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An evolutionary perspective on FoxP2: strictly for the birds?

Constance Scharff[1,2] and Sebastian Haesler[1,2]

FoxP2 mutations in humans are associated with a disorder that affects both the comprehension of language and its production, speech. This discovery provided the first opportunity to analyze the genetics of language with molecular and neurobiological tools. The amino acid sequence and the neural expression pattern of *FoxP2* are extremely conserved, from reptile to man. This suggests an important role for *FoxP2* in vertebrate brains, regardless of whether they support imitative vocal learning or not. Its expression pattern pinpoints neural circuits that might have been crucial for the evolution of speech and language, including the basal ganglia and the cerebellum. Recent studies in songbirds show that during times of song plasticity *FoxP2* is upregulated in a striatal region essential for song learning. This suggests that FoxP2 plays important roles both in the development of neural circuits and in the postnatal behaviors they mediate.

Addresses
[1] Max Planck Institute for Molecular Genetics, Ihnestrasse 73, 14195 Berlin, Germany
[2] Freie Universität Berlin, Department of Animal Behavior, Grunewaldstrasse 34, 12165 Berlin, Germany

Corresponding author: Scharff, Constance (scharff@molgen.mpg.de)

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Introduction

Language can be defined as the ability to communicate infinite meaning by combining a finite set of sounds (or gestures in the case of sign language) using the rules of grammar. Imitative learning influences which sounds or gestures are used, and how they are combined into sentences. There are good reasons to assume a genetic predisposition towards this learning, that is, a language instinct [1]. This could be reflected in neural circuits that determine the intrinsic hierarchal logic shared by all languages, named 'universal grammar' by Chomsky and co-workers [1]. In 2001 the chase for genes associated with language resulted in the identification of a mutation in *FoxP2* in individuals that share severe and characteristic core deficits of receptive and productive language. Comprehensive recent reviews summarize the behavioral phenotype and genetic, molecular and anatomical findings relevant to FoxP*2* function in humans [2,3].

Language is one of the few uniquely human traits. Other bastions of alleged human exclusivity, such as tool production and mental time travel, are now known to exist also in animals [4,5]. If language is uniquely human, is *FoxP2* a uniquely human gene? What about *FoxP2* in other species? Here, we review reports of the past two years that analyze FoxP2 function in different vertebrates and *in vitro* systems. We focus particularly on songbirds, because of the well-established behavioral and neurobiological parallels between speech learning in human infants and song learning in birds [6,7]. The emerging picture reveals that the DNA and protein sequences in addition to the overall brain expression patterns of *FoxP2* are highly conserved, from crocodile to human, regardless of their ability to learn vocally or not. We, therefore, speculate that FoxP2 is involved in the development of brain pathways that are essential for, but not limited to, the faculty of language. These comprise particularly the cortico–subcortical pathways that run through the cerebellum and the basal ganglia, which are involved in motor planning, sequenced behaviors and procedural learning. In addition, we summarize data that predict a role for FoxP2 in the postnatal function of these circuits, including those specialized for vocal learning. We conclude that unraveling the relevance of FoxP2 for language depends as much on considering its evolutionary conservation in non-human brains as on understanding the significance of its evolutionary innovation in the hominid lineage (see Box 1).

Molecular function

Pathomechanism

FoxP2 belongs to the large family of winged helix transcription factors that are characterized by a conserved Forkhead box (Fox) DNA-binding domain. The forkhead box binds to distinct sequences in promoter regions of a specific set of target genes, enabling their transcriptional regulation. Fox proteins affect cell fate and differentiation in various tissues, and mutations cause developmental disorders [8,9]. The common feature in all individuals with speech abnormalities caused by genomic alteration of *FoxP2* seems to be a reduction of functional FoxP2 protein by 50%. This haploinsufficiency results from the introduction of a premature stop codon in one patient [10], the disruption of the gene by a translocation in another patient or a substitution of arginine to histidine (R553H) in the DNA binding domain (Figure 2) in all affected members of the KE family, in which the speech phenotype was originally described [11]. Homology mod-

Box 1 Molecular Evolution of *FoxP2*

A comparison of synonymous mutations (i.e. base substitutions that do not alter the amino acid [AA] sequence) and non-synonymous mutations (i.e. base substitutions that alter the AA sequence) in the *FoxP2* sequences of mice, great apes and humans revealed that the gene was under selection pressure during recent human evolution [81,82]. After divergence from the great apes, two non-synonymous but no synonymous substitutions occurred. However, one of the two previously presumed human-specific amino acids also exists in non-human carnivores [83]. The functional significance of the AA that remains unique to humans is unclear as it lies in an uncharacterized protein domain. The pattern of *FoxP2* sequence variation among humans further suggests that the human-specific allele was fixed in the population as a result of positive selection rather than relaxation of negative selection. Fixation is assumed to have occurred within the last 200 000 years, during which proficient language also appeared [81].

