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Birdsong as a window into language origins and evolutionary neuroscience

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Humans and songbirds share the key trait of vocal learning, manifested in speech and song, respectively. Striking analogies between these behaviours include that both are acquired during developmental critical periods when the brain's ability for vocal learning peaks. Both behaviours show similarities in the overall architecture of their underlying brain areas, characterized by cortico-striato-thalamic loops and direct projections from cortical neurons onto brainstem motor neurons that control the vocal organs. These neural analogies extend to the molecular level, with certain song control regions sharing convergent transcriptional profiles with speech-related regions in the human brain. This evolutionary convergence offers an unprecedented opportunity to decipher the shared neurogenetic underpinnings of vocal learning. A key strength of the songbird model is that it allows for the delineation of activity-dependent transcriptional changes in the brain that are driven by learned vocal behaviour. To capitalize on this advantage, we used previously published datasets from our laboratory that correlate gene co-expression networks to features of learned vocalization within and after critical period closure to probe the functional relevance of genes implicated in language. We interrogate specific genes and cellular processes through converging lines of evidence: human-specific evolutionary changes, intelligence-related phenotypes and relevance to vocal learning gene co-expression in songbirds.

This article is part of the theme issue 'What can animal communication teach us about human language?'

1. Introduction

In the words of the Argentinean writer Borges [1], 'All language is a set of symbols whose use among its speakers assumes a shared past'. Spoken language primarily uses sounds as symbolic vehicles, a repertoire of learned and voluntarily controlled vocal elements that can be connected in a rule-based way to form more complex sequences. Despite its human uniqueness, spoken language shares some of its necessary components with vocal behaviour practised by at least one evolutionarily distant animal group. A robust body of evidence accrued over approximately 100 years demonstrates striking analogies between birdsong and speech, both learned forms of vocalization.

Birdsong and speech are acquired during developmental critical periods when the brain's ability for vocal learning peaks (see Tyack [2]). Both behaviours show similarities in the overall architecture of related brain areas, characterized by cortico-striato-thalamic loops and direct projections from cortical neurons onto brainstem motor neurons that control the vocal organs. These neural parallels extend to the molecular level, with certain song control regions sharing transcriptional profiles with speech-related regions in the human brain [3]. This offers an opportunity to decipher the shared neurogenetic underpinnings of vocal learning. This line of inquiry will additionally yield insight into human disorders of communication. Indeed, a major barrier in autism and schizophrenia research has been a lack of animal models with measurable behaviours relevant to core symptoms such as deficits in learned vocal communication [4–6]. With the advent of a well-annotated genome [7,8], the songbird model is poised to close the gap in the

available approaches for addressing language-associated neurodevelopmental disorders.

A key strength of the songbird model is that it allows for the delineation of activity-dependent transcriptional regulation driven by learned vocal behaviour. To capitalize on this advantage, we used published datasets that correlate gene expression networks to features of learned vocalization within and after critical period closure to probe the functional relevance of genes implicated in language [9,10]. Evolutionary changes relevant to human brain development include alterations in the timing of neuronal gene expression (e.g. heterochrony) as well as human-specific changes to the genetic sequence itself. We interrogate specific genes and cellular processes through converging lines of evidence: human-specific evolutionary changes, communication and intelligence-related phenotypes, and relevance to coordinated gene expression patterns related to learning in songbirds.

2. The slow but rewarding journey of becoming a vocal learner: intrinsic reward systems are central to the two-way evolutionary process between vocal learning and timing of sexual maturation

(a) Dopamine and song variability

Within a given songbird species, there is individual variability in both the acoustic structure of the vocal units themselves and in the order which they are sequenced. In zebra finches, a species in which song is sexually dimorphic and only males learn to sing, social context modulates song variability: it is typically reduced when a male sings to females (i.e. female-directed song—FD) relative to when he sings alone (i.e. undirected song—UD) [11]. While females prefer FD to UD song [12,13], the more variable UD song is thought to reflect vocal-motor exploration important for motor learning and reinforcement [14,15]. The same benefit of variability during training leads to more efficient motor learning and performance in humans [16–18].

Along these lines, a certain degree of variation in juvenile song is thought to enable vocal learning, as young birds explore a range of vocal gestures in search for motor patterns capable of producing vocal output that matches the template built from the tutor's song [19,20]. Similarly, in adult songbirds, variability appears fundamental for song maintenance, because it allows for the reinforcement of optimal motor patterns capable of producing auditory inputs that match the auditory template built from the bird's own song [21,22]. Hence, in a way, variation begets fidelity. Fidelity is fundamental for performance of species-specific song patterns and levels of stereotypy that are adequate to a species' sensory ecology (e.g. in species recognition), without which successful social interactions (e.g. enchanting females) are less likely [23]. On the other hand, the ability to introduce variation creates an openness to innovation and more complex patterns of cultural transmission, leading to increased song complexity, such as simultaneous learning from multiple tutors [24].

