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## Dopamine, Vocalization, and Astrocytes

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### Abstract

Dopamine, the main catecholamine neurotransmitter in the brain, is predominately produced in the basal ganglia and released to various brain regions including the frontal cortex, midbrain and brainstem. Dopamine's effects are widespread and include modulation of a number of voluntary and innate behaviors. Vigilant regulation and modulation of dopamine levels throughout the brain is imperative for proper execution of motor behaviors, in particular speech and other types of vocalizations. While dopamine's role in motor circuitry is widely accepted, its unique function in normal and abnormal speech production is not fully understood. In this perspective, we first review the role of dopaminergic circuits in vocal production. We then discuss and propose the conceivable involvement of astrocytes, the numerous star-shaped glia cells of the brain, in the dopaminergic network modulating normal and abnormal vocal productions.

### Keywords

astrocytes; basal ganglia; dopamine; glia; speech; vocalization

## 1. Introduction

Speech production is one of the most complex motor behaviors, requiring precise coordination of activities between multiple functional areas in the brain and more than 100 muscles in the body, including laryngeal, supralaryngeal, and respiratory muscles. The complete brain circuitry involved in vocal production is not fully identified; however, it has been established that both archetypal brain regions [i.e., nucleus ambiguus (NA),

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periaqueductal gray (PAG), and striatum] as well as highly developed areas [i.e., laryngeal motor cortex (LMC) and supplementary motor area (SMA)] are critically involved in the motor control and modulation of vocalizations (i.e. vocal production) (Alm, 2004; Jarvis, 2019a; Uwe Jürgens, 2002; Simonyan, 2014). Moreover, orofacial precision for articulation, synchronization of breathing behaviors with speech output, and higher level motor controls are critically involved and synchronized in successful generation of fluent speech (Jarvis, 2019a; Uwe Jürgens, 2002; Sommer, Koch, Paulus, Weiller, & Büchel, 2002). Better understanding the brain motor circuits controlling vocal communication may help identify pathophysiology of speech motor disorders.

Similar to other complex motor behaviors, elaborative circuitry and numerous neurotransmitters are involved in conducting the intricacies of vocal production circuits. It was proposed that vocalization is dependent on circuits stemming from the basal ganglia, a telencephalic brain region integral for initiation and maintenance of motor behavior, to multiple brain areas including the cerebral cortex, midbrain and the brainstem (Figure 1) (Creese & Iversen, 1975; Scheel-Krüger & Randrup, 1967). Moreover, studies in experimental animal models, including rodents, songbirds, and non-human primates (NHPs) (Arriaga, Zhou, & Jarvis, 2012; Ciucci, Vinney, Wahoske, & Connor, 2010; Jarvis, 2019a; Uwe Jürgens, 2002), suggest that dopamine, a neurotransmitter intimately involved in motor behaviors, plays a central role in vocal production circuits of the brain (Dastur, McGregor, & Brown, 1999; de Lanerolle & Youngren, 1978; Jenner et al., 1984; Rose, Nomoto, Jenner, & Marsden, 1989; Sasaki, Sotnikova, Gainetdinov, & Jarvis, 2006). These models, in conjunctions with human imaging studies, have been imperative for defining the dopaminergic circuitry controlling the vocal production network (Fuertinger, Zinn, Sharan, Hamzei-Sichani, & Simonyan, 2018; Simonyan & Fuertinger, 2015; Simonyan, Herscovitch, & Horwitz, 2013).

Similar to other communication systems, both production and perception of vocalization are critical aspects of vocal communication. Vocalization control circuits integrate a myriad of sensory functions and information from various brain regions, notably the auditory cortex (Eliades & Wang, 2003; Moore & Woolley, 2019), somatosensory cortex, cerebellum, and thalamus (Riecker, Kassubek, Gröschel, Grodd, & Ackermann, 2006). In doing so, communication can become a conversation through combining new information, articulating thoughts, producing meaningful speech and incorporating realtime feedback to correct mistakes (Chow & Chang, 2017). Although acoustic feedback control of speech is critical for vocal production, we do not discuss audio-motor interactions here, as it is reviewed comprehensively elsewhere (Poepfel & Assaneo, 2020). Moreover, it is critical to note a distinction between innate and learned vocalizations. While vocal communications with conspecifics in some species, such as humans and songbirds, is mainly learned, other species, such as rodents, mostly use innate vocalizations to communicate (Jarvis, 2007, 2019a; Petkov & Jarvis, 2012; Shu et al., 2005). This distinction is important when considering the brain regions involved in the vocalization circuits (Arriaga et al., 2012). In addition, it has been shown recently that astrocytes are critically involved in the control of complex motor behaviors (Morquette et al., 2015; Sheikhabaehi, Turovsky, et al., 2018) and can modulate dopaminergic neural circuits (Corkrum et al., 2020; Khan, Koulen, Rubinstein, Grandy, & Goldman-Rakic, 2001; Xin et al., 2019). In this perspective, we focus on vocal

production circuits in the brain and the role of dopamine in regulation of these circuits. We then discuss the role of dopamine and the basal ganglia in normal and abnormal vocal production. Lastly, we propose a possible mechanism for involvement of astrocytes in the dopaminergic modulation of vocalization. A disruption to the proposed mechanism might lead to speech disorders, including stuttering disorders.

## 2. Vocal production circuits

### 2.1 Physiological considerations in vocalization pathways

Breathing is vital for voice production. The normal breathing cycle consists of three behaviorally distinct sequential phases: inspiration, post-inspiration, and expiration (Del Negro, Funk, & Feldman, 2018; Richter & Smith, 2014). Breathing and vocalization are highly coordinated, as vocalization is restricted to periods during post-inspiration and expiration. Therefore, speech production requires a precise coordination of laryngeal muscle action with activities of brain circuits controlling orofacial and respiratory movements. In addition, proprioceptive input from mechanoreceptors and chemoreceptors in the larynx, orofacial region, and respiratory system that affect rhythm or pattern of breathing may provide feedback controls and might affect vocal production (Andalman, Foerster, & Fee, 2011; Dutschmann & Herbert, 2006; Forster, 2003; Uwe Jürgens, 2002; Mörschel & Dutschmann, 2009; Mulkey et al., 2004; O'Regan & Majcherczyk, 1982; Sheikhabaei, Turovsky, et al., 2018; Sheikhabaei, Gourine, & Smith, 2017; Sheikhabaei & Smith, 2017; Teppema & Dahan, 2010).

