synapses in *unc-116* mutants might represent the population of receptors originally destined for distal synapses and that the proximal synapses have more than enough slots to accommodate these bottlenecked receptors. This is an interesting point, as dendrites rely on passive propagation of potentials, which means the farther out on the dendrite, the less impact a synapse might have on triggering an axon potential at the cell body. Some arguments have been made for distance-dependent scaling of AMPARs, with distal synapses having larger surface levels of AMPARs compared to proximal synapses, as a mechanism by which neurons compensate for the passive decay of signals from distal dendrites (Shipman et al., 2013). Regulated motor delivery between populations of proximal and distal synapses would provide an interesting mechanism for such distance-dependent scaling.

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# A Variability-Generating Circuit Goes Awry in a Songbird Model of the FOXP2 Speech Disorder

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http://dx.doi.org/10.1016/j.neuron.2013.12.001

*FOXP2* mutations cause a monogenic speech disorder in humans. In this issue of *Neuron*, Murugan et al. (2013) show that knockdown of FoxP2 in the songbird basal ganglia causes abnormal vocal variability and excess bursting in a frontal cortical nucleus.

### Say the Word "Variability" Out Loud to Yourself Three Times

If you are like most adults, you just effortlessly moved your larynx, tongue, and lips in a coordinated fashion with millisecond timescale precision. But humans with mutations in a single gene, *FOXP2*, have severe articulation difficulties, including slurred and pathologically variable speech, as well as linguistic and grammatical impairment. The monogenic nature of these deficits, together with evidence that the *FOXP2* gene underwent intense selection pressures during a period of recent human evolution coincident with the emergence of language, suggest an exciting entry point into understanding the genetic and neural basis of a complex, learned, and uniquely human behavior.

The *FOXP2* gene was discovered by analyzing a multigenerational pedigree (the KE family) in which almost half of the members carried a mutated version of the gene and presented with speech and language pathology (Lai et al., 2001). *FOXP2* encodes an evolutionarily conserved transcription factor expressed in widespread brain regions associated with speech and motor control including cortex, striatum, thalamus, and cerebellum. These same brain regions are abnormally small in afflicted members of the KE family (reviewed in Enard, 2011). While testing the functions of the gene in humans poses obvious challenges, two experimental strategies in mice have begun to provide insights. A first approach has been to knock down FoxP2. Mouse pups with homozygous disruptions of *FoxP2* exhibit severe motor impairment and do not survive beyond 4 weeks after birth. Heterozygous *FoxP2*-disrupted mice survive but exhibit impaired motor learning on running wheels and accelerating rotarods and exhibit slightly increased exploration. A variety of abnormalities observed at the cellular level

