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EVOLUTION AND DEVELOPMENT OF LANGUAGE

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BACKGROUND

Isolating causal relationships within dynamic biological systems is challenging. Research in the past few decades has increasingly recognized the importance of understanding normal developmental events, because they are often points of evolutionary change and therefore serve as guideposts in understanding human biology. Studies of human development have shown, for instance, that human brain growth (Leigh and Park 1998), physical stature (Bogin 1999), and neural maturation (Petanjek et al. 2011) differ from those patterns observed in our nonhuman primate relatives. These observations consistently point to discrete differences between human and nonhuman primate biology that may be important in identifying and treating developmental disorders and disease. Accordingly, recent research in neurobiology has taken advantage of molecular techniques and under an evo-devo paradigm has led to a more nuanced understanding of neurodevelopmental disorders, such as schizophrenia and autism spectrum disorder (ASD) (Harris et al. 2009; O'Hearn et al. 2008; Zikopoulos and Barbas 2010). This research has also contributed invaluable evidence detailing the developmental trajectory of the neurobiological substrates of linguistic behavior. Specifically, research in the past decade has revealed a number of genes, regulatory molecules, signaling pathways, and neural systems crucial to the normal development of language (Konopka et al. 2009; Lai et al. 2001; Newbury and Monaco 2010; Rilling et al. 2008). These multiple independent lines of evidence suggest that the linguistic

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phenotype may indeed depend upon biological and social processes that only converge in human development to produce language (Enard et al. 2002b; Konopka et al. 2009; Nishimura et al. 2003; Passingham 1981; Sherwood et al. 2008). Although we currently lack a conclusive empirical demonstration of this hypothesis, future research will address this issue.

Language is not easily defined, and although any rigid definition offered will meet staunch opposition, a few basic properties are evident. First, language is, on a fundamental level, simply a system of differentially related signs (Culler 1986). As such, it is possible that manual gesticulation facilitated the evolution of language, but this remains controversial (Corballis 2009c). Second, molecular interactions produce the muscular and cellular anatomy that constitutes our vocal apparatus as well as the nervous tissue that innervates this apparatus and determines the physiological properties of vocal behavior. Therefore, the linguistic phenotype evolved through the natural selection of ancestral conditions (Mayr 2001). However, the details of these and related processes are currently debated, and there is another tradition rooted in computational science that emphasizes the brain's capacity to produce seemingly unbounded sequences of novel linguistic signs and the subjectively unprecedented associations among them (Hauser et al. 2002). Interestingly, these views are not as incompatible as they may appear, and each would agree that language is a sophisticated system of signaling subject to the physiological properties of the motor system and the anatomical constraints upon our vocal/manual apparatus. Therefore, in order to understand the evolution of language, the primary challenge is to move beyond hypotheses rooted in the form of communication we know and utilize today toward those that examine the ancestral aspects of signaling behavior capable of navigating the requisite biological and ecological terrain that ultimately gave rise to contemporary language. Exciting new research addresses this challenge through comparative application of cutting-edge techniques, such as next-generation sequencing (NGS), to identify important nodes of the underlying circuitry and signaling cascades crucial to the linguistic phenotype.

One of the more important trends in the last decade of research into the evolution and development of language is the parcellation of language, or the linguistic phenotype, into tractable subdivisions. For example, vocal learning is not the same as auditory learning. Vocal learning is the capacity to generate modifications to the acoustic properties or sequential arrangement of sounds produced (Jarvis 2004). Auditory learning, on the other hand, is the ability to make associations with auditory stimuli. Vocal learning, as opposed to auditory learning, appears to incorporate imitation and improvisation, suggesting this behavior is a primary candidate ancestral condition of human language (Figure 9.1). Language is a complex system of communication, and the observation that vocal learners are far less common than auditory learners suggests vocal learning requires a discrete neural pathway. Recent comparative research has identified a motor circuit-mediating vocal behavior that involves nuclei throughout the brain and may be homologous between humans and birds (Figure 9.2) (Jarvis 2004; Wada et al. 2004). Put another way, it appears as though humans and some birds use a similar solution for acquiring novel vocalizations that hinges upon a series of neuronal populations involved in motor function. Although the evolutionary forces behind this convergent adaptive response are not completely understood, an attractive candidate explanation involves the expression of genes involved in the plasticity of spines and synapses (Mello et al. 2004), perhaps as a result of sexual selection modifying the developmentally regulated expression of these genes. Although we do not fully understand the details of this circuit, it provides (a) support for the hypothesis that language is a constellation of more basic functions, and (b) an animal model that

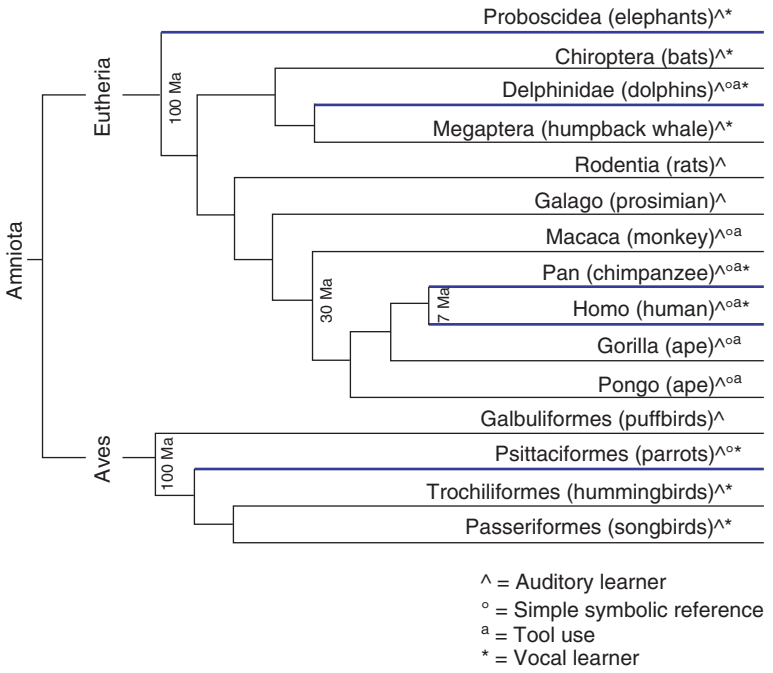

Figure 9.1. Phylogeny of candidate conditions in the evolution of language. Phylogenetic chart of select avian and mammalian taxa depicts the evolutionary history of possible candidate ancestral conditions to a language-like phenotype. The Latin name for genus is provided, followed by a common descriptor in parentheses. The avian (Johansson et al. 2008) and mammalian (Murphy et al. 2004) taxonomies are based upon DNA sequence data, and primate grouping is based on morphological as well as molecular data (Diogo and Wood 2011; Jameson et al. 2011). Illustrated taxonomic relationships are not exhaustive and are meant only to depict a simplified version of language evolution with regard to a few select species of interest. Candidate character states: ^ = auditory learner; ° = simple symbolic reference; a = tool use; * = vocal learner (Call and Tomasello 2007; Hopkins et al. 2007; Jarvis 2004; Peeters et al. 2009). Species of special interest are depicted with blue branches. It should be noted that most nonhuman primates are assumed not to be vocal learners; this is tentatively due to a lack of research in this area.

can be extensively tested at the behavioral and genomic level. This area of research will continue to be an exciting and productive source of information on the developmental constraints and biological processes crucial to a fundamental aspect of the linguistic phenotype—vocal learning. This line of research also holds great promise for understanding the regional recruitment of this circuit and its involvement in the suite of processes that ultimately facilitate human social cognition and language (Charvet and Striedter 2011; Deacon 2010).

