HOW CAN DEVELOPMENT AND PLASTICITY CONTRIBUTE TO UNDERSTANDING EVOLUTION OF THE HUMAN BRAIN?

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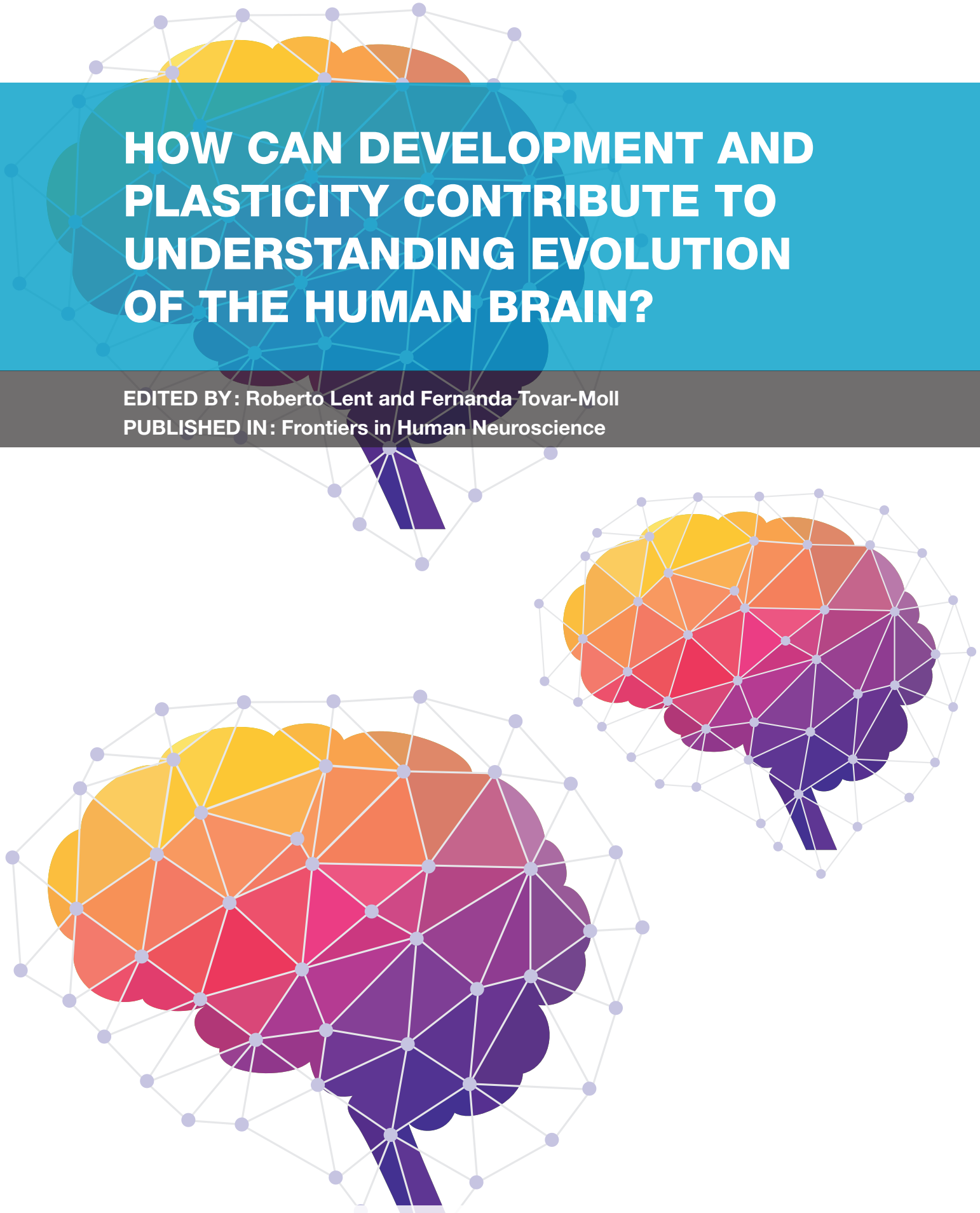

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HOW CAN DEVELOPMENT AND PLASTICITY CONTRIBUTE TO UNDERSTANDING EVOLUTION OF THE HUMAN BRAIN?

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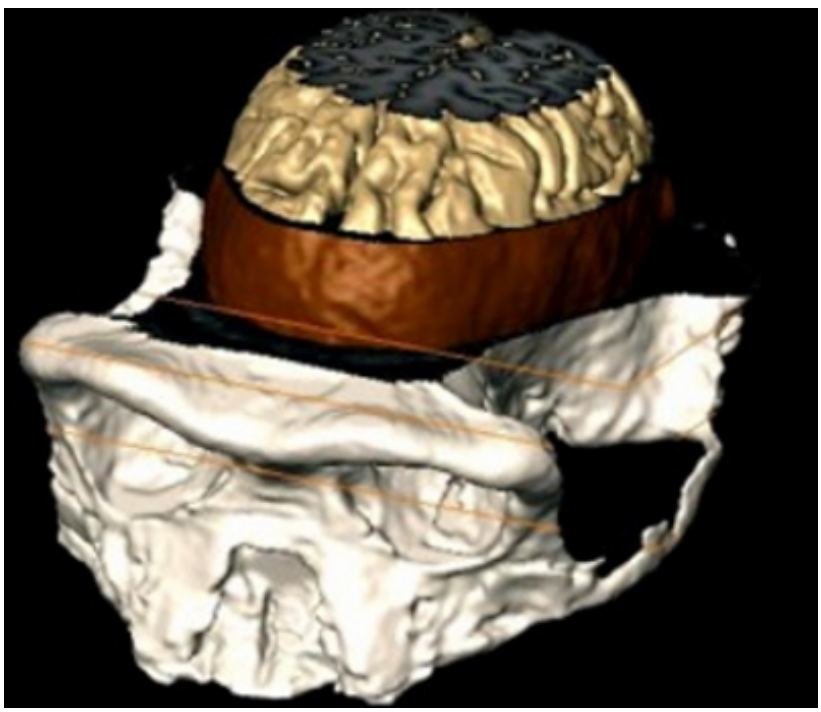

An example of magnetic ressonance imaging used to reveal the relationship between a chimpanzee brain (beige), its bone endocast (brown), and exocranium (white).
Image taken from: Hrvoj-Mihic B, Bienvenu T, Stefanacci L, Muotri AR and Semendeferi K (2013) Evolution, development, and plasticity of the human brain: from molecules to bones. Front. Hum. Neurosci. 7:707. doi: 10.3389/fnhum.2013.00707

Humans usually attribute themselves the prerogative of being the pinnacle of evolution. They have large brains with many billion neurons and glial cells, trillions of synapses and besides all, a plastic hardware that may change either subtly or strongly in response to the external environment and internal, mental commands. With this hypercomplex apparatus, they are capable of

very sophisticated inward computations and outward behaviors that include self-recognition, metacognition, different forms of language expression and reception, prediction of future events, planning and performing long streams of motor acts, subtle emotional feelings, and many other surprising, almost unbelievable properties.

The main challenge for research is: how do we explain this gigantic achievement of evolution?

Is it a direct consequence of having acquired a brain larger than our primate ancestors, with huge numbers of computational units? Would it be determined by a particular way these units came to relate to each other, building up logic circuits of powerful capacities? What along development has "made the difference" for the construction of such a complex brain machine? How much of this complexity is innate, how much is sculpted by influence of the external world, by social interaction with our human fellows, and by the history of our own mental trajectory along life?

