Cerebellum and Cerebrum in Chorus

How the Cerebellum Modulates Activity of the Basal Ganglia During Development and Production of Vocalisation; Insights from Humans and Songbirds

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Abstract

Vocal learning is an exceptional sensory-motor skill that is evolutionarily conserved between humans and songbirds. Songbirds serve as valuable models for studying the brain mechanisms underlying vocal learning, which have led to a well-established model of vocalisation in both mammals and birds. This model primarily consists of two components; a motor pathway for generating vocalisations and a feedback loop that ensures the produced sounds match an internal sound template. The motor pathway is associated with the cortex, while the feedback loop involves the basal ganglia and thalamus. This essay introduces the cerebellum as an extra component of the song system. The cerebellum is involved in the coordination and error correction of motor movements and has proven to play a significant role in human speech. Previously, it was believed that the cerebellum and cerebrum had separate functions in movement creation and interacted only at the level of the cortex. However, recent studies have shown that the cerebellum also interacts with the basal ganglia at the thalamic level and has direct projections to regions important for the feedback loop. This essay proposes a new song system model based on insights from both mammals and birds, that integrates the functions of both cerebellum and cerebrum.

Contents

1   Vocal Learning is a Complex Sensorimotor Skill

Vocalisation is an exceptional skill requiring precise coordination of motor control. It is the ability to modify acoustic and syntactic sounds, acquire new sounds via imitation, and generate vocalisations (Martins & Boeckx, 2020). This ability is not universal across the animal kingdom. Dogs for example can produce sounds, but lack the ability to imitate and modify specific sounds. In humans, speech acquisition forms the basis for the development of language (Stark, 1980). Humans learn to talk when they are a baby, at first this is done only by imitating the sounds of parents. Then in the first years of life, they develop their own speech through a combination of imitation and auditory feedback (Sharp & Hillenbrand, 2008).

However, the process is also not unique to humans. Songbirds for example learn to imitate a tutor song in a manner similar to how humans learn speech (Doupe & Kuhl, 1999). Two important phases can be distinguished during the development of vocalisation (see Figure 1a) (Derégnaucourt et al., 2004; Sakata & Yazaki-Sugiyama, 2020). The first is a sensory phase, where sounds from the environment are perceived. In the second phase, the sensorimotor period, sounds are not only perceived but produced as well. When

juvenile birds first start singing there is no phonetic structure to the production of sounds yet (Lipkind et al., 2013). In this period, the songbirds attempt to produce sounds that match their tutor's song. In the initial stage, there is minimal resemblance to the tutor song. The song in this stage is called the subsong. The subsong contains a lot of errors since the birds are still trying out different versions with the goal of finding what matches the tutor song best (Tchernichovski et al., 2001). With enough rendition, similarity to the tutor song increases and the song acquires a stable phonetic structure. For some species of songbirds, the song is not subject to much variation after this period and the birds are unable to learn a new song. These types of songs are called crystallised songs (White & Mooney, 1999).

Both in humans and birds the vocalisation in the sensorimotor period of vocal learning still contains a lot of variation (see Figure 1b). How do young birds or humans move from this flexible song or speech to vocalisation that matches the template better and becomes more crystallised? For both humans and birds, feedback plays an essential role in this developmental process (R. Chen & Goldberg, 2020; Tourville & Guenther, 2011). In humans, auditory and somatosensory feedback is used to compare the produced speech to the target speech. The target speech is an intrinsic template of speech that is acceptable to produce, which is usually the example juveniles hear from adults. When the produced speech falls outside the range of acceptable speech, this is perceived as an error. The speaker can subsequently adjust their speech to correct for this error (Tourville & Guenther, 2011). Studies show that this process is similar to song learning in birds (Nordeen & Nordeen, 2010).

The combination of producing sound while also processing feedback makes vocalisation a complex sensorimotor control system. Both motor control and sensory feedback control are vital components in the development and production of coherent sound. Since this process is extensively studied, there is already a comprehensive understanding of how vocal learning and production are regulated in the brain (R. Chen & Goldberg, 2020; Riters, 2011). However, there are still unexplored areas in the field of vocal learning.

This essay aims to explain the established mechanisms of vocal learning, while also discussing the current gaps in knowledge. There have been elaborate research on how cortico-thalamo-basal ganglia-cortical loops influence vocalisation. It is also well-known that the cerebellum is involved in motor coordination and error correction (Popa et al., 2016), however, its role in vocal learning is not well-researched yet. Therefore, the main focus of this essay is on the involvement of the cerebellum in the process of vocal learning. Further, insights will be provided on the function of various connections between the basal ganglia and the cerebellum. Moreover, experimental approaches will be proposed to examine the contribution of the cerebellum to vocal learning. Ultimately, this essay aims to offer a new perspective on the song system with the cerebellum as a contributor.
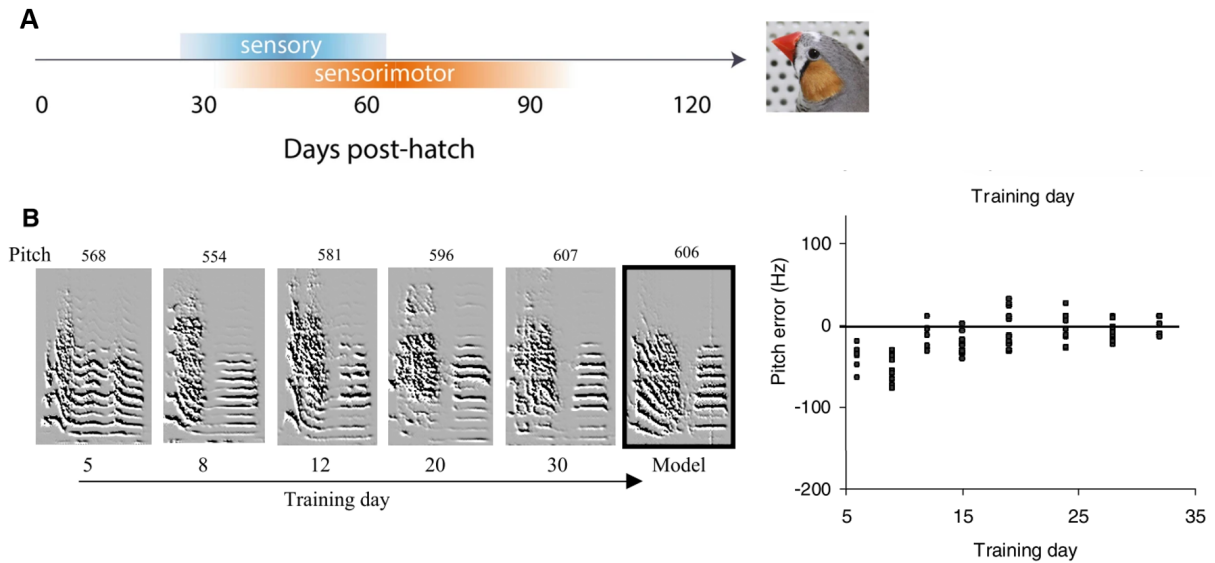
Figure 1: An example of song development in the Zebra Finch (*Taeniopygia guttata*). A) Vocal learning consists of a sensory phase where sounds from the environment are perceived, and a sensorimotor phase where the animal tries to imitate these sounds. While these periods overlap in the Zebra Finch, that is not the case for all birds. B) An example of the process of song imitation where pitch error gradually decreased until the trained song matches the model (Tchernichovski et al., 2001).