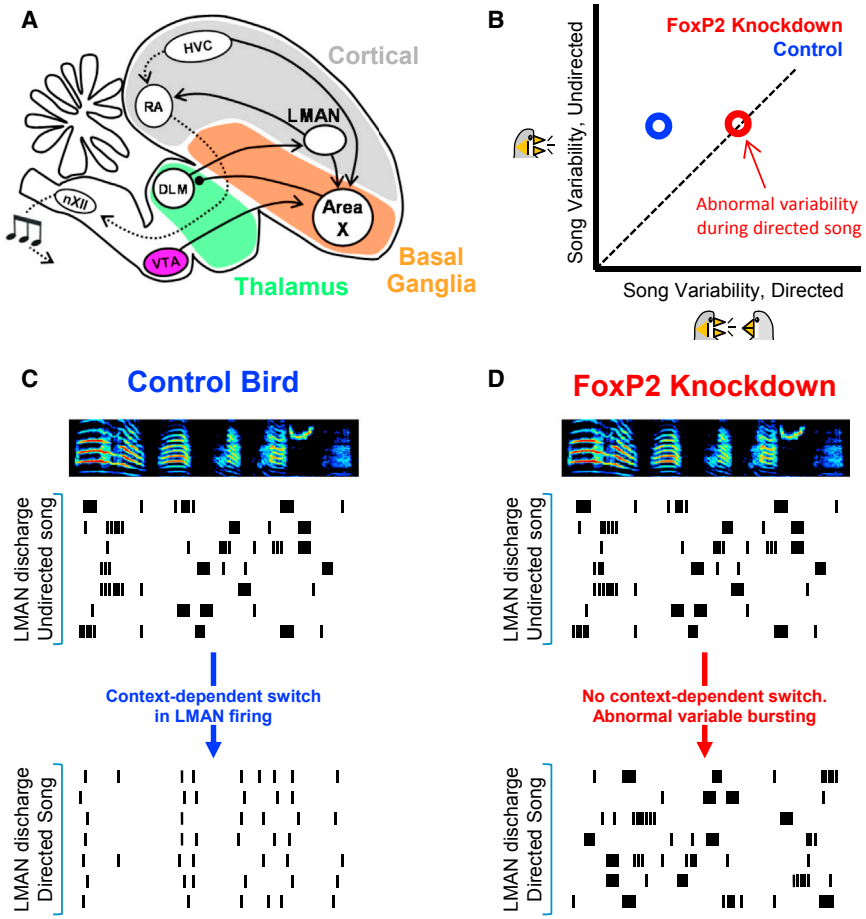


**Figure 1. FoxP2 Knockdown in the Songbird BG Leads to Dysregulation of Vocal Variability**
(A) Schematic of the avian song system. Area X is a striatopallidal nucleus in the basal ganglia and LMAN is a thalamorecipient portion of the BG-thalamocortical loop. LMAN drives song variability through its projection to RA, a motor cortex-like nucleus.
(B) Song variability is reduced when birds sing to a female (directed song), compared to when singing alone (undirected song). Knockdown of FoxP2 in Area X blocks this context-dependent reduction in variability.
(C) In control birds, LMAN neurons exhibit randomly timed bursts during undirected song but switch to tonic precise firing during directed song.
(D) FoxP2 knockdown prevents this switch in LMAN firing. Rasters are schematic representations of findings from Murugan et al. (2013).

suggest an important role for striatal medium spiny neurons (MSNs). MSNs exhibit abnormal morphology with reduced dendritic arbors and decreased spines, decreased corticostriatal long-term depression (LTD), and abnormally high firing rates during motor tasks (Enard, 2011; French et al., 2012). In addition, these mice exhibit unusually increased tissue concentrations of dopamine, an important regulator of corticostriatal function. A second experimental strategy has been to engineer mice that express the human variant of *FoxP2*, which includes two amino acid substitutions hypothesized to have played an important role in the evolution of speech and language. Intriguingly, these "humanized" mice express several behavioral and cellular-level changes that are opposite to the FoxP2 knockdown mice. At the behavioral level, they exhibit decreased exploration, and at the cellular level they have increased corticostriatal LTD, MSNs with more complex and spinous dendrites, and decreased tissue dopamine levels (Enard et al., 2009). Together, these studies suggest that FoxP2 in mice and humans act to regulate dopamine and corticostriatal function related to motor learning. Yet an outstanding challenge is to bridge the gap between the "high level" behavioral and motor learning deficits to the rather idiosyncratic and "low level" molecular, cellular, and structural abnormalities observed in *FoxP2* mutants. How does *FoxP2* dysfunction give rise to abnormal neural activity that, in turn, drives abnormal motor behavior?

Songbirds provide a powerful model system to address this question. First, like humans, songbirds learn their vocalizations through an imitative process of trial and error. For example, a juvenile zebra finch babbles, producing thousands of highly variable vocal units, or "syllables," per day. With practice, this babbling gradually acquires more temporal structure and begins to resemble the tutor song. As with speech, song learning involves a reduction in variability, occurs during a critical period early in life, requires auditory feedback, and ultimately results in stereotyped vocal sequences that require millisecond-timescale coordination of multiple vocal muscles. While birdsong does not appear to have a significant semantic component akin to human language, the dynamics of the learning process mirror human speech.