Because speech learning in humans necessitates vocal imitation, we and others investigated whether animals capable of vocal imitation, such as song-learning birds [32••], bats, whales and dolphins [84] harbor the human-specific AA in FoxP2. This is not the case. Furthermore, there is no correlation between a species' capacity for vocal learning and a particular version of their *FoxP2* coding region (Figure 1; Haesler S, Wada K, Enard W, unpublished). Thus, either *FoxP2* was not directly involved in the evolution of vocal-learning in birds or selection acted on the large non-coding regions of *FoxP2*. The latter possibility is supported by theoretical and experimental evidence that points out the importance of regulatory sequences in the evolution of complex traits [85].

eling of the FoxP2 forkhead domain structure in conjunction with electrostatic charge calculations predict a net reduction in positive charge on the DNA-binding surface of the R553H mutation, sufficient to disrupt DNA-binding [12].

Murine FoxP2 and the other three members of the FoxP family can act as transcriptional repressors, shown with reporter constructs in different cell lines [13,14••]. Thus, in patients with *FoxP2* mutations, reduced levels of functional protein are expected to attenuate transcriptional repression of a specific set of target genes. Their identity is still unknown, in part because the exact DNA motif to which FoxP2 binds has not been determined experimentally. However, the sequence to which FoxP1, the closest homolog of FoxP2, binds is known [15,16]. Interestingly, transcription reporter constructs containing the FoxP1 binding sequence also respond to FoxP2 [15], predicting a core motif to which both FoxP2 and FoxP1 can bind. This core motif is very similar to those of the two transcriptional activator families FoxO [17] and FoxC [18]. These mouse data suggest that Fox transcription factors are either functionally redundant or require additional protein interactions to specify target gene transcription.

Interaction partners

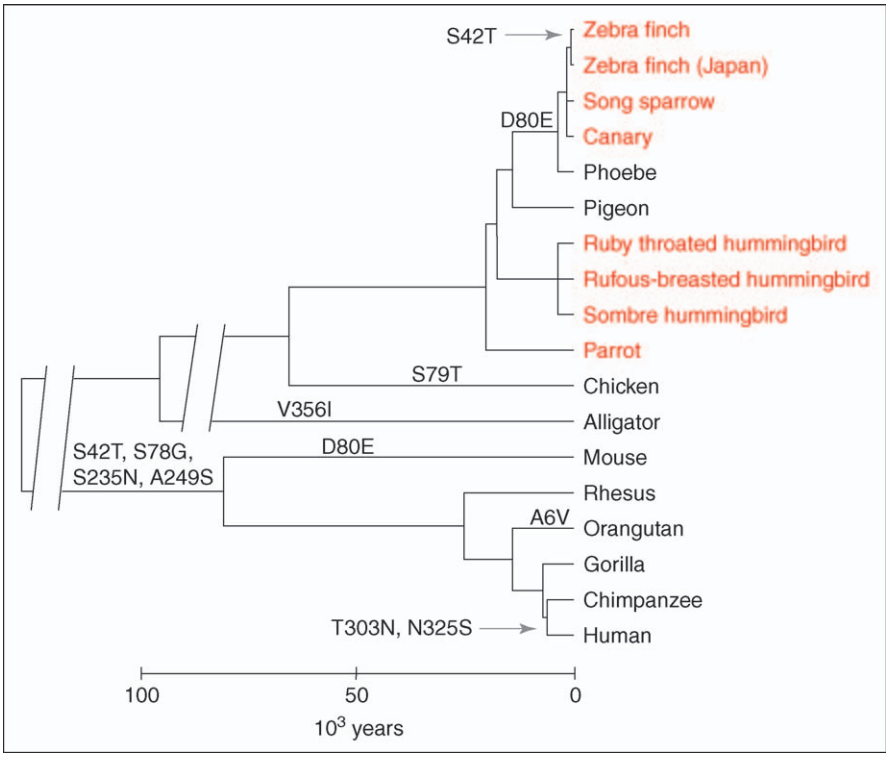
For transcriptional repression to occur, FoxP2 needs to dimerize with itself, with FoxP1 or with FoxP4 [14••]. This requirement distinguishes the FoxP family from the other Fox transcription factors. Dimerization depends on a conserved leucine zipper motif [14••]. A C2H2 type zinc finger adjacent to the leucine zipper might modulate the specificity of the interaction between FoxP proteins, as reported for FoxP1 [15]. FoxP1 and FoxP2, but not FoxP4, also interact with the transcriptional co-repressor C-terminal binding protein 1 (CtBP1). CtBP1 binding enhances, but is not essential, for transcriptional repression [14••]. A plethora of FoxP2 isoforms, including some that lack the forkhead box, add further complexity to the system [19].