2 Basal Ganglia Circuits Contribute to Speech in Humans

To understand the role of the cerebellum in vocal learning, the systems which are already known to be involved in vocalisation will first be examined. This involves understanding the fundamental principles of speech in humans. As previously highlighted, human speech is regulated by a combination of sensory feedback input and feedforward motor output (Tourville & Guenther, 2011). The feedforward motor output triggers the production of a sound. During the production of speech, a feedback system is incorporated where the produced speech is compared to an internal model of the intended speech. This feedback can be through auditory signals, for example, the sound heard while speaking, or somatosensory signals; the tactile perception and proprioceptive information from the movements involved in talking (Smith et al., 2020). If the produced speech does not resemble the intended speech then the model activates corrective motor actions to better match the intended speech. The regulation of this process in the brain involves cortico-thalamo-basal ganglia-cortical circuits (Ceravolo et al., 2021; Yoshida et al., 2022). This circuit consists of various regions in the brain, including the cortex, the thalamus, the striatum (which is the largest basal ganglia input nucleus), and basal ganglia output nuclei and ultimately forms a loop back to the cortex (see Figure 2). There are many brain nuclei involved, making it possible to activate different subnetworks through the loops in

the circuit. These differences make it possible for the basal ganglia to perform different functions in speech, such as initiating movement, stopping ongoing motor actions or suppressing unnecessary movements (Klaus et al., 2019). Various factors can manipulate the activation of the subnetworks, including the neurotransmitter dopamine.

Dopamine can modulate the basal ganglia loops, thus playing an important role in the production of speech (Gerfen & Surmeier, 2011). Dopamine activates the initiation of motor actions while inactivating the loop responsible for stopping movement. The importance of dopamine becomes especially clear when a problem with the level of dopamine arises. For example, patients with Parkinson's disease produce less dopamine, due to degeneration of dopamine-producing neurons in the substantia nigra pars compacta (SNc) (Klein et al., 2019; Surmeier, 2018). This results in multiple symptoms, including deficits in speech (Polychronis et al., 2019). Later sections will also cover the role of the neurotransmitter in vocalisation in birds and the role of the cerebellum.

The structure of these vocalisation circuits is evolutionarily conserved (Konopka & Roberts, 2016). Songbirds in particular share many similarities with the brain mechanisms behind vocalisation in humans (Bolhuis et al., 2010; Doupe & Kuhl, 1999). This makes the production of vocalisations in songbirds a good model for researching the workings of speech in humans (Zhang et al., 2023). Moreover, the neural mechanisms in songbirds can be easily manipulated. Experimental studies have provided a well-established understanding of the pathways involved in vocal learning in birds.

3 Basal Ganglia Circuits also Contribute to Vocal Learning in Songbirds

Birdsong is also regulated by a feedforward motor system and a feedback system (Sakata & Yazaki-Sugiyama, 2020). The feedforward system in songbirds is called the motor pathway. The motor pathway is responsible for creating the song output. It is thought that the HVC (abbreviation used as the proper name) is the songbird analogue of the premotor cortex in mammals and contains a memory of how the birdsong should be produced (Bolhuis et al., 2010; Colquitt et al., 2021). An experiment by Long & Fee (2008) shows that the HVC is also responsible for the timing of vocal production. Cooling the HVC slows down song speed while the structure of the song remains intact (Long & Fee, 2008). The HVC in birds is often compared to Broca's region in humans. Just like the experiment of Long & Fee (2008) showed, focal cooling of Broca's region also results in the manipulation of speech timing (Long et al., 2016). Later sections of this essay will delve further into how the cerebellum might be involved in time changes of vocalisation by modulating activity in the HVC. Projections from HVC to the robust nucleus of the arcopallium (RA), similar to the motor cortex, subsequently lead to the production of the
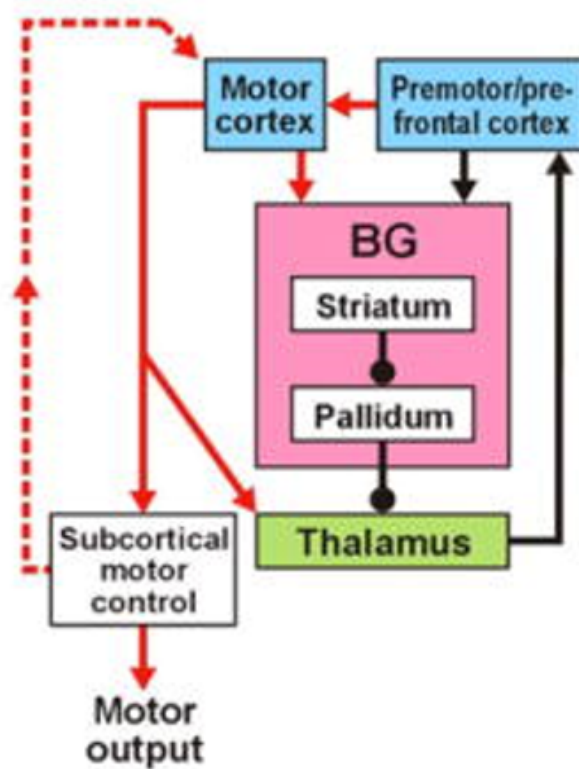
Figure 2: The mammalian brain nuclei involved in speech. Neurons from the cortex project to the Basal Ganglia (BG), which has a striatal and pallidal part. The basal ganglia project to the thalamus, which in turn projects back to the cortex. The motor cortex regulates signaling to the subcortical motor control area which ultimately creates motor output. (Brainard & Doupe, 2013)

template song. Ultimately, a sound is produced because of direct projections from the RA to the tracheosyringeal part of the hypoglossal nucleus (nXIIIs) which sends motor signals to the syrinx (see Figure 3).