### 2.2 Involvement of the Basal Ganglia

It has been shown that the basal ganglia and its main neurotransmitter, dopamine, have an important role in speech production (U Jürgens, 2009; Uwe Jürgens, 2002; Kristina Simonyan et al., 2013; Kristina Simonyan, Horwitz, & Jarvis, 2012). The conventional model suggests that neurons from the LMC project to the striatum (putamen and caudate nucleus) which itself sends projections to the NA, the brainstem motor nucleus that enervates laryngeal muscles (Uwe Jürgens, 2002; Kristina Simonyan & Jürgens, 2003; Kristina Simonyan, Ostuni, Ludlow, & Horwitz, 2009). In addition to NA, the motor nuclei of the trigeminal, facial (VII), and hypoglossal (XII) are also involved in vocal production (Uwe Jürgens, 2002) (Figure 1).

In addition to the established model, an "anterior pathway," including the anterior SMA, and vocal premotor cortex, namely premotor laryngeal motor cortex (preLMC) and inferior frontal gyrus (Broca's area), are also suggested to be involved in speech production (Jarvis, 2019b). Brain regions in this pathway send converging projections to the anterior striatum (Figure 1B). This information is integrated into the basal ganglia thalamo-cortical loop, a network that connects the motor circuits of the basal ganglia to the higher order processing centers in the cortex through the relay station in the thalamus. Specifically, the ventral tegmental area (VTA) as well as the substantia nigra pars compacta (SN) have been found in NHPs to send direct projections to LMC (Jürgens, 1982; K Simonyan & Jürgens, 2005). For speech motor learning, the anterior striatum sends projections to the anterior thalamus which relays back to the preLMC (Jarvis, 2019a).

As discussed above, various regions of the basal ganglia are involved in vocal production, however, the anterior striatum and the subthalamic nucleus receive direct dopaminergic input from the SNc and VTA (Hornykiewicz, 1966; Rice, Patel, & Cragg, 2011) and may have a direct role in speech production. In this setting, the striatum is proposed to have specific roles in speech initiation and vocal production and cessation of vocalizations (Price, 2010), the subthalamic nucleus may also be involved in initiation of speech production (Hebb, Darvas, & Miller, 2012).

### 3. Dopamine

Dopamine is one of the main catecholamine neurotransmitters in the central nervous system (CNS) (Hornykiewicz, 1966). The level of dopamine in the basal ganglia is well regulated via various mechanisms involves neurons and astrocytes (Adrover et al., 2020; Björklund & Dunnett, 2007; Rice et al., 2011; Y Smith & Kieval, 2000; Vaughan & Foster, 2013). Hypoactivity or hyperactivity of dopamine lead to a general inhibition or disinhibition of motor behaviors, respectively, that manifest in a range of motor control disorders, such as Parkinson's disease, amyotrophic lateral sclerosis (ALS), Tourette's Syndrome, and developmental stuttering (Alm, 2004; Bromberg-Martin, Matsumoto, & Hikosaka, 2010; Crocker, 1997; Groenewegen, 2003; Laverty, 1978).

#### 3.1 Dopamine synthesis

Catecholamines are synthesized through a number of steps with tyrosine hydroxylase catalyzing the rate limiting step of this process, converting tyrosine to Levodopa (L-DOPA). L-DOPA is then decarboxylated by amino acid decarboxylase to form an early form of dopamine (Kaushik, Gorin, & Vali, 2007; Vaughan & Foster, 2013). This predopamine transmitter is packaged into a vesicle along with other enzymes to continue dopamine synthesis inside the transmission vesicles in pre-synaptic neurons (Daubner, Le, & Wang, 2011; Hornykiewicz, 1966; Kaushik et al., 2007; Sourkes, 1971). Upon neuronal activation, dopamine is released into the synaptic cleft where it can bind to receptors on post-synaptic cell membranes. The excess dopamine is subsequently recycled back to the pre-synaptic neuron through the dopamine transporter (DAT) or is broken down by monoamine oxidase (MAO) and/or catechol-O-methyltransferase (COMT). This synthesis-release-reuptake process controls and regulates physiological dopaminergic responses to bodily demands (Blakely & Bauman, 2000; Rice et al., 2011; Vaughan & Foster, 2013).

#### 3.2 Dopamine functions

Dopamine is involved in activities of many brain circuits including those that control movement (Creese & Iversen, 1974; Hornykiewicz, 1973), cognition (Brozoski, Brown, Rosvold, & Goldman, 1979; Joseph, Frith, & Waddington, 1979; Nakajima et al., 2013), emotion (de Lanerolle & Youngren, 1978; Goschke & Bolte, 2014; Laverty, 1978), reward (Bromberg-Martin et al., 2010; Christie & Crow, 1971; Schultz, 2007; Shugart et al., 2004; Vaughan & Foster, 2013), and others. Interestingly, although dopamine is involved in a variety of behaviors, the majority of dopamine in the brain is released by a subpopulation of neurons in the SNc and VTA that provide the neurotransmitter dopamine to the rest of the brain (Björklund & Dunnett, 2007; Fürtinger, Zinn, & Simonyan, 2014; Fuxe, 1965;

Hornykiewicz, 1966; Lewis & Sesack, 1997; Rommelfanger & Wichmann, 2010; Simonyan et al., 2012).

#### 4. Dopamine in vocalization circuits

The structure and function of the vocal production circuits and the involvement of dopamine in this network has been studied in several animal models, including chickens, songbirds, rodents, and NHPs. As previously noted and in comparison to the innate vocalizations in chicken and rodents, speech and song in human and songbirds, respectively, are considered as learned vocalizations. In young chicks, where trill calls can be evaluated, injection of apomorphine hydrochloride, a dopaminergic receptors agonist, elicited a significantly higher rate of trill calls (de Lanerolle & Youngren, 1978) elucidating the possible role that dopamine is modulating chick vocal production. Songbirds are another animal model that has been used extensively to look at vocalization and in particular, vocal learning (Chakraborty et al., 2017; A. N. Chen & Meliza, 2020; Jarvis, 2019a; Kubikova et al., 2014). *In vivo* microdialysis (see also Appendix A for more details) of dopamine in awake, behaving songbirds has established that singing induces an increase in dopamine in area X, a nucleus located within the equivalent to the human striatum and similarly receives dopaminergic input from VTA and SNc, (Sasaki et al., 2006). Lesion studies in area X lead to increased syllable repetitions and a stuttering-like vocalization phenotype (Kubikova et al., 2014). Moreover, overexpression of N-methyl-D-aspartate (NMDA) subtype 2B glutamate receptor (*NR2B*) gene in lateral magnocellular nucleus of the anterior nidopallium (LMAN), a cortical region that has direct connections to area X, also induced changes in pitch and rhythmicity of vocalizations (i.e., stuttering-like vocalization) (Chakraborty et al., 2017). These studies help define a prominent role for both the basal ganglia and cortical-basal ganglia circuits in songbird vocalization.