The similarity between birdsong and speech extends to underlying neural circuitry. Songbirds have a specialized circuit for singing, "the song system," that evolved out of a highly conserved vertebrate brain architectural plan and includes cortex-like pallial nuclei and a dopamine-basal ganglia (BG) thalamocortical loop (Figure 1A) (Jarvis et al., 2005). This song system is highly tractable. RA (robust nucleus of the arcopallium) is analogous to mammalian primary motor cortex and has only two main inputs, HVC (used as a proper name) and lateral magnocellular nucleus of the anterior nidopallium (LMAN). These cortical inputs have distinct and well-understood functions. First, HVC neurons exhibit stereotyped, temporally precise activity that drives correspondingly stereotyped features of the song. In contrast, LMAN neurons exhibit variable, bursty activity that drives the correspondingly variable song components, including the vocal babbling of juveniles (reviewed in Fee and Goldberg, 2011). The relative contribution of these pathways controls the amount of song

variability, which is regulated in two ways. First, on the timescale of developmental learning (weeks), there is a gradual transfer of premotor control from LMAN, a "variability-generating pathway" for babbling, to HVC, a "stereotypy-generating pathway" for habit-like adult song. Second, adult birds can also flexibly modulate (on second timescales) the influence of these two pathways according to social context. When singing alone (undirected song), birds sing as if in a "practice mode" with substantial trial-to-trial variability that is driven by random, bursty spiking in LMAN. When singing to a female (directed song), birds sing highly stereotyped song, as if in "performance mode." During directed song, dopamine levels increase in the BG, and LMAN firing patterns become less bursty and more temporally precise (Brainard and Doupe, 2013) (Figures 1B and 1C).

Thus, the conceptual framework emerging from the songbird field is that trial-to-trial variability during babbling is not just the de facto output of an immature motor system but is instead "actively" injected into the song by variable bursting activity in LMAN. LMAN is the cortical output of a dopamine-BG-thalamocortical loop, raising the exciting possibility that the motor and cognitive impairments observed in BG-related neuropsychiatric disorders, including FoxP2-related speech dysfunction, might result from dysregulation of variability-generating functionalities—yet to be discovered in mammals—that are embedded in dopamine-BG cortical circuits.

Both *FoxP2* and BG circuits are highly evolutionarily conserved among vertebrates and *FoxP2* is also expressed in Area X, the striatopallidal component of the song system (Figure 1A) (Teramitsu et al., 2004). In studies that echo recent results in mice and humans, knockdown of FoxP2 in Area X impairs song learning and is associated with morphological abnormalities in MSNs, including decreased spine density (Haesler et al., 2007; reviewed in Fee and Scharff, 2010). These studies suggested similar FoxP2 functions in songbirds but as with mice and humans, a remaining challenge has been to connect the behavioral deficits that accompany *FoxP2* dysfunction to the cellular-level abnormalities that may underlie them.

In this issue of *Neuron*, Murugan et al. (2013) bridge this gap by combining lentiviral sh-RNA-mediated FoxP2 knockdown in Area X, biochemical and pharmacologic analysis of dopamine function, and awake-behaving electrophysiology (Murugan et al., 2013). Their experiments begin to paint a picture of how *FoxP2* deficits disrupt dopamine and corticostriatal function and cause excess bursting activity in LMAN that drives abnormal song variability. First, birds with FoxP2 knockdown in Area X can no longer execute the rapid context-dependent switch in song variability. They exhibit pathologically high variability in the presence of a female (Figures 1B and 1D). Previous studies underscored the role of dopamine in this context-dependent reduction of vocal variability: dopamine levels in Area X increase during directed song, and infusing D1 receptor antagonist into Area X eliminates the normal reduction in variability during directed song (Leblois et al., 2010). To test how FoxP2 knockdown might influence dopaminergic function, Murugan et al. (2013) perform immunoblots of Area X tissue samples and find that FoxP2 knockdown causes a slight reduction in the number of D1 receptors and a massive reduction in DARPP-32 (a key downstream protein in the D1 receptor signal cascade). To test how these molecular deficits might influence circuit-level functions, they next developed an in vivo assay to quantify signal propagation from HVC to LMAN, which requires a route through BG-thalamic circuits. In control birds, D1 agonists and antagonists delay and accelerate signal propagation through BG-thalamic circuits, respectively. However, in birds with FoxP2 knockdown in Area X, the propagation is abnormally fast and is insensitive to dopaminergic modulation. Next, to test whether FoxP2 knockdown in the BG influences neural activity in the "variability generator" of the song system, Murugan et al. (2013) chronically recorded LMAN neurons in FoxP2 knockdown birds during directed and undirected singing. Remarkably, LMAN neurons of FoxP2 knockdown birds exhibited increased firing rates and more randomly timed bursts during directed song compared to controls (Figure 1C). Thus, FoxP2 knockdown in Area X rendered songbirds unable to regulate their context-dependent variability.