Many specific questions can be asked (albeit not necessarily answered so far) to this purpose: (1) which genomic characteristics make us unique among primates? (2) which of developmental events during and beyond embryogenesis define our brain – prolonged neurogenesis? permanent circuit (re)formation? dynamic synaptogenesis? regressive sculpting of the hardware? all of them? (3) is there anything special about plasticity of the human brain that allows us to build the exquisite individual variability characteristic of our brains?

Neuroscience is in need of a synthesis. Perhaps associating concepts derived from developmental neurobiology with evolutionary morphology and physiology, together with those that photograph the human brain in action under influence of the external world, would turn on a light at the end of the tunnel, and we would be able to understand what humans do have that is special – if anything – to explain our success in the Earth.

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EDITORIAL
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How can development and plasticity contribute to understanding evolution of the human brain?

Roberto Lent[1]* *and Fernanda Tovar-Moll*[1,2]

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Keywords: neurons, cortex, evolution, molecular, chemical, development, evo-devo

Humans usually attribute themselves the prerogative of being the pinnacle of evolution. They have large brains with many billion neurons and glial cells (Lent et al., 2012), trillions of synapses and besides all, a plastic hardware that may change either subtly or strongly in response to the external or internal environment (Tovar-Moll et al., 2014). With this hypercomplex apparatus, they are capable of very sophisticated inward computations and outward behaviors that include self-recognition, metacognition, different forms of language expression and reception, prediction of future events, planning and performing long streams of motor acts, subtle emotional feelings, and many other exceedingly complex properties.

The main challenge for research is: how do we explain this gigantic achievement of evolution?

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This special issue of Frontiers addresses some of these intriguing issues. It is comprised of ten reviews by experts in the field.

A reductionist approach is taken by Seth Dobson from Dartmouth College, and Lauren Brent from Duke University, USA. They examine how genomic features of individuals link up to behavioral patterns, in health and disease. Their hypothesis is that polymorphisms of the serotonin transporter gene, typical of primates including humans, offer allelic diversity that make some of us more prone to face adverse social situations (those expressing low levels of the transporter proteins), while others deal better with nonconflictive daily situations (those with high levels). Having two different alleles, therefore, provides long-term benefits to the species to face diverse competition levels within the social group.

Branka Hrvoj-Mihic and her collaborators from the University of California at San Diego, USA, comment about an old suggestion by Greenough et al. (1987) on the two basic mechanisms of plasticity: *experience-expectant plasticity*, by which the brain is provided by development with exuberant hardware (connections, dendrites, synapses), sculpted postnatally to achieve the best configuration for survival; and *experience-dependent plasticity*, associated to the critical periods in development, by which our late-maturing brain allows change and modulation oriented by environmental input. They argue that the brain faces two opposing needs along life: one is to maintain its circuitry functionally stable, the other is to provide it with enough flexibility (=plasticity) to respond appropriately to the environment.

Franco Cauda and his colleagues from the University of Turin, Italy, review the role of an intriguing cortical cell—the von Economo's neuron—described almost 100 years ago (von Economo and Koskinas, 1925). Present in large-brained mammals, including humans, these

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fusiform neurons are thought to participate in the conscious perception of bodily states, related to the "sentient-self" as proposed by Bud Craig (2010), as well as to differentiation between the self, the others, and the external environment, a strong ability that humans acquired along evolution.

More common and universal than von Economo's neurons are the commissural ones. Commissures are inter-hemispheric connections that exist from lampreys to humans. In the latter, the number of commissures has increased to at least six, and the amount of commissural axons connecting the cerebral hemispheres has reached some hundred millions in humans. This evolutionary trajectory as related to developmental mechanisms is reviewed by Rodrigo Suarez and his colleagues from Queensland Brain Institute, Australia. The corpus callosum, in particular, is the target of their interest, and the knowledge of the developmental events underlying its formation is instrumental to unravel its striking *long-distance plasticity*, as shown in cases of humans born without it (Tovar-Moll et al., 2014).

Using a histological approach, on the other hand, Milos Judas and his colleagues from the Croatian Institute for Brain Research tackled the significance of the cortical subplate as a transient waiting compartment in the developing brain. Situated below the developing cortex, the subplate may possibly be involved in synchronizing and amplifying a period of neurogenesis that gets longer along the evolution of primates, and in relating it with the ingrowing afferent innervation from subcortical regions. Along the same line, Eric Lewitus and his colleagues from the Max Planck Institute of Molecular Cell Biology and Genetics at Dresden, Germany, examine the role of the subventricular zone on cortical folding, characteristic of large brains. They suggest that this region placed adjacent to the earlier ventricular zone becomes more and more complex along evolution, and constrains radial processes and proliferating precursors to assume a conical organization, ending up by mechanically forcing the tissue to fold and generate gyri and sulci.

Leah Krubitzer and James Dooley from the University of California at Davis, USA, take a more systemic approach: they review how the numerous functional areas of the cerebral cortex appear in evolution, related to developmental mechanisms and examples of epigenetic changes on the genome. They comment that cortical expansion follows scaling rules for the different mammalian groups, in line with what was found by Herculano-Houzel et al. (2006, 2007) for the different mammalian orders. The most important issue they tackle here is whether epigenetic influences can be incorporated into the genome and be transmitted across generations. They mention the example of maternal licking and grooming in rats, a behavior that causes increased glucocorticoid receptor transcription persistent along adult life because of a reduction in DNA methylation that can be transferred to the following generation (Kappeler and Meaney, 2010).

Similar to the rat example raised by Krubitzer and Dooley, Louis Lefebvre from McGill University, Montreal, Canada, brings to scene the intriguing examples of social learning that may appear at a given individual, and then prove so useful that becomes rapidly selected by evolution to stay engrained in the species. Even more intriguingly, he reveals that the same phenomenon was observed in tits (Fisher and Hinde, 1949) and chimpanzees (Kawai, 1965): convergent evolution of high cognitive abilities?

Ricardo Garcia and his collaborators from Universidad de Chile, Universidad del Desarrollo and Pontificia Universidad Catolica de Chile, tackle an even more complex cognitive ability, supposedly characteristic of humans: language. They review in detail the intricate circuits of monkey and human brains, point out similar features between them, and propose a "trajectory" for the evolution of language, from imitation of hand movements with communicative meaning, to a more complex system of manual and facial pantomimes, and finally a protospeech that opened way to full language.

Finally, Michael Anderson and Barbara Finlay, from the University of Maryland and Cornell University, USA, wrap up data on brain development, plasticity and evolution, providing a deep, broad, historical review about the concept of modularity of brain organization. They also end up by questioning if brain evolution has really been made possible only by increase or decrease of modules (neurons, connections, functional regions etc.), or if, alternatively, existing basic modules are simply reused in different ways to provide diversity in animal behavior and cognitive abilities.

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HUMAN NEUROSCIENCE

HYPOTHESIS AND THEORY ARTICLE
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On the evolution of the serotonin transporter linked polymorphic region (5-HTTLPR) in primates

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Some allelic variants of the serotonin transporter linked polymorphic region (5-HTTLPR) result in lower levels of expression of the serotonin transporter gene (*SLC6A4*). These low-expressing (LE) alleles are associated with mental-health disorders in a minority of humans that carry them. Humans are not the only primates that exhibit this polymorphism; other species, including some monkeys, also have LE and high-expressing (HE) variants of 5-HTTLPR. We propose a behavioral genetic framework to explain the adaptive evolution of this polymorphism in primates, including humans. We hypothesize that both LE and HE alleles are maintained by balancing selection in species characterized by short-term fluctuations in social competition levels. More specifically, we propose that LE carriers benefit from their hypervigilant tendencies during periods of elevated competition, whereas HE homozygotes cope best when competition levels do not deviate from the norm. Thus, both alleles have long-term benefits when competition levels tend to vary substantially over relatively short timescales within a social group. We describe this hypothesis in detail and outline a series of predictions to test it. Some of these predictions are supported by findings in the current literature, while others remain areas of future research.