The neural circuitry recruited in language spans numerous functional regions and involves a web of cortical and subcortical pathways (Lieberman 2002). Historically, the first evidence of language-specific brain regions came from the neurological reports of Paul Broca and Carl Wernicke, who identified areas involved in the production and comprehension of language, respectively. However, recent research has localized the neural activity related to human language to the inferior frontal operculum (including Broca's

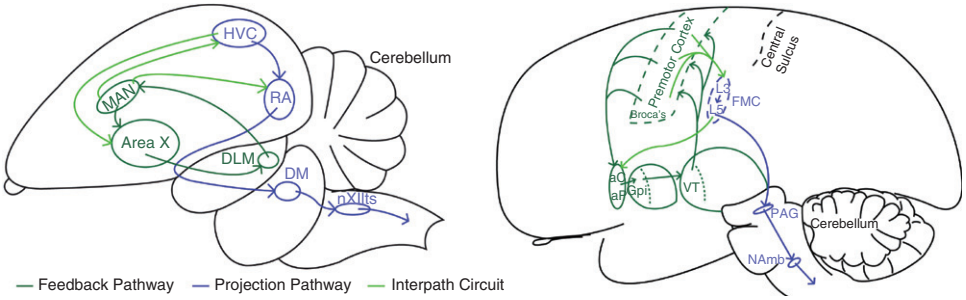

Figure 9.2. Neural circuitry of language evolution. Schematic in the sagittal plane of the circuitry underlying motor control of vocal behavior in an avian (left, songbird) and human (right) brain (based on Jarvis 2004; Jurgens 2002). Dashed lines depict cortical surface. Pathways depicted in the same color represent candidate convergent circuits underlying similar functions in these distantly related taxa. The blue path represents the posterior circuit in avian brains that may be homoplaseous with the efferent pyramidal tract of layer 5 pyramidal neurons in human facial motor cortex, here labeled the projection pathway. The dark green pathway represents the anterior path in avian brains that may be homoplaseous with the cortico-basal ganglia-thalamocortical pathway in humans. This circuit is labeled the feedback pathway because it is thought to constitute a similar feedback loop of cortical and subcortical motor processing in both species. The light green pathway, labeled the interpath circuit, depicts connections between the projection and feedback pathways, and may also be homoplaseous. Avian terminology: HVC, nidopallial vocal nucleus; RA, arcopallial vocal nucleus; DM, dorsal medial nucleus of the midbrain; xXIIts, tracheosyringeal subdivision of the hypoglossal nucleus; MAN, magnocellular nucleus of anterior nidopallium; Area X, area X of the striatum; DLM, medial nucleus of the dorsolateral thalamus. Human terminology: FMC, facial motor cortex; L3, layer 3; L5, layer 5; PAG, periaqueductal gray matter; NAmb, nucleus ambiguous; aC, anterior caudate nucleus; aP, anterior putamen; GPi, inferior globus pallidus; VT, ventral thalamus.

area, or the pars opercularis and triangularis) and the posterior perisylvian region (including the planum temporale, a subdivision of Wernicke's area) (Price 2010). The hypothesis that the human left neocortical hemisphere is functionally dominant in language was based upon Broca's work with lesion- or damage-induced aphasia(s), and has hence been related to anatomical asymmetry of the pars triangularis, pars opercularis, and the planum temporale. Studies of these regions in nonhuman primates have not found consistent asymmetries in vocal production pathways (inferior frontal operculum), but they have discovered that ape species exhibit population-level leftward asymmetry in the reception pathway (posterior perisylvian areas) (Cantalupo and Hopkins 2001; Cantalupo et al. 2009; Hopkins and Nir 2010; Jansen et al. 2010; Keller et al. 2007; Lyn et al. 2011; Schenker et al. 2010; Sherwood et al. 2003; Spocter et al. 2010). In addition, Rilling and colleagues (Rilling et al. 2008) did a comparative analysis of the arcuate fasciculus, an important fiber tract for vocal behavior because it connects these regions, and showed that this tract is more prominent in humans compared to chimpanzees and macaques. Interestingly, Sherwood et al. (2005) did not find hemispheric asymmetry in bats, another species with complex social vocalization (see Figure 9.1). Together, these observations suggest that hemispheric lateralization may not be directly tied to complex social vocal behavior (Keller et al. 2009). However, these studies do suggest a leftward lateralization of reception areas in ape species, further indicating that humans are unique in the leftward asymmetry of vocal

production structures and the enhanced overall connectivity of this circuit. It will be interesting to see in future studies, if other vocal learners, such as songbirds, have asymmetrical vocal reception or production pathways (Figure 9.1), and what molecular changes are involved. Together these observations indicate that humans may exhibit neuroanatomical specializations related to language, although this remains controversial as not all alternative explanations have been excluded (Corballis 2010; Keller et al. 2009).

GENES AND PATHWAYS

The molecular underpinnings of language remain mostly unknown. However, the sequencing of the human genome has permitted this area of research to blossom in the last decade. Three approaches have been utilized to provide insight into the molecular pathways underlying language. The first takes a comparative genomics approach to identify human-specific patterns of gene expression. The second assesses regional expression differences in the developing human brain. The third looks for causative genetic mutations in complex cognitive disorders with a language component. All three approaches have been successful in identifying both individual genes and signaling pathways that have likely played some role in the evolution of language.

The premise of comparative gene expression studies is that human-specific gene expression profiles should relate to human-specific functions such as language. The most informative of these studies compare gene expression in the brains of humans to that of our closest living genetic relative, the chimpanzee, and an additional primate out-group (e.g., macaque monkeys) to isolate expression changes specific to the human lineage. For the most part, these studies have only analyzed differences in single brain regions, likely due to the limited availability of nonpathological postmortem brain tissue. The microarray technology utilized to assess gene expression changes has also been limiting for nonhuman primate samples due to cross-hybridization issues of nonhuman primate samples on human microarrays (Preuss et al. 2004). Therefore, the advent NGS has been critical for this comparative genomics approach as NGS allows for unbiased inquiry into the transcriptome of any species (Konopka and Geschwind 2010). NGS allows not only for assessment of any species of interest, but also for identification of novel and alternatively spliced transcripts. Table 9.1 summarizes the findings of these comparative approaches using both microarrays and NGS (Babbitt et al. 2010; Brawand et al. 2011; Cáceres et al. 2003; Calarco et al. 2007; Enard et al. 2002a; Khaitovich et al. 2004, 2005; Lin et al. 2010; Liu et al. 2011; Marvanova et al. 2003; Somel et al. 2009; Uddin et al. 2004; Xu et al. 2010). The majority of these studies provide lists of human-specific patterns of gene expression, but the specific genes that are involved in language remain to be determined. More brain regions need to be assessed for human-specific profiles because there will likely be tissue- and region-specific expression differences. While those regions most relevant to language may be debatable, increased knowledge of gene expression in regions of interest would certainly be informative. Future technologies that accurately determine protein expression profiles also need to be harnessed for querying human-specific expression and posttranslational modifications.

