

MEETING REVIEW

How unique is the human neocortex?

 Zoltán Molnár^{1,*} and Alex Pollen²

ABSTRACT

The human cerebral cortex is generally considered the most complex organ, and is the structure that we hold responsible for the repertoire of behavior that distinguishes us from our closest living and extinct relatives. At a recent Company of Biologists Workshop, 'Evolution of the Human Neocortex: How Unique Are We?' held in September 2013, researchers considered new information from the fields of developmental biology, genetics, genomics, molecular biology and ethology to understand unique features of the human cerebral cortex and their developmental and evolutionary origin.

KEY WORDS: Brain development, Cortex, Evolution, Human, Neuron

Introduction

In 1664, Thomas Willis proposed that higher cognitive functions originate from the convolutions of the cerebral cortex and not from the fluid or other structures in the brain or other parts of the body (Molnár, 2004). Willis based his proposal on the sheer size of the cortex in humans compared with that of other animals and on his own clinicopathological observations of individuals with epilepsy and learning difficulties. The cerebral cortex constitutes half the volume of the human brain and is presumed to be responsible for the neuronal computations underlying complex phenomena such as perception, thought, language, attention, episodic memory and voluntary movement. Although there is basic structural similarity across the entire neocortex, different functions are clearly localized in a large number of distinct fields, characterized by their input and output connectivity, their cytoarchitecture, the proportions of cell types, their modular structure and their microcircuitry.

The questions formulated by Willis are still with us today. Is the human cerebral cortex unique? What features evolved specifically in human? How did the size, shape and cellular composition change during evolution to perform these unique functions? How are these evolutionary changes reflected in the fossil record and our genome? To tackle these important issues, The Company of Biologists Workshop 'The Evolution of the Neocortex: How Unique Are We?', organized by Arnold Kriegstein (University of California, San Francisco, CA, USA) and held at Wiston House (West Sussex, UK), brought together a multidisciplinary group of 30 scientists, with representatives from the fields of anthropology, paleontology, developmental biology, stem cell biology, genetics, genomics, molecular biology, clinical neurology and ethology. The meeting first provided a broad overview of the structure of the human brain in the context of scaling relationships across the brains of mammals, conserved principles in reptilian and avian forebrains, and recent changes in the human lineage inferred from cranial endocast and

genomic data from archaic humans. Next, speakers considered how changes to developmental processes might underlie these anatomical differences, with a focus on neural stem and progenitor populations, human-specific developmental processes, and the search for genomic events that may underlie the developmental and morphological differences that distinguish modern humans. By bringing together researchers from diverse backgrounds but with a common interest, and encouraging in-depth discussion between participants, this intimate workshop helped to identify key areas for future work to ultimately improve our understanding of human-specific brain evolution and of diseases related to higher cortical function.

Graceful scaling, functional channeling and areas in the mammalian cortex

Understanding how unique the human neocortex is necessarily begins with a discussion of comparative neuroanatomy. Barbara Finlay (Cornell University, Ithaca, NY, USA) discussed predictive relationships between the sizes of brain structures across species and argued that changes in neurodevelopmental schedules shape the evolution of major neuroanatomical differences. Notably, although different structures expanded in mammalian and avian lineages, within a lineage the overall scaling of brain structures remains predictable. Finlay presented a powerful tool for translating developmental time across 18 mammalian species based on 271 developmental events and 1010 empirical observations (www.translatingtime.net; Workman et al., 2013), arguing that, once the extensive comparative data are examined, most 'human exceptionalism' falls away (Finlay and Workman, 2013).