In rodent pups, injection of either an agonists of dopamine receptor D1 (D1R) or dopamine receptor D3 (D3R) reduced the frequency of ultrasonic vocalizations (Dastur et al., 1999), further suggesting a critical role for dopamine in the vocalization pathway of rodents too. These studies suggest that dopamine's effects within the basal ganglia and cerebral cortex dictate the ability to produce a vocalization. Dopamine may also have the capability to create proper pitch and fluidity of vocalization (Bragoni et al., 2000; Goberman & Blomgren, 2003; Uwe Jürgens, 2002; Lan et al., 2009; Poeppel & Assaneo, 2020; Simonyan et al., 2012). In particular, dopamine released in the striatum, may directly modulate neural activities of the speech motor regions in the basal ganglia and primary motor cortex (Crocker, 1997; Salamone, 1992). Similar to many motor behaviors, the basal ganglia-thalamo-cortical connections are also involved in speech production. The difference arises from where the dopamine release occurs; and for vocalization circuits, this termination occurs in the LMC (Boë, Fagot, Perrier, & Schwartz, 2017; Kumar, Croxson, & Simonyan, 2016; Mor, Simonyan, & Blitzer, 2018; Simonyan et al., 2012).

Clinical studies in humans further evaluated the involvement of dopamine in vocalization and speech (Bragoni et al., 2000; Goberman & Blomgren, 2003). The left hemisphere of the human brain is well-known for its particular involvement in speech production (Fuertinger et al., 2018; Jackson, 1915; Loring et al., 1990; Vigneau et al., 2006). Recently,

combinations of positron emission tomography (PET) with dopamine receptors radioligands, functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI) and/or diffusion-weighted MRI (Fuertinger et al., 2018; Simonyan et al., 2013) were used to show that during speech production, release of dopamine from the SNc and VTA was lateralized to the left ventromedial striatum (Fuertinger et al., 2018; Simonyan et al., 2013) and LMC (Fuertinger et al., 2018).

Evaluating the dopaminergic circuits in various animal models is crucial to understand how this system works and to gain insight on the role of dopamine in human brain. It is imperative that there be an understanding of similarities and differences between animal models and humans such that the information can be properly taken into account when treating human patients. An investigation of the basal level of plasma dopamine in various species, including rodents and humans, shed light on the fact that the resting dopamine values vary greatly between humans and rats (Bühler, da Prada, Haefely, & Picotti, 1978). Not only are the basal levels different, but the mechanisms of action to breakdown dopamine seem to differ as well. Whereas primates (including humans and NHPs) use MAO-A predominately, rodents seem to use MAO-B (Garrick & Murphy, 1980). However, while these differences exist, commonalities between species are apparent too. Most species seem to use the various dopamine receptors similarly (Bäckman et al., 2011; Seamans & Yang, 2004; Zahrt, Taylor, Mathew, & Arnsten, 1997) and commonalities in dopamine release into neural networks, particularly in motor control and reward circuits (Chini & Hanganu-Opatz, 2020; Grimm, Balsters, & Zerbi, 2020; Peters, Liu, & Komiyama, 2017; Walton & Bouret, 2019), have allowed investigators to confidently use various animal models to understand the dopaminergic circuits at large.

In addition to physiological functions, the role of dopamine in the control of speech production circuits can be further understood through its role in the pathophysiology of disorders that affect the control of motor circuits, such as Parkinson's disease and developmental stuttering disorder (Alm, 2004; Elgueta et al., 2017; Goberman & Blomgren, 2003; Yoland Smith & Villalba, 2008; Tani & Sakai, 2011). A precise control of dopamine release creates an intricate balance in the brain and modulation of dopamine release is associated with impairments in vocalization, such that a decrease in dopamine affects vocalization in Parkinson's disease, whereas an increase in dopamine level is associated with childhood-onset fluency disorder (also known as stuttering). In patients with Parkinson's disease, in which dopaminergic neurons in the striatum prominently degenerate, changes in vocalization quality, including a declined loudness, decrease in a range of vocal pitch, and a lack of expression during speaking are reported (Ciucci et al., 2010; Goberman & Blomgren, 2003; Walsh & Smith, 2011). Interestingly, Parkinson's patients treated with dopamine receptor antagonists report alterations in vocal production that reverse once the patients stops taking the medication (Newton-John, 1988; Warren & Thompson, 1998).

## 5. Dopamine in childhood-onset fluency disorder (stuttering)

Childhood-onset fluency disorder is a neurodevelopmental disorder (Ludlow & Loucks, 2003; Mawson, Radford, & Jacob, 2016; A. Smith & Weber, 2016; Watkins, Smith, Davis, & Howell, 2008) that affects normal fluency of speech which is not appropriate

for individual's age (American Psychiatric Association, 2013). Although the etiology of stuttering is not fully understood, many lines of evidence suggest that defects in dopaminergic circuits in the basal ganglia may be involved in the development of stuttering disorders in a subgroup of people who stutter; some adults who stutter may have three-times higher level of dopamine precursors in the basal ganglia (Wu et al., 1995, 1997).

This excess dopamine hypothesis of stuttering is supported by recent clinical and imaging studies (Alm, 2004; Chang & Guenther, 2019; G A Maguire, Riley, Franklin, & Gottschalk, 2000; Gerald A. Maguire et al., 2004; Gerald A Maguire et al., 2019; Gerald A Maguire, Nguyen, Simonson, & Kurz, 2020; Gerald A. Maguire, Yeh, & Ito, 2012; Gerald A. Maguire, Yoo, & SheikhBahaei, 2021). Because of this unique relationship, dopaminergic agents have been used as a potential therapy in clinical trials for patients with stuttering disorders. Although dopamine receptor D2 (D2R) blockers (such as risperidone, olanzapine, and haloperidol) reduce stuttering symptoms significantly, their broader effects on modulation of serotonin (5-HT), acetylcholine, and glutamate receptors, have limited their usage. Recently, Ecopipam, a selective D1R antagonist, and lurasidone, antagonist of D2, 5HT2a and partial agonist at 5HT1a, have been proposed as novel therapies for stuttering disorders (Charoensook & Maguire, 2017; Gerald A Maguire et al., 2019, 2020). Both clinical studies in humans and experiments on animal model further the importance of dopaminergic signaling in vocal production circuits of the basal ganglia.