The feedback system, on the other hand, is called the anterior forebrain pathway and is similar to the cortico-thalamo-basal ganglia-cortical circuit in humans (Doupe et al., 2004). Just like in humans, this basal ganglia network is necessary for song learning in songbirds (Brainard & Doupe, 2002; Ölveczky et al., 2005). The circuit is responsible for perceiving errors and correcting them. This pathway allows birds to modify their song when it does not correctly match the tutor song or the intended song. Studies that examine the perceiving and correction of errors do so by playing a noise while the bird is singing. This noise is perceived as an error by the bird. As a result, the bird starts to change its song. When specific syllables are targeted, for example, a high pitch, the bird compensates for this by singing a lower pitch. This is called error correction.

Error correction is the main mechanism behind vocal learning since it is used to match own vocalisations to a memorized template. The brain mechanism behind error correction in birds contains several interconnected regions. The model explaining the function of these regions is called the actor-critic model, and this model interprets the brain regions

as either actors or critics in the process of vocal learning (R. Chen & Goldberg, 2020). The actor experiments with motor control by creating more variation in the song. This variation increases the chance that through trial-and-error the produced song matches the memory of the tutor song. The produced song is subsequently evaluated by the critic. Through reinforcement, learning the song that closely matches the template song is rewarded and thereby reinforced.

Just like in humans, dopamine has an essential role here. It plays an important role in generating the rewarding signals essential for reinforcement learning, thereby modulating both song learning and performance. Dopamine is produced by the ventral tegmental area (VTA) and substantia nigra pars compacta (SNc). Dopaminergic neurons project from the VTA/SNc to Area X in the basal ganglia, where activity of dopaminergic neurons creates a reward signal (Woolley, 2019). Evidence supporting this is found in studies that expose birds to a noise during specific syllables of their song (i.e. syllable-triggered noise). Birds perceive this noise as an error in their song and subsequently change these syllables in an effort to correct the error. Syllable-triggered noise results in reduced firing of projections from the VTA/SNc to Area X. Furthermore, increased firing is observed when the noise is withheld, showing that this projection is important for error recognition. Thus, when a song is correct the dopaminergic projections from VTA/SNc to Area X reinforce these renditions of the song (Gadagkar et al., 2016). This is further supported by the study of Xiao et al. (2018) who show that syllable-specific inhibition of the VTA is enough to change the pitch, even when there is no error present. Furthermore, if you stimulate the VTA during high and low pitch, the song does not shift in pitch since the brain cannot tell which pitch is supposed to be correct. These studies indicate that activation of the VTA is important for being able to distinguish between correct and incorrect notes. Both the copying of songs by juvenile birds as well as reinforcement learning are dependent on VTA/SNc neurons and dopamine release into area X.

One of the inputs of area X is the lateral magnocellular nucleus of the anterior nidopallium (LMAN). The function of LMAN is to generate variability in the song sequences, meaning that multiple renditions of the same song will have slight variations from each other (Ölveczky et al., 2005). This variability is believed to underlie a trial-and-error-based system, allowing the evaluation of different song variants and reinforcing the most accurate one over time. This is important for pitch learning. As previously mentioned, when a bird is punished with noise for singing high notes, the bird compensates by shifting to a lower pitch. LMAN is involved in this response, as silencing of neurons in this nucleus prevents pitch adjustment (Hamaguchi & Mooney, 2012). This shows that LMAN activity is necessary for pitch learning. Thus, inactivating LMAN not only reduces acute song variability but also prevents pitch learning (Kearney et al., 2019).

Area X serves as the equivalent of the basal ganglia in mammals. Its main role involves assessing vocalisations that are sung and choosing accurate motor patterns, essentially

acting as a critic. It receives input from LMAN and sends projections to the dorsolateral thalamus (DLM). Area X evaluates the output from LMAN and provides feedback signals to guide song learning. The DLM, in turn, connects to the motor cortex RA via LMAN, playing a crucial role in modifying and refining the learned song by modulating the motor pathway.

The classical actor-critic system of vocal learning is well established (see Figure 3. However, the precise mechanism for error detection remains unclear. One study suggests that the auditory interface nucleus (Aiv) is responsible for this function. The Aiv receives input from auditory cortical regions, and the firing rates of the Aiv_VTA (Aiv neurons projecting to the VTA) increase when the bird produces a syllable that triggers playing of noise (Mandelblat-Cerf et al., 2014). No increase in firing rate is observed when the noise is not played. These observations imply that Aiv_VTA neurons play a specific role in detecting an error using auditory feedback and suppressing the activity of VTA_X neurons in response to syllable-triggered noise (Kearney et al., 2019).

Another alternative option for the brain mechanism responsible for error correction is the caudolateral mesopallium (CLM) described by Keller & Hahnloser (2009). This area contains neurons that fire when an error is detected. The neurons were largely inactive during singing, except when an auditory signal perturbed the song. These two areas currently remain the main possibilities for error detection systems in songbirds. However, the cerebellum is also known for its role in error detection and correction and is not currently integrated into the song system circuit. The following section will explore the functions of the cerebellum in motor coordination and planning, providing insights into why the cerebellum could be a promising candidate for involvement in vocal learning.

4   The Cerebellum Regulates Motor Coordination and Planning

Vocalisation is essentially a motor skill. Therefore, this section will first revise how the cerebellum is involved in other motor skills besides vocalisation.

The cerebellum is primarily involved in fine-tuning and coordinating voluntary movements, making it important for motor coordination and planning (Popa et al., 2016). It processes intended movement, the current position of the body and the sensory feedback coming from ongoing movements. The cerebellum is also important for the timing and rhythm of movements. It coordinates the sequence and timing of muscle contractions, making sure that the components of a movement are properly synchronised. Patients with a damaged cerebellum exhibit deficits in the control of the timing of movements (R. M. C. Spencer et al., 2003).