Finlay further demonstrated that such predictive relationships might extend to cortical microstructure, describing a general antero-posterior gradient of increasing neuron number per column and packing density that mirrors the developmental gradient of the duration of neurogenesis along the same axis (Charvet et al., 2013). Although certain brain regions have a higher neuron packing density than predicted by the model (Collins et al., 2010), the overall trend intimates a developmental mechanism that might impose a species-general 'progressive reduction of dimensionality' in the cortex, as information is relayed from cell-dense posterior regions to cell-sparse anterior regions. The larger the brain, the steeper the gradient, so the increased neuronal spacing in the frontal pole may be an exaggerated feature of the human cortex. Indeed, Kate Teffer (University of California, San Diego, CA, USA) found that humans have more spacing distance in the frontal pole than do apes (Semendeferi et al., 2011), and that both humans and chimpanzees share a protracted development of this neuropil spacing in the frontal pole (Teffer et al., 2013). Alexandra de Sousa (University of Bath, UK) found that species-specific differences in neuron packing density of the visual cortex are most closely linked to the size of structures in the visual system and not to brain size or body size (de Sousa et al., 2010).

Jon Kaas (Vanderbilt University, Nashville, TN, USA) defined cortical areas as the 'organs of the brain', explained the sources of

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evidence (histological and functional) needed to identify cortical areas, and elaborated how humans have more cortical areas and more varied neuron types than any other primate (Kaas, 2012). Kaas further highlighted several key features of the human brain: the pronounced specialization of cerebral hemispheres, the frontal granular cortex (which may be unique to primates), and the expanded posterior parietal cortex that allows for further steps in sensory guidance of motor actions and decisions. Together, these presentations highlighted the importance of interpreting unique human brain anatomy in the context of scaling relationships from comparative data.

Common principles between avian, reptilian and mammalian circuits?

Constance Scharff (Freie Universität Berlin, Germany) argued that bird brains are much more similar to mammals than generally appreciated, and that the field has a general ‘obsession’ with human uniqueness. For example, language has long been considered a distinctive feature of the human brain, but there are numerous parallels between human speech and birdsong (Scharff et al., 2013): both are auditory-guided vocal motor-learning behaviors that produce sound to communicate; both comprise similar neural networks; both are optimally learned during critical developmental periods; and both involve a tutor. For other aspects of language, absence of evidence in birds is often used as evidence of absence. Scharff emphasized that the same gene, *Foxp2*, is essential in humans for mastering fluent speech and is also required for birdsong learning. Thus, by identifying the targets of *Foxp2* in a basal ganglia region relevant for birdsong learning, the relative contribution of other *Foxp* genes and the changes in circuit properties, studies of the bird vocal learning circuit can contribute to understanding the molecular and physiological underpinnings of a trait considered distinctively human.

These issues generated intense debate among the participants: some questioned whether bird song and human language can really be considered similar behaviors mediated through similar circuits; some emphasized the long list of features that are not found in any other species and concluded that language is unique to humans. These discussions led to the critical evaluation of the similarity of circuit elements in avian and mammalian brains. Recent progress in our understanding of the molecular properties of mammalian cortical neuron subtypes allows for more systematic comparisons between avian and mammalian neural circuits. Tatsumi Hirata (National Institute of Genetics, Mishima, Japan) and Steve Briscoe (University of Chicago, IL, USA) argued that the expression of cortical neuron subtype marker genes in avian brains supports the notion that upper and deep layer neurons are present in avian brains but with a different distribution from those in mammals (Suzuki et al., 2012; Dugas-Ford et al., 2012). Although both groups agree that bird brains contain mammalian neocortical cell type homologs, they differ significantly in the details of their conclusions. Hirata showed that chick medial pallium selectively generates neurons with expression of deep layer genes, whereas lateral pallium predominantly generates cells expressing upper layer neuron markers. Interestingly, each pallial sector has the capacity to generate neurons with deep and upper layer markers *in vitro* (Suzuki et al., 2012). These results suggest that the mammalian neocortical neurogenetic program may have been present in stem reptiles, but is suppressed in different sectors of the pallium.