## 6. Astrocytes, dopamine and stuttering

Astrocytes, the numerous star-shaped glial cells of the brain, play a myriad of roles including regulation of extracellular concentration of ions and neurotransmitters, regulation of the blood-brain barrier, and have been proposed to regulate neuronal excitability and synaptic plasticity (Abbott, Rönnbäck, & Hansson, 2006; Alfonso Araque et al., 2014; Haydon & Carmignoto, 2006). Physiology of glial cells is managed by changes in their intracellular  $\text{Ca}^{2+}$  concentration ( $[\text{Ca}^{2+}]_i$ ) in a way that increases in  $[\text{Ca}^{2+}]_i$  triggers release of gliotransmitters (such as ATP/adenosine, D-serine, glutamate and others) (Heinrich, Andó, Túri, Rózsa, & Sperlág, 2012; Marina et al., 2018; Martineau et al., 2013; Sheikhabaei, Turovsky, et al., 2018).

Recent studies have suggested that in addition to their neuro-regulatory effects, astrocytes can directly modulate motor circuits *in vivo* and impact complex behaviors (Sheikhabaei, Turovsky, et al., 2018). While the exact role of astrocytes in motor circuitry remains elusive, key features of astrocytes provide evidence for their importance. For instance, changes of  $[\text{Ca}^{2+}]_i$  in astrocytes in response to neuronal activity not only triggers gliotransmitter release but also may modulate neuronal activity (A Araque, Carmignoto, & Haydon, 2001; Alfonso Araque et al., 2014; Haydon & Carmignoto, 2006; Marina et al., 2018; Pascual et al., 2005; Santello, Calì, & Bezzi, 2012). Accumulating evidence for this glia-induced modulation of complex behaviors is illustrated in many circuits. For instance, in locomotor circuits where it is postulated that rhythmic releases of  $[\text{Ca}^{2+}]_i$  modulate the neural circuit of locomotion (Christensen, Petersen, & Perrier, 2013; Hegyi et al., 2018; Hegyi, Kis, Holló, Ledent, & Antal, 2009), in mastication circuitry where astrocytes seem to be involved in the regulation of extracellular  $\text{Ca}^{2+}$  by release of s100 $\beta$  (Morquette et al., 2015), and

in respiratory circuitry where  $[Ca^{2+}]_i$ -dependent release of ATP from brainstem astrocytes regulate breathing rhythms (Sheikhabaei, Turovsky, et al., 2018), respiratory responses to hypoxia (low inspired oxygen) (Angelova et al., 2015; Rajani et al., 2018; Sheikhabaei, Turovsky, et al., 2018), hypercapnia (high inspired carbon dioxide), and determine exercise capacity (Sheikhabaei, Turovsky, et al., 2018).

One of the main functions of astrocytes throughout the brain is to maintain a level of homeostasis. One way in which astrocytes accomplish this goal is through the regulation of extracellular neurotransmitter concentrations (Barres, 2008; Clarke & Barres, 2013). As previously mentioned, dopamine has a number of reuptake mechanisms to regulate the levels of extracellular dopamine, and in addition to neurons, astrocytes also express DAT (which recycles the dopamine back to the cell), and COMT/MAO (which break dopamine down into metabolites) (Asanuma, Miyazaki, Murakami, Diaz-Corrales, & Ogawa, 2014; Hansson & Sellström, 1983; Karakaya, Kipp, & Beyer, 2007; Takeda, Inazu, & Matsumiya, 2002). Astrocytes from the rodent cortex have been found to be sensitive to various dopamine concentrations (Requardt et al., 2012; Vaarmann, Gandhi, & Abramov, 2010). It was shown that over 80% of cortical astrocytes took up and metabolized dopamine using COMT and MAO (Hansson & Sellström, 1983; Pelton, Kimelberg, Shipherd, & Bourke, 1981; Takeda et al., 2002). On the other hand, astrocytes from striatum and midbrain express DAT and recycle dopamine through this transporter and break it down into its precursor to be reused (Asanuma et al., 2014; Karakaya et al., 2007).

Astrocytes are heterogenous and may play a variety of modulatory roles depending on their regional location in the brain (Chai et al., 2017; Sheikhabaei, Morris, et al., 2018; Zhang & Barres, 2010). Recent comparative genomic, structural, and physiological studies have provided clear evidence for circuit-dependent specialization of astrocytes and their functional diversity (Chai et al., 2017; Doyle et al., 2008; Khakh, 2019). In dopaminergic circuits, dopamine-induced calcium transients in astrocytes is independent of neuronal activity (Fischer, Scheffler, & Lohr, 2020). Recently it was shown that even a moderate increase of astroglial resting  $[Ca^{2+}]_i$  can translate into a considerable increase of gliotransmitter release (King et al., 2020). Therefore, dopamine can induce release of gliotransmitters in a  $Ca^{2+}$ -dependent manner. This intimate relationship with dopamine seems to also extend throughout the ventral midbrain dopaminergic circuit where astrocytes have critical functions in the SNc, VTA (Xin et al., 2019) and NAc (Corkrum et al., 2020), and possibly in other regions. In these regions and in response to dopamine and in particular, D2R modulation, astrocytes show a change in  $[Ca^{2+}]_i$  activity which may lead to a release of gliotransmitters (such as ATP), (Corkrum et al., 2020; Khan et al., 2001; Xin et al., 2019) suggesting that astrocytes may be regulating the dopaminergic circuits in a similar fashion to other motor circuits (Figure 2A).

In addition to these physiological roles, astrocytes are proposed to be involved in the pathogenesis of numerous motor disorders, including Parkinson's disease (Booth, Hirst, & Wade-Martins, 2017; P.-C. Chen et al., 2009; Cressatti et al., 2019; Rappold & Tieu, 2010; Yun et al., 2018), amyotrophic lateral sclerosis (Haidet-Phillips et al., 2011; Meyer et al., 2014; Nagai et al., 2007; Yamanaka & Komine, 2018), and Tourette's Syndrome (de Leeuw et al., 2015; van Passel, Schlooz, Lamers, Lemmens, & Rotteveel, 2001). In



Parkinson's disease, for instance, one of the main pathological features is aggregation of protein alpha-synuclein ( $\alpha$ -syn).  $\alpha$ -syn will aggregate in the dopaminergic neurons but will also be released into the synapse and taken up by nearby astrocytes (Cressatti et al., 2019; Lee et al., 2011). The lack of available dopamine and the presence of this aggregated protein cause an increase in  $[Ca^{2+}]_i$  activity in astrocytes (Sonninen et al., 2020) which may lead to an increase in gliotransmitter release, in particular, adenosine. Adenosine will in turn affect the nearby neurons and cause motor symptoms seen in Parkinson's disease (Hosford et al., 2020; Rappold & Tieu, 2010; Sonninen et al., 2020) (Figure 2B).