Presumably, much of the structural groundwork for the neural systems responsible for cognition takes place *in utero* when neural specification and arealization occur (O'Leary and Sahara 2008). Therefore, developmental studies of the human brain may hope to uncover patterns of gene expression crucial to specializations such as language by illuminating the molecular dynamics that ultimately facilitate the functional specification of

TABLE 9.1. Comparative Genomics Studies in the Brain

Study	Brain Region	Species	Technology	Major Finding
Babbitt et al. (2010)	Frontal cortex	Human, chimpanzee, rhesus macaque	RNA-seq	Identification of conserved noncoding RNAs and differentially expressed genes under selection
Brawand et al. (2011)	Prefrontal cortex, cerebellum	Human, chimpanzee, gorilla, oranguatn, macaque	RNA-seq	Brain evolved more slowly than other tissues in amniotes
Cáceres et al. (2003)	Mixed cortical areas	Human, chimpanzee, rhesus macaque	Microarrays	Increased gene expression specifically in human brain
Calarco et al. (2007)	Frontal pole	Human, chimpanzee, rhesus macaque	Microarrays	Identification of alternatively spliced genes between humans and chimps
Enard et al. (2002)	Cortex (Brodman area 9)	Human, chimpanzee, orangutan	Microarrays	Increased changes in human brain gene expression compared to other tissues
Khaitovich et al. (2004)	Four cortical areas, caudate nucleus, cerebellum	Human, chimpanzee	Microarrays	Human–chimpanzee expression differences are similar across brain regions
Khaitovich et al. (2005)	Prefrontal cortex	Human, chimpanzee	Microarrays	Increased changes in human brain gene expression compared to other tissues
Lin et al. (2010)	Cerebellum	Human, chimpanzee, rhesus macaque	RNA-seq, microarrays	Over 500 genes alternatively spliced among the species
Liu et al. (2011)	Cerebellum	Human, chimpanzee, rhesus macaque	RNA-seq, microarrays	Platform comparison study demonstrating increased sensitivity using RNA-seq
Marvanova et al. (2003)	Prefrontal cortex	Human, chimpanzee, cynomolgous macaque, marmoset, orangutan	Microarrays	Validate the use of microarrays for comparative brain gene expression
Somel et al. (2009)	Dorsolateral prefrontal cortex, superior frontal gyrus, caudate nucleus	Human, chimpanzee, rhesus macaque	Microarrays	The timing of human gene expression is delayed compared to other primates
Uddin et al. (2004)	Anterior cingulate cortex	Human, chimpanzee, gorilla, rhesus macaque	Microarrays	Human is more similar to chimpanzee than to gorilla
Xu et al. (2010)	Cerebellum	Human, chimpanzee, rhesus macaque	RNA-seq	Identification of conserved intergenic transcripts

neuronal populations. One particular area of interest has been the search for differential gene expression between language-associated brain regions (see previous discussion) or hemispheric lateralization effects (Corballis 2009b). The anatomical localization of language to the left hemisphere has been attributed to potential asymmetry at numerous levels between the two cortical hemispheres (Galaburda et al. 1978) but remains controversial (Keller et al. 2009). Despite this controversy, one could *a priori* expect differences at the level of gene expression in each hemisphere based upon physiological recruitment differences (Friederici 2011). However, whole brain studies find few differentially expressed genes. An initial study identified 27 genes with differential expression between left and right hemispheres at around 12–14 weeks gestation, but these differences diminished by 19 weeks gestation (Sun et al. 2005). Additional studies using 18- to 23-week-old (Johnson et al. 2009) and 17- to 19-week-old (Lambert et al. 2011) human brains did not find any statistically significant differences. One explanation for these results is that hemispheric transcriptional regulation occurs early in development, and additional effects such as post-translational modifications may occur later in development. In contrast, region-specific expression studies in the developing human brain have uncovered numerous patterns of differential gene expression throughout midgestation (Abrahams et al. 2007; Johnson et al. 2009; Lambert et al. 2011). Thus, at the genomic level, differential expression between brain areas may be a bigger contributor to language development than differences between hemispheres.

Association of a gene or genes with language through causative mutations should provide direct evidence for the role of specific signaling pathways in language (see Table 9.2). Therefore, a major inroad into understanding the molecular basis for language was made upon the identification of a mutation in the gene for *FOXP2* in a large multigenerational family with verbal dyspraxia (Lai et al. 2001). Subsequent studies confirmed additional individuals with mutations or deletions in *FOXP2* concurrent with speech and language deficits (Feuk et al. 2006; Lennon et al. 2007; MacDermot et al. 2005; Shriberg et al. 2006; Zeesman et al. 2006). The study of FOXP2 within the framework of language signaling pathways is made more compelling by virtue of (1) its function as a transcription factor (Lai et al. 2001), (2) its peak expression in human fetal brain occurring during midgestation (Kang et al. 2011; Teramitsu et al. 2004), and (3) the molecular evolution of *FOXP2* which suggests that the human form of *FOXP2* may have acquired unique properties (Enard et al. 2002b; Zhang et al. 2002).

Functional studies of FOXP2 have yielded compelling results to support a role for FOXP2 in the evolution of molecular signaling networks for language and the corticofrontal-striatal circuitry underlying vocalizations. Human-specific transcriptional targets of FOXP2 are enriched for genes that are important in nervous system development (Konopka et al. 2009). Moreover, there is significant overlap with human-specific FOXP2 targets and genes differentially expressed in human and chimpanzee brain tissue (Konopka et al. 2009). Many of the genes differentially expressed between human and chimpanzee FOXP2 form a network of gene coexpression (Figure 9.3). This network is independent of one containing FOXP2 itself as well as the shared targets of human and chimpanzee FOXP2 (Konopka et al. 2009). These data highlight the unique and conserved transcriptional targets of human FOXP2. Further evidence for a dual role for FOXP2 in brain evolution comes from animal model studies. While mice and zebra finches with reduced *FoxP2* levels have disrupted ultrasonic vocalizations (USVs) and learned song, respectively (Haesler et al. 2007; Shu et al. 2005), mice with knock-in of human *FOXP2* display abnormal USVs (Enard et al. 2009). Together, these data suggest that FOXP2 regulates a transcriptional network that not only contains many conserved transcriptional targets that

TABLE 9.2. Genes Implicated in Language

Gene	Evidence	Reference
ATP2C2	Linkage analysis in SLI	Falcaro et al. (2008), Newbury and Monaco (2010), SLI Consortium (SLIC) (2004)
CFTR	Linkage analysis in SLI	Bartlett et al. (2004); O'Brien et al. (2003)
CMIP	Linkage analysis in SLI	Falcaro et al. (2008); Newbury and Monaco (2010); SLI Consortium (SLIC) (2004)
CNTNAP2	Associated with age at first word	Alarcon et al. (2005)
	Variants associated with autism	Alarcon et al. (2008); Arking et al. (2008); Bakkaloglu et al. (2008); Poot et al. (2010)
	Frontal/anterior cortex enrichment	Abrahams et al. (2007)
	Regulated by FOXP2	Vernes et al. (2008)
	Knockout mice have decreased ultrasonic vocalizations	Penagarikano et al. (2011)
FOXP1	Mutations associated with language deficits and/or autism	Carr et al. (2010); Hamdan et al. (2010); Horn et al. (2010); O'Roak et al. (2011)
	Overlapping expression with FOXP2	Ferland et al. (2003); Teramitsu et al. (2004)
	Physically interacts with FOXP2 to regulate gene expression	Li et al. (2004)
FOXP2	Mutations in patients with verbal dyspraxia	Lai et al. (2001); Lennon et al. (2007); MacDermot et al. (2005); Shriberg et al. (2006); Zeesman et al. (2006)
	Mutations/association in patients with autism spectrum disorders	Feuk et al. (2006); Laroche et al. (2008); Li et al. (2005)
	Association in patients with schizophrenia	Sanjuan et al. (2006); Tolosa et al. (2010)
	Human gene underwent accelerated evolution	Enard et al. (2002); Zhang et al. (2002)
	Knockout mouse has reduced ultrasonic vocalizations	Shu et al. (2005)
	Knockdown in songbird leads to altered song	Haesler et al. (2007)
	Humanized mouse has altered ultrasonic vocalizations	Enard et al. (2009)
	Human form has unique transcriptional activity	Konopka et al. (2009)
MET	Variants associated with autism	Campbell et al. (2008); Jackson et al. (2009); Sousa et al. (2009)
	Focally expressed in the temporal lobe in developing human brain	Mukamel et al. (2011)
	Regulated by FOXP2	Mukamel et al. (2011)
SRPX2	Associated with developmental verbal dyspraxia	Roll et al. (2006)
	Regulated by FOXP2	Roll et al. (2006)

are likely involved in vocalization circuitry, but also has unique target elements in human brain that may be important for language. Therefore, FOXP2 should not solely be considered as a regulator of the molecular machinery utilized for language, but rather as an orchestrator of signaling pathways required for complex motor movements that have been adapted in humans for language.