Keywords: serotonin transporter gene, group living, balancing selection, humans, macaques

INTRODUCTION

Understanding the neurobiological mechanisms that shape the production of behavior is a fundamental goal of neuroscience. Thanks to recent advances in genomics, it is now possible to investigate this question at the genetic level. A genetic variant that has received considerable attention in recent years is the serotonin transporter linked polymorphic region (5-HTTLPR), which is a promoter sequence that regulates the expression of the serotonin transporter gene (*SLC6A4*) (Canli and Lesch, 2007; Homberg and Lesch, 2011). Serotonin transporter (5-HTT) proteins mediate the reuptake of serotonin from the synaptic cleft, which serves to terminate neurotransmission and replenish serotonin stores in presynaptic terminals. *SLC6A4* expression is hypothesized to influence cortical development and consequently cognitive function, especially with regard to emotion regulation networks (Jedema et al., 2010).

Humans have two common versions of 5-HTTLPR, a "short" (S) allele, which consists of 14 tandem repeats, and a "long" (L) allele, which consists of 16 tandem repeats (Nakamura et al., 2000). There is geographic variation in the degree to which the L allele is more frequent than the S allele (Chiao and Blizinsky, 2010), and the latter is typically associated with lower quantities of 5-HTT resulting from reduced rates of *SLC6A4* transcription (Greenberg et al., 1999). However, some rare versions of the L allele, i.e., those characterized by additional single nucleotide mutations, also result in reduced amounts of 5-HTT (Hu et al., 2006). Given this complexity, we use the terms "low-expressing" and "high-expressing" to refer to functional variants of 5-HTTLPR.

The negative consequences of carrying low-expressing (LE) 5-HTTLPR alleles have been well documented (Caspi et al., 2010). For example, LE-allele carriers tend to score higher on personality tests that measure neuroticism, which is a risk factor for anxiety and depression (Lesch et al., 1996; Munafo et al., 2009). LE alleles do not necessarily result in mood disorders, however. Instead, environmental factors have been proposed to mediate the phenotypic effects of 5-HTTLPR throughout the lifespan (Homberg and van den Hove, 2012). Typically LE-allele carriers who experience stressful life events have a higher risk of depression than less-stressed LE carriers (Caspi et al., 2003).

Because most studies of 5-HTTLPR have tended to focus on mental-health disorders, relatively little attention has been paid to the potential benefits of LE alleles (Belsky et al., 2007; Homberg and Lesch, 2011). This is a glaring gap in our understanding of serotonin transporter polymorphisms for two main reasons. First, most people who carry LE alleles do not develop mental-health disorders, and in fact LE-allele carriers often respond more positively to environmental enrichment than high-expressing (HE) allele carriers (Belsky et al., 2009). Second, LE alleles are found in relatively high frequencies (>10%) in all human populations (Chiao and Blizinsky, 2010). These numbers are too high to be explained by mutation and gene flow alone, suggesting instead that this allele has been maintained by natural selection. Yet, it is highly unlikely for an allele with purely negative consequences to

be selectively maintained (Belsky et al., 2009; Homberg and Lesch, 2011).

In recent years, various benefits of the LE variant of 5-HTTLPR have been proposed. For example, LE carriers exhibit increased activity of the amygdala in response to emotionally relevant stimuli (Hariri et al., 2002; Caspi et al., 2010), a greater response of the HPA-axis to aversive stimuli (Gotlib et al., 2008; Mueller et al., 2010; Way and Taylor, 2010), and increased immune response, blood pressure, and epinephrine during stressful tasks (Ohira et al., 2009; Fredericks et al., 2010). These findings may explain why LE carriers have difficultly disengaging from negative or threatening stimuli, and why they respond more strongly to both negative and positive environmental cues (Homberg and Lesch, 2011). LE-allele carriers are also better able to change their responses in line with shifts in reward context, and have been described as more cognitively flexible (Vallender et al., 2009; Jedema et al., 2010). Yet, despite this flexibility, LE carriers generally demonstrate an aversion to risks in financial (Crişan et al., 2009; Kuhnen and Chiao, 2009) and social contexts (Watson et al., 2009). Taken together, these finding have led to the suggestion that LE-allele carriers are overly sensitive to external stimuli (Homberg and Lesch, 2011). Such "hypervigilance" may be moderately harmful in the day-to-day, but highly beneficial under circumstances that have major impacts on fitness, such as when life-threatening situations arise (Homberg and Lesch, 2011).

It is important to note that several studies of 5-HTTLPR have failed to replicate previously documented phenotypic associations. This is due in part to the fact that novel significant results are more likely to be published than failed replication attempts (Duncan and Keller, 2011), and initial findings of significant associations appear to have overestimated the true effect sizes (Munafo et al., 2008). Moreover, genome-wide association studies (GWAS) of human disease and personality have only infrequently identified 5-HTTLPR, or indeed other common genetic variants, as important loci (Flint and Munafo, 2013). While meta-analyses of published findings have found statistically significant associations between 5-HTTLPR and some phenotypes (Schinka et al., 2004; Sen et al., 2004; Munafo et al., 2008, 2009; Murphy et al., 2013), the amount of phenotypic variation attributed to the polymorphism is often less than 5%, which some authors have suggested is too small to be indicative of a causal factor in disease (Flint and Munafo, 2013).

A broader comparative perspective on 5-HTTLPR might help to mitigate some of these complexities. Humans are not the only primates to exhibit natural variation at this locus, nor are we the only primates for which the serotonergic system is important. Several species of monkey and all extant species of ape are polymorphic for 5-HTTLPR (**Table 1**). The taxonomic breadth of this polymorphism provides an excellent opportunity to generate and test hypotheses concerning the evolutionary pressures acting on this system, and to do so independently of the complexities of human neuropsychopathology.

The aims of this review are two-fold. First, we put forward an argument in favor of adopting an evolutionary perspective when studying 5-HTTLPR polymorphisms. Our intention is not to deny the important criticisms that have been raised regarding candidate genes studies. These are valid and should be taken into account when possible. However, we also believe that a broader, evolutionary perspective offers a valuable contribution to our understanding of this, and perhaps other common genetic variants. Second, we use this perspective to put forward a hypothesis for the evolution of 5-HTTLPR polymorphisms in primates. Our framework builds on previous (not entirely dissimilar) hypotheses and incorporates the most up-to-date findings regarding the primate serotonergic system. We make explicit links to primate social systems, and present an ecologically informed model that is generally applicable across the primate order. We conclude with a series of explicit predictions, some of which have already been supported by findings in the literature, while others remain areas for future research.

AN EVOLUTIONARY PERSPECTIVE

MECHANISMS OF POLYMORPHISM

A genetic polymorphism is defined as the presence of two or more alleles in a population at frequencies that are greater than expected by mutation and gene flow alone (Hedrick, 2009). Polymorphisms are actively maintained by balancing selection. This involves selection acting either through heterozygote advantage, frequency-dependence, niche divergence, or by the existence of two or more evolutionary stable strategies of roughly equal benefit. These mechanisms make very different predictions about the relationship between phenotypes and fitness. For example, under heterozygote advantage, carriers of one copy of the LE allele are predicted to do better than homozygotes for either the LE or HE alleles. This has important consequences for studies that lump LE homozygotes together with heterozygotes for the purpose of statistical analysis. Thus, any hypothesis that purports to explain the evolution of 5-HTTLPR polymorphisms must be explicit about the type of balancing selection that is implied.