FoxP2 contains an N-terminal glutamine-repeat that could function as a polar zipper to join other transcription factors that are bound to separate DNA segments [20], creating a multiprotein transcriptional unit. This hypothesis is consistent with the proximity of a binding site for FoxP1 to a number of other transcription factor binding sites in the *c-fms* promoter, a physiological target of FoxP1 [16]. Regulation of *c-fms* expression by FoxP1 depends on the polyglutamine repeat. Interestingly, the only neural sites of *c-fms* expression are the cerebellar Purkinje cells [21], which also strongly express FoxP2 (see below). The presence of a polyglutamine stretch in FoxP2 also prompted the search for pathogenic glutamine repeat extensions implicated in many neurodegenerative disorders [22]. However, the glutamine region of FoxP2 is neither expanded in the specific language impairment (SLI) patients studied to date nor in a set of 142 patients with progressive movement disorders [19]. The length of the polyglutamine tract could, however, be relevant for the molecular evolution of *FoxP2*, as suggested by recent fascinating correlations between speciation and length of repeat motifs in dogs [23].

The molecular factors that regulate *FoxP2* expression and the neural target genes of FoxP2 are still unidentified, leaving room for speculation. Analysis of signal transduction pathways relevant for the development of tissues in which *FoxP2* is expressed and comparison with molecular interactions of other *Fox* genes converge on the sonic hedgehog (Shh) pathway as a candidate for interactions with FoxP2. *FoxP2* is strongly expressed during lung morphogenesis [13], during which FoxA1 and FoxA2 regulate sonic hedgehog (Shh) [24]. Knockout of *FoxP2* (see below [25]) and transgenic overexpression of *FoxA2* in mice both disrupt cerebellar morphogenesis, which also depends on Shh signaling [26]. *FoxP2* could also lie downstream of Shh, similar to *FoxE1* [27], *FoxM1* [28] and *FoxF1* [29]. In addition, the zinc finger of FoxP2 is highly homologous to those of the major Shh downstream transcriptional effectors Gli1, Gli2 and Gli3 [13].

Taken together, dimerization of FoxP proteins and their potential interaction with other transcription factors

Figure 1



FoxP2 amino acid changes mapped on the phylogenetic tree of the species indicated. The seven song-learning avian species are marked in red, all other species, including the three non-song-learning birds, appear in black. Amino acid changes were inferred by parsimony and the phylogenetic tree of the birds is based on that of Wada *et al*. [86]. The topology of the tree inferred from silent substitutions in *FoxP2* agrees overall with the tree shown here (data not shown). Note that two amino acid changes have occurred two times independently (D80E and S42T) and that the direction of the four changes on the base of the tree cannot be inferred without an additional outgroup. Sequence positions are based on the human protein sequence. The timescale (in 10^3 years) offers a rough estimate for most divergence times.

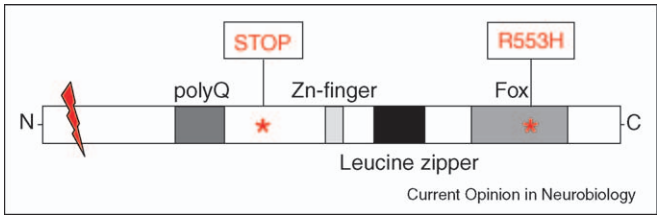
provide opportunity for complex patterns of target gene repression. In addition, the similarity of the predicted core DNA-motif, to which both FoxP1 and FoxP2 bind, raises the possibility that they can compensate for each other when co-expressed in the same cells.