Considering the anatomical and functional relationship between dopamine, the motor circuits, and astrocytes, it is plausible that astrocytes can have a significant role in pathogenesis of other disorder that affects motor patterns, such as developmental stuttering. Interestingly, in the newly established mouse models of stuttering (Barnes et al., 2016; Han et al., 2019) (see Appendix B for details), the number of astrocytes in the corpus collosum was decreased (Han et al., 2019). Although the role of astrocytes in the pathogenesis of stuttering is not defined yet, a recent study suggests that the effects of D2R blockers in increasing speech fluency in patients who stutter are mainly due to an increase of astrocytes' metabolism in the striatum (Gerald A. Maguire et al., 2021). According to this hypothesis, hypoactivity of striatal astrocytes due to excess dopamine concentration in the dopaminergic circuits of the basal ganglia could be one of the mechanisms that might lead to stuttering behavior (Figure 2B). We propose that similar to what is reported in the VTA (Xin et al., 2019), excess dopamine decreases the  $[Ca^{2+}]_i$  activity of striatal astrocytes. In this model, lower  $[Ca^{2+}]_i$  in astrocytes leads to less gliotransmitter release and imbalance activity of striatal neurons. Interestingly, it has been shown recently that decreases in  $[Ca^{2+}]_i$  in striatal astrocytes is linked to repetitive behaviors in rodents (Yu et al., 2018). More experiments are required to identify the main gliotransmitter released from astrocytes that may affect vocal production circuits, and in general, to further elucidate how astrocytes regulate striatal neurons, dopaminergic circuits, and vocalization behaviors.

## 7. Summary

In summary, dopamine projection from the basal ganglia to a variety of brain regions involved in motor functions, implicates its importance in voluntary and involuntary complex movements, especially in speech and other types of vocalizations. Recent studies illustrating dopaminergic release in vocal production regions further elucidates the strong possibility that dopamine plays an important role in vocal production. Further, recent data are uncovering the involvement of astrocytes in physiology of motor circuit activities and pathophysiology of motor disorders. This information, together with the fact that astrocytes have a close-knit relationship with the dopaminergic circuit strongly suggest that these glia cells have a critical role in modulating vocal production circuitry. Involvement of astroglial cells in these circuits will provide additional therapeutic target for disorders that affect motor control of speech production, such as stuttering disorder.

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## Appendix A I: Approaches to quantify dopamine in vivo

Four general approaches have evolved to quantify dopamine or its dynamics in the brain of humans and animals *in vivo*. They are governed by distinctively different principles, with contrasting advantages and disadvantages.

### Microdialysis.

The most common approach to measure tonic, extracellular dopamine at nanomolar concentrations is microdialysis coupled with analytical separations methods (Benveniste & Hüttemeier, 1990; Sasaki et al., 2006). Microdialysis is an invasive sampling technique based on diffusion of small molecules (< 20 kDa) through a semi-permeable membrane and into a perfusing fluid (artificial cerebral spinal fluid for neural samples) (Benveniste & Hüttemeier, 1990; Bucher & Wightman, 2015; Darvesh et al., 2011; Stenken & Patton, n.d.). The collected dialysate is then analyzed, typically with high performance liquid chromatography (HPLC) or capillary electrophoresis (CE) (Jaquins-Gerstl & Michael, 2015; Lu, Peters, & Michael, 1998; Shou, Ferrario, Schultz, Robinson, & Kennedy, 2006). Tonic concentrations of dopamine as small as nanomolar can be detected by microdialysis, with temporal resolution in order of minute, (Heien et al., 2005; Lu et al., 1998; Shou et al., 2006). Microdialysis probes are 200  $\mu\text{m}$  in diameter, and therefore spatial resolution and tissue damage are matters of concern (Cenci, Kalén, Mandel, & Björklund, 1992; Jaquins-Gerstl & Michael, 2009; Justice, 1993; Parsons & Justice, 1992). Tissue damage can elucidate immune response leading to ineffective sampling (Jaquins-Gerstl & Michael, 2009; Mitala et al., 2008).

### Electrochemical methods.

The most common techniques used to measure dopamine transients are amperometry (Dugast, Suaud-Chagny, & Gonon, 1994; Gulley, Larson, & Zahniser, 2007; D. J. Michael & Wightman, 1999; Willuhn, Wanat, Clark, & Phillips, 2010) and fast scan cyclic voltammetry (FSCV) (Bucher & Wightman, 2015; Heien, Johnson, & Wightman, 2004; Venton & Cao, 2020; Wightman et al., 1988). Dopamine undergoes oxidation at the surface of an active electrode, generating a current with an amplitude proportional to dopamine concentration. FSCV has been a gold standard for monitoring naturally occurring or stimulated changes in dopamine concentration by repeatedly applying a triangular potential waveform at high scan rates (> 100 V/s) to a carbon fiber electrode (5 – 40  $\mu\text{m}$  in diameter and 50 – 200  $\mu\text{m}$  in length), protruding from a sealed glass coating and inserted into tissue. Thus, high spatial resolution with minimal tissue damage at the tip is possible (Abdalla et al., 2020; Adrover et al., 2020; Nguyen & Venton, 2015; Roberts, Lugo-Morales, Loziuk, & Sombers, 2013). FSCV can detect sub-micromolar changes in dopamine, at sub-second time scales (Arbuthnott & Wickens, 2007; Roberts et al., 2013; Robinson, Hermans, Seipel, & Wightman, 2008; Robinson, Venton, Heien, & Wightman, 2003), and can be used to complement microdialysis. The high scan rate leads to a large charging current that must be subtracted to obtain the current from dopamine (Bucher & Wightman, 2015; A. C. Michael

& Borland, 2007), leading to challenges with detection of basal levels (Bucher & Wightman, 2015; Roberts & Sombers, 2018; Rodeberg, Sandberg, Johnson, Phillips, & Wightman, 2017). Amperometry, which does not suffer from large charging currents can measure basal levels, but it does not provide much information about the identity of the detected substance and therefore selectivity to dopamine is a major challenge unless the probe is inserted into areas known to include measurable amounts of dopamine (Ganesana, Lee, Wang, & Venton, 2017).