Context-dependent changes in song are correlated with key differences in gene expression in the songbird brain. The earliest indication of this came from the discovery of different patterns of immediate early gene expression in the brain between UD and FD, leading to the original proposal of catecholaminergic modulation in the male basal ganglia song control nucleus, Area X, in context-dependent changes in song [25]. Subsequent studies show that in contexts associated with increased song stereotypy, as in FD singing, extracellular dopamine (DA) levels in Area X are higher than in contexts associated with increased song variability, as in UD singing [26]. These changes are paralleled by another key molecule in vocal learning, the transcription factor FOXP2, for which Area X gene expression decreases during UD but not FD singing [27,28]. Rather than coincidental, these concordant changes between FOXP2 gene expression and dopaminergic regulation appear causative: experimental 'knockdown' of FOXP2 in Area X both disrupts the possibility of context-dependent modulation of vocal variability and decreases levels of dopamine receptor 1 (D1R) and DA- and cAMP-regulated neuronal phosphoprotein (DARPP-32), components in the D1R signalling cascade [29].

(b) A role for endocannabinoids in vocal learning

Darwin [30] noted that although the main function of birdsong during the breeding season is mate attraction, 'birds continue singing for their own amusement after the season for courtship is over'. Several studies now provide evidence supporting the hypothesis that song practice is indeed stimulated and maintained by intrinsic reward mechanisms [31]. These systems operate at two integrated levels: one regarding memetic aspects of song learning (i.e. of the reward-related memories) and associated dopaminergic neuromodulation, and the other regarding pleasure (i.e. elicited positive affective states), associated with opioid and endocannabinoid neuromodulation [32]. The role of cannabinoids in song variability and learning is substantiated by the reduction in stereotypy and number of learned notes in the songs of young birds exposed to an endocannabinoid agonist relative to songs of non-exposed juveniles [33]. Notably, the treatment had no measurable effect on the structure of already-learned song patterns in adults, indicating that the mechanisms underlying critical period learning are more sensitive to cannabinoid disruption. Here, we present further evidence supporting the involvement of the endocannabinoid system for vocal learning in humans and songbirds.

In prior work, our group applied an unsupervised weighted gene co-expression network analysis [34] to songbird brain transcriptomes and discovered groups of genes whose transcripts exhibit co-expression patterns, which in gene network terminology are referred to as 'modules'. As part of this unbiased approach, modules are assigned arbitrary colour names (e.g. darkgrey) [9,10]. Within the resultant network, some of the modules were unique to Area X and others were unique to the juvenile critical period for learning. Specifically, we tested whether the co-expression relationships observed in juvenile Area X were preserved in a non-song control brain region—neighbouring basal ganglia termed the ventral striato-pallidum (VSP)—and in adulthood (i.e. region-specific and age-dependent modules). Statistically significant correlations (q-value < 0.05) to song features were also reported including to song production (the number of motifs sung by the bird at the time of the experiment) or learning (the spectral similarity of a pupil's song to that of its tutor).

In another behavioural measure, we leveraged an experimental paradigm validated in several publications that

detect singing-induced changes in zebra finch (*Taeniopygia guttata*) song variation, as seen during natural social modulation [35]. Here, we refer to this as the 'variability induction' (VI) paradigm [35–38]. In these experiments, the variability of UD song after a period of non-singing is compared to the variability of UD song after an equivalent period of continuous UD singing. This comparison reveals that, on average, continuous UD 'practice' in the morning leads to increased song variability, while singing after a morning period of quiescence is more stereotyped, similar to FD song [35].

In this prior study, our group identified gene modules that were correlated to song-related behavioural features. Briefly, we found modules of genes whose co-expression was up- or downregulated by the amount of song that birds sang on the morning of the experiment. Strikingly, these 'song modules' were specific to Area X and observed in both adults and juveniles, speaking to the profound influence of singing behaviour on the transcriptome [9,10]. Excitingly, the analysis shows modules correlated to the amount of tutor song learning by a pupil, and these were restricted to juveniles. The gene co-expression pattern for these learning-related modules disappeared in adults that were beyond the critical period for learning, suggesting that they are important for the neural plasticity underlying critical period learning. Additional modules were correlated to the morning modulation of song variability as measured by the VI paradigm.

