that catalyzes the production of cAMP (Kheirbek et al., 2009). Reduced cAMP synthesis during D2R activation results in a reduction in phosphorylated PKA, which leads to decreased Ca^{2+} influx into dendritic spines through NMDARs (Higley & Sabatini, 2010). Furthermore, the reduction of PKA also results in decreased activation of regulator of G protein signaling 4 (RGS4), leading to disinhibition of mGluR signaling through G_q (Huang et al., 2007; Lerner & Kreitzer, 2012; Saugstad et al., 1998). In addition, by suppressing RGS4 activity in dSPNs, endogenous cholinergic signaling through M4Rs promotes LTD, while also preventing DIR-dependent LTP (Shen et al., 2015). M1Rs are also involved in LTD induction (Wang et al., 2006). D2R stimulation in striatal interneurons results in reduced release of ACh and decreased activation of M1Rs in SPNs, ultimately leading to disinhibition of L-type VGCC activity. In addition, activation of 5-HT receptors results in corticostriatal LTD, which may use similar presynaptic mechanisms as eCB (Mathur et al., 2011). Activation of μ or δ opioid receptors also induces LTD, but it is mechanistically distinct from eCB-LTD (Atwood, Kupferschmidt, & Lovinger, 2014).

3 | CORTICOSTRIATAL DYSFUNCTION AND ASD

ASD, the most prevalent neurodevelopmental disorders, is used to define a clinically heterogeneous group of disorders, while it generally exhibits two core symptoms, impaired social communication and repetitive behaviors (Bhat et al., 2014; Fakhoury, 2015). A large number of risk genes that are associated with ASD pathogenesis have been identified (Nakanishi et al., 2019; Verma et al., 2019). Studies on ASD-related genes have indicated altered axonal growth, imbalance of neural network excitation/inhibition, and impaired synaptic plasticity in the corticostriatal pathway (Fuccillo, 2016; Golden, Buxbaum, & De Rubeis, 2018; Kuo & Liu, 2019; Shepherd, 2013). Below we first discuss the current findings of corticostriatal dysfunction in experimental models of high-confidence ASD-associated genes (Table 1). As many studies have examined the role of striatal abnormality, but not specifically of corticostriatal dysfunction in other ASD genes, we also describe these findings in the next section, which may prompt future investigations of the dysfunction of the corticostriatal pathway.

3.1 | Role of ASD genes in corticostriatal dysfunction

3.1.1 | FMR1—Mutations in the human *FMR1* gene cause Fragile X Syndrome (FXS), the most common inherited form of intellectual disability (Bagni & Oostra, 2013). FXS individuals suffer from cognitive impairment, delayed language development, hyperactivity, epilepsy, repetitive behavior, and social withdrawal. *FMR1* encodes the fragile X mental retardation protein 1 (FMRP1), an RNA-binding protein that regulates cellular localization and translation of a large number of mRNAs encoding synaptic proteins. Impaired FMRP1

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function results in immature dendritic spines, excitation/inhibition imbalance, and altered mGluR-mediated LTD in many brain regions in mouse models of FXS, including the hippocampus and cerebellum (Dahlhaus, 2018). FMRP1 is abundantly expressed in the cortex and striatum (Bonaccorso et al., 2015). Neuroimaging studies in FXS children or adults show an abnormal growth of gray matter volumes in the caudate and an increased density of fibers of the ventral frontostriatal pathway, as compared with age-matched controls (Hallahan et al., 2010; Hass et al., 2009; Hoeft et al., 2010). Functional MRI brain imaging demonstrates that the frontostriatal circuit normally associated with response inhibition is dysfunctional in FXS patients (Menon et al., 2004). The corticostriatal circuitry that processes sensory information is hypoactive in *Fmr1* knockout (KO) mice (Zerbi et al., 2018). Furthermore, an enhancement in GABAergic synaptic transmission occurs in the striatum due to elevated presynaptic GABA release (Centonze et al., 2008). In these mice, 2-AG biosynthesis is compromised, leading to impaired mGluR-LTD in the ventral striatum (Jung et al., 2012). FXS patients treated with cannabidiol, an exogenous phytocannabinoid, show significant improvements in motor coordination, social anxiety and avoidance, and sensory processing (Targaglia, Bonn-Miller, & Hagerman, 2019). In addition, *Fmr1* KO mice show lower expression levels of M1Rs in the striatum; restoration of these receptors and inhibition of acetylcholinesterase activity by pharmacological treatments alleviate their locomotor hyperactivity (Qiu et al., 2016). Studies characterizing the functional state of the corticostriatal pathway in FXS animal models are lacking.