SMALL EFFECT SIZES

Natural selection acts on phenotypes not genotypes. This is because the relative fitness of a particular genotype depends on the benefits of the associated phenotype in a particular environment. If a beneficial phenotype is heritable at the population level, then selection will act to change allele frequencies over time. Phenotypic variation in a population does not have to be entirely, or even mostly, explained by genetic differences in order for natural selection to work. As long as there is a genetic association, even if it is relatively weak, selection acting on the phenotype will result in changes in allele frequencies.

This is an important point in light of the small effect sizes typically observed in genetic association studies of 5-HTTLPR. For example, in an early study of the relationship between 5-HTTLPR and anxiety-related traits, Lesch et al. (1996) observed that genotype explained only 3–4% of the total phenotypic variation in a large sample of 505 individuals. Subsequent meta-analyses have confirmed that the effects of LE alleles on individual differences in personality traits are relatively small (Schinka et al., 2004; Sen et al., 2004; Munafo et al., 2009). Similarly, early fMRI studies found that people with LE alleles tended to exhibit greater activation of the amygdala than HE-allele carriers (Hariri et al., 2002, 2005). But a recent meta-analysis of 31 imaging studies

Table 1 | Summary of 5-HTTLPR polymorphisms in primates and other species.

Species	Repeats	Polymorphic	Location	Repeat size	No of repeat elements	*n*	Allele frequencies	References
Gorilla gorilla	y	y	PL1	44 bp	18, 20	1	NA	Lesch et al., 1997
Gorilla gorilla	y	y	PL1	44 bp	16, 17, 18	14	54%(16), 14%(17), 32%(18)	Inoue-Murayama et al., 2000
Homo sapiens	y	y	PL1	44 bp	14,16	505	43%(14), 57%(16)	Lesch et al., 1996
*Homo sapiens**	y	y	PL1	44 bp	14, 16, 20	102	77%(14), 22%(16), 0.4%(20)	Inoue-Murayama et al., 2000
Hylobates muelleri	y	y	PL1	44 bp	15, 16, 17, 22, 23	15	7%(15), 3%(16), 50%(17), 7%(22), 33%(23)	Inoue-Murayama et al., 2000
Pan paniscus	y	y	PL1	44 bp	18, 20	1	50%(18), 50%(20)	Lesch et al., 1997
Pan troglodytes†	y	y	PL1	44 bp	18, 20	2	50%(18), 50%(20)	Lesch et al., 1997
Pan troglodytes verus	y	n	PL1	44 bp	17.5	16	100%(17.5)	Inoue-Murayama et al., 2000
Pongo pygmaeus	y	y	PL1	44 bp	18, 20	1	NA	Lesch et al., 1997
Pongo pygmaeus	y	y	PL1	44 bp	18, 20, 22	9	11%(18), 78%(20), 11%(22)	Inoue-Murayama et al., 2000
Macaca arctoides	y	NA	PL2	21 bp	24	2	100%(24)	Wendland et al., 2006
Macaca cyclopsis	y	y	PL2	21 bp	23, 24	1	NA	Shattuck, 2011
Macaca nemestrina	y	n	PL2	21 bp	24	12	100%(24)	Wendland et al., 2006
Macaca radiata	y	y	PL2	21 bp	23, 24	33	33%(23), 67%(24)	Chakraborty et al., 2010
Macaca thibetana	y	y	PL2	21 bp	22 ("*mti*")	3	100%(*mti*)	Wendland et al., 2006
Macaca tonkeana	y	n	PL2	21 bp	24	28	100%(24)	Wendland et al., 2006
Macaca fascicularis	y	n	PL2	21 bp	24	35	100%(24)	Wendland et al., 2006
Macaca mulatta	y	y	PL2	21 bp	23, 24	154	34%(23), 66%(24)	Lesch et al., 1997
Macaca mulatta	y	y	PL2	21 bp	23, 24, 25	289	26%(23), 74%(24), 2%(25)	Wendland et al., 2006
Macaca mulatta	y	y	PL2	21 bp	23, 24, 25	107	28%(23), 70%(24), 2%(25)	Brent et al., 2013a
Macaca munzala	y	y	PL2	21 bp	23, 24	24	2%(23), 98%(24)	Chakraborty et al., 2010
Macaca radiata	y	y	PL2	21 bp	23, 24	33	33%(23), 67%(24)	Chakraborty et al., 2010
Macaca silenus	y	n	PL2	21 bp	24	6	100%(24)	Chakraborty et al., 2010
Macaca sylvanus	y	y	PL2	21 bp	*"msy"*	87	100%(*msy*)	Wendland et al., 2006
Papio Anubis	y	NA	PL2	21 bp		1	NA	Lesch et al., 1997
Papio Anubis	y	y	PL2	21 bp	23, 24	NA	83%(23), 17%(24)	Simons et al., 2011
Theropithecus gelada	y	n	PL2	NA	undetermined	30	NA	Snyder-Mackler *pers. commun.*
Ateles geoffroyi	y	NA				2	NA	Lesch et al., 1997
Callithrix jacchus	y	n		20–23 bp	11	32	100%(11)	Pascale et al., 2012
Callithrix jacchus	y	NA				1	NA	Lesch et al., 1997
Cebus apella	y	n		20–23 bp	11	25	100%(11)	Pascale et al., 2012
Galago demidovii	n	n				4	NA	Lesch et al., 1997
Mus musculus	n	n				2	NA	Lesch et al., 1997
Tupaia belangeri	n	n				3	NA	Lesch et al., 1997

(orange, apes; blue, Old World monkeys; purple, New World monkeys; green, prosimians; red, non-primate mammals).

**Homo sapiens from Japan. †Subspecies unknown. Location = polymorphic location.*

found that only 1% of the variance in amygdala activation was explained by genotype (Murphy et al., 2013). Thus, the "endophenotype" approach promoted by researchers in imaging genetics (Hariri et al., 2006) might not be the solution to the problem of small effect sizes in genetic association studies (Flint and Munafo, 2007).

Given the polygenic nature of complex traits, it is not surprising to observe small effects in association studies of isolated candidate genes. This is because multiple genes interact with each other, and the environment, to produce complex phenotypes. While the phenotypic effect of any given candidate gene may be relatively small, in reality the influence of genetics on complex behavioral phenotypes may be much larger. This is because many other genes that might be involved are usually not examined directly in genetic association studies that typically focus on one or two isolated candidate genes. Similarly, just as single candidate genes acting in isolation do not produce complex behavioral phenotypes, single endophenotypes do not produce complex behaviors either. Complex behavioral traits arise from complex neural networks, and each area of the brain involved may influence the phenotype in a small but essential way. Thus, small statistical effect sizes can belie the biological importance of a candidate gene or endophenotype because of the complexity of the system.

Lastly, the use of narrow means to quantify complex phenotypes might result in small effect sizes. Many behavioral traits are continua, with pathology residing at the extreme ends of trait distribution. However, for most traits non-pathological continuous variation constitutes the majority of observed variance. By exploring only disease outcomes, or by quantifying complex traits using data from a small number of experimental tasks, researchers run the risk of capturing only a small portion of the phenotypic variance, thereby reducing their ability to uncover meaningful genetic associations. Broader and more exhaustive characterizations of behavioral phenotypes, including those that aim to capture normal variation not just pathology, might help to solve this problem.

PARSIMONY AND THE COMPARATIVE METHOD

The comparative method is a powerful tool for testing hypotheses about evolutionary convergence (Nunn and Barton, 2001). This approach models interspecific diversity as a series of natural experiments in the relationship between phenotypes and environments. When two or more species exhibit a similar phenotype, the comparative approach seeks to find a single adaptive explanation for every instance of convergence, rather than multiple species-specific explanations. This convention is an application of the principle of parsimony, which is the best place to start when formulating hypotheses about phenotypic similarities between species.