Other motor functions include error correction (Taylor & Ivry, 2014). The cerebellum
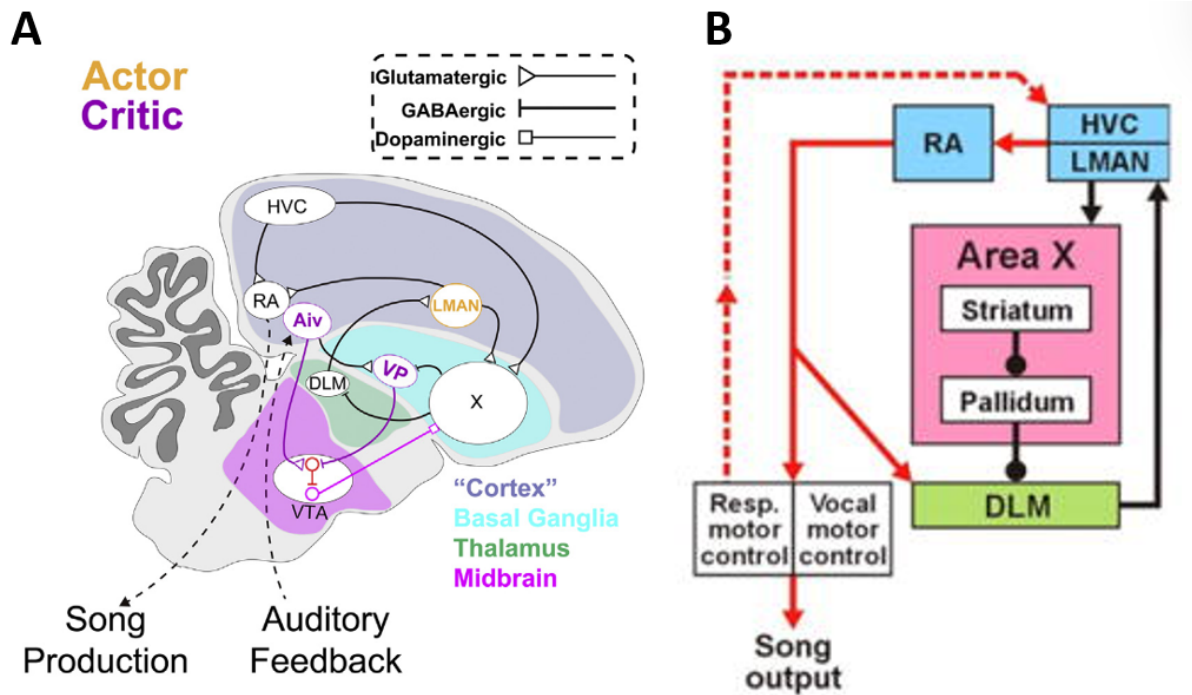
Figure 3: The avian brain nuclei involved in vocal learning. A) The actor-critic model from Mooney (2020). Background colours indicate the areas of the brain, while the text colours represent whether this area is an actor or critic. B) Cortico-striatal neurons in HVC project to Area X. Area X pallidal neurons send a signal to the DLM, which projects to LMAN, completing the cortical-basal-ganglia thalamo-cortical loop. LMAN projects both to the song motor cortical nucleus RA and back to Area X (Brainard & Doupe, 2013). (HVC (used as a proper name), RA (robust nucleus of the arcopallium), Area X (a song specialised region of the basal ganglia), DLM (dorsolateral thalamic nucleus), LMAN (lateral magnocellular nucleus of the anterior nidopallium), VTA (Ventral Tegmental Area), Aiv (ventral part of intermediate acropallium), VP (ventral pallidum))

continuously compares the actual created movements to the template of intended movements (see Figure 4). If the actual movement differs from the intended movement, the cerebellum creates a teaching signal. This teaching signal originates in the inferior olivary nucleus in the medulla oblongata and reaches deep cerebellar nuclei through climbing fibres. The errors are relayed from climbing fibres to Purkinje fibres to eventually signal to deep cerebellar nuclei (Narayanan & Thirumalai, 2019). The signal from the deep cerebellar nuclei travels to the thalamus and the cortex. These areas will correct the error and make sure that the corrected behaviour will be performed in the future (Kostadinov et al., 2019).

Besides playing a role in motor planning and correcting movements, the information from the climbing fibres also plays an important role in non-motor functions, such as learning and adaptation (Thompson et al., 1998). The cerebellum can refine its internal models based on the feedback received during movements. This allows for the optimisation of future motor actions, and could also play a role in other types of reinforcement learning.

To summarise, the cerebellum receives information from various sources, integrates this information, and then sends refined signals to the motor areas of the brain to optimise motor performance. Since vocalisation also requires motor performance, it is reasonable to assume that the cerebellum plays a role in this process as well. The next section will briefly cover what is already known about the influence of the cerebellum in the regulation of speech in humans.
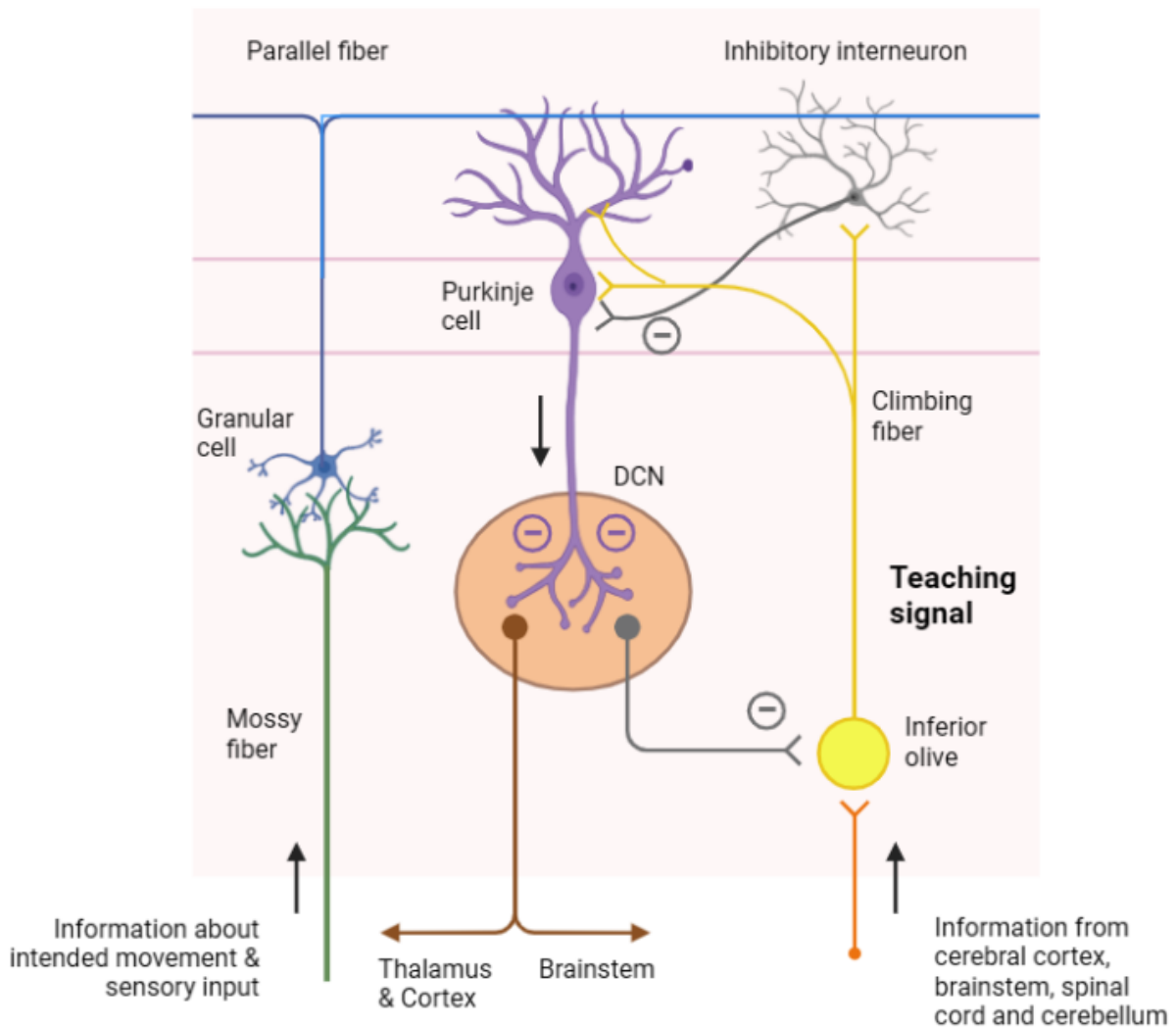