3.1.2 | KMT2A—The *lysine (K) methyltransferase 2a* (*KMT2A*) gene located on chromosome 11 encodes the H3K4 methyltransferase enzyme, which plays a key epigenetic role for gene transcription in the brain (Hyun et al., 2017). Gene sequencing studies have identified the correlation of *de novo KMT2A* variants with ASD occurrence (C Yuen et al., 2017; Lelieveld et al., 2016; Shen et al., 2014). Conditional KO (cKO) of *Kmt2a* in neurons of the mouse prefrontal cortex results in altered methylation at multiple genes important for emotion and cognitive function (Jakovcevski et al., 2015). Layer V pyramidal neurons in the medial prefrontal cortex in *Kmt2a* cKO mice show impaired short-term synaptic plasticity and temporal summation of synaptic responses. STDP-LTP evoked by stimulation of the anterior commissure is absent in SPNs of the ventral striatum (Shen et al., 2016). These mice also show heightened anxiety, which is consistent with increased expression of anxiety-related genes. Virally-mediated *Kmt2a* deletion in the ventral striatum is sufficient to replicate the ASD-like phenotypes, suggesting the involvement of *Kmt2a* in proper striatal function.

3.1.3 | GRIN2B—The GluN2B subunit encoded by *GRIN2B* is a major component of NMDARs that mediates excitatory synaptic transmission in the brain (Sun et al., 2018). Variants and *de novo* mutations in the human *GRIN2B* gene have been identified in several neurodevelopmental and psychiatric disorders, including ASD (Hu et al., 2016). *Grin2b* is highly expressed during the prenatal period and starts to decline after birth in mice, which suggest that it plays an important role in neuronal migration and differentiation, synaptogenesis, and circuit formation (Monyer et al., 1994). Indeed, *Grin2b* deficiency results in delayed migration, increased dendritic length and branching, and impaired developmental synapse elimination in the developing cortex (Jiang et al., 2015; Ohno et al.,

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2010). Conditional deletion of *Grin2b* in the hippocampus results in NMDAR-mediated excitatory postsynaptic currents (EPSCs) with altered kinetics, impaired synaptic plasticity, reduced synapse density, and learning deficits (Brigman et al., 2010), while its overexpression in the forebrain enhanced LTP at excitatory hippocampal synapses and spatial memory (Tang et al., 1999). It was reported that NMDARs containing the GluN2B subunit modulate action selection in corticostriatal system (Brigman et al., 2013). Both postsynaptic and presynaptic NMDARs are shown to be equally important for the induction of LTP at corticostriatal synapses (Park, Popescu, & Poo, 2014), although it is unclear whether GluN2B-containing NMDARs in presynaptic terminals are involved in this plasticity.

3.1.4 | SCN2A—Mutations in the human *SCN2A* gene encoding for the voltage-gated sodium channel $Na_v1.2$ have been identified as a prominent cause of ASD (Sanders et al., 2018). $Na_v1.2$ localizes to the axon initial segment and is involved in the initiation and propagation of action potential in neurons. Expressing the adult isoform of *SCN2A* in neonatal neurons results in increases in action potentials, seizure susceptibility, and risk-taking behavior (Gazina et al., 2015). In addition to its role in modulating neuronal excitability in early development, $Na_v1.2$ loss in mature neurons reduces action potential backpropagation and dendritic excitability, and impairs synaptic efficacy in a cell-autonomous fashion (Spratt et al., 2019). *Scn2a* haplodeficiency in mice results in deficit in spatial memory (Middleton et al., 2018). These mice also show impaired corticostriatal synaptic transmission, while the cortico-thalamic circuit is unaffected. Such altered corticostriatal synaptic transmission has been recognized as the cellular mechanism underlying absence seizures; however, whether it is also a mechanism responsible for motor and cognitive dysfunction in ASD has not been studied (Miyamoto et al., 2019).

3.1.5 | NLGN1—The *NLGN1* gene encodes a cell adhesion molecule that is primarily localized at excitatory synapses (Song et al., 1999). Copy number variants (CNV) analysis has implicated *NLGN1* as a susceptibility gene for ASD (Glessner et al., 2009). Mouse models deficient in *Nlgnl* or carrying missense variants demonstrate ASD-relevant behavioral abnormalities including repetitive grooming and social impairment (Blundell et al., 2010; Nakanishi et al., 2017). *Nlgnl* KO results in a decrease in NMDA/AMPA ratio in the dorsal striatum, which is correlated with repetitive behaviors (Blundell et al., 2010). Such reduction mainly results from decreased expression of GluN2A-containing NMDARs, and occurs exclusively at synapses between cortical afferent and dSPNs (Espinosa et al., 2015). No apparent difference in short-term plasticity at corticostriatal synapses was found in direct and indirectly pathways, but whether long-term plasticity such as LTP and LTD remains unaltered was not determined.