Here, we newly integrate those prior findings of behaviourally relevant gene co-expression modules in Area X of juvenile birds [9] with findings published by Pfenning *et al*. [3], who identified gene expression patterns that are conserved in the brains of humans and song-learning birds. Specifically, the authors analysed transcriptomes from multiple brain regions from humans and song-learning birds (zebra finch, parrot and hummingbird) as well as vocal non-learning birds (dove and quail) and a non-learning primate species (macaque). They found evidence for transcriptional convergence in vocal-learners' brains, including between Area X and the human putamen, a dorsal portion of the human striatum.

Our new analysis points to a total of 45 genes (electronic supplementary material, table S1) that form behaviourally relevant modules in the juvenile network and exhibit transcriptional convergence between Area X and the human putamen. Among these, monoacylglycerol lipase (MGLL) shows high intramodular connectivity that is specific to the Area X of juvenile birds, and for which expression correlates with a bird's ability to introduce variability in its song (electronic supplementary material, table S1). MGLL is responsible for the metabolism of endocannabinoid 2-arachidonoylglycerol (2-AG) [39]. These findings suggest that the regulation of MGLL metabolism of 2-AG in Area X allows for song variability in juvenile birds. Endocannabinoids such as 2-AG mediate activity-dependent changes in synaptic strength via activation of type 1 cannabinoid (CB1) receptors in several regions of the mammalian brain, including the striatum [40]. They retrogradely suppress both inhibition and excitation of dopaminergic neurons by inhibiting neurotransmitter release by GABAergic medium spiny neurons and glutamatergic terminals, respectively [41]. Endocannabinoid–DA striatal interactions seem to be conserved in songbirds, as components of both systems are regulated in Area X [26,42]. Thus, the regulation of MGLL metabolism of 2-AG in Area X during the juvenile critical period likely has consequences for FOXP2-mediated synaptic plasticity (e.g. [43,44]) and dopaminergic neuromodulation.

Sex hormones and related metabolites and enzymes are regulated in a context-dependent fashion and as a function of the developmental trajectory (see §2c below) in several organisms, including songbirds [45] and mammals [46]. In zebra finches, directed FD singing is associated with higher levels of circulating plasma testosterone than during more variable UD singing [47,48]. Moreover, the plastic period of juvenile song learning closes when zebra finches mature and testosterone levels rise [49,50]. These endogenous hormones have long been recognized to modulate DA in mammalian and songbird brains [51,52], and have more recently been investigated in endocannabinoid-associated reward systems in both animal groups [32,53–55]. Therefore, context-dependent surges in testosterone levels and changes in the timing of sexual maturation impact the function of intrinsic reward systems in both songbird and mammalian brains.

(c) Slow developmental trajectories and the evolution of vocal learning

Human development is delayed and prolonged relative to other great apes, and this distinction is key to understanding human uniqueness [56]. Songbird development is also delayed relative to non-vocal learning birds [57], suggesting that similar changes in the timing of development (heterochrony) contributed to the emergence of vocal learning in songbirds and humans. Charvet & Striedter argue that changes in the timing of development are a necessary prerequisite for the evolution of learned vocal communication [58]. Developmental timing, though not sufficient, may have been key to the evolution of complex vocal production learning, at least in songbirds and humans. Slowed development supports the vast metabolic demands of the developing songbird [59] and human brain [60]. This allows the generation of an expanded telencephalon, which is then capable of being adapted for learned vocalization circuitry. With prolonged development, the window of juvenile plasticity also expands, creating an opening for the evolution of complex learned behaviours [61].

In the wild, slow developmental trajectories reflect some of the most varied evolutionary processes, including the effects of limiting environmental conditions [62–64]. However, some cases of delayed developmental trajectories may evolve through a change in selective pressures whereby commonly found environmental sources of selection that work as constraints to behavioural plasticity and flexibility, such as predation, foraging and species recognition, are either superseded or overcome by sources of selection imposed by socialization [65,66]. This sort of change in evolutionary regime is also observed in processes of domestication [67]. Incidences of domestication thus serve as fruitful models for studying such evolutionary phenomena [68].

Domestication has reduced the time to sexual maturation in a variety of animals, including the domestic chicken. However, another parcel of domestic animals, likely following domestication practices other than selection for earlier reproduction, show slow developmental trajectories and retain in adulthood a suite of behavioural, physiological and morphological traits typically found at younger ages in the ancestral species (i.e. the domesticated phenotype/syndrome), a form of heterochrony called 'neoteny' [68,69]. This is reflected in

a reduction in sexually stereotyped traits (e.g. morphological and behavioural dimorphisms) and extended neuroplasticity and learning, which leads to behavioural flexibility and an openness to cultural transmission [70].