Tandem repeats in the 5-HTT promoter exist in all primates studied to date (**Table 1**), but not in species considered to be living analogues to the ancestor of primates, such as the tree shrew (Lesch et al., 1997). This suggests that repeats at this locus arose following the divergence of the primates from their common ancestor with other mammals. While a repeated element is found in the 5-HTT promoter of all primates, only some species express a variable number of repeats. For example, all tufted capuchin (*Cebus apella*) individuals have 11 repeats (Pascale et al., 2012). Variable numbers of repeats within the 5-HTT promoter occur at one of two known locations: polymorphic location number one (PL1), which is found in apes, and polymorphic location number two (PL2), which is found in Old World monkeys (Lesch et al., 1997). All species of ape genotyped to date ($n = 5$) are polymorphic at the promoter site, with repeat lengths ranging from 14 in humans, to 23 in gray gibbons (*Hylobates muelleri*) (**Table 1**). Most apes (hominoids) possess the 16-repeat HE allele (the "long" allele) along with a high prevalence of longer repeat lengths (18–20), whose impact on levels of 5-HTT expression are unknown (Lesch et al., 1997; Inoue-Murayama et al., 2000, 2008). Notably, humans are the only hominoid in which the LE 14-repeat allele has been found. In monkeys, 5-HTTLPR polymorphisms have been best characterized in the genus *Macaca*, the extant members of which are distributed mainly throughout Asia. The most common repeat lengths found in macaques are the shorter 23-length repeat, which is functionally analogous to the human LE allele, and the longer 24-length repeat, which is analogous to the human HE allele (Lesch et al., 1997). Of the 12 macaque species genotyped to date, five are polymorphic for the LE and HE alleles, while the rest are monomorphic for either the HE allele, or for a rare repeat of different length (e.g., the *msy* repeat found in *M. sylvanus*) (**Table 1**).

The presence of LE and HE 5-HTTLPR alleles throughout the primate order suggests that independent evolution has occurred multiple times at this locus. Thus, a strong argument can be made in favor of examining this genetic variant using a broad comparative approach. With this in mind, we have developed a behavioral genetic framework that attempts to explain the evolution of 5-HTTLPR polymorphisms in primates as a function of divergent strategies for coping with fluctuating levels of competition within groups.

BEHAVIORAL GENETIC FRAMEWORK

SOCIAL COMPETITION AND 5-HTTLPR

Group living is beneficial for animals mainly because it reduces the risks of predation (Van Schaik, 1983). Yet, along with such benefits come certain costs, including competition between group members for access to mates and resources (Sterck et al., 1997). Many primates rely on social strategies to mitigate these costs (Kudo and Dunbar, 2001), and variation in sociality is associated with differential survival and reproductive success (Silk et al., 2003, 2010; Majolo et al., 2012; Brent et al., 2013a).

Some researchers have suggested that carriers of the LE allele are better able to mitigate the costs of within-group competition because they are more sensitive to social stimuli (Jansen et al., 2010; Heiming et al., 2011; Homberg and van den Hove, 2012). However, this statement implies that LE allele carriers are more successful than HE homozygotes in competitive societies. If this were true, then we would expect highly competitive species like rhesus macaques (*M. mulatta*) to be monomorphic for the LE allele, which is not the case. Therefore, we suggest that a new hypothesis is required that posits either a heterozygote advantage in competitive contexts, or that attempts to explain why both the LE and HE alleles might be similarly beneficial in the face of competition.

We propose the following framework; as with previous authors, we suggest that 5-HTTLPR is associated with an individual's ability to cope with intra-group competition. However, unlike previous authors that have focused on average differences in competition levels between species, or between groups of the same species (Wendland et al., 2006; Chakraborty et al., 2010), we suggest that the driving force underlying the evolution of this system is *variance in competition levels within a group over time*.

FLUCTUATING COMPETITION LEVELS OVER SHORT PERIODS OF TIME

Physical and social environments are dynamic. Erratic changes can occur in the physical environment in the form of stochastic fluctuations in climate, predation pressure, and food availability. Similarly, variations in the social environment can result from demographic changes, breeding seasonality, and the varying demands of parental care (e.g., lactation and perceived infanticide risk). Any of these environmental changes can result in changes in the level of competition between members of a social group. These changes can occur over extended time periods (e.g., decades), but can also represent shorter periods, such as months or even days.

Figure 1 depicts how competition levels can fluctuate over a period of one year within a hypothetical primate group. In this example, competition levels do not deviate substantially from the mean most of the time. However, dramatic environmental changes occasionally result in competition levels that are substantially elevated (or substantially reduced) (**Figure 1A**). Given information on the extent to which competition levels vary over time, species can be classified into one of two groups: those for which competition levels are highly variable over short periods of time (**Figure 1A**), and those for which they are relatively stable (**Figure 1B**).

We propose that 5-HTTLPR polymorphisms evolve in primate species with levels of intra-group competition that are highly variable over short timeframes. As outlined in greater detail below, we hypothesize that LE-allele carriers cope best when intra-group competition levels are substantially elevated above average, whereas group members that are homozygous for the HE allele cope best when competition levels do not differ substantially from the norm.

DIFFERENTIAL SENSITIVITY TO COMPETITION

Rates of aggression are highest during periods of substantially elevated levels of intra-group competition (Brent et al., 2013b), making potentially fatal injuries more likely. Hypervigilance to social threats is likely to be beneficial in the face of elevated competition. Individuals can mitigate the risks of social aggression either by withdrawing from social interactions in general, or by continuing to engage socially while employing strategies to avoid conflicts. Commonly used conflict avoidance strategies include ritualized submissive gestures and low-cost signals of benign intent (Silk et al., 2000; Flack and de Waal, 2007). Risk avoidance is likely to be most adaptive during periods of elevated competition, when the potential benefits of risky behaviors are reduced relative to the costs of taking those risks.

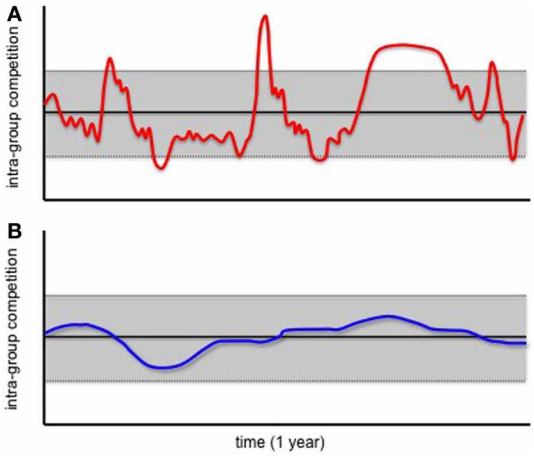

FIGURE 1 | Levels of intra-group competiton within hypothetical primate groups. One group has highly variable levels of intra-group competetion over the period of 1 year **(A)**, the other has relatively invariable levels **(B)**. Black lines indicate mean intra- group competition levels, while gray bars indicate one standard deviation above and below the mean.

LE-allele carriers tend to be risk averse and hypersensitive to both environmental stimuli and changes in reward context (Vallender et al., 2009; Jedema et al., 2010). As such, we propose that these individuals excel at attending to substantial fluctuations in competition levels and at adjusting their social strategies in response to those changes. Adjustments to social strategies that are likely to be beneficial during periods of elevated competition include heightened social vigilance and active avoidance of potentially hazardous social conflicts.

