Akt activity can be attributed in part to export of FOXO transcription factors from the nucleus and inhibition of glycogen synthase kinase 3β (GSK3β); the Erk1/2 cascade prolongs the transcriptionally active (serine 133 phosphorylated) state of CREB, and CREB activates brain-derived neurotrophic factor and PGC-1α. In contrast to these neuroprotective events, stimulation of extrasynaptic NMDARs can inhibit CREB transcriptional activity. Thus, neuroprotection might be produced by blocking extrasynaptic activity[5], but because NMDAR antagonists such as MK-801 block both synaptic and extrasynaptic activity, ROS-mediated damage occurs[1]. In contrast, memantine is an NMDAR antagonist that preferentially blocks excessive extrasynaptic NMDAR activity while relatively preserving synaptic activity[6,7]. Papadia *et al.*[1] corroborate this view by showing that memantine, unlike MK-801, does not produce oxidative damage to neonatal neurons, and indeed protects from bath-applied (extrasynaptic) NMDA exposure.

For the future, what remains to sort out is whether the synaptic and extrasynaptic dichotomy resulting in the life or death of neurons is mediated by different types of NMDAR subunits, as opposed to only distinct locations of the receptors. NMDARs are thought to be composed of four subunits chosen from NR1, NR2A–D and NR3A,B, with NR1 being mandatory. Some groups have maintained that subunit composition dictates whether receptor stimulation can become toxic, whereas other evidence supports the idea that receptor localization is the deciding factor. For example, as the current authors point out, the NR2B subunit predominates early in development, both synaptically and extrasynaptically, whereas in the adult brain, it is generally (though not universally) accepted that NR2A subunits predominate at synapses and NR2B subunits predominate at extrasynaptic sites. Different laboratories have reported seemingly conflicting evidence for the importance of synaptic versus extrasynaptic location[5] as opposed to NR2A or NR2B subunit composition[8] in determining the outcome of neuroprotection or neurodegeneration. The new work[1] reported here would seem to show that the location of the NMDAR is critically important in recruiting survival or death signaling pathways, but leaves open the possibility that subunit composition could also contribute. Only conditional NMDAR subunit knockout studies will answer this question.

Finally, Papadia *et al.*[1] show *in vivo* that overoxidation of Prx occurs after a focal ischemic insult (stroke) in mice, suggesting that such redox damage to this protective enzyme is pathophysiologically relevant. Another major direction for the future is to determine whether the synaptic and extrasynaptic dichotomy, leading to specific redox–mediated reactions, holds true in the many neurodegenerative diseases that are influenced by excessive glutamate receptor activity and its associated oxidative or nitrosative stress. Such stress generates free radicals that can contribute to disorders that include Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (Lou Gehrig's disease), multiple sclerosis and HIV-associated dementia. One recent example is Parkinson's disease, in which S-nitrosylation of Prx (forming SNO-Prx; **Fig. 1**) occurs in human brains, facilitating the overoxidation of Prx and preventing its neuroprotective effect[2].

Several of these neurodegenerative disorders appear to be mediated by aberrant, misfolded proteins. Although protein misfolding occurs in some cases because of mutation in the corresponding gene, the vast majority of neurodegenerative conditions are associated with aberrant proteins that potentially arise from oxidative or nitrosative damage, resulting in misfolding. Potential links to show how overactivation of glutamate receptors, with consequent altered redox signaling, can contribute to protein misfolding may provide critical mechanistic insight into the pathogenesis of these diseases[9–12]. Exploitation of the redox pathways influencing these reactions may be critical to future therapeutic intervention aimed at providing neuroprotection to the brain.

COMPETING INTERESTS STATEMENT
The author declares competing financial interests; details accompany the full-text HTML version of the paper at http://www.nature.com/natureneuroscience/.

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Language evolution: neural differences that make a difference

Asif A Ghazanfar

Language is unique to humans, but did it evolve gradually or suddenly, from a chance mutation or as a consequence of a larger brain? Two studies now suggest that language may have arisen gradually from precursors in other primates.