Figure 4: Information from the cortex, brainstem, spinal cord and cerebellum enters the interior olive, where a teaching signal is formed. The signal reaches the deep cerebellar nuclei (DCN) through an inhibitory interneuron and Purkinje cell. The DCN sends a signal to the thalamus, cortex and brainstem to correct the error. The DCN also receive information about intended movement and sensory input through mossy fibres. The horizontal lines indicate the three layers of the cerebellum, from top to bottom: molecular, purkinje and granular layer. Created in Biorender.

5   The Cerebellum Plays a Role in Speech

It is already well known that the cerebellum contributes to some extent to speech in humans. Evidence for this comes from patients with lesions or an impaired cerebellum. Lesion or dysfunction of the cerebellum causes ataxic dysarthria (Mathis et al., 2021). In ataxic dysarthria, speech is disturbed, with symptoms being the slowing down of articulatory movements, increased variability of pitch and loudness, monotonous and "scanning" speech, and impaired articulation (Ackermann & Ziegler, 1992). These symptoms imply that the cerebellum plays an important role in the timing and coordination of speech. Furthermore, the cerebellum is known to play an important role in movement preparation and programming, which could explain the abnormalities in the timing of speech when the cerebellum is impaired.

A recent study from Peng et al. (2021) showed a causal relationship between the cerebellum and auditory feedback control of vocal production. This study applied anodal transcranial direct current stimulation (a-tDCS) over the right cerebellum during a frequency-altered feedback task. In this task, young adults vocalised a pitch and simultaneously heard a pitch in real-time, different from the one they were producing. The auditory feedback system perceives this error, causing the subjects to compensate for their pitch. Compared to control subjects, participants that were exposed to a-tDCS compensated significantly larger and slower, indicating that the cerebellum plays a role in correction of auditory feedback errors and stimulation can alter the timing and size of pitch compensation (Peng et al., 2021). The authors discuss that the slowed compensations that emerge with cerebellar a-tDCS may be caused by an inhibition on the prefrontal cortex that exerts inhibitory control over vocal compensation behaviour. However, the mechanisms by which the cerebellum affects auditory compensation are still unclear.

A potential explanation for the influence of the cerebellum on motor skills could involve an interaction with the basal ganglia. It was long believed that the basal ganglia and the cerebellum influence motor systems separately. This view consisted of both the basal ganglia and the cerebellum sending projections to the cortex. It was hypothesised that signals from the cerebellum and basal ganglia only interact when they reach the cortex. However, recent developments challenge this idea, as there are projections found indicating that interaction of the cerebellum with the basal ganglia happens already at an earlier level. These projections might serve important functions regarding motor control, reward, and learning. In the following section, the connections between the cerebellum and the basal ganglia will be explored by examining the identified projections in mammals.

6 The Cerebellum and Basal Ganglia are Intricately Connected

One of the locations of communication between the cerebellum and basal ganglia is in the thalamus. In the brain, only the thalamus can directly 'talk' to the cortex. Thus, both the cerebellum and the basal ganglia need to project to the thalamus for their signals to reach the cortex. Regions of the basal ganglia also receive information from the thalamus. The zones of the thalamus that project to the basal ganglia overlap in the zones that receive information from the cerebellum, implicating that contact between the cerebellum and basal ganglia happens already at the level of the thalamus (Yoshida et al., 2022). Indeed, a study in rats used anterograde and retrograde tracing techniques to show that thalamic nuclei projecting to the striatum receive direct input from the cerebellum (Ichinohe et al., 2000).

Another study using mice showed that the so-called thalamostriatal projections are active a few milliseconds before initiating a movement sequence in an operant task (Díaz-Hernández et al., 2018), showing that these projections play a role in movement initiation in mice. Inhibition of their activity led to a delay in movement initiation, suggesting that the basal ganglia rely on the information from thalamostriatal projections on the millisecond timescale for movement initiation. Since the projection receives input from the cerebellum, it is likely that the cerebellum plays an important role in modulating movement initiation.

Indeed, it has been shown that the cerebellum and basal ganglia directly exchange information at timescales relevant for fast movements. Stimulating cerebellar projections to the thalamus influences striatal neurons through a short-latency pathway. Furthermore, blocking cerebellar activity to the basal ganglia to model pathological conditions causes disrupted movement, indicating that the disynaptic projections from the cerebellum to the basal ganglia are necessary for normal motor functioning (C. H. Chen et al., 2014).