Anatomy and behavior

Brain patterning

FoxP1 and *FoxP2* are expressed in a similar, partly overlapping pattern in all species studied, from crocodiles to humans [30,31••,32••]. Their restricted expression in

Figure 2



Functional domains of the FoxP2 protein. FoxP2 contains a glutamine-repeat region (polyQ), a C2H2 type zinc finger (Zn-finger), a leucine zipper and the forkhead box DNA-binding domain (Fox). All other FoxP family members (FoxP1, FoxP3 and FoxP4) have identical domain architecture with the exception of the polyQ region: in FoxP1, the polyQ stretch is shorter, varies in length among species and lies closer towards the N-terminus of the protein. FoxP3 and FoxP4 do not contain a polyQ region. The positions of the pathogenic alterations of the *FoxP2* gene are indicated. In one patient, *FoxP2* is disrupted by a balanced translocation (red flash). In another patient, a mutation introduces a stop codon (STOP). In the affected KE family members the mutation of arginine (R) to histidine (H) in position 553 of the AA sequence (*) disrupts the DNA-binding capacity of the Forkhead box (R553H).

primordia of the forebrain suggests that they belong to the set of orthologous genes that specify anterior development in *Drosophila* and that are vital for different aspects of forebrain development in amniotes, for example, distalless (*Dlx*), empty spiracles (*Emx*), and orthodenticle (*Otx*) [33]. Similar to that of *Dlx*, *Emx* and *Otx*, *FoxP* expression starts during early embryogenesis. *FoxP2* mRNA is first detected at embryonic day 13 in mouse brain and at an equivalent stage (E8∼HH26) in zebra finch. *FoxP1* expression lags by a day [32••,34]. In the rodent telencephalon, initial expression of *FoxP1* and *FoxP2* is largely limited to the lateral ganglionic eminence (LGE) [34,35], the mammalian subpallial germinal zone that gives rise to the striatal projection neurons of the basal ganglia and to the majority of cortical interneurons [36]. In birds, telencephalic *FoxP2* expression also begins in the striatal anlage and continues in the striatum after hatching. The LGE expression pattern of *FoxP1* and *FoxP2* in rodents and birds predicts a role in regional specification of ventral telencephalic structures, similar to the one played by members of the Dlx and Gsh gene families of transcription factors [37].

Within the LGE, *FoxP1* and *FoxP2* are expressed in the subventricular zone and mantle region but not in the proliferative ventricular zone, suggesting that expression is initiated in postmitotic neurons. This interpretation is also compatible with the additional expression site in the non-proliferative cortical plate of the developing cortex [34,35].

In the adult murine cortex *FoxP1* and *FoxP2* expression is layer-specific. Neurons that express *FoxP2* reside mainly in layer VI, whereas *FoxP1* expressing cells reside mainly in layers III–V. Given that projection neurons generally colonize the cortical layers in an age-dependent, inside-out manner, *FoxP2* expressing cells are expected to be born earlier than *FoxP1* expressing cells. If so, this could account for the slightly earlier onset of expression of *FoxP2* in the LGE. In the three-layered pallium of birds, FoxP1 is markedly expressed in the middle layer (mesopallium) and less in the other two 'cortical' layers [31••,32••]. Pallial *FoxP2* expression varies among bird species, with homogeneously low expression in oscine songbirds and a *FoxP1*-like pattern in their distant relatives the parrot and ringdove [32••].

Because the LGE gives rise to striatal medium spiny projection neurons, it fits that this cell type expresses *FoxP1* and *FoxP2* in mice and birds [30,32••]. Less congruent is the fact that *FoxP1* and *FoxP2* expressing neurons in the murine cortex are more layer-specific and less sparsely distributed than expected for LGE-derived interneurons [35,38]. Instead, the abundance and layer-restriction of cortical *FoxP1* and *FoxP2* expressing neurons suggest that they are projection neurons. In this case, *FoxP1* and *FoxP2* would deviate from the more common pattern of developmentally relevant transcription factors that mark either pallial or subpallial derivatives [37].