### **Genetically encoded fluorescent detectors:**

Changes in concentration of dopamine can be tracked by coupling the binding-induced conformational changes in dopamine receptors to changes in the fluorescence intensity of circularly permuted green fluorescent protein (cpGFP) (Patriarchi et al., 2018). Dopamine chemical sensors such as dLight1 (an intensity-based genetically encoded dopamine indicator which was developed from D1R) (Patriarchi et al., 2018) or GRAB<sub>DA</sub> (genetically encoded GPCR-activation-based-dopamine which was constructed from D2R) (Sun et al., 2018) indicate physiological or behaviorally relevant dopamine transients with high spatiotemporal optical resolution and provide high selectivity and sensitivity for dopamine dynamics (Patriarchi et al., 2018; Sun et al., 2018). Both dLight1 and GRAB<sub>DA</sub> demonstrate similar performance, however, GRAB<sub>DA</sub> has a narrower range of binding affinities (10 – 130 nM vs. 300 nM – 1.6 μM in dLight1) (Patriarchi et al., 2018; Sun et al., 2018). The second-generation GRAB<sub>DA</sub> has a 2–3-fold higher range for measuring dopamine dynamics (Sun et al., 2020). Other methods, such as Tango assays, in which the release of endogenous dopamine *in vivo* is reported as changes in the concentration, could be useful for circuit mapping, but they require longer signal amplification times (in order of hours) (Barnea et al., 2008; Inagaki et al., 2012). These methods are the latest trend in detection of endogenous dopamine in deep brain structures; however, they require implantation of optical probes (> 100 μm) that cause tissue damage and are incapable of measuring basal dopamine levels.

### **Positron emission tomography (PET).**

This non-invasive imaging technique has been used to assess dopamine systems in humans and animals (Drevets et al., 2001; Pal et al., 2001; Schiffer, Alexoff, Shea, Logan, & Dewey, 2005; Volkow, Fowler, Wang, Baler, & Telang, 2009). This method commonly uses intravenously-administered radiolabeled molecules, such as dopamine receptor ligands or precursors of dopamine, that decay and emit positrons, which upon encountering electrons in tissue create gamma rays that are detected by the PET camera. Ligands available for dopamine studies include [<sup>11</sup>C]raclopride for striatal dopamine receptors (Jonasson et al., 2014) and [<sup>11</sup>C]fallypride for those in amygdala and media temporal lobe (Badgaiyan, Fischman, & Alpert, 2009). These ligands are displaced by endogenously released dopamine (Ganesana et al., 2017; Volkow et al., 1996). The local dopamine concentration is correlated to the quantity of displaced ligand (Volkow et al., 1996). It is challenging to identify optimal ligands that compete with small molecules like dopamine (Volkow et al., 1996) that will bind to certain receptors and also avoid non-specific binding, which adds noise and lowers sensitivity (Badgaiyan, 2014). Studies of task-induced or drug-induced changes in dopamine

concentration have achieved a temporal resolution of 30 – 60 s and a spatial resolution of millimeters (Ganesana et al., 2017; Volkow et al., 1996).

## Appendix B I: Rodent models of speech disorders

Childhood-onset fluency disorder (stuttering) is a neurodevelopmental disorder (American Psychiatric Association, 2013) that affects more than 1 % of US adult populations (Yairi & Ambrose, 2013). It is now accepted that genetic substrates play a major role in pathophysiology of stuttering (Yairi & Ambrose, 2013). While a number of genes have been found to be important for speech (such as *FOXP2*, *CNTNAP2*, *GNPTAB*, *GNPTG*, *NAGPA*, *AP4E1*), three genes in particular, *FOXP2*, *GNPTAB*, and *CNTNAP2*, have been studied extensively.

### FOXP2.

*FOXP2* gene, located on chromosome 7q31, encodes a transcription factor with a forkhead and DNA binding domain (Lai, Fisher, Hurst, Vargha-Khadem, & Monaco, 2001; Shu et al., 2005). As a transcription factor, its activity in binding to DNA affects downstream genes, some of which (for example *CNTNAP2*) have also been implicated in speech disorders (Newbury & Monaco, 2010). A mutation in *FOXP2* and/or its translated protein reduces DNA binding and nuclear localization (Fujita et al., 2008) and causes speech deficits in humans as well as in rodents [such as reduced ultrasonic vocalizations and symptoms of developmental verbal dyspraxia (Castellucci, McGinley, & McCormick, 2016; Chabout et al., 2016; Fujita et al., 2008; Lai et al., 2001; Shu et al., 2005)]. In particular, the *Foxp2* mutant mouse was found to produce simpler sequences of ultrasonic vocalizations (USVs) and was less able to switch to more complex sequences when compared to wild type mice (Castellucci et al., 2016; Chabout et al., 2016). Thus, using this mutant mouse model, it has been suggested that a mutation in *Foxp2* in mice is similar to difficult in sequencing phonemes and syllable syntax to make complex words in humans (Chabout et al., 2016). Interestingly, *FOXP2* is highly conserved among species, such that the human *FOXP2* protein only varies from the mouse homolog by three amino acids (Shu et al., 2005). Additionally, although *FOXP2* expresses in a variety of regions including the basal ganglia, cortex and thalamus (Fujita et al., 2008; Shu et al., 2005), the expression is lower in the cortex (mostly restricted to layer VI) than in the striatum. In the thalamus, *FOXP2* expression is higher in the ascending sensory nuclei. There are no known cases of humans with a complete deletion of *FOXP2* mutation (Chabout et al., 2016). Similarly, mice with homozygous knockout of *Foxp2* are not viable. These animals have severe motor and respiratory impairments, inaudible vocalizations and die in 3 – 4 weeks (Enard et al., 2009; French et al., 2007; Fujita et al., 2008; Shu et al., 2005). Therefore, multiple heterozygous knockout mouse models with varying degrees of phenotypic changes have been generated (Enard et al., 2009; French et al., 2007; French & Fisher, 2014; Shu et al., 2005). In general, the heterozygous mouse models have fewer ultrasonic vocalizations and some motor impairments. A knock-in model of the *Foxp2* mutation has also been illustrated to show a decrease in ultrasonic vocalization and an increase in motor and respiratory impairments (Castellucci et al., 2016).