The thalamo-striatal pathway is not the only way through which the cerebellum and the basal ganglia communicate. As was earlier explained, the basal ganglia rely on information from midbrain dopaminergic nuclei such as the VTA and SNc. Earlier studies already showed that the cerebellum can influence these midbrain dopaminergic nuclei. Rogers et al. (2013) discovered an indirect pathway from the cerebellum to the VTA. Stimulating the cerebellum modulates dopamine release in the mouse prefrontal cortex. A recent study in mice showed that there is also direct input from the cerebellum to the VTA (Carta et al., 2019). Using optogenetic stimulation, the study showed that there are excitatory monosynaptic cerebellar inputs to the VTA (see Figure 5). Furthermore, stimulating these neurons in vivo increased the preference for the reward quadrant in a conditioned place preference test, indicating that stimulation of cerebellar-VTA neurons is rewarding. As explained before, dopamine released by the VTA is important for the

activation or inactivation of the direct and indirect pathways of the basal ganglia. Thus, it is possible that the cerebellum influences voluntary movements by modulating the dopamine released to the basal ganglia. The existence of connections from the cerebellum to the basal ganglia in rodents likely contributes to motor performance and learning. The question arises: do similar projections exist in songbirds?
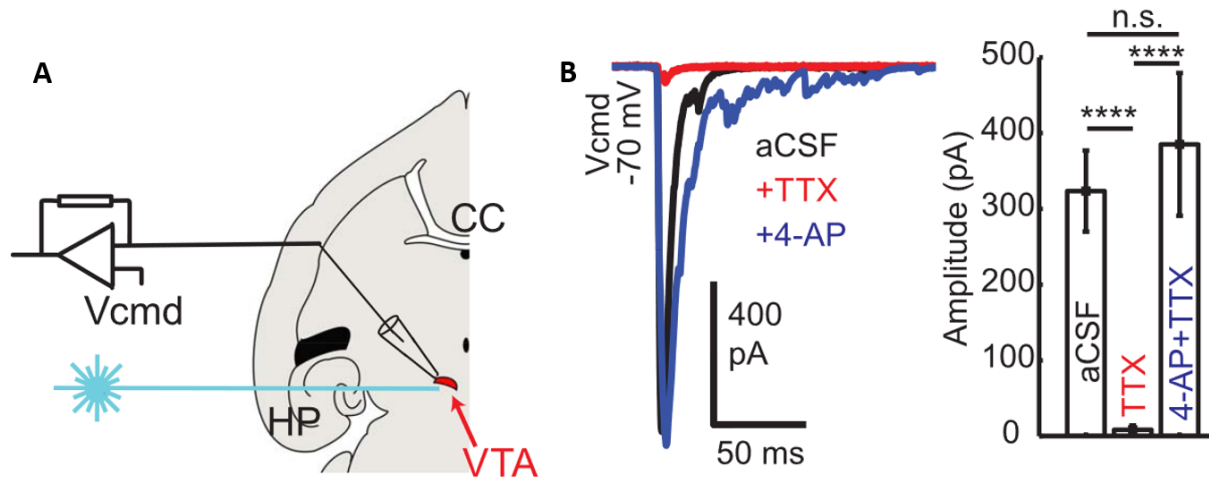

Figure 5: Cerebellar connections to the VTA in mice, adapted from Carta et al. (2019). a) Channelrhodopsin, an ion channel that can be activated with light, was expressed in the DCN. Light was used to stimulate the axons projecting from the cerebellum to the VTA. b) Cerebellar axons make direct connections with VTA neurons. To confirm that the connection was monosynaptic (direct from the cerebellum to VTA), the authors used a toxin (TTX) to block action potentials in the neurons from DCN to VTA. This caused a significant decrease in response. Afterwards, the drug 4-AP was added, which facilitates the occurrence of synaptic potentials. 4-AP enhances the depolarisation of neurons, making it easier for them to respond to direct synaptic inputs even without action potentials. When 4-AP restored the response, it demonstrated that the synaptic connection could still function without action potentials propagating along intermediate neurons. This recovery suggested that the cerebellar axons were making direct connections with VTA neurons.

7 Cerebello-Thalamostriatal Projections Contribute to Song Timing Processing in Songbirds

Anatomical studies in songbirds have shown a pathway from the cerebellum to the song-related basal ganglia (Person et al., 2008). A recent study confirmed that output from the cerebellar nuclei can reach the basal ganglia through thalamostriatal projections in the Bengalese finch (Nicholson et al., 2018). Specifically, dorsal thalamic neurons form synapses within the basal ganglia including Area X. Area X receives projections both from DLM and from the dorsal thalamus. These are targeted by projections of cerebellar nuclei. To examine whether projections from the cerebellum to song-related structures

were involved in vocal learning, another study examined the function of the pathway (Pidoux et al., 2018). This study confirmed the connection from the cerebellar nuclei to area X to the dorsal thalamic zone (DTZ) (see Figure 6). They then investigated whether electrical stimulation of the cerebellar nuclei would provoke a response in area X, which was indeed the case. Moreover, when glutamatergic signalling in DTZ was blocked, DCN stimulation failed to excite pallidal neurons of Area X, indicating that responses to DCN stimulation in Area X pallidal neurons are relayed by glutamatergic transmission in DTZ. The modulation of basal ganglia by the cerebellum propagates to LMAN via the thalamus and is then transmitted to premotor nucleus RA. Lastly, the authors investigated the function of this circuit in vocal learning and production and showed that lesioning the DCN caused impaired song learning, as it caused a significant drift in syllable duration. No change in fundamental frequency was found following the lesion. The authors therefore conclude that the cerebellum is mainly involved in timing processing.

The monosynaptic projection from the cerebellum to the VTA/SNc has not yet been identified in songbirds. However, the similarities between songbirds and mammals suggest the existence of such a projection. For the purpose of this essay, the assumption is made that such a projection is also present in songbirds. Based on the evidence provided in the previous few sections, the next part of this essay will outline potential roles for the thalamo-striatal projection and the cerebello-VTA projection in vocal learning and song production.

8 The Function of the Thalamo-striatal Projection and the Cerebello-VTA Projection

As aforementioned, the cerebellum plays a crucial role in the control of speech. This hypothesis was supported by studies demonstrating the involvement of the cerebellum in vocal production in both humans and songbirds. It is likely that the cerebellum controls speech in a similar way to how it controls other types of movement. This entails that the cerebellum receives input about information about the intended vocalisation, which would be the template. This information would then activate the planning of correct movement (see Figure 7).