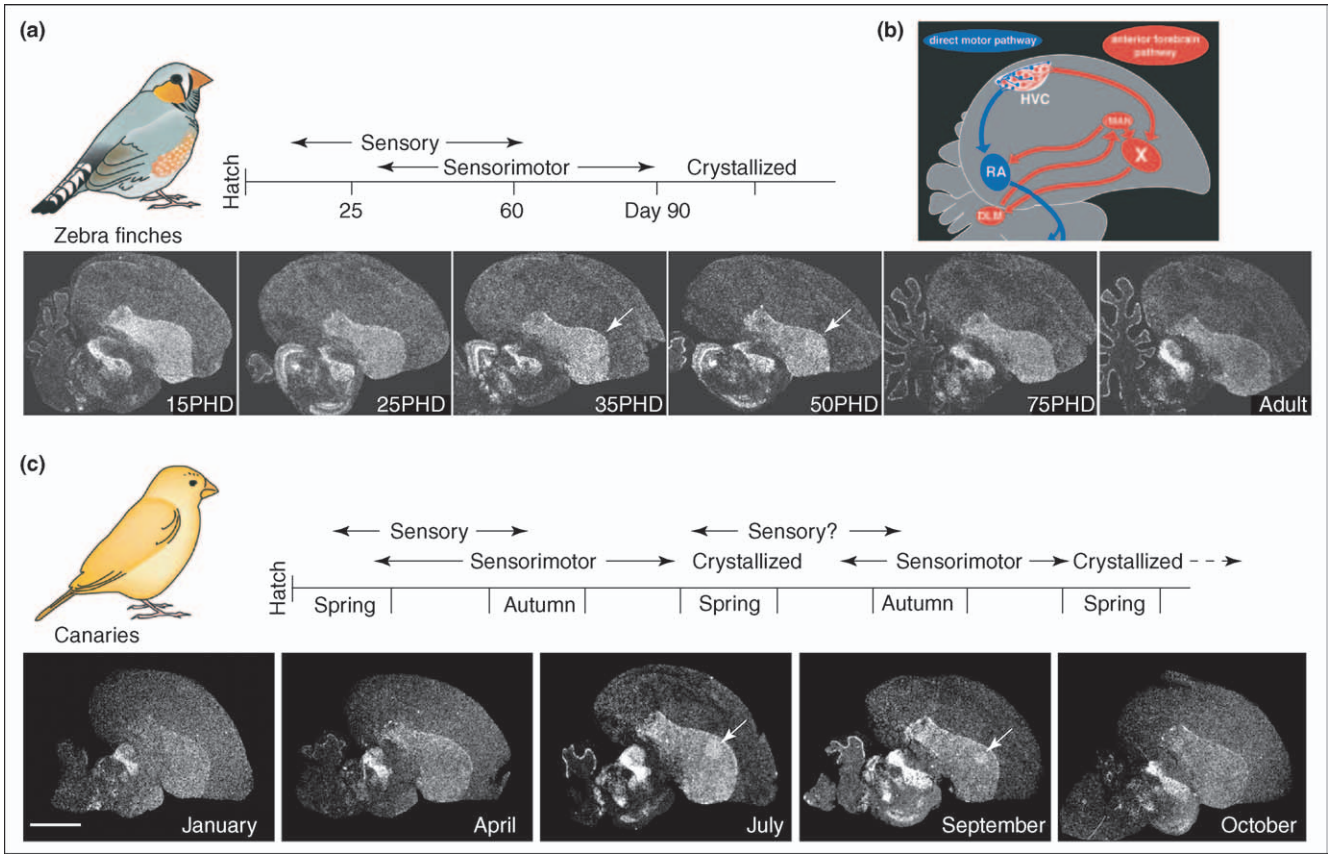
In addition to the striatum, species-conserved expression of *FoxP2* and *FoxP1* is prominent in regions of the thalamus that receive input from the basal ganglia, in midbrain visual processing regions and in the inferior olive of the medulla. Other regions, including the cerebellar Purkinje cells, deep cerebellar nuclei and sensory auditory midbrain structures express *FoxP2*, but not *FoxP1*. Importantly, *FoxP2* does not seem to be expressed in the majority of structures that form the trigeminal sensorimotor circuit that control the beak, tongue and oral cavity of birds [32••,39]. Although *FoxP2* expression in the human trigeminal circuit has not been investigated in detail, the avian expression data predict that the orofacial dyspraxia of patients with *FoxP2* mutations is not primarily linked to a role of *FoxP2* in peripheral orofacial sensory or motor circuits.