However, the equivalent circuit concept and the homologous developmental steps were not accepted by everyone. Luis Puelles (University of Murcia, Spain) pointed out that the genes marking

deep and upper-layer cortical neurons used by Suzuki et al. (Suzuki et al., 2012) and Dugas Ford et al. (Dugas Ford et al., 2012) are also expressed in other brain regions, including the claustramygdaloid and parahippocampal areas (Puelles, 2011) (Fig. 1). Thus, the developmentally independent medial and lateral regions of the avian pallium that express these markers are not necessarily homologous to cortical layers. Moreover, Zoltán Molnár (University of Oxford, UK) argued that systematically surveying all genes does not support the idea of homologous cell populations in the adult. In collaboration with the group of Chris Ponting (University of Oxford, UK), Molnár’s group recently conducted analyses comparing the expression patterns and gene networks of 5130 orthologous genes in adult mammalian cortical layers, claustrum, amygdala, hippocampus, striatum and various adult avian structures (Belgard et al., 2013). The study found conserved gene expression networks for ancestral features (striatum, hippocampus, oligodendrocytes), but largely divergent gene expression networks for avian structures proposed to share homology with cortical layers. Puelles argued that the sophisticated and powerful methods used for transcriptomic comparative analysis at adult stages did not produce more significant correlations in the case of the non-hippocampal pallium because the spatial and temporal tissue sampling might not have been optimal.

Nenad Sestan (Yale University, New Haven, CT, USA) investigated the specification of deep layer corticospinal neurons in mouse and discovered remarkable homology between mammals and birds in a key gene regulatory network. Sestan demonstrated that a conserved non-coding regulatory enhancer drives the expression of *Fezf2* in layer 5. Loss of this enhancer completely ablates corticospinal tract axons (Shim et al., 2012). Remarkably, binding motifs for *Sox4* and *Sox11*, and the activity of the enhancer are conserved between human, mouse and chicken, but not zebrafish, suggesting that crucial elements of a regulatory network for these projection neurons arose early in amniote evolution (Fig. 2A). Together, these talks highlighted how studies in even distantly related model organisms can contribute to our understanding of special features of the human brain, and how dramatic reorganization of brain structure can be studied by comparing mammals and birds.

Evidence for recent changes in the human lineage

Comparative studies necessarily focus on contemporary living species, but cranial endocasts from the Hominin fossil record provide actual evidence for the sequence of morphological changes in the human brain. Dean Falk (Florida State University, Tallahassee, USA) reviewed the history of ‘paleo-political’ debates. In the cases of the lunate sulcus and ‘Broca’s cap’, the misinterpretation of homologies between human and ape sulci and gyri has been counterproductive for the field. For example, the 1903 proposal based on the lunate sulcus position that the occipital lobe evolved before the rest of the cortex through ‘mosaic brain evolution’ was discredited only recently (Allen et al., 2006). Nonetheless, Falk considered the recent promising interdisciplinary research on the prefrontal cortex using modern imaging as a valuable way forward for the field.

DNA sequences from extinct archaic humans provide another window into the actual events that occurred during human evolution. Svante Pääbo (Max Planck Institute, Leipzig, Germany) presented improved methods for sequencing ancient DNA that have allowed his group to sequence the genome of Neanderthals and also of Denisovans, the first archaic human to be described on the basis of DNA sequences. Remarkably, the genome data imply a model of ‘leaky replacement’ in which modern humans migrating out of

