

Progressions

Cerebellar Contributions to the Basal Ganglia Influence Motor Coordination, Reward Processing, and Movement Vigor

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Both the cerebellum and the basal ganglia are known for their roles in motor control and motivated behavior. These two systems have been classically considered as independent structures that coordinate their contributions to behavior via separate cortico-thalamic loops. However, recent evidence demonstrates the presence of a rich set of direct connections between these two regions. Although there is strong evidence for connections in both directions, for brevity we limit our discussion to the better-characterized connections from the cerebellum to the basal ganglia. We review two sets of such connections: disynaptic projections through the thalamus and direct monosynaptic projections to the midbrain dopaminergic nuclei, the VTA and the SNc. In each case, we review the evidence for these pathways from anatomic tracing and physiological recordings, and discuss their potential functional roles. We present evidence that the disynaptic pathway through the thalamus is involved in motor coordination, and that its dysfunction contributes to motor deficits, such as dystonia. We then discuss how cerebellar projections to the VTA and SNc influence dopamine release in the respective targets of these nuclei: the NAc and the dorsal striatum. We argue that the cerebellar projections to the VTA may play a role in reward-based learning and therefore contribute to addictive behavior, whereas the projection to the SNc may contribute to movement vigor. Finally, we speculate how these projections may explain many of the observations that indicate a role for the cerebellum in mental disorders, such as schizophrenia.

Key words: Cerebellum; Basal-ganglia; dopamine; motor coordination; reward processing; movement vigor

Introduction

Coordinated movements leading to meaningful behavior require integration of sensory cues that inform the animal of its environment and the state of its body, activating and coordinating a multitude of skeletal muscles, and then ensuring that all movements are timed correctly and take place as intended (Ebbesen and Brecht, 2017). In addition, during goal-directed behavior, the brain computes what actions are optimal, and even what goals are worth pursuing. These are fundamental components of behavior and are thought to be processed by the brain's reward system, which computes motivation: the willingness to perform an action (Salamone and Correa, 2012; Berke, 2018). Even the simplest volitional behavior requires immense neural computation; therefore, the motor systems constitute a major component of the CNS. In mammals, voluntary movements are planned in the cerebral cortex and executed by spinal cord circuits. Two additional major structures of the brain, the basal ganglia and the

cerebellum, are also considered to be components of the motor system. By and large, these two systems control movement indirectly by regulating the activity of the upper motor systems of the cerebral cortex and brainstem.

The basal ganglia system ensures that the correct movements are initiated and maintained, while unwanted movements are suppressed (Klaus et al., 2019). In contrast, the cerebellum guarantees that movements take place in a smooth and coordinated way (D'Angelo, 2018). In addition to their motor functions, both the basal ganglia and the cerebellum are involved in processing sensory perception and higher-order cognitive functions (Middleton and Strick, 2000; Wagner and Luo, 2020). Both systems are also essential components of the brain's learning mechanisms (Bostan and Strick, 2018). The basal ganglia include the brain's so-called reward system, which controls both motivation and associative learning primarily as positive-reinforcement and classical conditioning. As with the prominent role of the basal ganglia in associative learning, the cerebellum also plays a central role in learning and memory. Cerebellar learning is primarily understood in the context of error correction in motor learning, for example, in learning to throw or catch a frisbee better and better (Popa et al., 2016). Borrowing terminology from Computer Science, cerebellar learning is often considered a form of error-based supervised learning (Raymond and Medina, 2018) because it uses feedback about

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the motor system's performance to adjust the system parameters and improve future performance. However, recent studies have indicated that cerebellar signals also process reward information, suggesting a role for the cerebellum in reward-based reinforcement learning (Taylor and Ivry, 2014).

All basal ganglia functions depend crucially on neuromodulation by dopamine (DA). DA release from midbrain nuclei to basal ganglia structures, especially the striatum, is essential for the initiation and vigor of movements (da Silva et al., 2018). Dysfunctions of DA neurons, as in Parkinson's disease, or their targets in the striatum, as in Huntington's disease, result in debilitating deficits of movement and action (Klein et al., 2019). DA in the basal ganglia is also essential for the reinforcement learning system (Lerner et al., 2021), and DA fluctuations are often considered a proxy for motivation and reward processing (Salamone and Correa, 2012).