3.1.6 | NLGN3—The X-linked *NLGN3* gene, another family member of *NLGN,* is associated with ASD (Quartier et al., 2019). Both *NLGN3* deletion and point mutations result in deficits in social behaviors, and repetitive and stereotyped movements (Rothwell et al., 2014; Tabuchi et al., 2007). NLGN3 plays a critical role in the development and plasticity of excitatory and inhibitory neurons, by interacting its presynaptic partner neurexin (Südhof, 2008). In the striatum, *Nlgn3* KO does not impair excitatory synaptic function in

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dSPNs and iSPNs (Rothwell et al., 2014). However, *Nlgn3* deletion causes a decreased inhibitory synaptic transmission onto dSPNs but not iSPNs in the ventral striatum. It remains unaffected in the dorsal striatum. Furthermore, LTD induced by pharmacological activation of CB1R was found to be normal in excitatory and inhibitory synapses in striatal dSPNs and iSPNs. However, HFS-LTD is affected at dorsal striatum excitatory synapses, which can be partially rescued by pretreatment of CB1R activation (Martella et al., 2018). These findings suggest that the effect of *Nlgn3* dysfunction on striatal function varies, depending on brain regions, synapse types, and experimental protocols.

3.1.7 | MET—*MET* is an ASD risk gene that encodes receptor tyrosine kinase required for many signaling events during neurodevelopment (Campbell et al., 2006, 2007). SNP in the *MET* promoter and CNVs lead to social and communication phenotype (Campbell et al., 2010). Mapping of MET expression in the brain shows high levels of the receptor in the cortex, hippocampus, and amygdala (Judson et al., 2009). Synaptic mapping in the anterior frontal cortex *Met* cKO mice shows stronger excitatory input to layer V corticostriatal neurons from layer M/III neurons, when compared with the local circuit in WT controls (Qiu et al., 2011). The intracortical hyperconnectivity is likely to impact downstream pathways in the subcortical region. Indeed, SPNs that receive corticostriatal afferents have a markedly increase in dendritic arborization and spine volume, although they do not express MET (Judson et al., 2010). Nonetheless, whether the morphological alteration is accompanied by changes in synaptic transmission and plasticity in this pathway remains unknown.

3.1.8 | CNTNAP2—Contactin-associated protein-like 2 (CASPR-2) is a neural transmembrane protein that belongs to the neurexin family (Dean & Dresbach, 2006) and is crucial for dendritic arborization and dendritic spine formation (Anderson et al., 2012). Genetic variants in the human *CNTNAP2* gene have been found in individuals with ASD (Klein et al., 2017; Varghese et al., 2017). Deletion of *Cntnap2* results in impaired cortical neuronal migration, decreased number of cortical interneurons, and altered neural network activity in the hippocampus and cortex (Penagarikano et al., 2011). Dendritic spine density is lower in *Cntnap2* KO mice, which is accompanied by lower synaptic levels of the AMPAR subunit GluA1 (Varea et al., 2015). *Cntnap2* is highly expressed in the striatum during development. Profiling the genome-wide 5-hydroxymethylcytosine (5hmC) in the striatum of *Cntnap2* KO mice discovered that this epigenetic modification is largely disrupted in many ADS-associated genes including *RELN* (Papale et al., 2015). In addition, the number of striatal PV-positive interneurons is lower in *Cntnap2* KO mice, which disturbs proper cortico-striato-thalamic circuitry activity important for language and speech, reward, and executive function (Lauber, Filice, & Schwaller, 2018).

3.1.9 | FOXP2—*FOXP2,* a member of the Fox family, has been shown to be associated with ASD; individuals with *FOXP2* mutations manifest spoken language disability (Vargha-Khadem et al., 2005). *FOXP2* interacts with several ASD risk genes, including *CNTNAP2* and *MET* (Mukamel et al., 2011; Vernes et al., 2008). In the mouse striatum carrying homozygous human *FOXP2* mutations, SPNs exhibit increased dendritic length and increased corticostriatal LTD (Enard et al., 2009). On the contrary, mice heterozygous for *FOXP2* mutations show impaired LTD at corticostriatal synapses and impaired motor skill

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learning (Groszer et al., 2008). The modulation of corticostriatal synapse formation by FOXP2 may be through its negative interaction with the synapse suppressor gene *myocyte enhancer factor 2C* (*Mef2c*), as the function of *Mef2c* can be repressed by FOXP2 (Chen et al., 2016). However, irrespective of homozygous or heterozygous deletion of *Foxp2,* the modulation of synaptogenesis by FOXP2 is positively regulated. Further investigation of how the deficiency of FOXP2 affects corticostriatal synaptic plasticity is necessary.