FoxP1, FoxP2 and learned vocalizations

The specific expression of *FoxP1* and *FoxP2* in brain nuclei that control bird song implicates the two genes in learned vocalization. The pallial nuclei HVC (proper name) and RA (Robust nucleus of arcopallium; for nomenclature of song nuclei see [40]) express substantially more *FoxP1* than their respective surrounding brain regions [31••,32••]. Moreover, in the striatal nucleus Area X, which is essential for song learning, *FoxP2* expression is elevated above the surrounding striatum during periods of vocal plasticity, both in juvenile zebra finches (Figure 3a) and in adult canaries (Figure 3c) [32••]. Area X belongs to a basal ganglia circuit, called the anterior forebrain pathway (AFP; Figure 3b). The AFP bears strong electrophysiological, neurochemical and functional parallels to the human basal ganglia [41,42•–44•]. The structural and functional abnormalities of the basal ganglia in KE family patients [2] support the notion that the basal ganglia play a role in learned vocalizations not only in birdsong but also in human speech. Therefore, the analysis of the role of FoxP2 in the AFP will be particularly informative.

FoxP2 expressing medium spiny neurons in Area X are in an excellent position to affect song plasticity. They are the site of convergent glutamatergic AMPA- and NMDA-mediated pallial input and ascending dopaminergic D1-receptor mediated input. By analogy with the mammalian system these cells might be involved in reward learning [41]. In avian slices, the medium spiny neurons show long-term potentiation [45]. Their patterns of activity indirectly set the temporal code of inhibitory postsynaptic potentials read by the thalamic neurons of song nucleus DLM (dorsal lateral nucleus of the medial thalamus; Figure 3b). This enables *FoxP2*-expressing neurons in

Figure 3



FoxP2 expression is increased during times of vocal plasticity. Zebra finches learn to sing by imitating the song of an adult tutor. During the 'sensitive learning phase' birds memorize the tutor song but vocalize little. During the 'sensory–motor phase' they start singing and use auditory feedback to modify their imperfect rendition of the memorized tutor song. This process culminates in a final, 'crystallized' song. **(a)** In zebra finches, adult song changes little, in contrast to canaries who continue to modify their song throughout life. **(b)** Before and after the breeding season they incorporate new syllables into their song, which correlates with seasonal plasticity in the neural circuits that mediate the learning and/or production of song. **(c)** The anatomy and connectivity of the song circuit. HVC and RA are part of the motor pathway necessary for song production (blue). HVC also provides input to the anterior forebrain pathway (AFP) (red). The AFP comprises the nuclei Area X, LMAN and DLM. It is essential for song learning during development and for periods of song plasticity in adulthood. *FoxP2* expression in Area X is elevated during times of song plasticity both in juvenile zebra finches (a) and in adult canaries (b).

Area X to gate the information passed on from DLM to the pallidal song nucleus LMAN (lateral magnocellular nucleus of anterior nidopallium; Figure 3b) through a rebound spiking mechanism [46•]. Recent elegant experiments confirm the hypothesis posited from earlier lesion work [47] that LMAN ensures variability during song learning. When LMAN is transiently inactivated young zebra finches sing uncharacteristically stable song sequences instead of the variable juvenile ones [48]. Whether the variability that is vital for the process of song imitation is intrinsic to LMAN or is created 'upstream' by the combined action of Area X and DLM remains to be determined. The AFP circuit continues to be important in adult birds that keep their song fairly stable once they have mastered it, which was predicted by indirect experiments [49,50] and has now been shown directly [51].

What determines how much *FoxP2* Area X expresses? In zebra finches the amount and the variability of singing do not seem to influence the levels of *FoxP2* expression [32••], in contrast to their effects on the expression of the immediate early gene *ZENK* [52,53•]. The seasonal expression of *FoxP2* in Area X of adult canaries could be related to seasonal changes in the morphology of song nuclei that depend on photoperiod, hormones and behavior [54,55]. For instance, during the fall months HVC grows in size and recruits more adult-born neurons both in canaries and in song sparrows [56,57]. Area X also changes seasonally in size but does not recruit more new neurons in wild-caught adult male song sparrows [58]. Although rates of seasonal neuronal recruitment are not known for Area X in adult canaries, the data from song sparrows suggest that rates of neural replacement and regulation of *FoxP2* expression in Area X are not linked.