Language may well be what makes us human. As far back as 400 BC, Isocrates suggested that we avoid "living like animals" through our ability to communicate to each other via language, which gives us the capacity to build cities, make laws, invent art and so on. The uniqueness of speech and language to humans is indisputable, but how did it happen? Did language evolve gradually via communication precursors in the primate lineage or did it arise spontaneously through a fortuitous confluence of neuroanatomical changes that are found only in humans?

Many argue that, unlike traits such as the opposable thumb or color vision, where there is clear evidence for a gradual evolution, language essentially arose *de novo*. Even Thomas Huxley, Darwin's irascible promoter of the theory of evolution by natural selection, found the idea that language could evolve gradually through animal precursors to be too difficult to swallow. Huxley[1] wrote, "Believing, as I do…, that the possession of articulate speech is the grand distinctive character of man…, I find it very easy to comprehend

The author is at the Neuroscience Institute and Department of Psychology, Green Hall, Princeton University, Princeton, New Jersey 08540, USA.
e-mail: asifg@princeton.edu

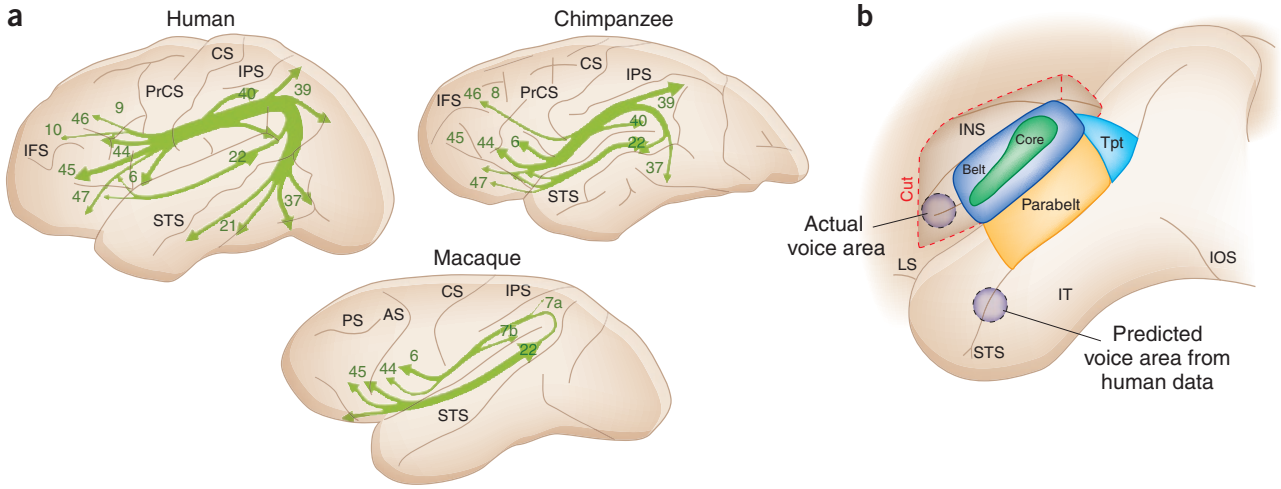

Figure 1 Changes to the communication-related neural circuitry in humans occurred gradually in the primate lineage. (**a**) Changing patterns of connections between frontal cortical areas and the temporal lobe in humans, chimpanzees and macaque monkeys. AS, arcuate sulcus; CS, central sulcus; IFS, inferior frontal sulcus; IPS, intraparietal sulcus; PS, principal sulcus; PrCS, precentral sulcus; STS, superior temporal sulcus. (**b**) The voice area in the rhesus macaque relative to other auditory cortical areas and where the voice area would be if it were in a similar location as the human voice area. LS, lateral sulcus; IOS, inferior occipital sulcus; STS, superior temporal sulcus; other labels refer to cytoarchitectonic areal designations. The lateral sulcus is cut open to reveal the superior temporal plane. In this plane, the core region is thought to contain 'primary-like' areas, responding best to pure tones, whereas the surrounding belt areas are more responsive to complex sounds. The voice area in macaques is anterior to the core and belt regions. INS, insula; IT, inferotemporal cortex; Tpt, temporoparietal area.

that some…inconspicuous structural differences may have been the primary cause of the immeasurable and practically infinite divergence of the Human form from the simian strips." Although this scenario may be implausible to those who expect evidence of gradualism in all evolved traits, it is possible that small changes in regulatory gene expression during development could lead to profound changes in brain growth and/or patterns of connectivity. There is even evidence of heritable, nongenetic influences on behavior that can occur in a single generation[2].