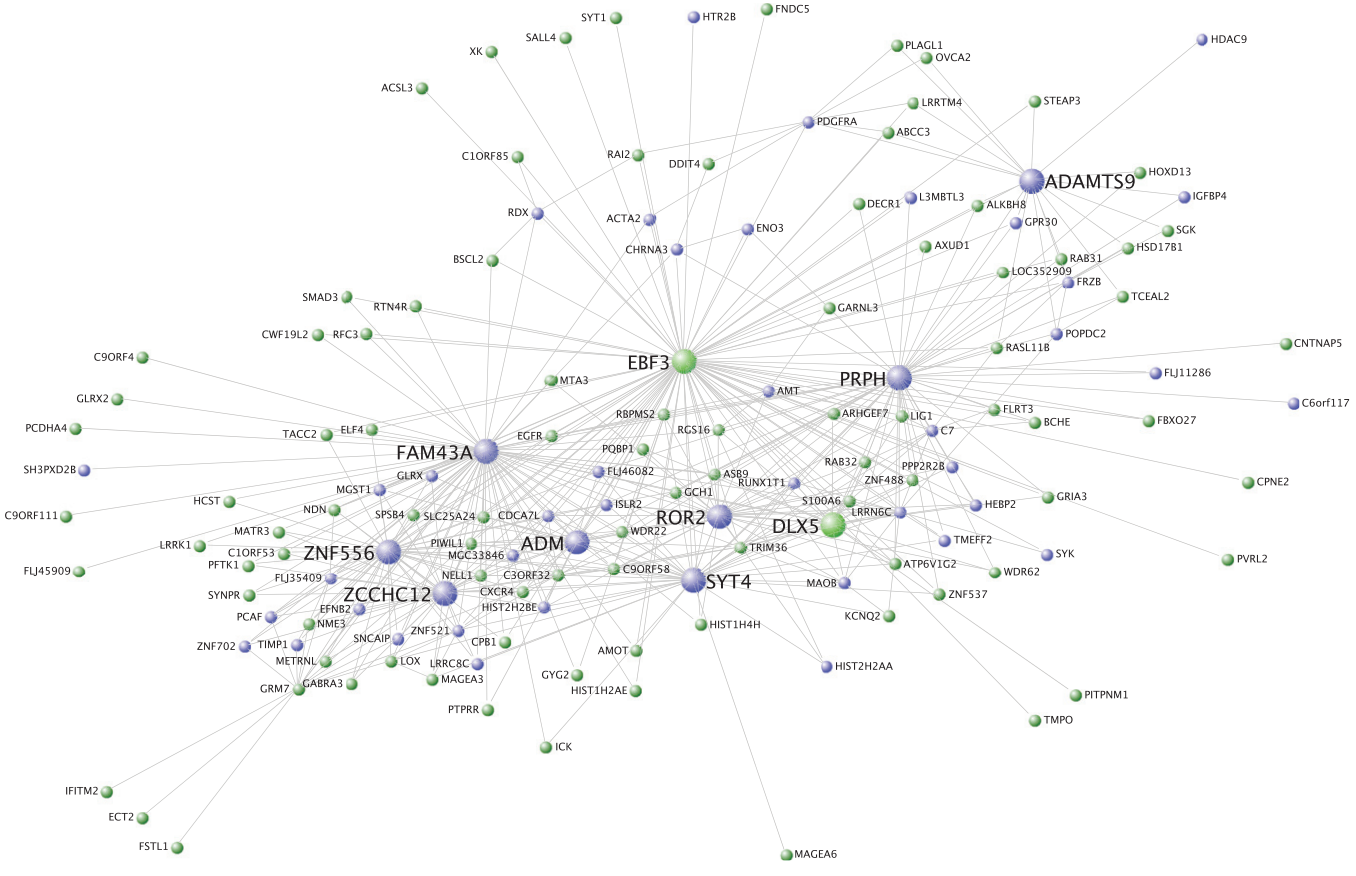

Figure 9.3. Example of coexpression network for genes differentially regulated by human and chimpanzee FOXP2. Visualization of coexpressed genes from neuronal cells expressing either the human or chimpanzee form of FOXP2. Differentially expressed genes are depicted in purple whereas hub genes, or the most connected genes, are depicted using larger circles. Adapted from Konopka et al. (2009).

FOXP2 appears to be central to the molecular circuitry of language as two other genes with strong association with language, *FOXP1* and *CNTNAP2*, both have relationships with *FOXP2*. FOXP1 is highly homologous to FOXP2 and can heterodimerize with FOXP2 to regulate gene expression (S. Li et al. 2004). In addition, FOXP1 has some overlapping expression patterns with FOXP2 in the human brain (Ferland et al. 2003; Teramitsu et al. 2004). Several studies have identified individuals with either deletions or mutations in *FOXP1* and speech and language deficits; however, most of these cases are complicated by comorbidity with intellectual disability or autism (Carr et al. 2010; Hamdan et al. 2010; Horn et al. 2010; O'Roak et al. 2011). As will be discussed later, since language impairment is a key facet of disorders such as autism, untangling the genomic architecture of the language component in these diseases will be challenging.

CNTNAP2 fits all three approaches for uncovering the molecular underpinnings of language. *CNTNAP2* has enriched expression in anterior cortical areas, and this enrichment is not seen in rodent brain (Abrahams et al. 2007). Its expression also appears to be associated with vocalization and expression in related song nuclei in zebra finch (Panaitof et al. 2010). Mutations in *CNTNAP2* are associated with epilepsy and intellectual disability, including language abnormalities (Strauss et al. 2006), specific language impairment (SLI) (Vernes et al. 2008), and similar to *FOXP1*, variants in *CNTNAP2* are also associated with autism (Alarcon et al. 2008; Arking et al. 2008; Bakkaloglu et al. 2008; Poot et al. 2010). Furthermore, knockout mice for *Cntnap2* have reduced ultrasonic vocalizations (Penagarikano et al. 2011). Interestingly, variants in *CNTNAP2* have been linked to frontal lobe connectivity (Scott-Van Zeeland et al. 2010). These data fit well with the anterior enrichment of *CNTNAP2* in human brain as the anterior frontal pole is an area of recent evolutionary importance for cognition (Semendeferi et al. 2011). Finally, *CNTNAP2* appears to be a directly repressed target of FOXP2 (Vernes et al. 2008). *CNTNAP2* may not be the only target of FOXP2 that is associated with cognition and language, as FOXP2 can also regulate expression of *MET*, an autism gene with focal expression in human temporal lobe (Figure 9.4) (Z. Mukamel et al. 2011), and *SRPX2*, a gene involved in epilepsy and developmental verbal dyspraxia (DVD) (Roll et al. 2010). Thus, FOXP2 appears to be central to the molecular signaling pathways underlying language. In addition, FOXP2 expression is enriched in frontal cortex and perisylvian areas in the developing human brain (Johnson et al. 2009), suggesting that FOXP2 target gene regulation during human brain development was critical for the evolution of language.