However, there are potential downsides to monitoring changes in the environment too closely. If small perturbations in the local environment do not reflect substantial changes in competition levels within the group as a whole, then it can be costly to monitor and respond to this type of random "noise." Moreover, vigilance takes both time and energy, and interrupts other important behaviors, such as feeding (Chang et al., 2013). This in turn can reduce feeding efficiency and result in a reduction in total food intake. During periods in which competition levels do not deviate substantially from the mean, we propose that LE-allele carriers tend to waste time and energy monitoring and responding to relatively unimportant changes in their local environments. In contrast, because HE homozygotes are less responsive to fluctuations in competition levels in general, they can conserve time and energy when competition levels are not substantially elevated. This would give HE homozygotes an advantage over LE-allele carriers when environmental conditions are typical.

In **Table 2**, we summarize the behavioral "best practices" to cope with highly variable levels of intra-group competition. We predict that, due to their risk aversive tendencies and biased attention to social threats, LE-allele carriers will be best suited to situations in which competition levels are substantially elevated above average. In contrast, we predict that, due to their greater willingness to take (sometimes beneficial) risks, and their

Table 2 | Behavioral "best practices" in primates with fluctuating levels of within-group competition over time.

	Average competition levels	Elevated competition levels
Social tendencies	Normal amounts of vigilance, occasionally engage in risky social interactions	Hypervigilance, strictly avoid risky social interactions
Sensitivity to changes in competition level	Ignore small fluctuations	Respond quickly to large fluctuations
Which genotype is better?	HE homozygotes	LE-allele carriers

tendencies to conserve time and energy by not being overly vigilant or attending to minor changes in competition levels, HE homozygotes will be best suited to situations when competition levels are not substantially different from mean levels (**Table 2**).

Crucially, our hypothesis assumes that levels of intra-group competition are balanced over the lifetime of group members such that LE allele carriers and HE homozygotes have similar levels of long-term survival and reproductive success. It is for this reason that we have focused mainly on fluctuations in competition levels that occur over short timescales. Otherwise, balancing selection would not occur. It should also be noted that during periods of substantially reduced competition we expect selection pressures to be relaxed. In other words, all individuals cope well with periods of relative peacefulness, regardless of their behavioral tendencies. Finally, we would like to emphasize that highly variable levels of intra-group competition can occur in groups with both high and low baseline competition levels. For example, we have no reason to believe that substantial changes away from low levels of competition are less meaningful to group members than substantial changes in groups with relatively high baseline competition levels.

TESTING THE PREDICTIONS

AT THE SPECIES LEVEL

To date, the only primates for which there is evidence of a functional 5-HTTLPR polymorphism are humans and five species of macaque (**Table 1**). It is not known whether the other species with this polymorphism exhibit differences in serotonergic functioning. Interestingly, humans and rhesus macaques (*M. mulatta*) are the two most widely distributed species of primate in the world, with humans occupying all continents, and rhesus macaques ranging from the Indian sub-continent, through the Himalayas to South-East Asian and China. The wide geographic range and behavioral flexibility of these two species have previously been linked to the presence of the LE allele (Suomi, 2006). However, the distributions of the other macaque species with the LE allele are relatively limited. Lion-tailed macaques (*M. silenus*), for example, are found only in a tiny section of Southern India (Molur et al., 2003). This suggests that geographic range size is not a good predictor of the presence/absence of the LE allele.

Alternatively, some researchers have argued that macaque species with less-tolerant social styles are more likely to have both LE and HE versions of 5-HTTLPR (Wendland et al., 2006; Canli and Lesch, 2007). However, this correlation has been rejected by more recent evidence of polymorphism among socially tolerant macaques (Chakraborty et al., 2010). One problem with the social style concept (Thierry, 2007) as applied to the question of 5-HTTLPR evolution is that it does not take into account variability in competition levels within social groups. Until classification schemes with explicit consideration of within-group variability are created, it will remain unclear whether intra-group competition levels are more variable in polymorphic compared to monomorphic species of macaque, or indeed other primates. The potential role of phylogenetic inertia (Blomberg and Garland, 2002) should also be considered in any interspecific analysis, as the genotypes of closely related species may be determined by their common ancestries more than their current socio-ecological conditions (Di Fiore and Rendall, 1994; Thierry et al., 2000).

Clearly there is also a general need for a greater understanding of 5-HTTLPR allele distribution and function across the primate order. Thus far, we have very little information about this promoter region in haplorhine primates outside of macaques, and we know almost nothing about this locus in strepsirhines. For many species that have been genotyped, sample sizes are often too small (e.g., $n = 1$) to definitively conclude whether the promoter is polymorphic or not (**Table 1**). Targeted genotyping of additional animals in a broader range of species will improve our understanding of this locus and its role in the evolution of primate behavior.

AT THE INDIVIDUAL LEVEL WITHIN SPECIES

Perhaps a more promising approach to testing our hypothesis is to examine the reproductive success of each genotype within species. However, fitness is challenging to measure in the best of circumstances, and this is especially true of long-lived animals that are slow to reproduce like primates. Nevertheless there are some tractable proxies, including number of offspring sired and subject morbidity. One study of free-ranging male rhesus macaques living on the island of Cayo Santiago, Puerto Rico, found that individuals with different 5-HTTLPR genotypes did not differ in the total number of offspring sired (Krawczak et al., 2005). That is, carriers of the LE allele had as much reproductive success as HE homozygotes. These findings suggest that balancing, rather than directional, selection is underway in the Cayo Santiago macaques, which supports our hypothesis. We can test this hypothesis further by examining differences in morbidity between individuals with different 5-HTTLPR genotypes. That is, we expect LE-allele carriers to receive fewer injuries during periods of elevated competition levels compared to HE homozygotes. This is because hypervigilance and high emotional reactivity in LE carriers should enable them to avoid aggressive encounters more effectively. In other words, the increase in morbidity associated with elevated competition levels should be greater in HE homozygotes than in LE-allele carriers.

Another approach would be to examine the response of the HPA-axis. Hormones, such as cortisol, are released in response to disruptions of homeostasis. This system triggers behavioral and physiological processes that help individuals to cope with stressors, and restore homeostasis (McEwen, 1998; McEwen and Seeman, 1999; Sapolsky, 2000; McEwen and Wingfield, 2003). Cortisol levels are therefore a good physiological indicator of how well individuals are coping with their current environments, with elevated baseline levels being indicative of frequent homeostatic disruptions. Due to their greater sensitivity to external stimuli, we predict that LE-allele carriers will have higher baseline cortisol levels compared to HE homozygotes, regardless of the competitive context. We also predict that LE-allele carriers will experience a more rapid increase in cortisol levels than HE homozygotes in response to increasing competition levels. In males, we may also expect a similar pattern for testosterone, with LE-allele carriers exhibiting a more rapid increase in testosterone levels compared to HE homozygotes in preparation for increased levels of competition. Data are currently being collected on Cayo Santiago to test these predictions in free-ranging rhesus macaques.

CONCLUSIONS

Most research on 5-HTTLPR has emphasized the negative consequences of LE alleles under adverse environmental conditions. But the sheer prevalence of these so-called "risk alleles" within human populations, and among some non-human primates, suggests that LE-allele carriers enjoy a substantial amount of reproductive success. In this paper, we have outlined a detailed hypothesis for how 5-HTTLPR polymorphisms evolved in relation to ecologically relevant selective pressures in primates. It is clear that much more work needs to be done to test the predictions of our hypothesis. But we argue that the time has come for the fields of psychiatry and imaging genetics to take evolution more seriously.