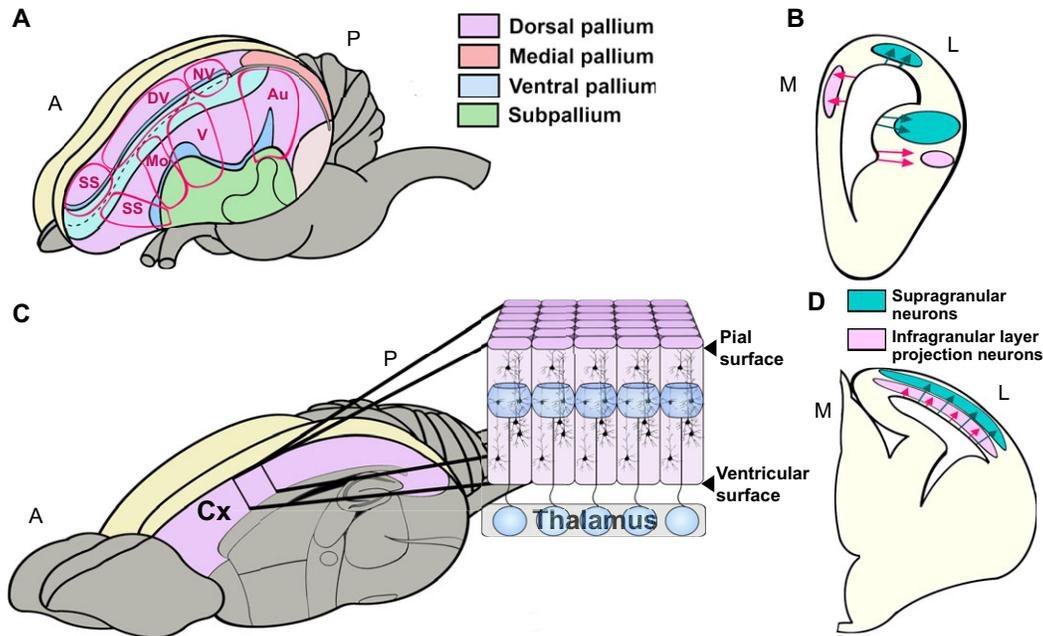


Fig. 1. The organization of avian and mammalian brains. In the avian brain (A,B) the cells of the co-activated networks are derived from different sectors of the pallial neuroepithelium and assemble across these sectors. Different sectors produce different cell populations that combine perpendicularly to the radial trajectories to form functional columns. In mammals (C,D), the diverse elements of the functional columns are produced within the same sector of cortical neuroepithelium, extending across the layers of the cerebral cortex perpendicular to the pial surface. The 'functional columns' have been defined by co-activation patterns of neurons during a specialized sensory or motor activity in mammalian and avian brains (Montiel and Molnár, 2013). Both mammalian and avian functional columns contain similar sets of specialized neurons, but the overall logic of their developmental origin is very different. A, anterior; Au, auditory; DV, day vision; L, lateral; M, medial; Mo, motor; NV, night vision; P, posterior; SS, somatosensory; V, ventral. Adapted from Montiel and Molnár (2013).

Africa interbred with archaic human populations. Indeed, Neanderthal sequences represent 1-4% of the genomes of Europeans and Asians (Green et al., 2010), and Denisovan sequences represent 4-6% of the Melanesian genome. Based on the size of Neanderthal haplotypes, interbreeding likely occurred 47,000-67,000 years ago (Sankararaman et al., 2012).

Pääbo provided a framework for identifying functional modern human-specific mutations and speculated that such mutations contributed to rapid technological innovation and expansion of modern human populations. Only about 30,000 nucleotide substitutions are fixed in the genomes of modern humans and Pääbo highlighted a relatively small number of key candidate mutations affecting fewer than 100 proteins and a few thousand regulatory elements. Some regions of the genome are particularly strong candidates for containing mutations involved in the evolution of modern human traits, such as those with abundant sequence changes since our divergence with Neanderthals and those with a complete absence of introgressed Neanderthal alleles. Functional studies of mutations specific to modern humans may eventually reveal unique aspects of modern human brain function.

Developmental processes that may contribute to brain expansion

The developmental processes that could underlie human cortical expansion and folding were a major topic of discussion at the meeting. In particular, several groups focused on changes in the behavior and gene expression of radial glia, the neural stem cells of the cortex, and of intermediate progenitor cells. Arnold Kriegstein (University of California San Francisco, USA) and Colette Dehay (INSERM, Lyon, France) discussed the behavior of a recently identified progenitor cell population, the outer radial glia (oRG, also