LIFE HISTORY

Comparative studies suggest that numerous biological processes have undergone substantial developmental modification in human evolution. The molecular mechanisms underlying the neural circuitry recruited during language are prime candidates for research into the possibility that these observations apply to human language. As an example, consider that the size of the adult human brain is achieved by maintaining the third trimester gestational brain mass growth rate through the first year of life (Leigh 2004). Since we know that brain organization changes as brain size increases, we are confronted with a need to explain how the threefold size difference between human (~1350 cc) and chimpanzee (~400 cc) brains is reflected in their organization. Additional work indicates that gene expression patterns related to postnatal development of the prefrontal cortex (PFC) are delayed in humans compared to chimpanzees and macaque monkeys (Somel et al. 2009). Furthermore, postmortem studies indicate the ancestral developmental trajectory

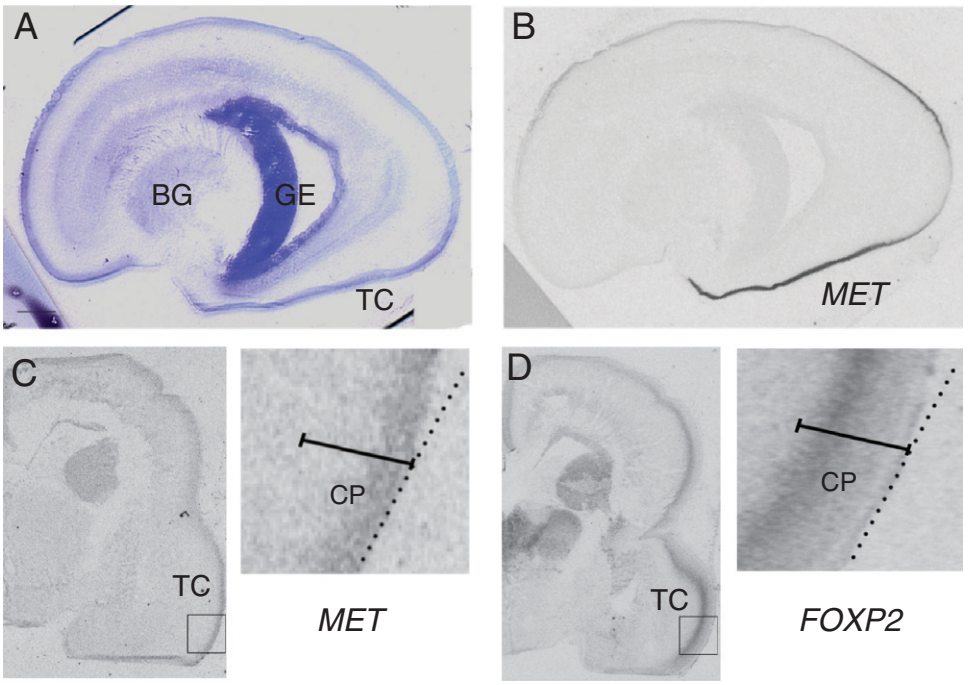

Figure 9.4. Inverse expression of *FOXP2* and *MET* in the developing human brain. (A) Cresyl violet staining of sagittal section from human fetal brain (20 gestational weeks). (B) *In situ* hybridization showing focal enrichment of *MET* in the temporal cortex. (C and D) *In situ* hybridization of coronal sections of human fetal brain (19 gestational weeks) showing inverse expression of *MET* and *FOXP2* in the cortical plate (magnified insets) within the temporal cortex. BG, basal ganglia; GE, ganglionic eminence; TC, temporal cortex; CP, cortical plate. Modified with permission from Z. Mukamel et al. (2011).

of synapse maturation (Huttenlocher and Dabholkar 1997; Petanjek et al. 2011), and axon myelination (Gibson 1970; Yakovlev and Lecours 1967) is prolonged in humans compared to our closest living relatives (Figure 9.5) (Miller et al. 2012). The PFC is an important node for a variety of behaviors, including language, and the processes of synaptic and axonal maturation are responsive to function-related activity, suggesting that the developing human brain may differentially respond to social learning, of language for example, in these closely related species (Defelipe et al. 2010; Fields 2010; Ishibashi et al. 2006; Llorens et al. 2011; Stevens et al. 2002; Wake et al. 2011). Together, these observations indicate that a marked delay in the developmental schedule of the human brain may play an important role in the differentiation of regions and growth of connections that contribute to human-specific cognition and language. Illustrating the molecular basis of these changes is therefore crucial to furthering our understanding of the evolution and development of language.

The most salient differences between humans and other primates are tool use and language (McComb and Semple 2005; Peeters et al. 2009). Tool use and manufacture take chimpanzees a long time to learn (Boesch and Boesch 1990), and may be determined by rule-learning biases that differ among life history stages and species (Crain 1991; Poulin-Dubois et al. 2009; Tomasello et al. 2005). Intriguingly, although great apes are capable

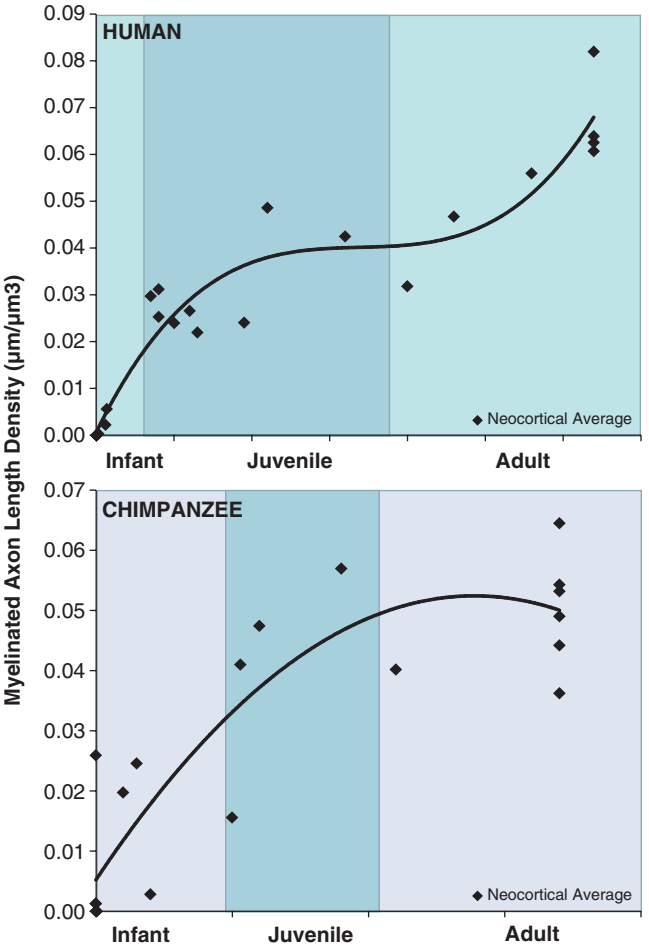

Figure 9.5. Myelin: an example of evolutionary change via development. Best fit curves for data in humans (top, cubic, n = 24) and chimpanzees (bottom, quadratic, n = 20) arranged by life history stage (horizontal axis). The vertical axis depicts myelinated fiber length density per unit volume ($\mu m/\mu m^3$). All points represent average neocortical myelinated fiber length density for a single individual. Vertical shaded area depicts developmental period between species-typical age at weaning and sexual maturation. Adapted from Miller et al. (2012).