Humans may have undergone a similar process, but one in which we were the solo protagonists of our own domestication (i.e. self-domestication) [71]. Sources of relaxation of selection during human evolution include the development of collective ambushing strategies to hunt for stronger prey; taking part in 'traditional learning' (i.e. the cultural transference of information from generation to generation), and division of labour that allows for the optimization of tool-making, hunting-and-gathering as well as long-range trading, among other fundamental human activities. In addition, increases in affiliative behaviours towards the elderly, children and disabled individuals, minimize the fitness consequences of their vulnerability. In these contexts, human sociality would have entered a feedback loop, reducing common environmental selective pressures, but making itself the main source of selection in our species. Individuals showing more tolerance to social stress, and more cooperative—instead of aggressive—behaviours would have gained selective advantages. Several unique traits that define our species, including language, could have evolved associated with these selective pressures for more peaceful and cooperative living.

Like language, the evolution of birdsong is challenging to study because song is not directly reflected in non-perishable or fossilizable forms. As Don Kroodsma, a pioneer in the field, has pointed out, 'perhaps the best hope for understanding why some birds learn is to examine far more recent evolutionary events […] in which we can better identify the social circumstances that led to the origins [and] loss of vocal learning' [72, p.110]. To that goal, recent studies have added the evolution of more complex patterns of vocal learning, such as learning from multiple tutors and more variable song. A preeminent example of this type of evolutionary change is the domesticated Bengalese finch (BF; *Lonchura striata domestica*) [73].

Beginning approximately 250 years ago, BFs were caught and domesticated from their wild Chinese ancestor, the white-backed munia (WBM; *Lonchura striata*). According to extensive historical reports, the BF was never bred for its singing ability, yet it evolved a much more complex vocal behaviour than that found in WBMs, marked by increased sequence variability and simultaneous learning from multiple tutors. Together with less aggressive and less neophobic (i.e. fear of novelty) behaviours, these features complete a suite of neotenic traits in the BF that enhance exploration. Female choice has been proposed as a major selective force leading to the increase in BF's vocal complexity [74]. Additionally, relaxation of sources of selection present in the wild, such as species recognition and environmental stress [75,76], may have been crucial in allowing for new or continuing sources of positive selection to operate towards the evolution of more complex vocal behaviour in the BF (i.e. female choice for more complex songs) [77,78].

To sum up thus far, the delayed developmental trajectories in both humans and songbirds hold parallel implications for reward systems leading to the evolution of vocal learning. Evidence suggests that, rather than the work of a single evolutionary force, this was the product of a similar interplay of adaptive pressures relating to the enrichment of social over environmental demands in both groups. This advance holds timely relevance to the current path of our species in meeting modern-day socio-political and climate-related challenges on the global scale.

3. From slowing down to speeding up: the role of human-specific and intelligence-related genes in learned vocal behaviour

(a) Human accelerated regions and vocal learning

Human accelerated regions (HARs) are segments of DNA that are conserved among our closest relatives but have undergone recent selection in humans [79,80]. HARs are identified by higher rates of single-nucleotide substitutions in the human lineage [81] or by segmental duplication and copy number variation [79]. HARs are typically found in non-coding regions of the genome. These areas are often poorly annotated yet likely regulate gene expression [82].

Among the approximately 3000 currently identified HARs with potential biological effects, a subset have been directly linked to brain development and function [83]. A popular method for validating the functional relevance of HARs to human-specific traits is to create transgenic reporter animals or cell lines and monitor how the human versus the chimpanzee region differentially regulates gene expression during development [82]. We tested for the presence of 10 highly validated HAR-related genes within juvenile and adult activity-dependent gene expression networks [9,10]. Eight were detected within juvenile Area X modules that were correlated to vocal learning (AUTS2, PTBP2, SRGAP2, NPAS3, CUX1, FZD8, GPC4, ARHGAP11A) and five were correlated to the modulation of song variability in juveniles as measured in the VI paradigm (NPAS3, CUX1) or to the amount of singing (i.e. the number of motifs sung on the day of the experiment) in adults (AUTS2, PTBP2, SRGAP2). We discuss the implications of these relationships for evolutionary neuroscience and developmental disorders of vocal communication for two of these, below.