3.1.10| TSHZ3—The *teashirt zinc finger homeobox 3* (*TSHZ3*), encoding the transcription factor TSHZ3, has an essential role in cortical development (Kang et al., 2011). A genome-wide association study indicates that *TSHZ3* is a susceptibility gene for ASD (Hussman et al., 2011). Postnatal *Tshz3* cKO from cortical projections induces altered expression of a large number of genes, many of which have the human orthologue known to be involved in ASD (Chabbert et al., 2019). In the corticostriatal synapses of these mice, presynaptic release probability is decreased and the ratio of NMDAR- and AMPAR-mediated synaptic transmission is enhanced, the latter of which may be responsible for LTD deficit but spare LTP (Chabbert et al., 2019). In contrast, constitutive *Tshz3 heterozygous* mice demonstrate some opposite synaptic features, increased release probability, normal NMDA/AMPA ratio, and enhanced LTP (Caubit et al., 2016). These discrepancies may be due to the induction difference of *Tshz3* loss and the involvement of the compensatory mechanism.

3.1.11| SHANK3—The *SH3 and multiple ankyrin repeat domains 3* (*SHANK3*) gene encodes the protein SHANK that is localized at the core of the postsynaptic density (Sheng & Kim, 2000). *SHANK3* mutations have been implicated in ASD because its haploinsufficiency causes ~1% of all individuals with ASD (Uchino & Waga, 2013). Shank regulates excitatory synapse structure and function by interacting with scaffolding proteins and glutamatergic receptors via protein binding domains (Ehlers, 1999). Consistently, lower dendritic spine density and impaired function of AMPARs and NMDARs are common deficits in mice with *Shank3* mutations (Jaramillo et al., 2016; Sala et al., 2015). In *Shank3* KO mice, surface expression of several glutamate receptors is downregulated in the striatum (Heise et al., 2018). Consistently, corticostriatal synaptic transmission is reduced in these mice (Peca et al., 2011); unexpectedly, this study also shows increased dendritic complexity. Notably, SHANK3 mediates mGluR5 signaling in the striatum, and pharmacological enhancement of this pathway rescues behavioral deficits in *Shank3* KO mice (Vicidomini et al., 2017). The striatum is also known to specifically contribute to preservative exploratory behaviors, which is different from the cortex where the grooming behavior is expressed (Bey et al., 2018). Furthermore, a report shows the indirect, but not the direct, striatal pathway is involved in repetitive behaviors (Wang et al., 2017). At the molecular level, proteomic analysis striatal samples from *Shank3* KO revealed a downregulation of several proteins that are encoded by ASD susceptibility genes (Reim et al., 2017).

3.2 | Role of ASD genes in striatal abnormality

3.2.1 | PTEN—*Phosphatase and tensin homolog* (PTEN) dephosphorylates phosphatidylinositol 3,4,5-trisphosphate (PIP3) to generate PIP2, thereby suppressing the activity of phosphoinositide 3-kinase (PI3K) pathway (Sun et al., 1999). The human *PTEN*

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gene, located on chromosome 10q23, has been identified as the susceptibility gene for macrocephalic ASD (Hobert et al., 2014). Consistently, mice deficient in *Pten* have increased cell number and size, and abnormal social interactions (Groszer et al., 2001; Kwon et al., 2006). Conditional deletion of *Pten* in Purkinje cells (PCs) also results in autistic-like features in adult mice, and these PCs show altered morphology and impaired synaptic function (Cupolillo et al., 2016). In addition, PTEN acts as regulator of DAergic signaling in an animal model of Parkinson's disease induced by 6-OHDA (Stavarache et al., 2015). However, it is unknown whether PTEN dysregulation alters the functional state of the corticostriatal pathway.