Both the basal ganglia and the cerebellum systems receive input from the cerebral cortex and sensory systems, and both communicate back to the cortex, via mostly distinct thalamic nuclei (Percheron et al., 1996; Sakai et al., 1996). Thus, either system can be considered a component of a cortical loop, and these two loops have been historically thought to interact at the cortical level. Yet, early functional and anatomic studies (Li and Parker, 1969; Snider et al., 1976; Nieoullon et al., 1978; Nieoullon and Dosticier, 1980) as well as human brain imaging (Kwon and Jang, 2014; Milardi et al., 2016) had suggested the possibility of more direct connections between these structures. The development of modern anatomic techniques allowed for the discovery of interactions between the cerebellum and the basal ganglia independent of the cortical loops (Hoshi et al., 2005; Bostan et al., 2010), leading to a renewed interest in unraveling the nature of interactions between these two important brain structures (Cacciola et al., 2017; Caligiore et al., 2017). In the past decade, a handful of studies used modern techniques in viral-genetic circuit mapping, imaging, optogenetics, and electrophysiology to show that the cerebellum also provides a direct input to the basal ganglia DA centers (Watabe-Uchida et al., 2012; Beier et al., 2015; Carta et al., 2019; Washburn et al., 2022), increasing the dimensions by which the cerebellum can contribute to movement and cognition. Nevertheless, the detailed function of these connections or their mechanism of action remains unclear. In this article, we will review these recent findings and discuss the contribution of the subcortical pathways that connect the cerebellum to the basal ganglia to the processing of (1) movement initiation and coordination and (2) reward-based learning in the basal ganglia. Although there is also strong evidence in support of subcortical connections from the basal ganglia to the cerebellum (Kizer et al., 1976; Ikai et al., 1994; Meissner et al., 2005; Bostan et al., 2010; Sutton et al., 2015; Jwair et al., 2017; Flace et al., 2021), we will not discuss these connections in this review.

Basic cerebellar anatomy and projections to the basal ganglia

Cerebellar processing is performed by the cerebellar cortex, whose anatomic organization is primarily a uniform, repetitive three-layer neuronal circuit. The cellular processing units of the cerebellar cortex are the Purkinje cells, which receive primarily inputs from the pontine nuclei and the inferior olive. The pontine nuclei axons (mossy fibers) synapse onto granule cells, the most abundant cells in the vertebrate brain. Purkinje cells integrate inputs conveyed from the parallel fibers, the granule cell axons, and from climbing fibers, the axons of the inferior olivary neurons. Purkinje cells are tonically active (pacemakers) and have inhibitory GABAergic output. Their axons mainly project

to the neurons in the deep cerebellar nuclei (DCN), the cerebellar output nuclei whose efferent projections are sent to other brain regions. As with the Purkinje cells, the DCN neurons are also tonically active. Inhibition by the Purkinje cells results in changes in the pattern and frequency of firing of DCN neurons (Cerminara et al., 2015; Hull and Regehr, 2022).

The DCNs are bilateral and, on each side, are composed of three primary nuclei: the dentate, the interposed, and the fastigial nucleus, each of which somatotopically receives inputs from their overlying cerebellar cortex. Classical studies suggested that the dentate and interposed nucleus neurons project mainly to the thalamus and the midbrain, while the brainstem and spinal tracts are targeted mainly by the fastigial nuclei (Ito, 1984; Voogd, 2014). While in broad strokes these observations remain valid, recent data show heterogeneity in DCN neurons and broad projections from each nucleus to similar but mostly nonoverlapping target regions (Kebschull et al., 2020), suggesting that each nucleus may have a potentially different functional influence on the target regions. Moreover, historically it is thought that the cerebellar nuclei may serve distinct functions, with the fastigial and interposed nuclei primarily contributing to motor execution, and the dentate to motor planning (Manto and Oulad Ben Taib, 2010; Gao et al., 2018).

Although early anatomic studies (discussed below) linked the cerebellum with some components of the basal ganglia, recent advances on tracing techniques combined with cutting-edge approaches, such as optogenetics and fiber photometry, have allowed a more rigorous characterization of the details and possible functions of the pathways involved in the cerebellum-basal ganglia connections. Below, we will discuss the evidence linking the cerebellum with the basal ganglia, specifically the pathways through the thalamus and the midbrain DA centers (Fig. 1), and then delineate the possible roles of the cerebellum in these different circuits in terms of motor control, motivation, and reward-related behaviors.

The thalamic pathway and its influence on motor coordination

The cerebellum and basal ganglia have been traditionally considered to be interconnected via the cerebral cortex (Haber and Gdowski, 2004; Nieuwenhuys et al., 2007; Voogd and Ruigrok, 2012). However, both the basal ganglia and the cerebellum communicate to the cortex through the thalamus, albeit through different thalamic nuclei (Percheron et al., 1996; Sakai et al., 1996), although some degree of convergence exists (Hintzen et al., 2018). The thalamus, in turn, has a myriad of connections to subcortical structures, so the idea that the cerebellum and the basal ganglia may have connections through the thalamus has been present for a long time. Interestingly, such connections have been examined in nonmammalian vertebrates. Both the cerebellum and the basal ganglia are brain structures that have been conserved throughout the vertebrate evolutionary history (Nieuwenhuys, 1967; Grillner and Robertson, 2016), and both by far predate the evolution of the neocortex (Van Essen et al., 2018). Many studies have examined the role of these structures in a variety of behaviors in nonmammalian vertebrates (Reiner et al., 1998; Gómez et al., 2010; Brown et al., 2011; Montgomery and Perks, 2019). In songbirds that learn song by imitation, both structures have been implicated in song learning (Ziegler and Ackermann, 2017; Daou and Margoliash, 2021). Connections from the cerebellum to the song-related components of the basal ganglia had been suggested by anatomic studies (Vates et al., 1997; Person et al., 2008; Nicholson et al., 2018), but the functional significance of these connections to sensorimotor learning in

