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TITLE: Basal ganglia circuits: Bursting with song

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The songs of mature zebra finches are notoriously repetitious, or 'crystallized'. Despite this stability, new work reveals that chronic pharmacologically-driven bursting of cortical inputs to the basal ganglia can drive cumulative and lasting changes to multiple vocal features, including phenomena reminiscent of human stuttering.

"I never had professional therapy, but a couple of nuns taught me to put a cadence to my speaking, and that's why I spent so much time reading poetry – Emerson and Yeats," In this quote from US Joe President Biden, he shares advice on how iterative behavioral practice can largely overcome certain motor disabilities, in his case, childhood stuttering.

The basal ganglia are key brain structures for learning complex behaviors including speech; when these circuits malfunction, speech can go awry[1]. Songbirds are useful model organisms to understand brain mechanisms for speech due to significant parallels in how songs and speech are developmentally acquired and actively maintained in maturity[2]. This evolutionary convergence acts at multiple levels, all the way from transcriptional expression profiles in vocal control regions[3] to the functional effects of cooling brain tissue on vocal output[4]. A recent paper by Moorman *et al.[5]* makes expert use of the zebra finch songbird model to show that the crystallized songs of adult birds can be induced to change and that these changes can persist, likely via transfer to vocal command pathways in the brain. Fortuitously, the brains of zebra finches and related songbirds possess well-defined vocal control circuitry dedicated to learned song. These anatomically tractable regions include a posterior vocal motor control pathway, essential for song production, and an intersecting cortico-basal ganglia loop called the anterior forebrain pathway (AFP), required for vocal plasticity during critical period learning (Figure 1A). The AFP is also crucial for active song maintenance in adulthood. Moreover, the crystallized song of male finches provides a readily quantifiable behavior.

Despite the repetitious stability of zebra finch song, work from multiple groups (reviewed by Woolley and Kao[6]) demonstrates that adult finches can acutely adjust their songs when they are experimentally subjected to perturbed auditory feedback. In many experiments, perturbation is made feasible by the fact that there is a slight rendition-to-rendition variation in the fundamental frequency of certain syllables that is actively generated by the premotor cortical AFP region known as the lateral nucleus of the anterior neopallium (LMAN). Reinforcement paradigms can thereby 'punish' birds when the fundamental frequency is outside an experimentally determined value by delivering a blast of white noise. Birds respond by shifting their fundamental frequencies away from this target range, thereby avoiding the aversive stimulus. Perturbed auditory feedback also acutely alters human speech, notably by inducing stuttering (reviewed in Cynx & Von Rad[7]). In both cases, these immediate effects are transitory with songs and speech returning to baseline once the perturbations cease.

In the songbird brain, the AFP largely contributes to these acute vocal changes. Kojima and colleagues[8] found that lesions of LMAN permanently eliminate rapid within-syllable variation as do lesions of Area X, the song-dedicated basal ganglia portion of the AFP. Direct electrical perturbation of LMAN drives fluctuations in fundamental frequency that mimic naturally occurring within-syllable variability. In a similar vein, Heston *et al.* found that pharmacogenetic manipulations involving designer receptors exclusively activated by designer drugs (DREADDs) in LMAN and Area X transiently and bidirectionally alter the microstructure of song syllables[9]. Together, these results demonstrate that nodes in the AFP comprise a central source of rapid behavioral variation in adult birds that is lost when these regions are lesioned. What was unknown is whether chronic perturbation in the intact AFP can drive behavioral alterations that are transferred to the motor program, long-

term; and whether these long-term changes may be reversed when the experimental perturbation ends. If so, then the door for not only experimental, but also therapeutic intervention in motor function and dysfunction in maturity creaks slightly more ajar.

Moorman *et al.[5]* directly test the influence of changes in LMAN activity to song stability by chronically altering LMAN activity pharmacologically with infusion of bicuculline methiodide (BMI; Figure 1B), a drug that blocks $GABA_A$ receptors and a calcium-activated potassium channel. Chronic infusion of this drug resulted in bursting activity in individual LMAN neurons (Figure 1C). For the first time, they demonstrate that these long-term increases in bursting activity result in distorted syllables with variable sequencing as well as three core symptoms of human stuttering (Figure 1C). They go on to show that these behavioral changes are consolidated, producing long-term changes in song structure. Given the mechanistic convergence of biological systems that support learned vocal communication, these findings provide important insight into motor function/dysfunction and highlight nodes of intervention.