3.2.2 | CHD8—Chromodomain helicase DNA-binding protein 8 (CHD8) is an ATP-dependent chromatin remodeling protein that plays a critical role in transcriptional regulation during development (Barnard, Pomaville, & O'Roak, 2015). The human *CHD8* gene has been identified as one of the most consistently replicated ASD genes (Ayhan & Konopka, 2019; Tammimies, 2019). Whereas homozygous deletion of *Chd8* is embryonically lethal in mice as a result of severe apoptosis (Nishiyama et al., 2009), *Chd8* haploinsufficiency mouse models display the large brain volume and mild social deficits reminiscent of some features of individuals with ASD harboring *CHD8* mutations (Gompers et al., 2017; Katayama et al., 2016; Suetterlin et al., 2018). Gene expression studies in *Chd8* haploinsufficiency mice have demonstrated widespread upregulation and downregulation of many genes known to be important for cell cycle regulation, and chromatin and histone modification (Durak et al., 2016; Gompers et al., 2017; Katayama et al., 2016). Notably, *Chd8* deficiency results in altered activation of the RE-1 silencing transcription factor (REST) and lower levels of Wnt-β-catenin signaling. *In utero* knockdown of *Chd8* in embryonic cortical neurons results in altered neural proliferation, reduced complexity of dendritic arborization, and lower dendritic spine density (Durak et al., 2016). Mice carrying human mutant *CHD8* show sexually dimorphic changes in excitatory and inhibitory synaptic transmission, and neuronal firing (Jung et al., 2018). RNAi-mediated *Chd8* knockdown results in delayed neuronal migration, altered callosal projection, and reduced axonal and dendritic arborization (Xu et al., 2018). Synaptic dysfunction was also found in SPNs of the ventral striatum. *Chd8* loss-of-function mice show increased excitatory and decreased inhibitory activity in the striatal circuitry (Platt et al., 2017). Interestingly, although locomotion is reduced in these mice, acquired motor learning is improved, which has been observed in other ASD mouse models (Rothwell et al., 2014); however, whether synaptic activity in the dorsal corticostriatal pathway is dysfunctional was not determined. To date, the consequences of enhanced excitation and impaired inhibition in the striatum on specific ASD-like behaviors is unknown.

3.2.3 | MECP2—Methyl-CpG binding protein 2 (MeCP2) is the founding member of the family of methyl-DNA-binding proteins, and initially described as a transcriptional repressor of genes with methylated CpG islands in their promoter regions (Guy et al., 2011). Loss-of-function mutations in the human *MECP2* gene, located on chromosome Xq28, are the cause of Rett syndrome (RTT), a neurodevelopmental disorder with severe neurological and cognitive deficits, including ASD-like features during the regression phase of the disease (Neul et al., 2010). Because of the severity of their neurological symptoms, boys

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hemizygous for *MECP2* mutations perish during early infancy, while girls heterozygous for these mutations due to X-chromosome inactivation survive longer, albeit with RTT. Individuals with RTT develop typically until 6–18 months when a constellation of neurological and cognitive symptoms begins to develop (Li & Pozzo-Miller, 2012; Neul et al., 2010). Mouse models of *Mecp2* deletion and loss-of-function result in subtle changes in the morphology and function of brain cells and synapses, but with profound consequences on neural network activity (Li & Pozzo-Miller, 2012). A wealth of evidence has pointed to the involvement of striatal dysfunction in the pathogenesis of RTT. Volumetric analyses from MRI brain imaging studies in RTT individuals revealed reductions in the caudate nucleus, a major component of the striatum (Dunn et al., 2002; Naidu et al., 2001; Reiss et al., 1993; Subramaniam, Naidu, & Reiss, 1997). Consistently, *Mecp2*-based mouse models of RTT exhibit characteristic hind limb clasping and reduced striatum volume (Chen et al., 2001; Guy et al., 2001). Selective *Mecp2* deletion in the striatum is sufficient to cause the same RTT-like motor deficits that occur in constitutive *Mecp2* KO mice, while *Mecp2* re-expression locally in the striatum improves motor function (Su et al., 2015). Expression levels of AMPARs, NMDARs, and GABARs are affected in the striatum of RTT individuals (Blue, Naidu, & Johnston, 1999). In RTT, the levels of D2Rs and DAT are altered in the caudate nucleus and putamen, but D1Rs are not affected (Chiron et al., 1993; Harris et al., 1986; Wenk, 1995; Wong et al., 1998). In addition, the striatum of *Mecp2* KO mice expresses lower levels of the dopamine synthetic enzyme TH (Panayotis et al., 2011), and dopamine release from afferent axons of substantia nigra pars compacta (SNpc) into the striatum is reduced in *Mecp2* KO mice (Gantz et al., 2011). Despite these early observations, however, it is currently unknown whether the cortical input to SPNs is altered in *Mecp2*-based mouse models.