songbirds was unknown. A recent study confirmed the presence of a disynaptic connection between the cerebellum and Area X, a striatal nucleus of the songbird basal ganglia, through the thalamus. This pathway is mediated by the dorsal thalamic zone, which is the bird homolog of the mammalian intralaminar, midline, and mediodorsal nuclei (Veenman et al., 1997). Electrical stimulation of the DCN in anesthetized zebra finches provoked a strong increase in the firing rate of Area X neurons, indicating that cerebellar activity can drive these striatal neurons. In addition, DCN lesions resulted in lower imitation scores in song learning, suggesting that the cerebellar projection to the basal ganglia contributes to song learning (Pidoux et al., 2018).

Does a similar pathway exist in mammals? An early anatomic study in the rat used double labeling with traditional tracers and electron microscopy to show an overlapping distribution, in the central lateral nucleus (CL) of the thalamus, of retrograde-labeled neurons of the dorsolateral striatum and anterograde-labeled cerebellar dentate nucleus axon terminals (Ichinohe et al., 2000). The presence of a similar connection was shown using modern anatomic retrograde rabies virus tracing methods in the macaque monkey. This study showed that both the motor and the nonmotor domains of the dentate nucleus are linked to the striatum via a disynaptic connection (Hoshi et al., 2005), and suggested that the intralaminar thalamic nuclei (Smith et al., 2004; Xiao et al., 2018) (which include the CL and the parafascicular nucleus [PF]) may be the intermediary connection between the two structures. The physiological properties of such a connection were explored more recently, in behaving rodents, in a study that specifically examined the connections from the dentate nucleus to the dorsal striatum (DS)-projecting CL thalamic nucleus neurons (Chen et al., 2014). Optogenetic stimulation of the cerebellar axons in the thalamus evoked rapid (~10 ms) excitation of dorsal striatal neuronal activity, which was abolished by the inactivation of the thalamic CL, but not of the cerebral cortex. This was the first physiological proof that, in mammals, the cerebellum communicates with the basal ganglia independent of the classical cortical route. This study further showed that the cerebello-thalamostriatal pathway can adjust long-term plasticity of cortical projections to the striatum by switching LTP of the corticostriatal synapse to LTD, thus pointing to a potential function of simultaneous activity in these two pathways. Although the basal ganglia connections cover the anterior-medial parts of the thalamus, the cerebellum mainly projects to the posterior-lateral regions of the thalamus. Nevertheless, the existence of overlapping zones, mainly through medial thalamic and intralaminar nuclei, supports the presence of a similar thalamic interaction between the two systems in humans.

What potential function may the cerebello-thalamostriatal (Cb-CL/PF-DS) pathway serve? Cerebellar activity correlates with movement kinematics and is necessary for the real-time adjustment and optimization of the muscle activity (Ito, 1984), while it is thought that the basal ganglia are primarily concerned with the selection of optimal motor commands (Mink, 1996; Doya, 1999; Redgrave et al., 1999; Doya, 2000). It is possible that the real-time muscle kinematics conveyed by the Cb-CL/PF to the basal ganglia would be of value to its selection of the optimal motor commands for complex