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Evolution, development, and plasticity of the human brain: from molecules to bones

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Neuroanatomical, molecular, and paleontological evidence is examined in light of human brain evolution. The brain of extant humans differs from the brains of other primates in its overall size and organization, and differences in size and organization of specific cortical areas and subcortical structures implicated into complex cognition and social and emotional processing. The human brain is also characterized by functional lateralizations, reflecting specializations of the cerebral hemispheres in humans for different types of processing, facilitating fast and reliable communication between neural cells in an enlarged brain. The features observed in the adult brain reflect human-specific patterns of brain development. Compared to the brains of other primates, the human brain takes longer to mature, promoting an extended period for establishing cortical microcircuitry and its modifications. Together, these features may underlie the prolonged period of learning and acquisition of technical and social skills necessary for survival, creating a unique cognitive and behavioral niche typical of our species. The neuroanatomical findings are in concordance with molecular analyses, which suggest a trend toward heterochrony in the expression of genes implicated in different functions. These include synaptogenesis, neuronal maturation, and plasticity in humans, mutations in genes implicated in neurite outgrowth and plasticity, and an increased role of regulatory mechanisms, potentially promoting fast modification of neuronal morphologies in response to new computational demands. At the same time, endocranial casts of fossil hominins provide an insight into the timing of the emergence of uniquely human features in the course of evolution. We conclude by proposing several ways of combining comparative neuroanatomy, molecular biology and insights gained from fossil endocasts in future research.

Keywords: pyramidal neurons, plasticity, neuropsin, brain evolution, development, amygdala, endocast, human evolution

INTRODUCTION

The search for the evolutionary emergence of neural features underlying human cognitive and behavioral specializations represents a persistent field of inquiry spanning several disciplines. From comparative neuroanatomy through molecular biology and paleoanthropological reconstructions, years of research have yielded numerous insights into features unique to the human brain, their morphological correlates, evolutionary pathways, and context of their appearance. Compared to other primates, extant humans are unique in the nature of their sociality, ecological adaptations, and, most importantly, in a complete reliance on culture as the extrasomatic, transgenerationally transmitted behavioral adaptation (Alexander, 1989; Kaplan et al., 2000; Hill et al., 2009). Throughout the evolution of the genus *Homo*, the fossil record demonstrates an increase in brain size and appearance of cortical asymmetries suggestive of functional lateralization (Falk, 1987; Holloway et al., 2004). At the same time, comparative neuroanatomical studies suggest that, in addition to an increase in size, human brain evolution was characterized by selective enlargement and reorganization of specific cortical areas (Semendeferi and Damasio, 2000; Semendeferi et al., 2001, 2011) and subcortical structures (Barger et al., 2007, 2012), potentially promoting information processing unique to our species. In parallel, human life history is characterized by an extended period of offspring dependency compared to chimpanzees, delayed onset of reproductive maturation, and long post-reproductive life-span (Bogin and Smith, 1996; Flinn, 2005; Hawkes, 2006), enabling prolonged cognitive maturation, acquisition of skills necessary for survival, and their transmission across generations.

The importance of complex morphological structures and flexible behaviors – allowing for novel responses to newly encountered selective pressures – was proposed as the key adaptation of the hominin lineage (Potts, 1998). In this sense, variability selection approached human evolution from a perspective different from fluctuating selection and developmental plasticity; it

emphasized the evolutionary emergence of traits capable of providing selective advantage to hominins in unstable conditions, without invoking changes in the reaction norm or the need for genetic polymorphisms (Potts, 1998). Among these traits, expansion of the brain and behavioral complexity emerged as the key features carrying a selective advantage during the course of human evolution.

Behavioral variability, together with a more general cognitive complexity, has been typically considered in the context of overall encephalization. However, the relationship between the brain size of fossil hominins and their behavioral complexity inferred from the archaeological remains is neither simple nor straightforward (McBrearty and Brooks, 2000; Teyssandier, 2008). Whereas the first wave of increase in brain size early in the Pleistocene coincides with the appearance of first bifacial tools, the relationship becomes less clear later in human evolution, especially when assessing cognitive capacities of early modern *H. sapiens*. Although it has been proposed that novel tool technologies, new food procurement strategies, and the emergence of representational art appeared suddenly and concurrently at 50–40 kya (Klein, 2000; Bar-Yosef, 2002), recent reports provide evidence that aspects of behavioral modernity may have already been present much earlier than that (McBrearty and Brooks, 2000; Brown et al., 2012). At the same time, anatomically modern humans were characterized by only a modest increase in the brain size compared to their predecessors (Ruff et al., 1997) leading some to suggest that the emergence of behavioral modernity may have been accompanied by subtle changes in cortical organization that cannot be inferred from the fossil record (Klein, 2000). The debate on the origin of behavioral modernity aside, changes in brain size are accompanied by numerous modifications in organization and connectivity. In the case of the neocortex, an expansion in cortical size tends to be accompanied by changes including absolute or relative size of cortical fields, enlargement of areas devoted to processing relevant sensory inputs, and changes in the amount of areas devoted to processing specific types of stimuli (Krubitzer and Kaas, 2005). Cortical expansion is often accompanied by an increase in modularity and a reduction in long axonal projections, thus decreasing the distance between neurons subserving the same set of information processing (Kaas, 2000).

A growing body of research suggests that neocortical pyramidal neurons – the basic units of cortical microcircuitry (DeFelipe et al., 2002) – display variations in homologous areas across primates, possibly underlying differences in cognitive potentials across taxa (Elston et al., 2006). As such, natural selection may have acted specifically on the morphology and organization of neurons, favoring a particular type of information processing in a given species (Kaas, 2000). When compared across primates, pyramidal neurons in humans tend to display more complex morphologies (Elston, 2003) that are capable of sampling from larger inputs and of participating in more extensive cortical networks (Jacobs and Scheibel, 2002). In all primates examined to date, pyramidal neurons are characterized by extensive morphological changes during post-natal maturation and remodeling throughout life, potentially underlying flexible behavioral responses typical of all primates. Pyramidal neurons in the human neocortex display a prolonged period of development compared to other primates (Cupp and Uemura, 1980; Petanjek et al., 2008, 2011), especially in the cortical areas characterized by expansion during human evolution, including selected areas in the prefronal cortex (PFC). Similar developmental differences can be observed in gene expression studies, with delayed peak activity of genes involved in synaptogenesis and neuronal plasticity in humans compared to chimpanzees and macaques (Liu et al., 2012). At the same time, certain genes implicated in neuronal plasticity display mutations unique to humans (Lu et al., 2007, 2009), potentially suggesting differences in regulation of these processes between humans and non-human primates.

Even though insights into the microstructure of the cortex gained from comparative neuroanatomical studies cannot be directly compared with the fossil crania, certain features of human brain development and cortical organization allow for a synthesis of paleontological, neuroanatomical, and molecular evidence in reconstructing human brain evolution. In this review, we will combine these lines of research to examine plasticity in the human brain from an evolutionary perspective. We will specifically address maturation, cortical asymmetries, and lifelong changes in human neocortical pyramidal neurons, molecular aspects underlying neocortical plasticity, and a potential time-frame for the evolution of increased plasticity in the human brain based on the insights gained from fossil endocasts. Where possible, we will refer to the evolution of subcortical structures, especially in relation to social and ecological adaptations unique to our species. Several specificities of the human brain, including its size, development, and hemispheric dominance can be examined in extant primates, traced through the course of human evolution, considered in the context of developmental patterns unique to the human brain, and supplemented by insights from molecular studies.

HUMAN BRAIN EVOLUTION: INSIGHTS FROM THE NEURONAL PHENOTYPES

During the course of human evolution, the brain underwent an increase in its overall size (Falk et al., 2000; Holloway et al., 2004), in the relative size of some of its gross components (Finlay and Darlington, 1995; Semendeferi and Damasio, 2000), and a selective enlargement of specific cortical areas and subcortical nuclei (Semendeferi et al., 2001; Barger et al., 2007). Along with changes in size came subtle modifications in organization, indicating possibly significant alterations in microcircuitry at the cellular level (Semendeferi et al., 2011; Barger et al., 2012). From an anatomical perspective, morphological characteristics of a particular cortical region reflect the number, size, and distribution of neurons within that region (DeFelipe et al., 2002). Thus, an analysis of properties and organization of neurons in homologous areas across species forms the basis for examining cortical organization from an evolutionary point of view (Kaas, 2000). Increasingly there is interest in the level of individual neurons and how they vary across functionally different cortical areas, across species, and how they change across the lifetime (Jacobs et al., 2001; Sherwood et al., 2003a; Bianchi et al., 2012). Analyses at the neuronal level enable the development of testable hypotheses linking the morphology of information processing units and their function. They can also provide insights into plastic responses to environmental

circumstances across different cortical areas, the limits of the plasticity, and possible differences in the nature or extent of plasticity across species.