3.2.4 | DYRK1A—Dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) modulates various intracellular signaling cascades by interacting with cytoskeleton proteins in the cytoplasm (Hämmerle, Elizalde, & Tejedor, 2008), and its gene is highly conserved and located in the Down syndrome regions of chromosome 21. In addition, *DYRK1A* mutations have emerged as a high-confidence cause for ASD that manifests with microcephaly, intellectual disability, speech impairments, seizures, and abnormal gait (Courcet et al., 2012; van Bon et al., 2011). Homozygous *DyrklA* KO mice die in the mid-gestational phase, while *DyrklA* heterozygous mice survive into adulthood, but exhibiting delayed brain development and motor impairments (Fotaki et al., 2002, 2004). *DyrklA* gene dosage is critical for neuron development, because both its overexpression and loss-of-function result in impaired dendritic complexity and lower dendritic spine density in cortical neurons (Benavides-Piccione et al., 2005; Martinez de Lagran et al., 2012). Mice carrying one copy of human *DYRK1A* gene show altered bidirectional synaptic plasticity in the hippocampus, as well as impaired spatial learning (Ahn et al., 2006). Also, mice harboring a frame-shift mutation in *DyrklA* show DYRK1A haploinsufficiency and as a result exhibit deficits in ultrasonic commutations and social contacts (Raveau et al., 2018). Intriguingly, reducing Dyrk1a levels only in the striatum is sufficient to rescue several corticostriatally-dependent phenotypes, such as hypoactive behavior, coordination impairments, and sensorimotor gating (Oritz-Abalia, et al., 2008).

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3.2.5 | RELN—The large secreted glycoprotein Reelin binds to the extracellular domains of very-low-density-lipoprotein receptor (VLDLR) and apolipoprotein E receptor 2 (APOER2), and their signaling is then transduced to intracellular adaptor protein Disabled-1 (DAB1). Phosphorylated DAB1 can activate many downstream effectors, including the kinases PI3K and AKT. Thus, the Reelin-DAB1 signaling pathway plays a critical role in controlling neuronal migration and aggregation, and neurite branching and synaptic function (Hirota & Nakajima, 2017; Wasser & Herz, 2017). Several single nucleotide polymorphisms (SNPs) in the human *RELN* gene, located in chromosome 7 (Armstrong, Anderson, & McDermott, 2019), are associated with an increased risk of ASD (Lammert & Howell, 2016). Homozygous *Reln* mutant mice show abnormal social behavior (Salinger, Ladrow, & Wheeler, 2003). Reelin, VLDLR, APOER2, and DAB1 are all highly expressed in the striatum (Sharaf et al., 2015). In heterozygous *Reln* mice, the expression levels of D2Rs are higher in the striatum, while 5-HT levels are lower (Nullmeier et al., 2014; Varela et al., 2015). However, the role of Reelin in corticostriatal synaptic dysfunction in ASD models is unclear.

3.2.6 | FOXP1—*FOXP1,* a member of the Fox family, encodes the transcriptional factor FOXP1 (Kaestner, Knochel, & Martinez, 2000). *Foxpl* is highly expressed in multiple brain regions, including the striatum (Ferland et al., 2003), and especially in precursor and mature SPNs where it is responsible for their differentiation and expression of the characteristic biomarker DARPP-32 (Precious et al., 2016). Individuals with deletions, point mutation, or translocations in the human *FOXP1* gene have delayed development, speech, and motor activity (Bowers & Konopka, 2012). Constitutive *Foxpl* KO mice die at the embryonic phase (Wang et al., 2004), while conditional *Foxpl* deletion in neurons results in altered morphology, excitability, and increased synaptic transmission in the striatum and hippocampus (Bacon et al., 2015). *Foxpl* deficiency results in altered neuron proliferation-related pathways in the striatum, as well as increased dendritic branching, impaired social behavior, repetitive behavior, and hyperactivity. Furthermore, FOXP1 directly regulates ASD-relevant genes in the striatum, and differentially influence excitability of dSPNs *vs.* iSPNs (Araujo et al., 2015). However, the role of FOXP1 in corticostrial synaptic transmission and plasticity is still unclear.

3.2.7 | SYNGAP1—SynGAP1 is a postsynaptic protein that is encoded by *SYNGAP1* and functions downstream of NMDARs and the scaffolding protein postsynaptic density-95 (PSD-95). Its activity is regulated by Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) (Kim et al., 1998). SynGAP1 acts to restrict the insertion of AMPARs by negatively regulating RAS-GTPase activity. Mutations in the human *SYNGAP1* are common in sporadic ASD (Berryer et al., 2013; Parker et al., 2015). Heterozygous *Syngapl* KO mice display significant behavioral abnormalities, including reduced seizure threshold, hyperactivity, stereotypic behaviors, and learning and cognitive deficits. *Syngapl* deficiency is associated with accelerated maturation of glutamatergic synapses and enhanced synaptic transmission (Clement et al., 2012). SynGAP1 is highly expressed in both glutamatergic and GABAergic neurons in the striatum (Porter et al., 2005). One study reports that there is no alteration in seizure threshold, anxiety levels, and learning in *Syngapl* cKO mice lacking SynGAP1 only in GABAergic interneurons, including SPNs (Ozkan et al., 2014); however,

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it was not tested whether corticostriatal synaptic function and ASD-related phenotype are altered in these *Syngapl* cKO mice.