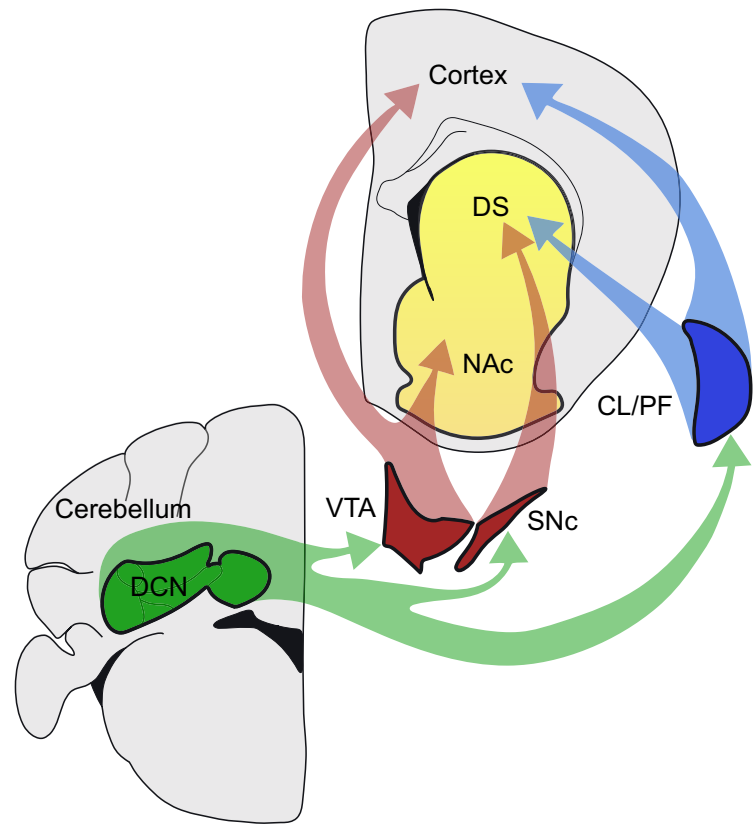


Figure 1. Anatomical pathways connecting the cerebellum with the basal ganglia. The figure refers only to the noncanonical pathways described in this review. The traditional cerebello-thalamo-cortical pathways are omitted. The DCN of the cerebellum connect with the DS via the thalamic nuclei (CL and PF), and with the NAc and DS via the VTA and the SNc, respectively. The thalamic pathway conveys fast glutamatergic signals to the striatum, contributing to motor coordination. Projections via the VTA and SNc allow the cerebellum to directly contribute to DA release in the DS and the NAc. The VTA, as well as the thalamus, also projects to the cerebral cortex. VTA cortical projections suggest that the cerebellum can directly contribute to cortical DA levels via direct projections to the VTA (this connection is not discussed in this review).

motor tasks, particularly for movements that require high temporal precision and thus synchronization between the two structures. In support of this hypothesis, Diaz-Hernandez et al. (2018) reported that thalamostriatal projections were activated for several milliseconds before a mouse initiated movement sequences in an operant task, and that inhibition of their activity led to a delay in movement initiation, suggesting that the basal ganglia relies on this information on the millisecond timescale for movement initiation. Studies of dystonia also supported this idea. In a mouse model of cerebellar-induced dystonia, it was shown that the Cb-CL projections erroneously transmit irregular high-frequency activity to the striatum, causing the dorsal striatal neurons to fire in high-frequency bursts. Interrupting the Cb-CL activity rescued the dystonia in these mice (Chen et al., 2014). Together, these studies indicate that the Cb-CL-DS signaling is essential for intact motor coordination, and inappropriately timed or excessive signaling from the cerebellum to the striatum via the thalamus can aggravate or cause abnormal movement disorders, such as dystonia.

Interactions through the midbrain dopaminergic nuclei

Midbrain DA nuclei are a key brain region in charge of providing DA to the basal ganglia and the cerebral cortex. DA release in the basal ganglia is necessary for reward processing and movement initiation, and impairment in DA release dynamics could produce severe behavioral consequences in motor and nonmotor domains. Recent evidence showing that the cerebellum directly

contributes to midbrain dopaminergic activity in behaving animals suggests that cerebellar input plays a direct role in basal ganglia DA levels, and proposes that this circuit might play a central role in linking the cerebellum to motor and nonmotor dysfunctions. Below, we review the recent work supporting this idea.

Projections to the VTA and their potential influence on motivation and reward evaluation

The ventral tegmental area (VTA) is a ventromedial midbrain nucleus, and is one of the major sources of DA in the brain together with the substantia nigra. The VTA plays a role in a variety of brain functions, such as positive and negative reinforcement, decision-making, salience, and aversion (Ungless et al., 2004; Berridge, 2007; Matsumoto and Hikosaka, 2009; Bromberg-Martin et al., 2010; Lammel et al., 2012; Fry et al., 2021). The VTA receives inputs from different brain regions, including the PFC, NAc, lateral habenula, and the ventral pallidum (Geisler et al., 2007; Watabe-Uchida et al., 2012; Ogawa et al., 2014; Beier et al., 2015; Faget et al., 2016) and sends dopaminergic projections to several brain regions, primarily through two major pathways: the mesolimbic pathway to the NAc (Fallon and Moore, 1978; Mogenson et al., 1980; Phillipson and Griffiths, 1985) and the mesocortical pathway to the PFC (Swanson, 1982) (see Fig. 1). The mesolimbic pathway has been involved in reward-related behaviors, motivation, and aversion (Salamone, 1994; Cardinal et al., 2002; Carelli, 2002; Yun et al., 2004; Goto and Grace, 2005). The VTA is mainly composed of DA neurons, while the rest of the neurons are GABAergic or (a smaller fraction) glutamatergic. The GABAergic and glutamatergic subgroups include both local interneurons and projection neurons, and some fraction of these co-release DA as well (Morales and Margolis, 2017).