of learning aspects of language, such as syntax and symbolic reference, this process takes longer than in humans and may also be more easily mastered at a young age (Lyn et al. 2011; Savage-Rumbaugh et al. 1988). These observations suggest that altering the developmental time point at which an individual is exposed to complex communication systems, such as language and its precursors, may directly impact their facility with that system. An attractive candidate mechanism for this process is modification to the developmental time course of spine and synapse pruning in the motor system underlying vocal learning and gesticulation. Indeed, mirror neurons and gestural communication may be an important aspect of the hypothesized gradual exaptation of cortical and subcortical motor circuitry in the evolution of language (Aboitiz and Garcia 2009; Arbib et al. 2008; Corballis 2009a, 2010; Rizzolatti and Arbib 1998). Recent molecular research supports these hypothesized mechanisms by demonstrating that mutations affecting these

motor pathways, such as in *FOXP2* (Reimers-Kipping et al. 2011), produce verbal dyspraxia in humans (Lai et al. 2001) and altered vocalizations in other animals (Enard et al. 2009; Haesler et al. 2007). However, language depends upon multiple constituent abilities such as imitation, vocal learning, joint attention, and theory of mind (Kuhl 1994; Sherwood et al. 2008; Subiaul 2010; Tomasello et al. 1997, 2005). Therefore, it is possible that language and tool use arise from a common constellation of behaviors that placed selective pressure upon the developmental trajectory of the brain and the molecular structure of the relevant pathways. Furthermore, similar selective pressures could act upon a subset of these processes to produce the hypothesized parallel evolution of distinct aspects of the linguistic phenotype in other species, such as songbirds. Brain growth and maturation may thus intersect in novel ways with behavioral strategies to produce adaptive solutions to biological and ecological challenge. Unfortunately, mutations that modify the molecular dynamics of developing circuitry can have profoundly deleterious consequences, and the evolution of specializations such as language may involve unanticipated risks for developmental and neuropsychiatric disorders. Future studies, particularly ongoing work with avian and primate species using NGS and transgenic approaches, are in prime position to investigate these fundamental questions about cognition, behavior, and disease.

DISORDERS OF LANGUAGE

One of the potential consequences of the evolution of neural specializations such as language is the emergence of neurodevelopmental and neurodegenerative disorders. Disruption of language frequently occurs in neurodevelopmental disorders, including, but not limited to, SLI, autism, and schizophrenia. Emerging evidence suggests that all of these disorders share some overlapping causal mechanisms including both the genes and brain structures involved. Identifying these unique and common etiologies are an important first step for reconciling disrupted structure with abnormal function, as phenotypes for these diseases range from fairly normal language function (high-functioning autism), to isolated issues in syntax and/or phonology (SLI), to disordered speech (schizophrenia), or a complete absence of language (autism).

SLI is a common developmental disorder affecting approximately 7% of school-age children (Tomblin et al. 1997). SLI encompasses generalized difficulties in language that can be defined by specific clinical measures. SLI is thought to be genetic in origin with a complex genetic architecture (Bishop 2002), and a number of genes have been shown to have strong association with SLI including *CFTR* (Bartlett et al. 2004; O'Brien et al. 2003), *CNTNAP2* (Vernes et al. 2008), *ATP2C2*, and *CMIP* (Falcaro et al. 2008; Newbury et al. 2010; Newbury and Monaco 2010; SLI Consortium (SLIC) 2004). The finding associating *CNTNAP2* with a specific endophenotype of SLI, nonword repetition defects (Vernes et al. 2008), is particularly compelling because it points to a possible convergence of molecular pathways for SLI and ASD. This fits with the regulation of *CNTNAP2* by FOXP2 as some individuals with *FOXP2* mutations have language deficits but not ASD (e.g., members of the KE family) (Vargha-Khadem et al. 1995). Thus, in some instances, dysfunction of *CNTNAP2* downstream of FOXP2 leads to ASD, and in other instances, it leads to SLI. This divergence is likely due to interaction with other factors, whether they be genetic, epigenetic, or environmental. One of the challenges in uncovering the etiology of SLI is that it likely encompasses a constellation of language phenotypes that are all currently being classified into one disorder (Bishop 2009). Thus, more sensitive phenotyping combined with whole genome sequencing may lead to the identification of additional molecular pathways that underlie language disorders.

Perhaps the most well-studied disorder with a language component is autism. One of the defining hallmarks of autism, or the more broadly categorized ASD, is the disruption of language and communication (Geschwind 2011). Thus, all autistic individuals by definition have some form of language impairment, with the exception, on one end of the spectrum, of high-functioning individuals. Therefore, taking this spectrum of phenotypes into account, language impairment in ASD ranges from fairly normal language to a complete absence of language.

Although the etiology of ASD is still unknown, there is clearly a strong genetic component. While a few rare single gene mutations are associated with ASD, the majority of patients likely have a complex genetic architecture with combinations of common and copy number variants that lead to disease (Geschwind 2011). Even given this seemingly complex genetic etiology, the disorder appears to emerge from a convergence of molecular signaling pathways involved in nervous system development (Bill and Geschwind 2009). One obvious pathway to investigate, given its role in speech and language, is the signaling hierarchy regulated by *FOXP2*. Variants in *FOXP2* itself have been investigated for direct association to ASD. However, while a few studies found some evidence for *FOXP2* variants in ASD (Feuk et al. 2006; Laroche et al. 2008; H. Li et al. 2005), the majority of these studies did not uncover a significant link (Gauthier et al. 2003; Gong et al. 2004; Marui et al. 2005; Newbury et al. 2002; Wassink et al. 2002). In contrast, targets of FOXP2 have been directly linked to ASD. Genome-wide searches have uncovered a number of ASD-associated genes downstream of *FOXP2* (Konopka et al. 2009; Spiteri et al. 2007). In addition, more detailed analyses have described FOXP2 regulation of two candidate ASD genes, *CNTNAP2* (Vernes et al. 2008) and *MET* (Z. Mukamel et al. 2011). Finally, as mentioned earlier, the related transcription factor FOXP1 appears to be directly related to ASD (Hamdan et al. 2010; O'Roak et al. 2011). Thus, due to the diagnostic requirement of language impairment in ASD, it is difficult to tease apart the relative contribution of a specific gene to a particular phenotype, whether the dysfunction is specific to language or more general dysfunction.

Although schizophrenia is a well-established neurodevelopmental disorder (Rapoport et al. 2005), symptoms do not typically manifest until early adulthood (van Os and Kapur 2009). Symptoms can be positive (delusions, hallucinations, etc.) or negative (ahedonia, catatonia, etc), and can include general cognitive defects (van Os and Kapur 2009). Of particular interest, patients with schizophrenia exhibit abnormal speech and language. This deficit is thought to derive from a general disruption of higher cognitive processes and may indicate an underlying defect in cerebral cortex asymmetry (Crow 1997; X. Li et al. 2009; Morice and Igram 1983). Due to the incidence of language impairment in schizophrenia, several groups have looked for association of *FOXP2* with schizophrenia. While a number of genetic association studies did not find that *FOXP2* correlates with disease (Laroche et al. 2008; Sanjuan et al. 2005), at least two studies have found positive association of polymorphisms in *FOXP2* with schizophrenia (Sanjuan et al. 2006; Tolosa et al. 2010). However, because individuals with *FOXP2* mutations or deletions do not have symptoms consistent with schizophrenia, direct disruption of *FOXP2* is not likely to be a major contributing factor. A possible role for *FOXP2* in schizophrenia is in the disruption of the expression or regulation of FOXP2 target genes. In line with this, a number of known schizophrenia candidate genes have been identified downstream of FOXP2 through either promoter binding studies (Spiteri et al. 2007) or gene expression studies (Konopka et al. 2009).