3.2.8 | NRXN—Neurexins are heterophilic cell adhesion molecules present in presynaptic terminals that bind ligands such as neuroligins (NLGN1) and cerebellin/GluD complexes localized in postsynaptic compartments and mediate trans-synaptic signaling during synapse differentiation and maturation (Südhof, 2017). The human Neurexin (*NRXN*) gene consists of *NRXN1, NRXN2,* and *NRXN3,* each encoding α-neurexin and β-neurexin under control of different promoters (Kasem, Kurihara, & Tabuchi, 2018). CNVs and point mutations in *NRXN* (particularly in *NRXN1*) have been associated with ASD (Reichelt, Rodgers, & Clapcote, 2012). *Nrxn2α-deficient* mice exhibit impaired social interaction and heightened anxiety (Born et al., 2015). α-Neurexin is also required for presynaptic Ca^{2+}-triggered transmitter release and VGCC function (Dudanova et al., 2006), and its deletion results in an impairment of neurotransmitter release at both excitatory and inhibitory synapses. A single-cell mRNA profiling study shows that a spliced isoform of neurexin1 is preferentially expressed in dSPNs of the ventral striatum (Fuccillo et al., 2015). Whether this specific expression pattern contributes to a unique role for corticostriatal circuitry in ASD models has not been determined yet.

4 | CONCLUSION

The corticostriatal pathway that conveys sensory, motor, limbic information to the striatum plays a critical role in motor control, action selection, and reward. Dysfunction of this pathway is associated with many neurological and psychiatric disorders. However, the study elucidating its role in ASD is in their infancy. When the repertoire of ASD-related genes is expanded, finding a convergent neuronal pathway that underlies such a heterogeneous etiology can be efficiently targeted by therapeutics. Interrogating the synaptic, cellular and network mechanisms of corticostriatal pathway dysfunction in experimental models of ASD is thus a fundamental undertaking for ASD research.

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Significance

The majority of cortical areas send monosynaptic excitatory projections to the striatum, which contribute to diverse sensorimotor and cognitive processing tasks. This glutamatergic corticostriatal pathway is strongly modulated by dopaminergic, cholinergic, GABAergic, and purinergic signaling. Corticostriatal dysfunction has been involved in many neurological and psychiatric disorders. This review summarizes current the understanding of corticostriatal connectivity and describes its functional role in the context of autism spectrum disorders.

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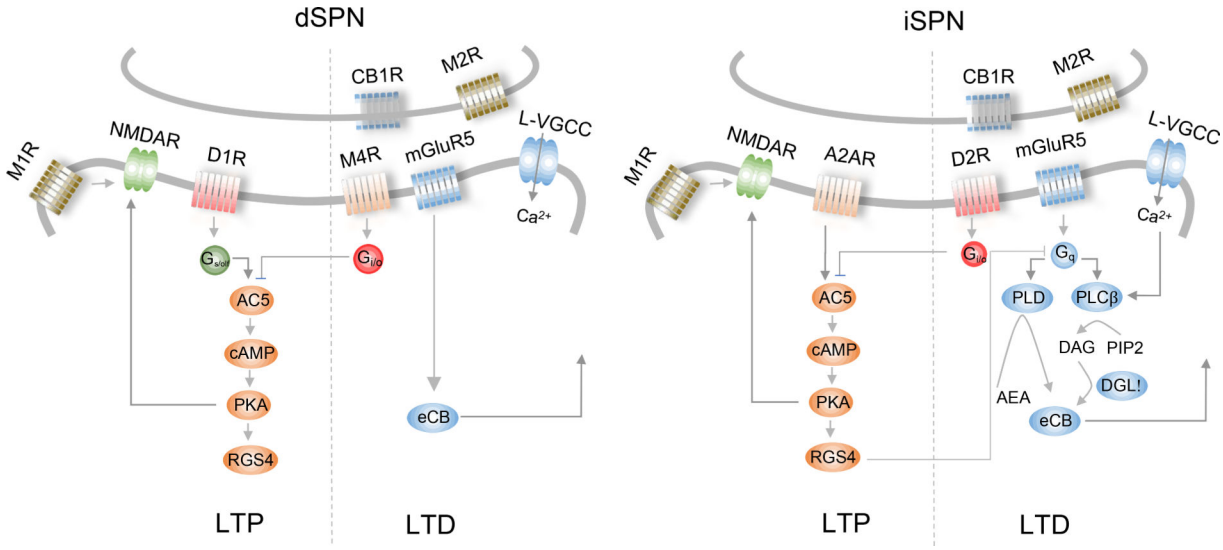

FIGURE 1.