Almost 50 years ago, some anatomic studies pointed out cerebellar projections to the VTA, but there were no follow-up explorations of this pathway until the recent development of modern tracing methods. The early studies performed tracing experiments using post-lesion staining of degenerating projections, and anterograde or retrograde tracing in cats and rats, and showed that all three DCNs contribute to VTA projections (Snider et al., 1976; Phillipson, 1979; Teune et al., 2000). The development of transsynaptic anterograde and retrograde viruses allowed researchers to corroborate these results. Using transgenic mice lines combined with retrograde viruses to selectively target specific cell types, it was demonstrated that the DCN send direct projections to VTA DA, GABAergic, and glutamatergic neurons (Watabe-Uchida et al., 2012; Beier et al., 2015; An et al., 2021). There are, however, some disagreement in these studies on the DCN origin and identity of these projections. Baek et al. (2022) have observed projections in the dorsolateral VTA mainly from the dentate nucleus and to a lesser extent from the interposed nucleus, but not from the fastigial nucleus. However, by using a transsynaptic anterograde virus to label postsynaptic target cells, another study has shown that the posterior fastigial nucleus also contributes to these projections (Fujita et al., 2020). Results from our group have also corroborated this pathway. Similarly, we have observed cerebellar inputs coming from the three cerebellar nuclei, targeting DA and GABAergic VTA neurons. Projections from each DCN nuclei target different, but overlapping regions in the VTA, suggesting potentially specific contributions of each DCN to the VTA pathway (Oñate and Khodakhah, unpublished observation). Physiologic characterization of the DCN projections that used optogenetic stimulation to demonstrate the presence of functional

monosynaptic cerebellar projections to the VTA only found excitatory connections (Carta et al., 2019; Baek et al., 2022).

In order to understand the possible functional roles of this pathway, it is important to identify the targets of the VTA neurons that receive cerebellar input. A major output of the VTA is through the mesolimbic projections to the NAc. Anatomical tracing experiments to trace the input of cell type-specific neurons in the VTA based on the output suggested the existence of a disynaptic pathway from the cerebellum to the accumbens through this pathway that involves GABAergic, glutamatergic, and dopaminergic neurons (Beier et al., 2015, 2019). Corroborating this circuit, a recent study (D'Ambra et al., 2021) showed an overlap in the VTA neurons that receive input from the DCN (tagged using an anterograde viral tracer) and those that project to NAc (tagged using a retrograde tracer). In addition, intersectional tracing using a transsynaptic virus combined with an anterograde virus showed cerebellar VTA projections to accumbens (D'Ambra et al., 2021). Data from our group have also confirmed these results. Using a combination of transsynaptic anterograde and retrograde virus tracing, we mapped and identified the cells in the DCN and in the VTA that form this disynaptic pathway. We found that neurons from all three DCN nuclei project to DA and non-DA neurons in the VTA (the Cb-VTA pathway) that then send extensive projections to all regions of the NAc (Oñate and Khodakhah, unpublished observation).

Previous data from our group have also shown that the Cb-VTA pathway is functionally active. The DCN sends monosynaptic excitatory projections to both dopaminergic and nondopaminergic neurons of the VTA (Carta et al., 2019). Given that VTA sends major projections to the NAc, this suggests that cerebellar activity could trigger excitation of the VTA neurons and consequently modify the mesolimbic neuronal activity. A similar study used amperometry measurements of DA to show that electrical stimulation of the dentate nuclei evokes DA release in the NAc (Holloway et al., 2019). Using fiber photometry to measure DA activity with the fluorescent sensor dLight, we also recently found that optogenetic stimulation of the Cb-VTA pathway can drive DA release in the NAc (Vera and Khodakhah, unpublished observation). Interestingly, stimulation of this pathway evoked not only DA release but also fast excitation of NAc single units (D'Ambra et al., 2021; Vera and Khodakhah, unpublished observation), suggesting that cerebellar activity can have strong influence in the activity of the NAc.

Although the cerebellum has been traditionally thought to process mainly motor-related information, it is well known that it also contributes to a variety of other brain functions, such as sensory and cognitive processing (Rapoport et al., 2000; Noroozian, 2014; Bostan and Strick, 2018; Schmahmann, 2019). Pertaining to our topic, several recent studies have reported that the cerebellum encodes and processes reward-related signals (Ohmae and Medina, 2015; Wagner et al., 2017; Heffley et al., 2018; Heffley and Hull, 2019; Kostadinov et al., 2019; Larry et al., 2019; Kostadinov and Hauser, 2022), functions that are typically attributed to the limbic system and are also the purview of the basal ganglia. But is this reward-related information conveyed to the basal ganglia?