The last section showed that the cerebellum has intricate connections to various parts of the basal ganglia, one of which is the input from the cerebellum to the thalamo-striatal projections. This connection might be in place to enable the basal ganglia and the cerebellum to synchronise and coordinate their activities during movement that requires high precision, such as singing. The coordination observed may occur due to the disynaptic connection, enabling the predictions generated by the cerebellum to reach the basal
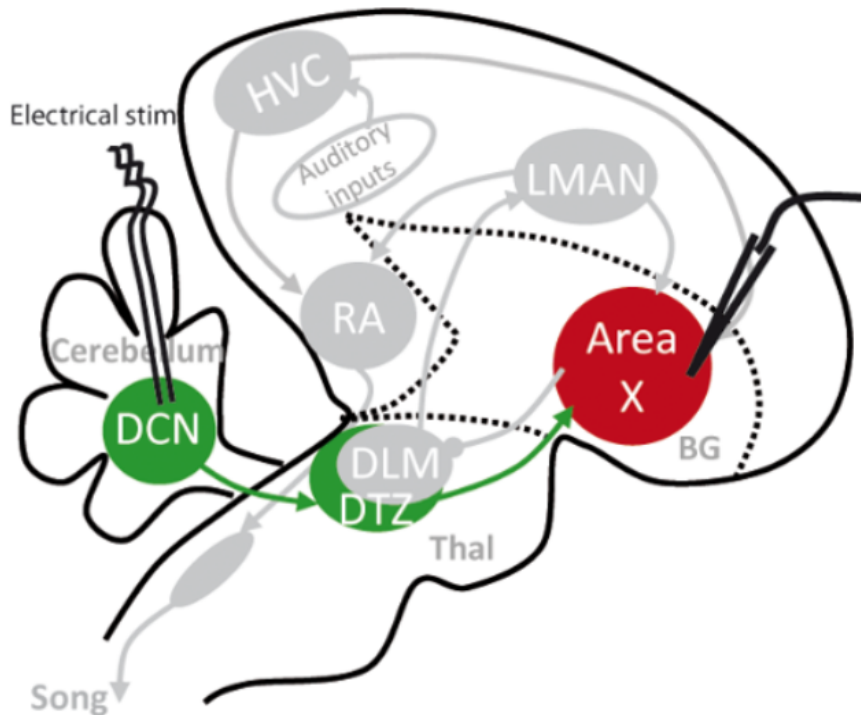
Figure 6: The deep cerebellar nuclei (DCN) were electrically stimulated, which revealed a direct pathway to the dorsal thalamic zone (DTZ) and the signal propagated to Area X where neurons also responded (Adapted from Pidoux et al. (2018)).

ganglia. One potential significance of this coordination could be the precise timing of movements. As explained earlier, the cerebellum is important for the timing and rhythm of movements (R. M. C. Spencer et al., 2003). The thalamo-striatal pathway could be responsible for this since this projection is responsible for the smooth initiation of sequences of movement (Díaz-Hernández et al., 2018). This is the case for vocalisation as well. As observed in songbirds, disruption in the deep cerebellar nuclei causes a drift in syllable timing (Pidoux et al., 2018), indicating that not only motor movement but also timing of vocalisation needs input from the cerebellum. Birdsong consists of several syllables, which is also a sequence of movements. Therefore, the cerebellum could be responsible for relaying information about the basal ganglia for the correct timing and smooth performance of these aspects of the song.

An additional aspect of vocalisation involves recognising an error and subsequently correcting it. As aforementioned, dopaminergic activity from VTA to Area X is necessary to relay this error signal. Area X receives a reward prediction error from the VTA that is necessary and sufficient to drive song learning (Gadagkar et al., 2016; Xiao et al., 2018). The connection between the cerebellum and the VTA, which was shown in mice, could also play a role in reinforcement learning. Carta et al. (2019) already showed that stimulation of cerebellar-VTA neurons is rewarding. In my view, the process unfolds as follows: as sound is produced, efferent copies of motor neurons reach the cerebellum, which also receives auditory feedback of the actual sounds produced and somatosensory information.

These are compared to the speech template. Furthermore, the difference between target and actual somatosensory information is hypothesised to map through the cerebellum to the cortex (Guenther et al., 2006). This means that the cerebellum receives both auditory and somatosensory information and is likely an integral part of the feedback loop. This information goes via mossy fibres to granule cells to parallel axons to Purkinje cell, which makes predictions and sends them to deep cerebellar nuclei.

If the predictions do not match the generated movement, the inferior olivary nucleus sends teaching signals via climbing fibres through the cerebellum. This signal is projected through the cerebellum, where information about the error is transformed into a signal that can act on other systems to correct the error (K. A. Spencer & Slocomb, 2007). The teaching signals reach the deep cerebellar nuclei, where Purkinje cells send information to update the template, which could mean that signals are sent to the HVC. This new pathway from cerebellum to dorsal thalamus to MMAN to HVC remains to be characterised (Pidoux et al., 2018). The cerebellum further sends projections to the dopaminergic areas of the midbrain (VTA/ SNc) to modulate dopaminergic release and thereby can send reinforcing or corrective signals. When there is a difference between the intended vocalisation and the actual auditory signal that the cerebellum receives, this represents an error signal. If an error is detected, the cerebellum withholds the signal to the VTA, less dopamine is released and the specific error is not reinforced. Since the VTA is not activated, LMAN activity increases, which subsequently causes an increase in song variability. The increase in song variability allows for error compensation. Pidoux et al. (2018) already showed that DCN stimulation elicited strong responses in LMAN neurons, indicating that cerebellar responses are conveyed to LMAN and RA through the basal ganglia loop. However, this response occurred through the thalamo-striatal pathway and not via the monosynaptic pathway to the VTA. More research is needed to check if DCN stimulation can indeed reinforce the song or correct the song by increasing LMAN activity down the line. If the system indeed functions in this way, the cerebellum could be assumed to play a crucial role in both the learning of a song and the maintenance of correct vocalisation in adulthood. It would continuously monitor whether the produced vocalisation aligns with the intended vocalisation. The reward prediction error signal from the VTA and the cerebellar error correction signal could cooperate within the basal ganglia to achieve faster and more efficient sensorimotor learning.