## CNTNAP2

Contactin-associated protein-like 2 gene is located on chromosome 7q35 (Petrin et al., 2010; Rodenas-Cuadrado, Ho, & Vernes, 2014). The gene codes for CASPR2 protein which is part of the neurexin superfamily (Peñagarikano et al., 2011; Peñagarikano & Geschwind, 2012). Interestingly, in the common fruit fly (*Drosophila Melanogaster*), the homolog of this gene codes for neurexin IV and is intimately involved in the neuron-glia interactions necessary for myelination of axons in the cortex (Peñagarikano & Geschwind, 2012). *CNTNAP2* has been found to be implicated in a variety of neurological disorders including schizophrenia and Tourette's syndrome (Rodenas-Cuadrado et al., 2014), however, it is most well-known for its prominent role in neurodevelopmental disorders such as Autism Spectrum Disorder (ASD), epilepsy, and language impairment disorders (Peñagarikano et al., 2011; Peñagarikano & Geschwind, 2012; Rodenas-Cuadrado et al., 2014; Selimbeyoglu et al., 2017). A *Cntnap2* knockout mouse model shows similarities to human features of ASD and is created to evaluate behavioral and pathological features of ASD (Brunner et al., 2015; Peñagarikano et al., 2011; Peñagarikano & Geschwind, 2012; Selimbeyoglu et al., 2017). The interesting overlap between the *Cntnap2* knock out mouse model used to study neurodevelopmental disorders and speech impairments is further elucidated through a chromosomal relationship. Interestingly, intron 1 of *CNTNAP2* gene contains a binding spot for *FOXP2* (mentioned above) (Peñagarikano & Geschwind, 2012). Thus, when *CNTNAP2* is mutated, and a region containing intron 1 is deleting from the gene, aside from neurodevelopmental delays, language impairments, and in particular stuttering is apparent.

## GNPTAB.

*GNPTAB* codes for the N-acetylglucosamine-1-phosphate transferase alpha and beta subunits, an enzyme involved in the intracellular trafficking pathway (Kazemi, Estiar, Fazilat, & Sakhinia, 2018; Newbury & Monaco, 2010; Raza et al., 2016). Four coding mutations in *GNPTAB* located in chromosome 14q that are linked to stuttering disorders have been identified so far (Kang et al., 2010; Kazemi et al., 2018; Raza et al., 2016). Along with this gene, a number of other genes closely related to *GNPTAB* and its function (i.e., *GNPTG*, *NAGPA*, *AP4E1*) have also been implicated in developmental stuttering.

The original transgenic mouse model of stuttering incorporated a *Gnptab* Glu1200Lys mutation (Barnes et al., 2016). Generated mice were on all accounts normal except for a deficit in the fluency of ultrasonic vocalizations (Barnes et al., 2016; Han et al., 2019). While this mutation seems to recapitulate the deficits seen in human stuttering disorders, other mutations in this gene have been tested too and a Ser321Gly mutation created a similar decrease in pup's vocalizations (Han et al., 2019). In these mice, the number of astrocytes in the corpus callosum was lower, which suggests that astrocytes might play a significant role for proper vocalization (Han et al., 2019).

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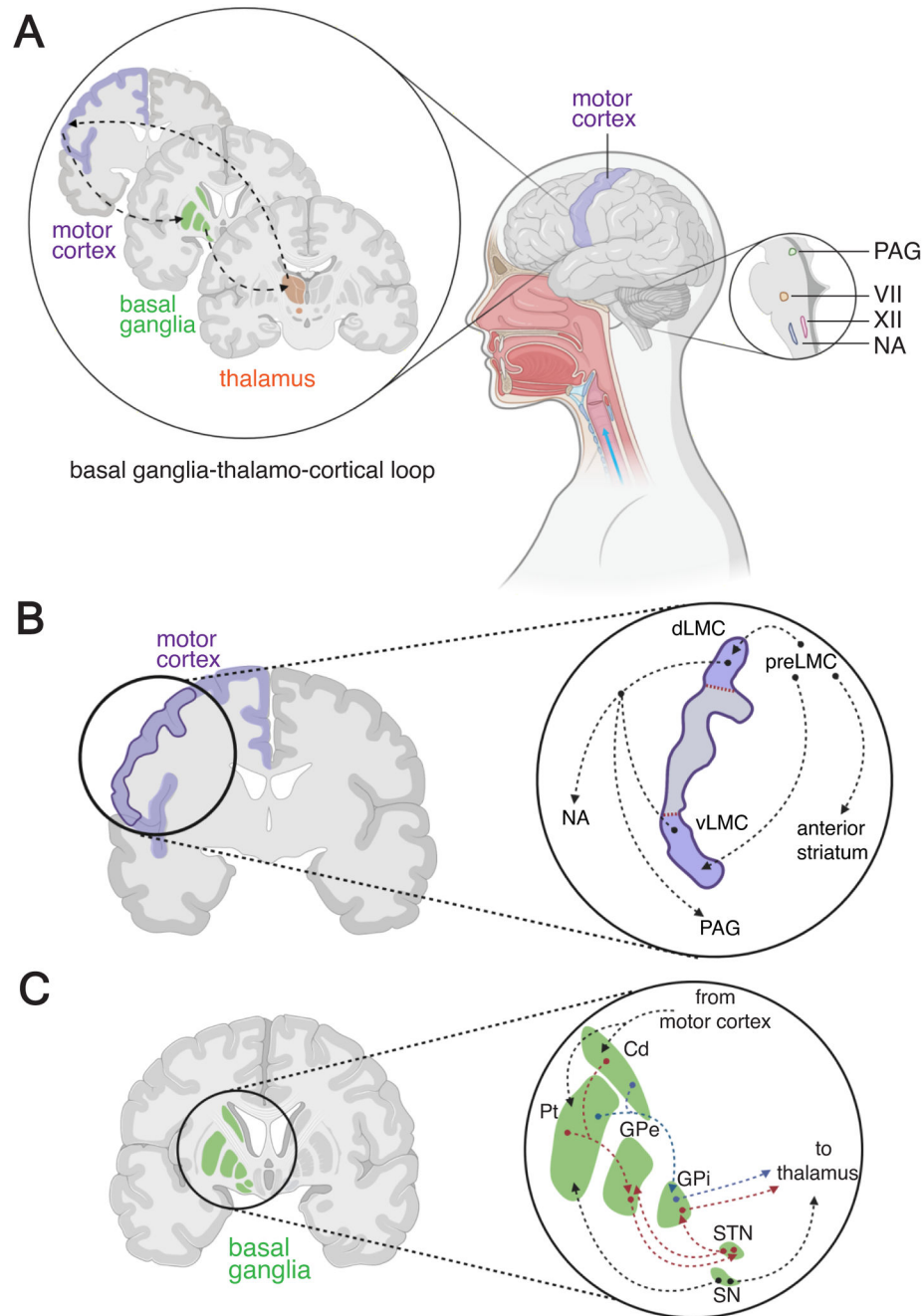
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**High lights:**

Dopamine's role in regulation of motor circuits is accepted, but its function in speech production is not fully understood.