Some clues from earlier studies suggest an answer to this question. Impairment in Purkinje cells, granule cells, or the DCNs could cause a reduction in motivated behaviors (Berntson and Schumacher, 1980; Caston et al., 1998; Bauer et al., 2011). As we described above, the cerebellum has direct projections to the VTA dopaminergic neurons. It is well known that VTA dopaminergic neurons, in particular the projections to the NAc, play a central role in reward-driven motivated behaviors and in

reward-based reinforcement learning (Saunders et al., 2018; Mohebi et al., 2019). Interestingly, time-restricted optogenetic inactivation of the VTA-accumbens projection does not affect ongoing movements (Lee et al., 2020) but influences upcoming future behaviors (Chang et al., 2016; Lee et al., 2020). These findings suggest that the Cb-VTA-NAc pathway may contribute to the computation of motivation and influence learning processes. Indeed, fiber photometry measurement of the fluorescent calcium indicator GCaMP in behaving mice showed that the activity of the Cb-VTA projection was increased during social interaction, compared with exploration of an empty chamber (Carta et al., 2019), and scaled with reward value in a Pavlovian task (Yoshida and Khodakhah, unpublished observation). In addition, optogenetic stimulation of the Cb-VTA projection produced conditioned place preference, and its optogenetic inhibition impaired social interactions in a three chamber test (Carta et al., 2019).

The mesolimbic DA pathway is known to be an essential component of brain processes underlying addiction (Nestler, 2001; Koob and Volkow, 2010). The fact that the Cb-VTA projection is involved in motivational processing therefore indicates that this projection may also contribute to the pathologic mechanisms underlying addiction. Although the cerebellum is not generally considered as part of the neural circuitry responsible for drug abuse and addiction, studies of drug-dependent humans have consistently yielded tantalizing evidence, suggesting cerebellar involvement in reward processing and in addiction (Volkow et al., 2006; Thomas et al., 2008; Miquel et al., 2009, 2016, 2019, 2020; Moulton et al., 2014; Wagner et al., 2017; Guarque-Chabrera et al., 2022). For example, cerebellar gray matter volume is reduced in long-term addicted individuals compared with controls (Moulton et al., 2014; Miquel et al., 2016). Even more compellingly, functional imaging studies show that the cerebellum is activated in human subjects receiving methylphenidate, cocaine, or nicotine (Volkow et al., 1997, 2006; Domino et al., 2000; Risinger et al., 2005; Zubieta et al., 2005). Moreover, in drug abusers, cues predictive of drugs activate the cerebellum (Grant et al., 1996; Schneider et al., 2001; Bonson et al., 2002; Anderson et al., 2006), and the strength of these activations correlates with subjective ratings of craving (Grant et al., 1996; G. J. Wang et al., 1999; Sell et al., 2000; Kilts et al., 2001; Schneider et al., 2001; Bonson et al., 2002; Risinger et al., 2005; Anderson et al., 2006; Lou et al., 2012). These striking and consistent correlations seen in human subjects suggest that the cerebellum may participate in craving, relapse, and even primary drug reinforcement. Recent studies in rodents find that chronic cocaine treatment causes structural plasticity in cerebellar Purkinje cells (Vazquez-Sanroman et al., 2015), and that cerebellar granule neurons exhibit c-Fos activation in mice expressing a cocaine-conditioned place preference (Carbo-Gas et al., 2014), leading to strong evidence for cerebellar involvement in cocaine-induced habit formation (Domino et al., 2000; Miquel et al., 2019, 2020; Gil-Miravet et al., 2021; Sanchez-Hernandez et al., 2021). These studies strongly indicate that the cerebellum is one of the brain regions involved in the pathologic mechanisms of addiction, possibly by its modulation of the mesolimbic pathway.

The cerebello-nigrostriatal pathway and its possible role in movement vigor

Another dopaminergic center in the midbrain is the substantia nigra pars compacta (SNc), located in the ventrolateral region, next to the VTA. Like the VTA, the SNc mainly contains DA

neurons; and although it also includes GABAergic and glutamatergic neurons, DA neurons dominate by far (Nair-Roberts et al., 2008). The major output of the SNc is through its (nigrostriatal) projections to the DS, where the release of DA modulates the properties of target neurons and their synapses. DA release in the DS has been associated with motor control, primarily because degeneration of DA neurons in the nigrostriatal system, a primary hallmark of Parkinson's disease, is linked to difficulty in initiating movements (hypokinesia) and rigidity, and its hyperactivity could favor hyperkinetic movements (Wang et al., 2013). Notably, studies using MRI for fiber tracking have suggested the presence of cerebellar connections with the substantia nigra and the VTA in healthy humans (Kwon and Jang, 2014; Milardi et al., 2016), and that the relative connectivity with these two regions is modified in patients with Parkinson's disease (O'Shea et al., 2022), suggesting that cerebellar activity is a required input for these dopaminergic centers in humans.