(i) AUTS2

AUTS2 was among the shared set of genes upregulated throughout the songbird and human striatum detected by Pfenning *et al*. [3]. In the juvenile network that we identified [9], AUTS2 exhibited high module membership in the cyan song-related module (0.85; $p = 0.000005$). In humans, three unique intronic regions of Autism Susceptibility Candidate 2 (AUTS2) have undergone accelerated evolution [84,85]. Notably, in a scan for selective sweeps in humans versus Neanderthals, AUTS2 was within the region with the greatest significance, containing 293 consecutive single-nucleotide polymorphisms within non-coding regions throughout the first half of the gene [86]. Functionally, AUTS2 has been implicated in transcriptional repression [83] as well as regulation of neuritogenesis and neuronal migration [84]. Knockdown of AUTS2 in zebrafish leads to a reduced head size, reduced movement and a smaller number of midbrain neurons, suggesting that the human-specific evolutionary changes could be associated with expanded brain size [87].

AUTS2 was first identified in a pair of monozygotic twins concordant for autism [88]. Given that deficits in social communication are one of the three key diagnostic criteria that

define autism spectrum disorder, this indicates that AUTS2 may be important for social communication. In addition to autism, AUTS2 variants have been linked to information processing speed [89] and dyslexia [90], further suggesting a role in language-related processes. AUTS2 has also been linked to human intelligence [91]. Expression quantitative trait loci (eQTLs) are single-nucleotide variants that increase or decrease expression of a gene and are correlated to a trait (see §3b). Intelligence-related eQTLs in AUTS2 increase its expression as measured in whole blood, which is often used as a proxy for brain tissue [91,92]. In juveniles, AUTS2 was significantly correlated to the darkgrey Area X gene co-expression module that is enriched for human intelligence-related genes.

As noted above, birdsong is procedurally learned and associated with basal ganglia reward systems, so specializations of the underlying processes become of interest. AUTS2 is highly expressed in reward-related brain regions, including tyrosine hydroxylase-positive dopaminergic neurons of the substantia nigra and the ventral tegmental area [93]. Variants in AUTS2 are linked to alcohol consumption [94], and AUTS2 mRNA and protein levels decrease in the nucleus accumbens after chronic heroin administration [95], further supporting a link between the underlying genetics of reward and vocal learning.

(ii) SRGAP2

Another HAR gene with relevance to vocal learning is Slit-Robo Rho GTPase activating protein 2 (SRGAP2) [79]. The ancestral SRGAP2 gene has undergone three consecutive partial duplications in humans, resulting in paralogues SRGAP2 B, C and D. SRGAP2 B and D are RNA genes, whereas C encodes a human-specific truncated form of the ancestral protein that arose 2–3 Ma. The truncated form acts as a dominant negative to suppress the function of ancestral SRGAP2 [96–99]. The SLIT-ROBO pathway regulates axon guidance and neuronal migration [100]. Human mutations in SRGAP2 lead to intellectual disability and psychomotor delay [101]. SRGAP2 negatively regulates neuronal migration [102] and promotes dendritic and synaptic maturation [99,103]. The human-specific SRGAP2C inhibits the ancestral SRGAP2A to prolong the phase of spine development and retain a more plastic, neotenous neuronal phenotype [103].

The role of SLIT-ROBO signalling in vocal learning has been well characterized by Jarvis and co-workers [104]. SLIT1 is selectively downregulated in the primary motor cortex song control nucleus, known as RA, of vocal learning birds. RA neurons make direct projections onto tracheosyringeal motor neurons. Conversely, the SLIT1 receptor, ROBO1, is upregulated in RA during developmental critical periods for vocal learning [104]. In humans, SLIT1 is also downregulated in the primary motor cortex, specifically in a region that directly projects to laryngeal motor neurons, reinforcing the molecular and functional parallels of neural circuitry for vocal learning in both species.