In this perspective, we reviewed the modulatory role of dopamine in vocal production circuits of the basal ganglia.

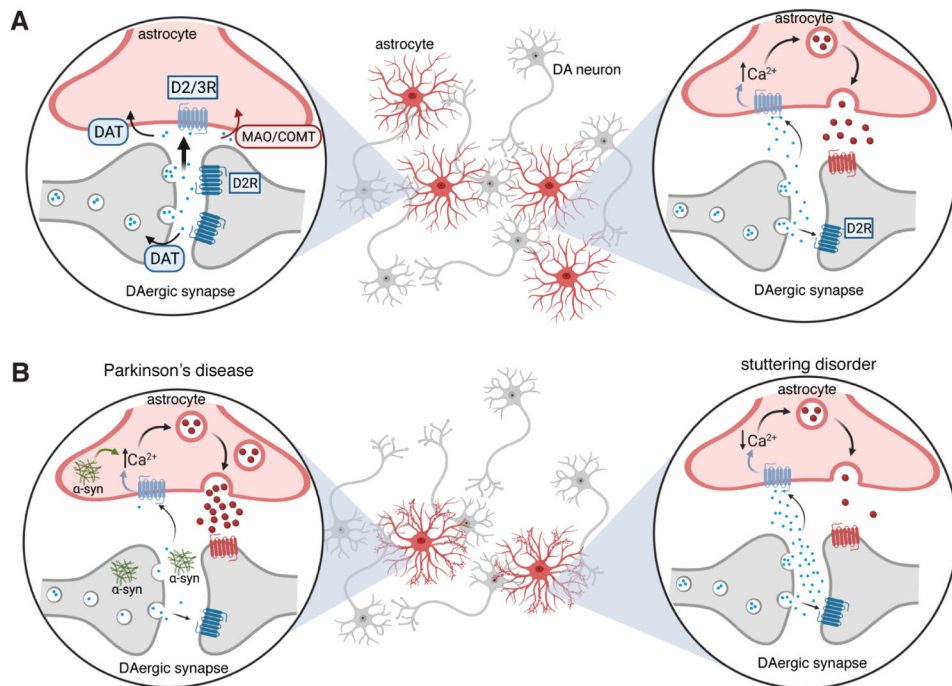
We proposed a modulatory role for astrocytes residing in the dopaminergic circuits of the basal ganglia in vocal productions.



**Figure 1 | Basal ganglia and motor control of speech production circuits.**

(A) The basal ganglia thalamo-cortical loop that connects the motor circuits of the basal ganglia to the laryngeal motor cortex through a relay station in the thalamus is important for speech production. The higher order brain structures, directly or indirectly [via periaqueductal gray (PAG)], modulate activities of orofacial and laryngeal motor neurons of facial (VII), hypoglossal (XII) nuclei and nucleus ambiguus (NA) located in the brainstem. (B) The laryngeal motor cortex (LMC) is located towards the ventro-lateral portion of primary motor cortex, and divided into dorsal (dLMC) and ventral (vLMC) regions. Both portions of LMC are involved in the vocal production circuits. Neurons in the preLMC sends

direct connections to dLMC and vLMC as well as to the anterior striatum. dLMC and vLMC neurons send projections to PAG and NA . (C) The Basal ganglia region includes the striatum (caudate and putamen), globus pallidus [external (GPe) and internal (GPi)], subthalamic nucleus (STN) and substantia nigra (SN). The intricate connectivity between these regions allows for proper execution of motor behaviors. Information from motor cortex is inputted to the striatum which in conjunction with dopaminergic inputs from the SN, sends information to two parallel pathways in the basal ganglia. In the first pathway (red arrows), the GPe received inhibitory signals from the striatum and relays inhibitory signals to the subthalamic nucleus. The subthalamic nucleus then send an excitatory signal to the GPi which in turn sends an output signal to the thalamus. In the second, parallel pathway (blue arrows), the striatum ends a direct inhibitory signal to the GPi which directly sends an output signal to the thalamus. By integrating inhibitory and excitatory signals, these two pathways can delicately modulate motor behaviors control, including speech production. Abbreviations: Cd – caudate, dLMC – dorsal laryngeal motor cortex, GPe – globus pallidus external, GPi – globus pallidus internal, NA – nucleus ambiguus, PAG – periaqueductal gray, preLMC – premotor laryngeal motor cortex, Pt – putamen, SN – Substantia Nigra, STN – sub thalamic nucleus, vLMC – ventral laryngeal motor cortex, VII – facial nucleus, XII – hypoglossal nucleus.



**Figure 2 | Astrocytes in dopaminergic circuits of basal ganglia.**

(A) (*left*) Presynaptic dopaminergic neuron releases dopamine (DA) into synaptic cleft, in which, DA binds to the postsynaptic DA receptor (such as D2R) and is also recycled back into the presynaptic neuron by DAT. However, some dopamine transmitter may also be recycled back through astrocytes potentially through DAT and/or COMT to recycle or break down dopamine, respectively. (*right*) Following the release of dopamine from the presynaptic terminal, dopamine may also bind to the D2R on astrocytes and lead to an increase in the levels of intracellular calcium ( $[Ca^{2+}]_i$ ), which in turn facilitates the release of gliotransmitters (such as ATP/adenosine and others). The released gliotransmitters affect neurons in the region. (B) (*left*) Dopaminergic neuronal synapse in a Parkinson's diseased brain where DA degeneration is prominent and less DA is released into the synapse. In addition to release of DA is release of aggregate alpha-synuclein ( $\alpha$ -syn). DA and aggregated alpha-synuclein are taken up by astrocytes, which causes a dysregulation of  $[Ca^{2+}]_i$  and an increased release of adenosine. (*right*) Presynaptic dopamine release increases in the case of developmental stuttering disorder which accumulates in the synapse where it can bind to the postsynaptic receptors, be taken back up by the presynaptic neuron or by the nearby astrocyte. In the proposed model, this increase in DA causes a decrease in  $[Ca^{2+}]_i$  activity and a reduction in release of gliotransmitters. Abbreviations:  $[Ca^{2+}]_i$  – intracellular calcium concentrations, COMT - catechol-O-methyltransferase, D2R – dopamine receptor D2, D3R – dopamine receptor D3, DA - dopamine, DAT – dopamine transporter, MAO - monoamine oxidase.