While the presence of the cerebello-thalamo-basal ganglia and the cerebellar-VTA pathways suggests a significant potential for cooperation between the cerebellum and the basal ganglia in sensorimotor learning, much remains to be uncovered. Further studies are necessary to establish a causal role for these circuits in vocal learning.
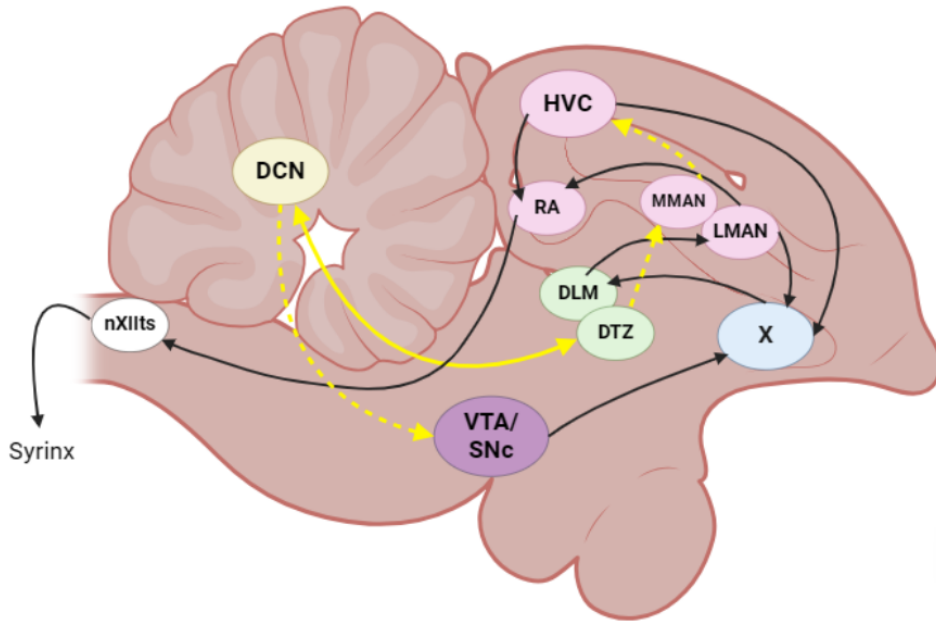
Figure 7: Proposed song system in the bird. Solid lines depict existing connections between brain areas black lines represent the song system as already established, yellow lines indicate the connections that are added to the song system as discussed in this essay. Dotted lines represent hypothesised areas. The colours of the brain areas indicate whether it is part of the cortex (pink), basal ganglia (blue), midbrain (purple), thalamus (green) or cerebellum (yellow).

9   Proposed Future Experiments

In this section, I will propose a few studies to further investigate the role of the cerebello-thalamostriatal and the cerebello-VTA pathway in vocal learning. The cerebello-thalamostriatal connections likely allow the cerebellum and basal ganglia to coordinate, which might regulate the timing and regulation of song syllables. While in the study of Pidoux et al. (2018) lesioning the deep cerebellar nuclei did not affect the variability in fundamental frequency, the authors also discuss the possibility that only a small amount of lesions were performed. Moreover, other areas of the song system could compensate for the lesions, therefore it cannot be ruled out that the cerebellum is involved in the regulation of fundamental frequency. Furthermore, the authors discuss a possible new pathway from the cerebellum to the dorsal thalamus to a region next to LMAN to HVC which remains to be characterised. The existence of this pathway could possibly explain the way in which the cerebellum updates the template song.

For the cerebello-VTA pathway, a role was proposed in error correction and song learning. To further investigate the nuclei involved in the song system it ought to be established if the cerebello-VTA pathway is actually present in songbirds. Characterisation of avian cerebellar areas projecting to the dopaminergic midbrain can be done through retrograde and anterograde tracing. To check the functional implications

it should also be determined whether these neurons are active during singing, both in learning juveniles and adults.

Another methodology that has proven very efficient in determining the function of projections with regard to error correction is to present vocal errors in real time during singing. This method allows for checking whether cerebellar neurons projecting to VTA/SNc exhibit error-related auditory responses during singing. In combination with this method, conducting targeted lesion studies can selectively disrupt specific connections between the cerebellum and the basal ganglia or dopaminergic midbrain nuclei to assess the impact of these lesions on vocalisation timing, sequence accuracy, and error correction.

Optogenetic stimulation or inhibition could also be valuable methods to check the effect of activating or inactivating the cerebello-thalamostriatal pathway or the cerebello-VTA pathway. Specifically, it would be interesting to perform an experiment where the effect of the cerebello-VTA pathway is examined. For example, this pathway can be stimulated while presenting vocal errors in real-time during singing. If the cerebellum is indeed sufficient for the relay of error signals to the VTA, then stimulating these projections during an error signal will result in the VTA sending reinforcing signals to Area X. It would be interesting to see the effect of this on LMAN and on the variation in the following songs. If the cerebello-VTA pathway is also sufficient for error correction, then stimulating these projections could lead to the reinforcement of those specific errors. Furthermore, investigating the opposite by lesioning or inhibiting would also be interesting. Inactivating the projections would mean that VTA is not activated by the cerebellum. If the cerebello-VTA projections are necessary to create a reinforcing pathway, then lesioning these neurons will have the effect that all signals are seen as errors. These studies would tell us more about the causal effect of these neurons. Further research using the described techniques could allow us to unravel the current gaps in knowledge.

10   Conclusion

This essay discussed the regulation of sensory feedback and motor control essential for vocalisation. We can conclude from it that the basal ganglia play a crucial role in human speech. The songbird system is highly similar to the human speech system and is therefore a very useful model for examining vocalisation in more detail. In songbirds, the basal ganglia also play a major role in the feedback system to optimise the song. This essay also emphasised the cerebellum, which is still relatively unexplored in its function in song performance and song learning. Human patient studies and transcranial stimulation show the role of the cerebellum in motor coordination and speech, indicating a deeper understanding is needed of how the cerebellum and cerebrum together regulate motor control mechanisms.

Examining rodent models shows that the cerebellum influences movement initiation and potential modulation of dopamine release through the cerebello-thalamostriatal and cerebello-VTA projections. In songbirds, anatomical studies indicate a cerebellar pathway to the basal ganglia, impacting timing processing in vocalisation. However, a direct cerebellum-VTA projection remains to be elucidated. Additional research is warranted to further investigate the cooperation between the cerebellum and basal ganglia in sensorimotor learning and its function in vocalisation. Research in this area can be insightful to investigate the role of the cerebellum in disorders involving the disruption of the basal ganglia by degeneration of dopaminergic neurons.

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