Mechanistically, how can burst firing contribute to plasticity in song? Mehaffey and Doupe[10] uncovered a long-sought-for synaptic plasticity from LMAN to the primary motor region, the robust nucleus of the arcopallium (RA). Bursts of activity in LMAN neurons that precisely followed bursts of action potentials from HVC (acronym used as the proper name), the premotor input to RA (Figure 1A), potentiated synaptic responses in RA neurons. In addition, pharmacologically blocking inputs from LMAN to RA prevented song plasticity induced with perturbed auditory input (as described above). Therefore, bursts of activity in LMAN neurons appear to be important for driving plasticity in premotor neurons and changes in behavior. This idea is supported by experiments in which adult birds are deafened. Deafening produces an aberrant, though experimentally elusive, auditory signal[11] and leads to degradation of song that occurs over several weeks in adult birds[12, 13]. Kojima and colleagues[14] showed that lesioning the basal ganglion input to LMAN followed by deafening reduces burst activity and removes deafening induced plasticity. The experiments by Moorman *et al*.[5] support the hypothesis that bursts of activity in LMAN drive plasticity in premotor regions of the brain, producing long-lasting behavioral changes.

It is noteworthy that Moorman *et al*.[5] expertly employed classic pharmacological and electrophysiological techniques that do not rely on trendy optogenetic or chemogenetic methods. Given the requirement for input timing-dependent plasticity in LMAN, it would be unlikely to produce the long-lasting behavioral changes shown here using methods in which intrinsic neuronal bursting is difficult to mimic. We predict typical tonic optogenetic stimulation would not be as effective. Rather, deployment of optogenetic pulses that mimic natural activity patterns, as done electrically in Mehaffey and Doupe[10], or clever implementation of diverse stimulation paradigms[15] will be required to use the brain's 'code' for altering behavior.

This contribution provides important insights for the function and dysfunction in mammalian basal ganglia. For example, parkinsonian monkeys as well as humans with Parkinson disease who undergo surgical treatments have an increase in bursting activity in basal ganglion neurons driven by hyper-synchrony[16]. In addition, one treatment of Parkinson's is to lesion the basal ganglia (pallidotomy[17]) suggesting aberrant activity is worse than an absence of activity. The experiments by Moorman *et al*.[5] show that bursting activity can be maladaptive, leading to long-term deficits in vocalizations, including stuttering-like behavior. This parallels results in primates which suggest that bursting in basal ganglia neurons drives some of the behavioral problems in disease states[16]. These experiments also indicate that interventions involving patterned activity, as with dynamic and closed-loop stimulation[18][19], are an additional avenue for treatment in basal ganglia circuitry.

Deafening birds generates a-yet-to-be-detected error signal that drives plasticity of adult song, thus the clear follow up experiments to this work should deafen birds and record changes in LMAN activity. We predict the error signal driven by aberrant auditory feedback will result in an increase in bursting activity in LMAN neurons.

Among basal ganglia-based disorders, vocal motor deficits can be less responsive to pharmacologic treatment and deep brain stimulation therapies than are limb-motor functions. While progress has been made with certain types of speech therapy[20], these iterative and time-intensive treatments –which also harness the brain's own activity patterns– could be augmented by a better understanding of the neural mechanisms for

speech. Notwithstanding the lack of a common ancestor with the capacity for vocal learning, neural circuit-breaking work in songbirds, like that of Moorman *et al.[5],* may 'burst' open the door to overcoming human speech disorders.

Declaration of interests
The authors declare no competing interests.

FIGURE LEGEND:
Figure 1. Bursts of action potentials in LMAN neurons, the output of songbird anterior forebrain pathway, drives song 'stuttering'. A. Schematic sagittal section shows vocal control circuitry dedicated to learned song in the zebra finch brain. The anterior forebrain pathway comprises cortical LMAN (blue) which projects to the basal ganglia nucleus Area X, which forms a loop through the thalamus back to LMAN. LMAN also projects to the primary motor nucleus RA, which receives synaptic input from the premotor nucleus HVC. Coordinated bursts of action potentials in LMAN and HVC drive synaptic plasticity in RA[10]. The grey line shows the approximate location of the coronal section in B. D, dorsal. P, posterior. B. Illustration of the experimental infusion of bicuculline methiodide (BMI) bilaterally into LMAN. L, lateral. C. Infusion of BMI into LMAN produced bursts of action potentials (blue vertical lines) during song.

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