called basal radial glia) (Hansen et al., 2010; Fietz et al., 2010), that is rare in the mouse brain but abundant in species with larger brains (Wang et al., 2011; García-Moreno et al., 2012; Kelava et al., 2012; Reillo et al., 2011). Kriegstein described a distinctive behavior of oRGs in humans, mitotic somal translocation, and the possible cellular mechanisms of this behavior, whereas Dehay described a previously unappreciated diversity in the morphology, behavior and lineages of primate oRGs (Betizeau et al., 2013). Wieland Huttner (MPI Dresden, Germany) discussed the role of astral microtubules on mitotic division plane and cell fate in apical progenitor cells, and the mechanisms regulating symmetric versus asymmetric division of these cells. Luis de la Torre-Ubieta (University of California, Los Angeles, USA) presented data on the extent to which *in vitro* systems can be used to model *in vivo* human cortical development and Caroline Pearson (University of California, Los Angeles, USA) reviewed the shared and unique functions of Foxp proteins in neural stem cell maintenance and differentiation (Rouso et al., 2012).

Victor Borrell (CSIC and University of Miguel Hernandez, Spain) emphasized that, although oRGs are abundant in large-brained near-lissencephalic mammals, their abundance correlates well with the degree of brain folding (Kelava et al., 2012; García-Moreno et al., 2012). Borrell also noted that, although major folds are specified prior to axonal connections, this model is not incompatible with a later refinement of folds to reduce neuronal wiring length driven by axonal tension (Van Essen, 1997). The degree and importance of cortical folding across evolution was a recurring theme: Wieland Huttner presented comparative data on cortical folding and life history traits across mammals to suggest that gyrencephaly is an ancestral mammalian trait, which generated a spirited discussion.

Looking at other progenitor cells in the cortex, Zoltán Molnár showed lineage analysis indicating that *Tbr2* intermediate

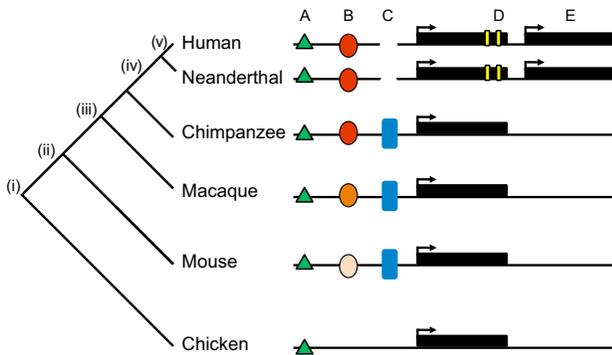


Fig. 2. Potential genomic changes underlying neocortex evolution. (i-v) Select events in neocortex evolution: (i) possible conserved neurogenetic program in amniote common ancestor (Suzuki et al., 2012); (ii) six-layered neocortex evolves in common ancestor of mammals; (iii) emergence of frontal granular cortex in primates; (iv) threefold expansion of human brain prior to divergence with Neanderthal; (v) possible additional events in modern human lineage supporting rapid technological innovation. (A-E) Genomic changes that may be associated with changes in brain structure: (A) conserved regulatory elements (e.g. Shim et al., 2012); (B) regulatory elements with functional changes in many lineages; (C) human-specific deletion of conserved regulatory elements (e.g. McLean et al., 2011); (D) human-specific coding substitutions (e.g. in *FOXP2*); (E) human-specific gene duplication (e.g. Charrier et al., 2012).

progenitors contribute to all cortical layers (N. A. Vasistha, F. Garcia-Moreno, S. Arora, A. F. P. Cheung, S. J. Arnold, E. J. Robertson and Z.M., unpublished), and Stephen Noctor (University of California, Davis, USA) highlighted the surprising finding that microglia phagocytosis of neural precursor cells could regulate brain size and leave the brain vulnerable to inflammation during development. Collectively, these talks painted a picture of the diverse behaviors of neural stem and progenitor cells during development and the contribution of these processes to evolution and disease.