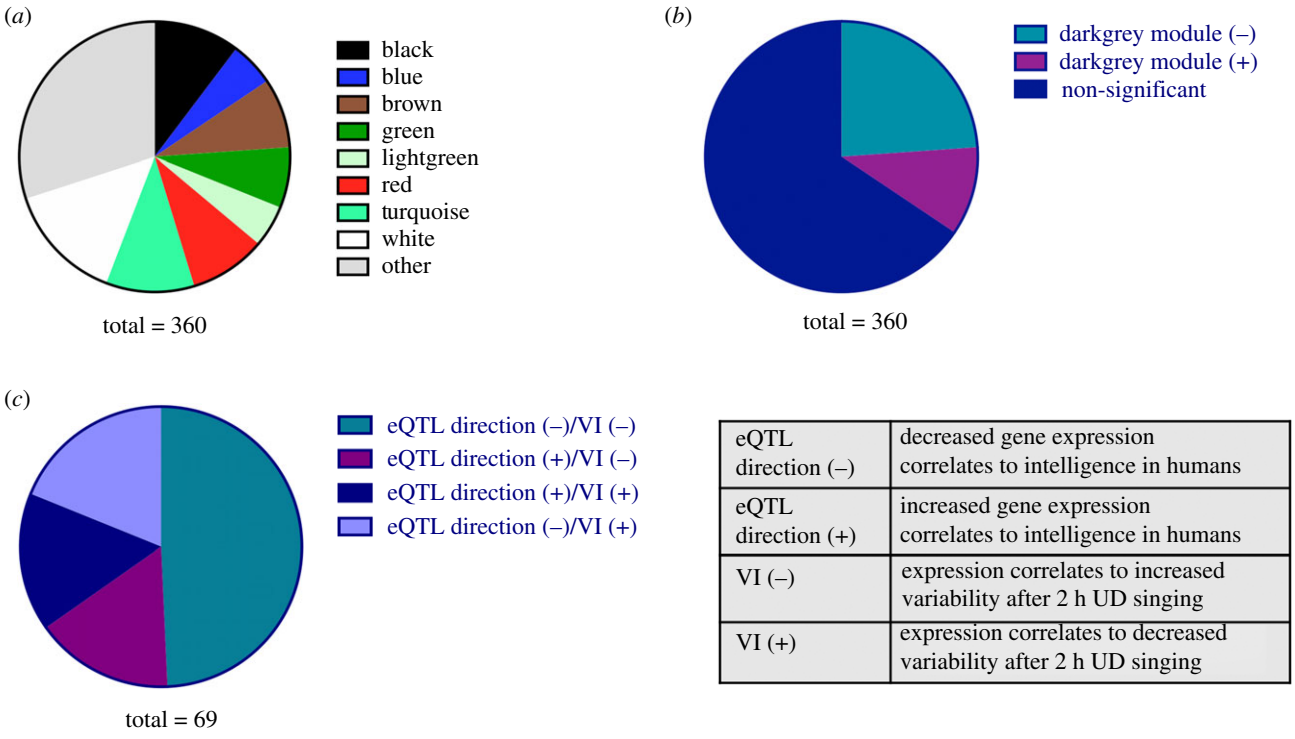
In the Area X gene co-expression networks, *SRGAP2* is downregulated during singing in adult birds [10]. Likewise, in juveniles, SRGAP2 levels are inversely correlated with the song- and learning-related modules. Although a truncated form has not been identified in songbirds, these observations suggest that singing-driven inhibition of SRGAP2 expression promotes learning-related plasticity mechanisms.

(b) Human intelligence-related genes and vocal learning

A meta-analysis of 2748 twin studies showed that human intelligence is a highly heritable trait [105], although a consensus about the theory, definition or model of human intelligence is currently lacking [106]. A subsequent meta-analysis of 269 867 individuals identified eQTLs in 1016 genes associated with intelligence, as determined by various measures operationalized to index a common latent *g* factor capturing multiple dimensions of cognitive functioning [91]. Expression quantitative trait loci (eQTLs) are single-nucleotide variants that alter the expression of a gene and are correlated to a phenotype. Notably, intelligence-related eQTL genes were most strongly expressed in medium spiny neurons, the major striatal cell type. Historically, studies of human cognition have focused primarily on cortical regions, but there is mounting interest in how the basal ganglia contribute to systems-level circuits for complex behaviour, like speech and language.

We examined the overlap between these 1016 intelligence-related genes and the 10 348 genes in the Area X juvenile vocal learning network. Among these 1016 intelligence-related genes, orthologues of 412 were found in our juvenile dataset [9]. The human genes include 360 variants in non-coding regions and 52 genes with non-synonymous variants in protein coding exons (electronic supplementary material, tables S2 and S3) [9,91]. We next looked for enrichment of human intelligence-related genes within specific modules [9]. Rather than a 'winner take all' approach where each gene is assigned to only one module, we included all genes significant for a module as determined by the false discovery rate-corrected *p*-value, *q*, on the grounds that a single gene can play an important role in multiple modules. One module, darkgrey, was significantly enriched for human intelligence-related genes as measured by a hypergeometric gene-set enrichment test ($p = 7.8 \times 10^{-3}$, R Gene Overlap package) (electronic supplementary material, figure S1) [107]. This was the only module correlated to overall song stability and one of several modules correlated with the morning modulation of song variability measured in the VI paradigm. As a control, we compared an equivalent number of brain-expressed chicken genes to this dataset and did not find any gene enrichment relationships, demonstrating that the association was not simply owing to using gene lists for brain-expressed genes [108].