Interestingly, ASD and schizophrenia appear to have many overlapping features. Both ASD and schizophrenia are considered complex genetic disorders that manifest due to

multigenic insults. Many of the chromosomal loci, copy number variations, and candidate genes are overlapping in the two disorders (Cook and Scherer 2008; Crespi et al. 2009; Mefford and Eichler 2009). On a cognitive level, patients with either ASD or schizophrenia display disruptions to frontal-striatal circuitry (Pantelis et al. 1997; Takarae et al. 2007) and exhibit defects in frontal executive functions (Barch 2005; O'Hearn et al. 2008). Neuroanatomical correlates of these and other cognitive deficits may be due to pathology in the dorsolateral PFC, temporal lobe, cerebellum, and white matter tracts (Andreasen and Pierson 2008; Barch 2005; Courchesne et al. 2007; Goldberg et al. 2002; Lawrie et al. 2008; White et al. 2008). Thus, the genetics, molecular biology, anatomy, and cognitive defects in both schizophrenia and ASD provide converging evidence for disruption of the neural circuitry underlying language.

A significant difficulty in understanding complex disease etiology derives from the incompletely understood evolutionary history of the anatomical, chemical, and molecular organization of the differentially expanding cortical regions of the human brain. One hypothesis suggests that ASD and schizophrenia are disorders on either end of the same spectrum: schizophrenia is the "overdeveloped" and autism is the "underdeveloped" social brain (Crespi and Badcock 2008). An additional hypothesis draws upon potential imbalance in the ratio of excitatory and inhibitory neurons within the circuit (Rubenstein 2010; Yizhar et al. 2011). Mutations in the regulatory mechanisms acting upon the growth and development of language-related circuits in the course of human evolution, such as the effect of gene expression on the corticofrontal-striatal system, provide opportunities to test these hypotheses in an effort to better understand how language emerges from neural circuitry, evolved in phylogenetically distantly related organisms, and mediates normal human social behavior. A future challenge will be to determine how developmental insults to the same pathways result in quite different disorder phenotypes.

FUTURE DIRECTIONS

Unraveling the origins of a uniquely human feature such as language may never be fully realized due to the practical difficulties of conducting many types of experimentation in humans. However, several technical breakthroughs may bring us closer to a more complete picture of the molecules and circuitry underlying language. As discussed earlier, one of the most important technological advances that will assist in ascertaining this goal is the availability of NGS. This platform has assisted in sequencing the genome, exomes, and transcriptomes of numerous species and tissues (Konopka 2010). As NGS becomes less expensive and we enter the era of personalized genomics, whole genome sequencing of cohorts of patients with language dysfunction including SLI, autism, and schizophrenia will identify more genes directly associated with language function.

One application of NGS that may provide insight into the evolution of language is the examination of extinct hominid genomes. Both the Neandertal and "Denisovan" genomes have been sequenced using NGS (R. E. Green et al. 2010; Reich et al. 2010). Since it is likely that we will only ever be able to examine DNA and not gene expression or regulation from these rare bone samples, insight into cognitive processes will be limiting. Even examination of one "language gene" such as *FOXP2* has led to inconclusive results. The finding that the sequence of *FOXP2* in the Neandertal genome is the same as that of human suggested either that the change in the two amino acids that differ between human and chimpanzee occurred before the common ancestor of Neandertals and humans, or that there was admixture between humans and Neandertals (Coop et al. 2008; Krause

et al. 2007). Interestingly, recent data support admixture between archaic humans and Denisovans (Abi-Rached et al. 2011). Regardless of which conclusion regarding *FOXP2* sequence is "correct," it will still remain unknown whether Neandertals had language *per se*. In addition, *FOXP2* is one of the rare examples of a gene where changes at the genomic level have led to a coding change with known functional implications along the human lineage. Most other important evolutionary changes at the molecular level are likely in the form of gene regulation or expression (King and Wilson 1975). Finally, no one would argue that the presence of one form of one gene would lead to the emergence of language. As discussed in this chapter, many factors and developmental processes need to come into play simultaneously. In particular, the substantial role of the environment on language acquisition and development need to always be considered (Hayiou-Thomas et al. 2012). It is, however, interesting that the majority of known genes linked to language are also associated with *FOXP2* (Table 9.2).

To address the developmental and conserved aspects of language, animal models with alterations in vocalization-related circuitry will prove extremely informative. These studies are currently being done in mice by either traditional knockout technology as in the case of *Foxp2* (Shu et al. 2005) or *Cntnap2* (Penagarikano et al. 2011), and also by "humanizing" the mice by replacing a mouse gene with the corresponding human gene such as *FOXP2* (Enard et al. 2009). In particular, detailed examination of gene expression changes in animal models like these will provide insight into the broader framework of molecules involved in vocalization. In addition to conducting these genomic studies, data analyses that appreciate the inherent underlying structure of functional genomics need to be applied. For example, weighted gene coexpression network analysis (WGCNA) can uncover novel relationships among genes and permit prioritization of the genes most likely to be important in the process being studied (see Figure 9.3) (Geschwind and Konopka 2009).

Combining transcriptomic approaches with transgenic/optogenetic studies in more closely related model systems such as monkeys should prove very valuable for connecting genes to circuitry to behavior (Figure 9.6). To date, transgenic rhesus macaques have been generated (Chan et al. 2001; Sasaki et al. 2009) and viral approaches in monkeys have also been used for gene therapy (Mancuso et al. 2009). These approaches have been utilized to model human disease in a system more closely related to the human brain than the typical lab model, the mouse (Yang et al. 2008), and could be adapted for investigating language-related pathways if specific molecular, neuroanatomical, or behavioral correlates can be identified. Integration of optogenetics (Deisseroth 2011) into songbird or monkey studies will allow for cell-specific and conditional, developmentally timed manipulation of neural circuits. Thus, one will be able to directly assess the impact of altered neural circuitry on vocalizations and/or other conserved forms of sensory-motor integration in real time. Of course, all of these studies still await the discovery of additional genes from human patients as well as the identification of the critical cells and regional tissues that are functionally homologous to those in human brain. Therefore, future studies on the evolution of language will not only depend upon the most recent genomic technologies, but also on continued investigations into the neuroanatomy of all vocal learners.

Another technological advance that should impact both the developmental and evolutionary understanding of the human brain and its function is the use of induced pluripotent stem cells (iPSCs). These cells are typically derived from easily accessible tissues such as skin and can be transformed into a multipotent state from which numerous cell types can differentiate, including neuronal cells. Studies in which neurons derived from patient-supplied skin biopsies in several human diseases hold promise for potential personalized therapeutics (Konopka 2010). In addition, direct conversion of neurons from

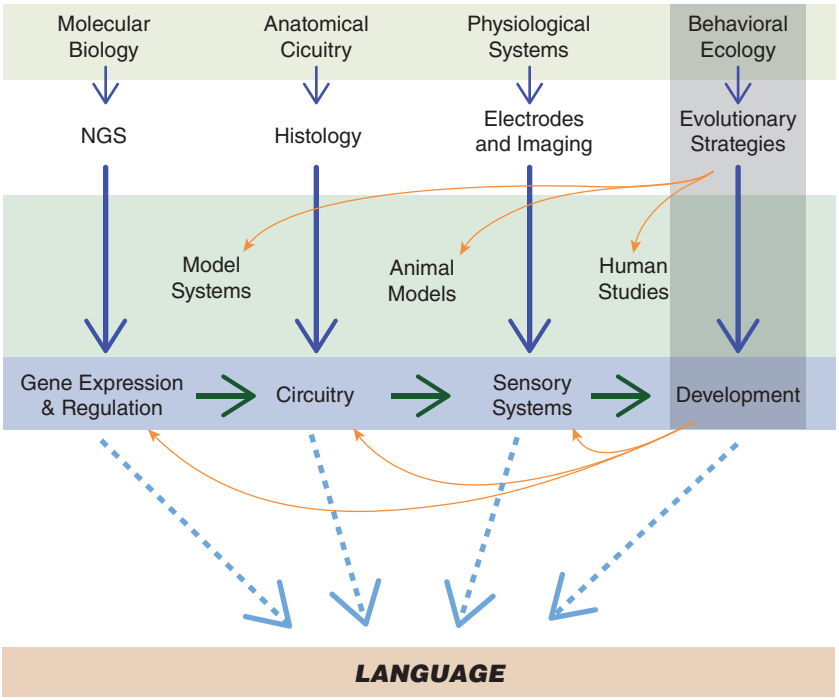

Figure 9.6. Summary of logistics and mechanisms in language evolution. Flow chart summarizing the disciplines (top row), techniques (second row), materials (third row), and logistics (fourth row) involved in the reconstruction of language evolution. Bold blue arrows indicate subject matter hierarchy. Bold green arrows indicate bottom-to-top flow of data ramification. Thin orange arrows indicate top-down feedback. Dotted lines indicate converging input from types of evidence to evolution of language. Shaded vertical box highlights impact of theoretical paradigm upon data generation and interpretation.