Human-specific anatomy and developmental processes

Despite the emphasis on the shared structural and developmental features of mammalian brains, Pasko Rakic (Yale University, New Haven, USA) argued that the field may be too focused on mouse development and often neglects dramatic differences that distinguish the primate and human brains (Clowry et al., 2010; Geschwind and Rakic, 2013). Indeed, the human brain is over 1000 times larger than the mouse brain, the period dedicated to cortical neurogenesis is 20 times longer, the transient subplate is several-fold larger and more compartmentalized, cell cycle duration is three to four times longer, birth occurs during later stages of cortical development, and postnatal maturation lasts for much longer prior to reproduction. Structurally, the human neocortex is highly folded, whereas the mouse brain is smooth, and cortical areas are modified in human compared with mouse.

Rakic described developmental processes that also differ qualitatively: the developing subventricular zone and the subplate are both compartmentalized in human, and the transient subplate granular layer is absent in rodent. Some migratory pathways may even qualitatively distinguish human brain development from other primates, including prominent neuronal migration from the ganglionic eminence to the thalamic nucleus pulvinar – a phenomenon that cannot be identified even in monkeys (Letinic and Rakic, 2001). Rakic concluded that we are now in a position to take advantage of the advances made in molecular genetics to study

evolutionary novelties directly in neuronal stem cells and tissues of the developing cortex in human and non-human primates. Gavin Clowry (University of Newcastle, UK) presented evidence based on gene expression that another migratory pathway differs between human and mouse: the generation of a population of interneurons very early in cortical plate development and preferentially from frontal lobe (Al-Jaberi et al., 2013). Kriegstein questioned this notion based on recent birthdating experiments (Hansen et al., 2013), and the conference agreed that more work is needed to trace clones of developing inhibitory neurons.

Neural activity, including connections between thalamus and cortex, may contribute to developmental processes that generate cortical areas. Andre Goffinet (Université Catholique de Louvain, Brussels, Belgium) reviewed the role of planar polarity proteins *Celsr1-Celsr3* and *Fzd3* in brain wiring (Tissir and Goffinet, 2013), and showed examples where the mouse cerebral cortex forms normal layers but lacks modules such as the barrel cortex after connectivity has been eliminated between thalamus and cortex. Denis Jabaudon (University of Geneva, Switzerland) discussed another activity-dependent process, showing that assembly of inhibitory circuits in the dorsal lateral geniculate nucleus (dLGN), the principal visual relay nucleus of the thalamus, is modulated by visual activity. Interestingly, humans show an increased proportion of interneurons in the dLGN and other thalamic relay nuclei (Arcelli et al., 1997).

Ed Lein (Allen Institute for Brain Science, Seattle, USA) noted that such dramatic species-specific differences may explain why many discoveries in mouse do not translate well to human. Lein presented insights about distinctive changes in the human brain derived from large-scale analyses of gene expression in mouse, human and primate (Ng, et al., 2009; Hawrylycz et al., 2012; Bernard et al., 2012). The excellent tools developed by the Allen Brain Institute (<http://www.brain-map.org>) were universally appreciated by all participants. Michael Oldham (University of California, San Francisco, USA) described an innovative approach for comparing gene expression in specific developmental cell types between mouse and human. Nonetheless, to conclude that gene expression patterns are either primate or human specific requires closer contrasts and outgroups than mouse. Genevieve Konopka (University of Texas Southwestern Medical Center, Dallas, USA) compared gene expression in adult human and chimpanzee brain regions using macaque as an outgroup and discovered an abundance of human-specific gene expression patterns in the frontal lobe but not in more conserved brain regions. She also demonstrated that human differentially expressed genes correlate with autism susceptibility genes, and both gene classes have increased expression in the human neonatal brain. Also addressing questions of the developmental basis of human disorders, Nenad Sestan discussed the molecular basis for a striking pattern of *NOS1* protein expression in minicolumns of layer 5 in the mid-fetal frontal operculum. Although the *NOS1* transcript is transiently widely expressed in developing mouse and human excitatory projection neurons, only primate transcripts have gained a sequence motif for binding to fragile X mental retardation protein (FMRP) that enables efficient translation (Kwan et al., 2012). Sestan showed that individuals with fragile X syndrome that lack FMRP express reduced *NOS1* protein in this domain, demonstrating the importance of understanding human-specific expression differences for modeling human diseases.