These findings raise several important questions. First, at the cellular, circuit, and behavioral levels, FoxP2 knockdown in Area X appeared to mimic in the BG a functionally hypodopaminergic state, which in mammals is also associated with increased bursting in motor cortical areas (Costa et al., 2006). Yet while dopaminergic control of corticostriatal activity is well known, it remains unclear exactly how dopamine action in the BG controls burst generation in target cortical regions, and how this bursting might in turn drive variability. Second, FoxP2 knockdown appears to provide the BG with a curious gain of function: it has the opposite effect as Area X lesion, which results in abnormal absence of bursting in LMAN during singing (Kojima et al., 2013). Third, this study did not address possible roles of *FoxP2* in the cerebellum, which remains largely unstudied in the songbird model system.

Finally, a compelling prediction of this study is that dyspraxia in humans arises not from a simple lack of coordination resulting from damaged or impaired circuits but instead might be actively driven by regions of frontal cortex with excess, randomly timed bursts that occur during speech. Perhaps the biggest obstacle to testing this prediction is our lack of understanding of if, and if so, how, variability is actively generated in the mammalian brain in the first place. What is the mammalian equivalent of LMAN? In the songbird, LMAN is a discrete thalamorecipient portion in a BG-thalamocortical loop. But mammalian motor circuits are much more complex and no such "nucleus" exists. Instead, this thalamic projection targets upper and middle layers distributed throughout frontal and motor cortices. Intriguingly, variability in songbirds also requires the BG-recipient thalamus (Goldberg and Fee, 2011), which has a clear human homolog. Thus, if verbal dyspraxia in humans truly results from forebrain variability circuits gone awry, then lesion or deep brain stimulation of the vocal motor thalamus might paradoxically restore vocal coordination in afflicted patients.

In summary, Murugan et al. (2013) showed that FoxP2 knockdown in the songbird basal ganglia interferes with

dopamine function, impairs signal propagation through corticostriatal circuits, and leads to excess bursting in a thalamorecipient motor cortical area, resulting in abnormal vocal variability. Extending this model to mammals and humans requires a better understanding of how variability—the "trial" part of trial-and-error learning—might be actively generated by the mammalian brain.

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# Prefrontal-Amygdala Interactions Underlying Value Coding

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http://dx.doi.org/10.1016/j.neuron.2013.11.027

**Dissociating the source and function of value-related signals is a major challenge for understanding the role of reward in neural processing. In this issue of *Neuron*, Rudebeck et al. (2013) provide insight into the neuroanatomical origins of a subset of these signals.**

Neurons throughout the brain are affected by an encounter with a valuable item. Some neurons are activated while others are suppressed. Some have brief, phasic responses, while others exhibit more prolonged changes. It is likely that different value-related signals play distinct roles in neural processing, contributing, for example, to affect, perception, motivation or learning. Some putative value signals are better explained by the degree to which a stimulus is salient (Leathers and Olson, 2012) or surprising (Hayden et al., 2011; Kennerley et al., 2011). But because these functions can all correlate with reward value, dissociating them is a major challenge in understanding the neural substrates of motivated behavior (Wallis and Rich, 2011).

Despite the prevalence of reward signals in the brain, the ability to use reward information to guide future behavior depends primarily on a subset of brain regions, among them the orbitofrontal cortex (OFC), medial frontal cortex (MFC), and amygdala. Damage to these structures causes impairments in value-based learning or choice, whereas damage to other structures does not. However, the precise contribution of each of these areas remains unclear, and relatively few studies have been able to demonstrate functional dissociations.

In a new study, Rudebeck et al. (2013) provide insight into one aspect that distinguishes some of these reward signals in the frontal cortex. In order to functionally dissociate value signals, the traditional approach uses behavioral manipulations to tease apart cognitive or emotional variables. In contrast, Rudebeck et al. (2013) employed the unique approach of combining neuron recording with selective neurotoxic lesions to identify value signals that depend on particular neuroanatomical circuits. Given their role in value-based behavior, this study focused on three brain regions, OFC, a region of MFC that lies within the dorsal anterior cingulate cortex, and the amygdala. All three of these regions encode value signals and are anatomically interconnected in a bidirectional manner (Ghashghaei