Unfortunately, brains do not fossilize. One way of moving from speculation to an empirical foundation is to compare the communicative behavior and neurobiology of existing nonhuman primates with those of humans. Although there are numerous studies of gross anatomical differences between the brains of different mammals, the advent of magnetic resonance imaging allows researchers to use the same experimental protocol across species to make circuit-level comparisons. Two recent magnetic resonance imaging studies in *Nature Neuroscience* used this approach to address the neural bases for the evolution of speech and language. Rilling *et al.*[3] investigated the putative differences in connectivity between the frontal and temporal lobes, a pathway that is essential for language, by comparing humans, chimpanzees and macaque monkeys. Petkov *et al.*[4] explored whether, similar to humans, macaques have a cortical area dedicated to processing voices exclusively. Results from both studies suggest that a gradual evolutionary change led to the neural circuitry underlying human communication.

The study by Rilling *et al.*[3] focused on the fiber tract connecting the temporal lobe to the frontal lobe in humans. This tract is the arcuate fasciculus, and it is essential for language. Lesions to this pathway result in conduction aphasia, in which, among other deficits, patients can comprehend speech, but cannot repeat what was said. Given its importance, it is a good target for investigating connectivity differences between species of primates that may partially explain why only humans have language. Using diffusion-tensor imaging to track white matter, Rilling *et al.*[3] found that the organization of cortical terminations between the temporal and frontal lobes was strongly modified in the course of human evolution, but, crucially, this modification was gradual (**Fig. 1a**). In humans, the terminations of the arcuate fasciculus connect the superior, middle and inferior gyri of the temporal lobe with the following frontal regions: ventral premotor cortex, pars opercularis, pars triangularis and middle frontal gyrus. Examination of the same pathway in the chimpanzee using the identical imaging protocol revealed extensive frontal terminations similar to humans, but the terminations in the middle and frontal temporal gyri were much less numerous. In macaques, these temporal lobe terminations were entirely absent; the arcuate pathway connects the frontal lobe with extrastriate visual areas dorsal to the inferior temporal gyrus. Two other fiber tracts with no predicted differences across species were very similar, revealing both the robustness of the diffusion-tensor imaging method and the specific selective pressure on the arcuate fasciculus.

Chimpanzees are phylogenetically between macaques and humans in the primate lineage, and the similarly 'in between' pattern of their arcuate pathway terminations strongly suggest a gradual evolution of this pathway. However, if changes in connectivity along this pathway are a major contributor to the evolution of language, then what are the functions of those pre-existing cortical areas in macaques and chimpanzees? They may not receive the same patterns of projections from the frontal lobes, but all three primate species possess a shared subset of cortical areas in the temporal gyrus, although they may vary in number[5]. These temporal areas are nodes in a variety of networks that presumably mediate a variety of behavioral functions, but exactly what do the new connections with the frontal cortex add to the human behavioral repertoire? It could be language or syntax, but it could also be related to species differences in locomotion, tool use, social structure or reproductive strategies (among other factors). Thus, although the evolution of the arcuate pathway may be gradual, language is still likely an emergent property of a variety factors that include, but are not limited to, changes in neuroanatomy.

In the typical scenario, language is mediated through speech, but voices also carry other important information related to the identity

and physical characteristics of the speaker[6]. Indeed, there is a 'voice' area in the anterior superior temporal sulcus of the human brain that processes human voices with priority over other animal vocalizations and natural sounds[7]. This voice area may be unique to humans because of the importance of speech in mediating language. To test this idea, Petkov *et al.*[4] carried out an elegant functional imaging study on macaques, comparing auditory responses to their own species-specific calls with responses to control sounds that had the same spectral profile and duration, as well as to other animal vocalizations and natural sounds. What they found was surprising; macaques do have a voice area that is especially sensitive to conspecific vocalizations in the same manner as the human voice region, but the anatomical location is entirely different. The macaque voice area is located in the anterior superior temporal plane that lies in the lateral sulcus. By contrast, the human voice area lies in the superior temporal sulcus, well below the lateral sulcus (**Fig. 1b**). This again suggests that the neural circuitry related to voice processing in humans is modified from an ancestral voice area that was present in the common ancestor of macaques and humans.