To better understand the relationship between variability and human intelligence variants, we compared directional changes in the expression of the 860 intelligence-related gene eQTLs to directional expression changes in the 2064 genes correlated to juvenile song modulation. Based on the total distribution, we would expect to see 66% negatively correlated to variability, 34% positively correlated to variability and an even split for intelligence eQTL gene expression (figure 1*a*). Instead, we found a bias for downregulation of genes associated with greater variability after 2 h of undirected singing (χ^2 11.81, $p = 0.008$; figure 1*b*). This relationship was observed in the full dataset of 19 birds and preserved within a subset of three control birds [9]. As a control, we compared the same intelligence genes to an equivalent number of genes not correlated to variability. Broadly construed, these parallels suggest links between cognition and the modulation of vocal variability in both humans and songbirds.



eQTL direction (–)	decreased gene expression correlates to intelligence in humans
eQTL direction (+)	increased gene expression correlates to intelligence in humans
VI (–)	expression correlates to increased variability after 2 h UD singing
VI (+)	expression correlates to decreased variability after 2 h UD singing

Figure 1. Pie charts illustrate relationships between human intelligence eQTLs and songbird gene expression. (*a*) The expected distribution of overlap if there is no correlation between intelligence gene expression and genes underlying vocal variability in songbirds. (*b*) The observed correlation showing that, among directional gene expression changes correlated to intelligence, genes correlated to higher variability in songbirds are more likely to be downregulated in humans. (*c*) A control dataset showing a random distribution when using songbird genes with no correlation to vocal variability.

We interpret this to suggest that the ability to control variability is advantageous in the evolution of vocal learning. An athlete able to make very subtle modifications to their free throw is going to more precisely hone in and perfect their shot. This also suggests that functional validation of at least a subset of human intelligence genes could be carried out in songbirds using a vocal variability paradigm, particularly shared mechanisms in the basal ganglia.

Five intelligence-related genes that were related to prolonged stereotypy were also among the convergent genes in the songbird and human striatum: ARPP21, CACNA2D3, CACNA1E, FOXP1 and SMPD3. Below, we characterize three intelligence-related genes relevant for vocal learning.

(i) ARPP21

One intelligence-related gene selectively expressed in DA-innervated brain regions is cAMP-regulated phosphoprotein 21kD (ARPP21) [109]. Computational modelling suggests that ARPP21 and DARPP-32, both downstream effectors of cyclic AMP, work together to coordinate the timing of calcium and DA signal integration in medium spiny neurons of the basal ganglia [110]. Rehfeld *et al*. [111] recently demonstrated that ARPP21 is important for regulating dendrite formation: knockdown leads to reduced dendritic complexity, whereas complexity is enhanced by ARPP21 overexpression. ARPP21 works as an mRNA binding protein to interact with eukaryotic translational initiation factor eIF4F to positively regulate transcription.

Interestingly, one intron of ARPP21 includes miR-128, a brain-enriched microRNA previously implicated in procedural learning and memory [112,113] and neurodevelopment [114–116]. ARPP21 prevents miR-128-mediated repression of a subset of genes related to neural development, suggesting that the interplay between host gene and miRNA may be important for striatal function and cognition [111]. Molecular mechanisms that change over development are prime candidates for mechanisms that could be altered by heterochrony. Expression of miR-128 increases over pre- and post-natal development, peaking in adulthood [112,114–116]. This makes miR-128 and ARPP21 promising candidate mechanisms underlying the link between heterochrony and vocal learning.

Multiple lines of evidence suggest that ARPP21 and miR-128 are relevant for cognition in humans. Mutations affecting ARPP21 lead to intellectual disability [117,118], and miR-128 is aberrantly elevated in autism [119,120]. ARPP21 is convergently regulated in the songbird and human striatum, suggesting a role in vocal learning. In songbirds, higher expression of ARPP21 correlates to higher variability after 2 h of undirected singing in juveniles, and ARPP21 levels decrease with singing in adults. Human eQTLs related to intelligence are associated with downregulation of ARPP21, following the broader trend described in figure 1*c* [91].