fibroblasts circumventing the iPSC stage altogether may eventually prove to be even more useful than iPSCs themselves (Pang et al. 2011; Vierbuchen et al. 2010). These types of studies are relevant to the study of evolutionary systems as they potentially bypass the need for access to brain tissue for specific focused studies in species such as the great apes. For example, iPSCs have been generated from at least two endangered species (Friedrich Ben-Nun et al. 2011). Thus, for example, one could manipulate expression of language-related genes in neurons derived from iPSCs from numerous vocal learners and assess the resultant transcriptional changes. In addition, transplantation studies of human or great ape induced neurons into mouse or monkey models followed by behavioral assessments might be feasible and permit insight into conserved pathways for vocalizations. Combinations of these approaches will bring us closer to modeling aspects of a human-specific function in nonhuman systems.

While this chapter has primarily focused on what makes human language unique such as the genes and brain anatomy, studies of shared capabilities among vocal learners is an active area of focus for future studies. For example, a recent study demonstrated that the Bengalese finch can exhibit evidence of recursion within their calls (Abe and Watanabe 2011). This possibility had been previously documented (Gentner et al. 2006); however,

these authors utilized a more complex paradigm that showed syllables within calls could be matched over a long distance. This type of matching is indicative of the complex hierarchical structure of much of human language. In addition, the authors also implicate a brain structure in songbirds that may be critical for this recursive process through lesion experiments. This brain structure receives output from the bird equivalent of the basal ganglia, and therefore correlates well with language and syntactic-related structures described in human brain (see Figure 9.2). Therefore, even while nonhuman studies of vocal learners that support conserved features of mechanisms underlying language may at first seem to detract from the "uniqueness" of human language, these studies are necessary to parse out the specific aspects of language that truly are unique, no matter how small the final tally may eventually be.

The future directions described earlier account for the use of animal models and genomic and cellular models from human tissues in the study of language. However, while we certainly cannot conduct invasive studies in humans, the use of imaging, particularly when coupled with genomics, may be the closest we can get to understanding language *in vivo*. One recent example of this direction examined a link between variation in *CNTNAP2* and cortical connectivity. Using functional imaging on genotyped patients, the authors found that individuals with specific *CNTNAP2* risk alleles were more likely to have disrupted long range connectivity between the frontal and temporal lobes and also less lateralized activity to the left hemisphere (Scott-Van Zeeland et al. 2010). This study demonstrates the power of harnessing the few tools available for human research: genetic and biomarker analysis using blood and structural and functional brain assessment using imaging. While this example examines the role of one gene implicated in both ASD and SLI, similar future studies can be undertaken to examine the relationship between other genes associated with language and specific language tasks while imaging.

One exception to the lack of invasive studies in humans might be the rare example of direct recording from human brain that is undertaken during neurosurgical procedures. More than 70 years ago, Penfield and colleagues pioneered this type of experimental paradigm to map cortical areas related to language (in order to avoid resecting language areas during surgery for epilepsy) (de Almeida et al. 2008). Similar but increasingly complex approaches have been used throughout the past few decades to obtain information on neural activity related to cognitive processes such as language (Engel et al. 2005; Ojemann 1991). More recently, such *in vivo* recordings have been used to monitor the response of mirror neurons in real time to specific stimuli and directly provide evidence for the existence of mirror neurons in the human brain (R. Mukamel et al. 2010). As mirror neurons are thought to be a neuroanatomical correlate for theory of mind (TOM) (Schulte-Ruther et al. 2007), and TOM may have been necessary groundwork for language evolution (see previous discussion and Penn et al. 2008; Premack 2007), these recording experiments could be integrated with knowledge of brain regions involved in language from imaging experiments to map language circuits. In addition, this link between mirror neurons and TOM has led to the suggestion that the autistic brain may have deficits in the mirror neuron system (Williams 2008). Thus, the study of the electrophysiological properties of specific neurons in human brain may provide insight into one of the cellular phenomenon that needed to evolve for language and how this process may become disrupted in disorders with a language component such as autism.

While all of these technologically advanced studies are critical for understanding language on multiple levels, there are still some basic properties of the human brain that require further study before a complete picture of language can emerge. One key aspect

of human brain development and evolution that is understudied is the dynamic role of brain development for processes like language. As discussed earlier, one hypothesis for the ability of humans to evolve higher cognition is the prolonged developmental time course in human brain compared to other species, including great apes. Recent evidence also suggests that there are molecular correlates to this protraction specifically in the human brain that potentially contribute to this developmental modification (Somel et al. 2009). In addition, comparative neuroanatomical studies are uncovering other potential contributing factors (see Figure 9.5). These few examples underscore the importance of taking developmental time courses into consideration when conducting any study related to language. Often, most studies are limited in the number of time points that can be examined due to lack of patient or tissue access. However, experimental design should include as many developmental time points as practical whenever possible.

Another basic fact of the human brain that is still poorly understood is multisensory integration. This form of complex processing requires the integration of several peripheral sensory stimuli to yield a new internal comprehension of stimuli, which may allow for a faster or deeper understanding of the inputted stimuli (A. M. Green and Angelaki 2010). Such integration not only requires intact processing of each peripheral stimuli stream, but also higher level functioning such as attention (Talsma et al. 2010). This type of information processing is likely critical for cognitive processes such as language. Auditory and visual input, together with attention and working memory, need to coordinate for language comprehension. Then, a reverse process needs to occur for the sequential motor output required for language production. While the basic mechanisms of these processes are acknowledged, the underlying connectivity and integrative mechanisms are poorly understood. Interestingly, in addition to previous anecdotal evidence, recent evidence has demonstrated a compelling link between deficits in multisensory integration and ASD (Russo et al. 2010). Thus, a deeper appreciation of the neurobiology of multisensory integration should be very beneficial toward comprehending language evolution and development.

Language is arguably the most complex cognitive function that humans possess. Understanding the origins of language requires integration of knowledge from numerous disciplines, including development, evolution, genetics, cognitive science, neuroscience, anthropology, linguistics, and psychiatry. Due to the uniqueness of language within the human domain, there are certain aspects of language that will never be modeled within another animal system. Thus, many conclusions about the development or evolution within the human brain can only be taken as unproven hypotheses. However, as this chapter attempts to describe, there are certain features of language that are conserved, and therefore can be studied in other organisms. Moreover, the emergence of genome resequencing and genome-wide transcriptomics allows for the identification of molecular pathways involved in language that can be studied in model systems. Finally, noninvasive imaging technology can provide another layer of insight into the neural systems at play during language use and malfunction. Together, these approaches are elucidating the mystery of our most unique feature and are providing therapeutic leads for patients affected with neurodevelopmental disorders.

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