That both humans and macaque monkeys have a voice area that is sensitive to conspecific voices begs the question of what is so special about conspecific voices. One possibility is that there is nothing special about conspecific voices, but that the neurons in this area are sensitive to formants. Formants are acoustic signatures related to the shape and length of the vocal tract (the oral and nasal cavities above the larynx). As sound travels from the larynx through the vocal tract, it gets filtered, so that some frequency bands are enhanced (the formants), whereas others are suppressed. As an individual's vocal tract is uniquely shaped and has a length dependent on body size, formants are acoustic cues to both individual identity and other physical characteristics[8,9]. Petkov *et al.*[4] indirectly tested this idea by showing that the response of the voice area, in essence, habituates to different calls (for example, a grunt and a coo call) from the same individual (and thus similar formant signatures), but does not habituate when two calls of the same category (a coo and a coo), but from different individuals (and thus, different formant signatures), are presented. These data suggest sensitivity to formants more generally, regardless of the species producing the vocalization. This idea is ripe for testing.

Debate on how language came to be involves many branches of knowledge—philosophy, artificial intelligence, anthropology and now neuroscience—but this discussion is often very speculative, and there are few hard data. In contrast, the studies by Rilling *et al.*[3] and Petkov *et al.*[4], capitalizing on the power of both imaging and comparative functional anatomy, provide a much-needed empirical foundation for our understanding of the origins of human communication. Together, their results suggest that the neural circuitry in humans evolved gradually from primate precursors, which parallels findings from ethology that indicate a gradual emergence of vocal sophistication in the primate lineage[10,11]. The human language circuits did not appear *de novo* through a chance mutation or as a 'spandrel' of increased brain size, as some have argued, but instead have their basis in modified versions of neural structures shared by related species.

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What's in your mind?

Brian A Wandell

Previous 'mind-reading' studies have differentiated patterns of brain activity without understanding the underlying processes. A new study in *Nature* uses a model of neural encoding mechanisms to identify brain activity patterns.

There is a provocative claim that functional magnetic resonance imaging (fMRI) of the human brain can provide an objective measure of a person's sensory experience and thoughts. The possibility of such mind reading has led to various applications and engaged broad public interest. Some propose to use fMRI to reveal whether a person is telling the truth[1]. Others use the method to measure "unconscious evaluation of Black and White social groups"[2]. Economists and marketing experts want to measure the brain to determine how much a person values a product[3]. Clinicians seek to use biofeedback to help patients control their thoughts and feelings[4]. The research and applications have triggered discussions about privacy, ethics and free will[5].

Now comes a paper by Kay *et al.*[6], who used fMRI brain measurements to estimate what a subject was seeing. The authors made this estimate in two steps. They first measured primary visual cortex (V1) signals while a subject viewed a large set of gray-scale natural images (**Fig. 1a**). From these measurements, the authors derived a model of the populations of neurons in the subject's V1–V3; the model is based on fundamental principles of receptive fields derived from physiology and psychophysics[7]. They used the model to predict the responses to a large set of new images and estimate which image the subject is viewing by finding the best match between the model predictions and the observed fMRI response (**Fig. 1b**). Their work is the most advanced result in the mind-reading literature.

Such experiments before Kay *et al.*[6] provoked a wide range of reactions in the scientific community. For some, the possibility of using sensory and motor signals to infer what a subject is seeing, hearing or doing seems to be nothing more than a parlor trick. For example, we can classify whether a signal is seen or heard simply by noting whether the response is in auditory or visual cortex; in visual cortex, we can classify the location of a signal in the visual field from its position in the visual field map in V1 (ref. 8). Furthermore, we can determine whether the stimulus is likely to be moving or still, colored or achromatic, or a face or a texture from the relative amplitudes in other portions of visual cortex. The ability

The author is in the Psychology Department, Stanford University, Stanford, California 94305, USA.
e-mail: wandell@stanford.edu