Seasonally and developmentally changing hormone levels could influence *FoxP2* expression. This hypothesis is compatible with the observations that first, *FoxP1* is co-regulated with the estrogen receptor α in cancer cells [59], second, gene regulation by this estrogen receptor requires FoxA1 [60], third, androgens can negatively regulate other FOX genes [61], fourth, mouse striatal medium spiny neurons depend on estrogens for their maturation *in vitro* [62] and fifth, steroids potently shape dendritic attributes and synaptic function in adult avian and mammalian brains [63,64]. If steroids influence *FoxP* expression in Area X, it would be an inhibitory relationship, because circulating testosterone levels are low in young finches and adult canaries [54] when *FoxP2* expression is high. Hormone interactions with FoxPs in Area X could be distinct from those occurring in the surrounding striatum, because hormones can act trans-synaptically through the projection neurons from HVC to Area X [54]. Finally, melatonin receptors in Area X of starlings have a strikingly similar seasonal pattern to *FoxP2* expression in canaries, being highest in the non-breeding fall months. Changing melatonin levels have been interpreted to play a role in downregulating cellular activity via the inhibitory action of melatonin on second messengers and transcription factors [65].

Double duty of transcription factors

FoxP2 is implicated in both brain development and postnatal behavior. Might the molecular mechanism of its regulation and function be similar in both contexts? Examples for a conservation of transcription factor function throughout the life of a cell are Dlx1 [66••] and the *engrailed* genes [67]. They are required in neonatal and adult mice for the survival of a subset of cortical interneurons and midbrain dopaminergic neurons, respectively. Because FoxP2 might be important for fate-specification of striatal projection neurons during brain development, one wonders whether it fulfils a similar function during times of song plasticity in birds. Behavioral plasticity often entails changes in cell-type specific attributes of neurons, altering their connectivity and electrophysiological properties. These changes might actually challenge the maintenance of cell fate. An upregulation of *FoxP2* might, thus, be needed to counterbalance the effects of neural plasticity to preserve the identity of the cell. Alternatively, increased *FoxP2* expression in Area X during song learning could promote neural and behavioral plasticity. However, this seems less compatible with a hypothesized function of *FoxP2* in regional specification of the embryonic brain.

FoxP2 knockout mouse

Whereas heart defects in *FoxP1* knockout mice cause embryonic lethality [68], mice with disruption of both *FoxP2* alleles live for three weeks after birth [69]. They are developmentally delayed, and are impaired in tests of motor function. Heterozygous mice perform only moderately worse than wild types, and catch up by their second week of life. Adult heterozygous *FoxP2* knockout mice show no deficits in the Morris water maze, which requires coordinated movement of the limbs and measures spatial learning abilities. Spatial learning depends on the hippocampus, which does not express *FoxP2* in mice [35,70] and would, therefore, not be expected to be strongly impaired in *FoxP2* knockout mice.

Consistent with the conserved cerebellar *FoxP2* expression [32••,35,70], *FoxP2* knockout mice display cerebellar abnormalities. These include abnormal Bergmann glia and the delayed and incomplete postnatal resolution of the external granular layer, suggesting impaired cell migration. In addition, the molecular layer in heterozygous animals is thinner, the Purkinje cells have underdeveloped dendritic arbors and are misaligned. It is possible that the cerebellum is particularly vulnerable to the absence of *FoxP2*, because it lacks coexpression of *FoxP1* [30,31••,32••]. FoxP1 might compensate for the absence of FoxP2 during development in regions that normally express both, for example, the basal ganglia and the thalamus. The basal ganglia that strongly express *FoxP2* and *FoxP1* during development do not exhibit gross histological abnormalities in *FoxP2* KO mice. As KE family patients do have structural abnormalities of the basal ganglia [71], it will be interesting to analyze the anatomy and behavioral function of the basal ganglia in *FoxP2* KO mice in more detail.

Homozygous *FoxP2* knockout pups vocalize less in the sonic range than heterozygote and wild type animals when separated from their mothers. In the ultrasonic range, both homo- and heterozygote knockout animals utter fewer whistles. Interestingly, the acoustic structure of the vocalizations is preserved in *FoxP2* KO pups, indicating that the motor areas controlling acoustic features of sound production are intact. Ultrasound communication in adult homozygotes could not be tested because they die too early [69]. Because FoxP2 is implicated in cellular differentiation of the developing lung, pneumatic function might be compromised in the knockout mice, which could affect vocalizations. In fact, hypoxia strongly decreases the rate of postnatal vocalizations [72]. Given the speech pathophysiology of patients with *FoxP2* mutations, it is particularly interesting that vocal behavior in the KO mice is impaired. However, it is important to bear in mind that although both humans and mice vocalize, only speech is learned.