As discussed for the VTA in the previous section, older anatomic tracing studies had implicated the presence of direct cerebellar projections to the SNc. Lesions in each DCN nucleus, followed by a staining method to detect neuronal degenerated terminals revealed that the DCN projects to the substantia nigra, targeting medial and lateral regions of the SNc (Snider et al., 1976). This work was not followed up for several decades, until the development of modern neuronal tracing techniques (as discussed above) allowed for a more rigorous reevaluation of these connections. Using a retrograde viral approach to target specific neuronal cell types shows inputs in the cerebellum projecting to DA, GABAergic, and glutamatergic neurons in the SNc (Watabe-Uchida et al., 2012; An et al., 2021). More recently, this result was corroborated by multiple groups. Using a transsynaptic anterograde virus to label all target cells, Fujita et al. (2020) showed that, specifically, the caudoventral region of the fastigial nucleus sends projections to SNc DA and non-DA neurons. Our own anatomic work using the same approach, but targeting the entire DCN, confirmed these projections to both DA and non-DA neurons of the SNc. By mapping the target cells in detail, we found cells throughout the entire SNc. Additionally, injection of a retrograde virus in the SNc to map all originating neurons demonstrated that cerebellar inputs come from all three DCN (Washburn et al., 2022). In a similar study, to label the input of SNc-DA neurons based on their output, particularly to the striatum, input cells in the cerebellum were observed, providing anatomic data for the existence of this disynaptic circuit (Menegas et al., 2015). In addition to anatomic studies, both older and recent studies have explored the functionality of this pathway. Electric stimulation of the DCN was shown early on to alter DA levels in the striatum (Nieoullon et al., 1978; Nieoullon and Dusticier, 1980). More recently, our group showed that the projections from DCN neurons to the SNc (the Cb-SNc pathway) form monosynaptic glutamatergic synapses, targeting AMPARs and NMDARs, with both DA and non-DA neurons. Optogenetic stimulation of this pathway in slice preparations produced fast excitatory synaptic currents in SNc neurons. Additionally, *in vivo* optogenetic stimulation of this pathway increased SNc single-unit activity and evoked DA release in the DS, as measured with the fluorescent DA sensor dLight (Washburn et al., 2022). Finally, *in vivo* optogenetic activation of the Cb-SNc pathway increased the probability of locomotion in head-fixed animals ambulating on a treadmill. Together, these data show that cerebellar projections to the SNc can play a prominent role in the DA modulation of the basal ganglia and may constitute an additional pathway by which the cerebellum contributes to movement coordination.

All movements underlying natural behavior are initiated and executed with a specific delay, speed, frequency, and with appropriate force, attributes that are collectively referred to as movement vigor. All components of movement vigor are flexible and subject to change depending on behavioral need. A large body of research in primates, including humans, and rodents shows that the basal ganglia play a central role in controlling movement vigor (Berardelli et al., 2001; Boecker et al., 2008; Palmiter, 2008; Howe and Dombeck, 2016; da Silva et al., 2018; Shah et al., 2020) and that nigrostriatal DA plays a critical role in adjusting movement vigor (Panigrahi et al., 2015; Mendonça et al., 2021). It is also known that the DCN activity precedes movement onset (Thach, 1970, 1975; Armstrong et al., 1979; Fortier et al., 1989) similar to what has been observed for the SNc DA neurons (Boecker et al., 2008; Howe and Dombeck, 2016; da Silva et al., 2018), and that inhibiting the activity of the cerebellar nuclei slows reaction times in motor tasks (Meyer-Lohmann et al., 1977; Trouche and Beaubaton, 1980; Miller and Brooks, 1982; Tsujimoto et al., 1993). Although the cerebellar thalamocortical pathway is known to contribute to movement initiation (Dacre et al., 2021), as discussed above, recent work from our laboratory has also shown that the Cb-SNc projection directly influences the activity of the SNc DA neurons and their DA release in the DS. Interestingly, in a simple Pavlovian task where animals were given a liquid reward following a sensory cue, the Cb-SNc projections showed activation to water reward and a much higher activation to sweet water reward, indicating that this pathway conveys information on the reward value (Washburn et al., 2022). The cerebellum is commonly thought as a “learning machine” that uses cortical and sensory input to learn to predict the neural activity needed to coordinate posture and movement (Ito, 1984, 2006). Knowing that the cerebellum computes reward value information, it is plausible that the cerebellum uses sensory and cortical signals to compute reward likelihood and communicate this information to the SNc. The SNc then can use this information, together with those arriving from other brain regions, to determine the appropriate movement vigor.