(ii) BCL11A

Among the gene specializations exclusive to vocal-learners identified by Pfenning *et al*. [3], two were independently identified as human intelligence-related genes: BCL11A and PCDH17 [91]. BCL11A encodes B-Cell CLL/Lymphoma 11A, a zinc-finger transcription factor and a putative member of the BAF SWI/SNF chromatin-remodelling complex [121]. BCL11A is an intellectual disability gene associated with language delays, dysarthria and childhood apraxia of speech [121,122].

While loss of BCL11A is associated with severe speech and language deficits, BCL11A is upregulated in William's Syndrome (WS), a developmental disorder associated with low non-verbal intelligence yet strikingly enhanced verbal

fluency and speech production [123]. WS results from haploinsufficiency of approximately 25 genes on chromosome 7 including Williams Syndrome Transcription Factor, also known as BAZ1B [124]. The knockdown of BAZ1B during zebrafish development results in defects in neural crest migration and maintenance, a severe version of a milder phenotype posited to reflect a 'domestication syndrome' [68,69]. In this sense, BAZ1B may be connected to neural crest changes that occur during neotenization, and influence a subset of specialized traits including verbal fluency and sociality that are enhanced in WS patients.

Notably, BCL11A was among the most highly interconnected genes in a transcriptional network generated from peripheral blood from WS patients [123]. In the juvenile Area X, expression levels of BCL11A and BAZ1B positively correlate with levels of morning song modulation measured by the VI paradigm [9]. These parallels suggest links between the modulation of vocal variability and fluency in verbal production in both humans and songbirds.

4. On the horizon: key questions for future research

Over the past decades, exciting progress has been made in relating the previously separate fields of language evolution and birdsong. Below, we propose new horizons of investigation based on these insights of convergent evolution, with a focus on the implications of songbird neurogenomics to evolutionary medicine and developmental disorders of speech and language.

(a) Can songbird genes be used to drive discovery of novel syndromic intellectual disability genes?

With more than 1200 human intellectual disability genes identified in our juvenile gene expression dataset alone [9], it is increasingly apparent that convergent mechanisms govern vocal learning in songbirds and humans. Genes causing deficits in humans have been manipulated in songbirds to determine how they affect song, but could this approach also work both ways? We predict that in the future consortiums such as the undiagnosed diseases network [125] will capitalize on gene lists from the songbird model of vocal learning to pinpoint mutations in humans that could be validated for their causal effect.

(b) Can song-related gene expression modules be used to identify subtypes of autism?

Autism is a highly heterogeneous disorder that varies between affected individuals at every level of analysis—from underlying genetics to developmental trajectories [126–128]. New strategies are needed to identify subtypes of autism and accurately predict how a patient will respond to treatment. Lombardo *et al*. [129] have pioneered this approach by linking gene expression in songbirds and humans to early language outcome subgroups. They found that 902 of the 1267 differentially expressed genes that we identified in adult Area X [10] were present in their autism gene-related modules. Future work could use songbird gene expression data to identify shared modules of genes that can best be targeted for therapeutic intervention. For example, modules that persist in adulthood could be targeted directly, whereas critical period modules may require pharmacological restoration of critical period plasticity [130] to have an effect.

(c) Can songbirds model the negative symptoms of schizophrenia?

Neuropsychiatric disorders are highly polygenic, with autism and schizophrenia being particularly well correlated [131]. Given that the negative symptoms of schizophrenia centre on deficits in social expression and verbal communication, songbirds may offer novel ways to model schizophrenia and identify interventions to normalize symptoms.

5. Conclusion

Birdsong and human speech are highly convergent at multiple levels of analysis. A better understanding of the convergently evolved patterns of gene regulation that govern learned vocalization will accelerate progress towards deciphering the mechanistic basis for this complex behaviour. As we enter the era of songbird transgenics, we predict that the similarities between human and songbird will also yield the development of better animal models of disorders affecting communication [6], which can then generate breakthrough progress in translational research.

Data accessibility. The datasheets supporting this article have been uploaded as part of the electronic supplementary material.

Authors' contributions. S.A.W. participated in the initial workshop that led to the journal special edition. C.M.A., M.F.-V and S.A.W. conceived the scope of the manuscript. While all authors contributed to and edited the entire manuscript, M.F.-V. primarily wrote the introduction (§1) and §2; C.M.A. primarily wrote §§3–5 and contributed figure 1 in the main manuscript. M.F.-V. contributed electronic supplementary material, table S1. C.M.A. contributed electronic supplementary material, tables S2 and S3 and figures S1 and S2. S.A.W. integrated all author contributions.

Competing interests. We declare we have no competing interests.

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