Conclusions and future directions

The original suspicion that FoxP2 would be primarily involved with control of oro-facial muscles and, thus, would be only peripherally interesting for understanding neural substrates for speech and language, is not supported by the gene expression and mouse KO data. Instead, the strong expression of *FoxP2* in cerebellar

and basal ganglia circuits points towards functions that include sensory–motor integration important for sequenced behaviors and procedural learning. For language it has been proposed that a basal ganglia-dependent procedural memory system mediates the 'how', that is, the implicit, non-declarative aspect of how language is put together sequentially using rule-governed computations [73]. By contrast, the 'what' of language depends on the explicit 'mental lexicon' of words, what they mean and any unpredictable, non rule-governed grammatical exceptions [73]. The beauty of the idea that language uses a procedural memory system is that one can easily imagine how language evolved onto 'procedural' and 'declarative' memory systems that already existed in animals [74]. By analogy, Area X in songbirds could have evolved from a striatum mediating general procedural learning and adapted this ability for song acquisition [75]. Circuits evolved for vocal learning could then continue to mediate general procedural and declarative processing, or lose this ability. In SLI patients, there is evidence for procedural deficits that affect both language and other functions [73]. However, it is unlikely that Area X in songbirds functions in procedures that are unrelated to singing. Adult Area X lesions do not hinder zebra finches in learning an operant conditioning task that requires procedural memory for initiating a sequence of events in a stimulus-dependent manner [76]. In mammals, procedural memory is thought to depend on sleep [77], although this is controversial [78]. In zebra finches, sleep is definitely important for song learning [79••]. In light of the controversy concerning the role of sleep on procedural memory in mammals, it will be interesting to test whether the effect of sleep on song learning is mediated via the basal ganglia. This would strengthen the notion that sleep facilitates procedural memory.

When *FoxP2* mutations were first linked to speech and language, the hope that a single gene might provide insight into such a complex trait was met with considerable skepticism. Four years later the accumulated knowledge encourages cautious optimism that studying FoxP2 function will help us to understand the neural mechanisms of learned vocal communication. Yet many questions remain. Some of these are summarized in Box 2.

Box 2 Open questions:

1. Which genes are regulated by FoxP1 and FoxP2?
2. What regulates *FoxP2* expression, particularly in Area X?
3. Does FoxP1 play a role in human speech and birdsong?
4. What is the identity of the pallial and/or cortical *FoxP1* and *FoxP2* expressing neurons?
5. Is there a causal relationship between *FoxP2* expression levels in Area X and song plasticity?
6. Is the striatum surrounding Area X involved in procedural learning and memory?
7. Does the cerebellum participate in song learning and production?

The human experience is based on traits that are unique to our species and traits that we share with other animals. Language combines aspects of both. In his 'Essay concerning Humane Understanding' [80] the English Philosopher Locke wrote in 1689 under the heading 'Brutes have memory': ''Birds learning of Tunes and the endeavors one may observe in them to hit the notes right put it past doubt with me, that they have Perception, and retain Ideas in their Memories and use them for Patterns. (. . .) It cannot with any appearance of Reason, be suppos'd (much less proved) that Birds, without Sense and Memory, can approach their Notes, nearer and nearer by degrees, to a Tune played yesterday''. By turning to birds to understand the role of FoxP2 in song learning we might in turn discover something about how language evolved for the purpose of 'Humane Understanding'.

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- • of special interest
- •• of outstanding interest

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thalamic DLM nucleus, because of its net inhibitory action on the thalamus. These authors suggest the 'direct' pathway to be HVC → Substance P^+, GABAergic medium spiny striatal neurons (SN) → AF neurons → DLM, because of its net excitatory action. Note that in this scenario the direct pathway has one more synapse than the indirect pathway. Based on their findings that many presumed AF projection neurons in Area X do not project to DLM but contact other AF neurons, Farries *et al.* [44•] hypothesize that the net inhibitory indirect pathway could involve a series of three inhibitory synapses, that is, pallial glutamatergic HVC neurons → SN neurons → locally projecting AF neurons → AF neurons → DLM.

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