Given the evidence showing the strong activation of the SNc DA neurons by the Cb-SNc activity, it is logical to think of this pathway in the context of Parkinson’s disease. Parkinson’s disease is caused by the degeneration of SNc DA neurons (Damier et al., 1999; Dauer and Przedborski, 2003; Michel et al., 2016). A key feature of Parkinson’s disease is the difficulty in initiating movements and the movements of Parkinsonian patients, once initiated, tend to be slower (Benecke et al., 1987; Jahanshahi et al., 1992; Pascual-Leone et al., 1994; Chen et al., 2001), both indicative of a deficit in movement vigor. Therapeutic approaches that increase DA receptor activation, such as increasing DA release by administering levodopa, are effective in alleviating these vigor deficits early in the disease (Ehringer and Hornykiewicz, 1960; Hornykiewicz, 1975; Birkmayer and Hornykiewicz, 1998; Hornykiewicz, 2006), indicating that reduced DA is the major cause of the motor symptoms. Recent studies have shown a rapid increase in the activity of SNc DA neurons immediately preceding movement onset (Boecker et al., 2008; Howe and Dombeck, 2016; da Silva et al., 2018) and have demonstrated that SNc DA plays a central role in the control of movement vigor (Berardelli et al., 2001; Mazzoni et al., 2007; Palmiter, 2008; Turner and Desmurget, 2010; Panigrahi et al., 2015; Mendonça et al., 2021). As described above, the Cb-SNc projection can convey movement vigor information to the basal ganglia by increasing the activity of SNc DA neurons and

striatal DA levels. Although the Cb-SNc pathway is not the sole projection that contributes to regulation of SNc DA neurons, it is nonetheless plausible that increasing the activity of the Cb-SNc pathway may alleviate the Parkinson’s-like motor symptoms if the DA neurons are only partially lost. This hypothesis could be readily examined in animal models of Parkinson’s disease with optogenetic excitation of the Cb-SNc pathway. If excitation of the Cb-SNc pathway can reduce Parkinson’s-like vigor deficits, activation of this pathway provides a potential therapeutic substrate by deep brain stimulation or transcranial magnetic stimulation of DCNs that can be readily targeted in Parkinsonian patients.

Beyond reward and movement: thoughts on the potential role of the cerebellum and basal ganglia interactions in schizophrenia

Both the cerebellum and basal ganglia are implicated in diverse functions, such as motor, cognitive, reward, and emotional processing. As discussed, recent findings have revealed an extensive set of direct, cortex-independent, pathways by which the cerebellum communicates with the basal ganglia. These pathways allow the cerebellum to transmit information at multiple timescales, with neurotransmitters, such as glutamate, enabling fast, short-latency communication with millisecond time resolution, and neuromodulators, such as DA, supporting slower modulation of the basal ganglia in the 100 ms to seconds timescale. As discussed above, a cardinal feature of the cerebellar circuitry is its ability to provide predictive outputs based on learned associations between a wide array of sensory and cortical inputs. It is plausible, therefore, that the cerebellum constantly samples the environment and one’s intent using its extensive sensory and cortical inputs, and via its direct projections provides the basal ganglia with predictions that help formulate diverse sets of behaviors, ranging from movement to reward processing, motivated behavior, and cognition.

Further scrutiny of such potential functional frameworks might allow for formulation and test of hypotheses to better understand the brain, and also to account for the diversity of nonmotor disorders in which the cerebellum is implicated. As an example of the latter, it might be interesting to briefly consider the role of the cerebellum in schizophrenia. In patients, a substantial decrease in cerebellar size (Laidi et al., 2015; Moberget et al., 2018, 2019) changes in cerebellar connectivity with the cortex and basal ganglia (Cao et al., 2018; Moberget et al., 2018; Anteraper et al., 2021), and cerebellar, cortical, and striatal hypoactivity (Lungu et al., 2013) are some of the most common and consistent findings. A major debilitating feature of schizophrenia is the presence of negative symptoms, cardinal among which are apathy and amotivation (Millan et al., 2014; Mosolov and Yaltonskaya, 2021). Given that motivated behavior requires reward processing by the midbrain DA centers that target both the PFC and the ventral striatum, the negative symptoms of schizophrenia might be the consequence of the reduced interactions between the cerebellum and the basal ganglia DA network as described here. Such a failure in communication between the cerebellum and basal ganglia might prevent the cerebellum from conveying to the basal ganglia its predictions related to desirability of upcoming behaviors, leading to apathy and amotivation. Indeed, in support of such a possibility, preliminary reports suggest that transcranial magnetic stimulation of the cerebellum can partially restore its functional connectivity with the cortex and the basal ganglia, and concurrently lessen the severity of the negative symptoms in patients (Demirtas-Tatlidede,

et al., 2010; Tikka et al., 2015; Garg et al., 2016; Brady et al., 2019; Basavaraju et al., 2021; Zhu et al., 2021; Bègue et al., 2022).

The recent advances in our understanding of the nature of the interactions between the cerebellum and basal ganglia, and the potential contributions that these interactions may make in motor and nonmotor functions of the brain, have generated significant excitement in the field and have forced reevaluation of many long-held beliefs. No doubt, the fertile ground thus generated will motivate a large number of exciting new hypotheses that need to be rigorously tested in the coming years.

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