Molecular mechanisms of corticostriatal synaptic plasticity. Accumulating evidence suggests that LTP and LTD can be induced in both dSPNs and iSPNs, and that signaling interplays in this opposite synaptic plasticity. Note that lines that end with arrowheads indicate signaling activation whereas lines that end with perpendicular bars indicate inhibition. In dSPNs, stimulation of D1Rs results in activation of the AC5-cAMP-PKA pathway via $G_{s/olf}$, which in turn activates RGS4 that is involved in LTP. LTP involves NMDAR activity, which can be induced by M1Rs and PKA. LTP can be repressed by activation of postsynaptic M4Rs via $G_{i/o}$ and presynaptic M2Rs. LTD was also found to be induced by mGluR5 activation in dSPNs, which is likely involved in eCB synthesis and release, and presynaptic activation of CB1Rs. In iSPNs, LTP involves the same signaling pathway as in dSPNs, but it is initiated by A2AR stimulation. LTD in iSPNs is well known to be involved in eCB signaling that is initiated by mGluR5 via G_q. eCB can be synthesized by two pathways: PLD catalyzes AEA to eCB, and PLCβ and DGLα catalyze DAG to eCB. PLCβ activation is controlled by VGCC activity in addition to mGluR5. Additionally, D2R activity is responsible for LTD by inhibiting the AC5-cAMP-PKA pathway via $G_{i/o}$. LTD can be prevented by activation of this pathway via RSG4.

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Table 1.

Striatal pathogenesis in ASD

Gene	Loci	Protein function	Striatal function, pathology and phenotype
FMR1	Xq27.3	Regulating cellular mRNA localization and translation	Increased fiber density in frontostriatal pathway; hypoactive corticostriatal circuitry; elevated GABA release; impaired mGluR-LTD; decreased M1R expression
KMT2A	11q23.3	Modulation of gene transcription	Impaired STDP-LTP; anxiety and depression
GRIN2B	12p13.1	NMDAR subunit; mediating excitatory synaptic transmission	Impaired action selection
SCN2A	2q24.3	Initiation and propagation of action potential	Reduced corticostriatal synaptic transmission; absence seizures
NLGN1	3q26.31	Cell adhesion molecule	Reduced NMDA/AMPA ratio; repetitive behaviors
NLGN3	Xq13.1	Cell adhesion molecule	Reduced inhibitory synaptic transmission onto dSPNs; HFS-LTD defect in excitatory synapses
MET	7q31.2	Receptor tyrosine kinase	Increased dendritic arborization and spine volume
CNTNAP2	7q35-q36.1	Modulation of cell adhesion; dendritic arborization and spinogenesis	Reduced PV-positive interneurons; disturbed cortico-striato-thalamic circuitry
FOXP2	7q31.1	Transcriptional factor; interacting with *MEF2C*	Increased dendritic branching and LTD in *Foxp2* homozygous mice but impaired LTD in heterozygous striatum; hyperactivity; altered dSPN and iSPN excitability
TSHZ3	19q12	Transcription factor; modulation of cortical development	Decreased release probability, increased NMDAR- and AMPAR-mediated transmission, and LTD deficit in cKO; increased release probability, normal NMDA/AMPA ratio, and increased LTP in constitutive heterozygous mice
SHANK3	22q13.33	Regulation of excitatory synapse structure and function	Altered mGluR5 signaling; reduced expression of ASD susceptibility genes; impaired preservative exploratory behavior
PTEN	10q23.31	Suppressing PI3K pathway	Altered PC morphology and impaired PC synaptic function
CHD8	14q11.2	Chromatin remodeling protein	Increased excitatory but decreased inhibitory activity; reduced locomotion; improved acquired motor learning
MECP2	Xq28	Chromatin modification; processing mRNA	Reduced striatal volume; altered levels of AMPARs, NMDARs, GABARs, D2Rs, DAT, and TH
DYRK1A	21q22.13	Modulation of intracellular signaling cascades	Hypoactive behavior; impaired coordination; aberrant sensorimotor gating
RELN	7q22.1	Activating kinases PI3K and AKT	Increased D2R levels; low TH
FOXP1	3p13	Transcriptional factor; modulation of cell differentiation	Increased dendritic branching; hyperactivity; altered dSPN and iSPN excitability
SYNGAP1	6p21.32	Postsynaptic protein; restricting AMPAR restriction	Highly expressed in both glutamatergic and GABAergic neurons
NRXN	2p16.3	Modulation of synapse differentiation and maturation; regulation of transmitter release and VGCC function	Expressed in dSPNs of the ventral striatum