Genomic screens for key human-specific mutations

Chris Ponting (University of Oxford, UK) presented the challenges of identifying adaptive mutations in the human genome. Of the

millions of human-specific mutations, many will be neutral or deleterious and – due to the low effective population size of humans – are likely to have been fixed in the genome by drift and not by adaptive selection, whereas many others are likely to fall in regions of the genome that are not functional. Indeed, only 1.2% of our genome is protein coding, and Ponting's work suggests that only ~7% of our genome is likely to be functional. Some of the non protein-coding sequences are transcribed as long intergenic non-coding (linc) RNA that can have diverse phenotypic consequences in mouse (Young and Ponting, 2013), whereas other non-coding sequences can act as regulatory enhancers that control the expression of nearby genes.

Alex Pollen (University of California, San Francisco, USA) presented one strategy for identifying human-specific mutations that are likely to be functional. As Ponting noted, structural mutations tend to have larger effects than base pair substitutions, and regulatory mutations tend to underlie evolutionary changes in natural populations. Based on these signatures of evolutionary change, Pollen and colleagues identified 510 human-specific deletions that remove sequences conserved between chimpanzee, mouse and macaque (McLean et al., 2011) (Fig. 2C). By filtering the list to identify deletions that may affect the expression of tumor-suppressor genes, and potentially releasing a brake on neurogenesis, Pollen identified two human-specific mutations that affect specific neural stem and progenitor populations. Future work to 'humanize' mice at these loci by re-creating the human-specific mutations will reveal the extent to which these mutations affect brain development.

Franck Polleux (The Scripps Research Institute, La Jolla, CA, USA) studied another type of structural mutation: segmental duplications (Fig. 2E). Approximately 30 gene families show human gene duplications, including the *SRGAP2* gene. A segmental duplication that arose 2.4 million years ago created a human-specific paralog *SRGAP2C* (Charrier et al., 2012; Dennis et al., 2012). Polleux provided functional data that this new gene acts as dominant negative to inhibit the normal function of *SRGAP2A* in promoting synaptic spine maturation. This gene duplication is predicted to contribute to a significant increase in the total number of excitatory synapses, which alone might be expected to lead to aberrant neural activity and hyperexcitability. Polleux presented data showing that the *SRGAP2A* gene may coordinate the maturation of both excitatory and inhibitory synapses, illustrating the power that a single gene duplication might have during human cortical evolution.

Taking a different approach, Christopher Walsh (Boston Children's Hospital and Harvard Medical School, Boston, MA, USA) described how genetic studies of human neurodevelopmental disorders can reveal genes that are crucial for the development of key regions of the human brain, such as the frontal lobe. By examining the evolutionary history of these loci, coding and regulatory mutations in genes likely to have strong effects on human cortical development can be identified. Using this approach, Walsh's group identified a regulatory region necessary for proper folding of the perisylvian gyrus in humans and demonstrated that the activity of this regulatory region has changed across mammals (Fig. 2B). The gene *Foxp2* was also first identified by a similar genetic mapping approach as being necessary for normal language development, and Svante Pääbo provided an update on the functional significance of two human-specific amino acid substitutions in the gene (Fig. 2D). Mice 'humanized' at these two positions show improved synaptic plasticity in the lateral striatum and improved procedural learning. Collectively, these genomic screens illustrate a powerful new approach for identifying key genomic changes in the human lineages and for relating these back

to developmental and physiological processes that distinguish the human brain.

Summary

The meeting was extremely productive in sharing ideas and resolving more controversial issues. The presentations and discussions identified key areas for future work to ultimately improve understanding of diseases related to higher cortical function. The repertoire of interdisciplinary approaches available to study brain development and evolution is impressive, but overall, the meeting identified our ignorance of human-specific traits. We must channel these diverse approaches to study human brain development and resolve fundamental questions related to human uniqueness. As Voltaire said: 'The human brain is a complex organ with the wonderful power of enabling man to find reasons for continuing to believe whatever it is that he wants to believe'.

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Competing interests

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