At the cellular level, the neocortex consists of excitatory pyramidal and spiny stellate neurons, and of various classes of inhibitory neurons (Nieuwenhuys, 1994; Hof and Sherwood, 2007; DeFelipe et al., 2013). Despite this cellular diversity, neocortical pyramidal neurons constitute the principal class of neurons in the cortex, accounting for 70–85% of all cortical neurons (DeFelipe and Fariñas, 1992) and have been the target of a considerable number of developmental, comparative, and evolutionary studies. Pyramidal neurons form the basic units of cortical microcircuitry, determining the pattern of inputs and outputs into a particular cortical area (DeFelipe et al., 2002). In this review, we focus specifically on this morphological class of neurons. Pyramidal neurons are typically characterized by a pyramidal- or ovoid-shaped soma, the presence of one apical dendrite directed toward the pial surface, several basal dendrites emerging from sides of the soma, an axon emerging from the base of the cell body or from the proximal parts of basal dendrites, and the presence of spines representing sites of excitatory inputs onto dendrites (**Figure 1**; DeFelipe and Fariñas, 1992; Nieuwenhuys, 1994; Spruston, 2008).

In the cortex of adult primates – more specifically, macaques, chimpanzees, and humans – pyramidal neurons vary across cortical areas in the length of dendrites, branching complexity, and in number and density of dendritic spines (Cupp and Uemura, 1980; Jacobs et al., 1997, 2001; Elston, 2007; Bianchi et al., 2012). Pyramidal neurons in the primate neocortex also tend to display two trends: an increase in complexity in relatively larger cortical regions, and an increase in complexity from primary to higher-order sensory processing areas (Elston, 2003; Elston et al., 2006). In all three species, pyramidal neurons in the prefrontal cortex (PFC) tend to be longer, more branched, and more spinous compared to primary sensory areas. Across species, pyramidal neurons in the human cortex typically emerge as morphologically the most complex when compared to homologous areas of other primates, with the difference being particularly prominent in PFC pyramidal neurons (Elston, 2000; Elston et al., 2006; Bianchi et al., 2012). The prefrontal cortex comprises several cytoarchitectonically defined areas, and many of them, especially the ones within the dorsolateral PFC, are involved in complex cognitive tasks and executive functions in primates (Goldman-Rakic, 1987; Barbas, 1995). During the evolution of the human lineage, parts of the prefrontal regions, notably the frontopolar part, underwent an increase in size (Semendeferi et al., 2001) and changes in neuronal organization (Semendeferi et al., 2011), potentially indicating localized microanatomical changes related to cognitive complexity typical to humans. Analyses of pyramidal neurons in macaque, chimpanzee, and human cortex suggest that an increased complexity of PFC neurons in all species may reflect a trend toward emphasis on executive functions shared by Old World monkeys, apes, and humans (Elston, 2000; Elston et al., 2009; Bianchi et al., 2012), while the integrative role of PFC and its complex behaviors became even further emphasized in humans.

Reorganization observed in the human neocortex has been argued to parallel reorganization in some subcortical structures (Barton and Harvey, 2000). Among those, the amygdala emerges as critical in mediating social and emotional behavior in both human and non-human primates. While subcortical structures are generally considered to be conserved during primate evolution, the amygdala is anatomically connected with many neural

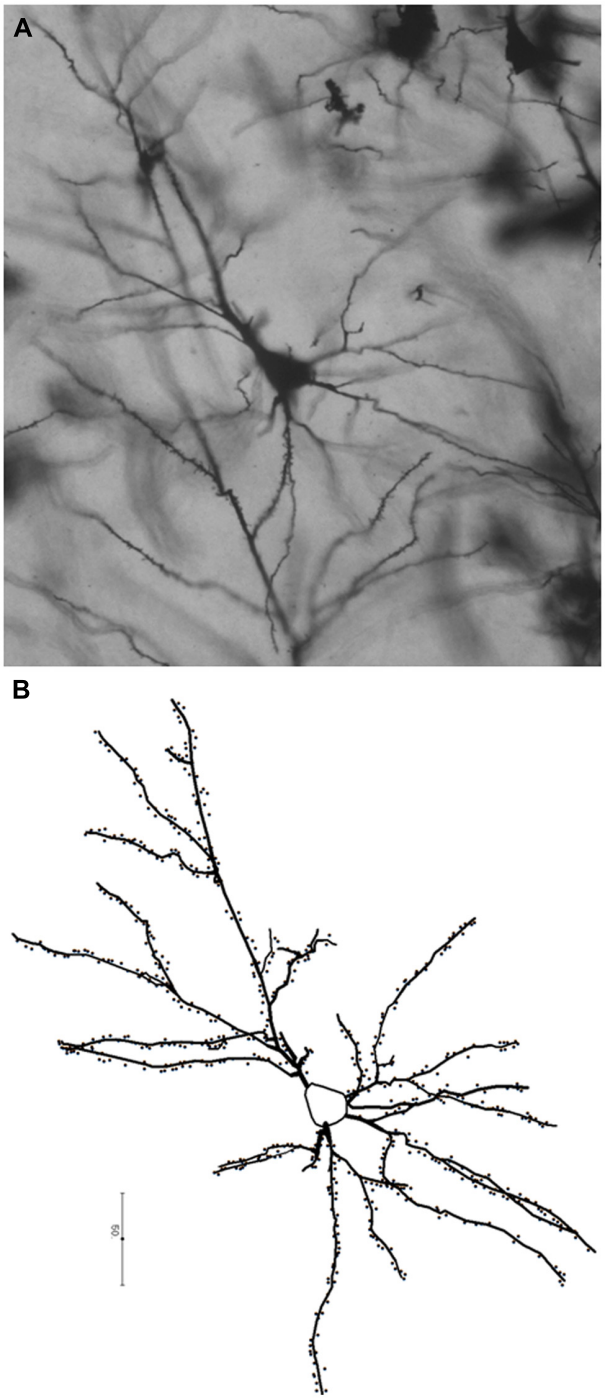

FIGURE 1 | Photomicrograph (A) and a schematic representation (B) of a pyramidal neuron from the human prefrontal cortex (BA 10) processed with the Golgi–Kopsch method. Scalebar in **(B)** is in microns.

systems that are differentially expanded in humans, such as parts of the prefrontal cortex and the temporal lobe (Stefanacci et al., 1996; Semendeferi and Damasio, 2000; Semendeferi et al., 2001; Stefanacci and Amaral, 2002). Amygdala connections with the prefrontal cortex are an important component of the social brain circuitry. Between 85 and 95% of neurons in the basal nucleus of the amygdala that project to the prefrontal cortex are pyramidal cells immunoreactive for the excitatory amino acids glutamate or aspartate (McDonald, 1996), suggesting the excitatory nature of amygdaloid inputs into the PFC.

When compared to the other members of the family Hominidae, namely chimpanzees, gorillas, bonobos, and orangutans, the amygdala in humans displays disproportional enlargement in the lateral nucleus (Barger et al., 2007, 2012) – both in terms of volume and number of neurons – suggesting a reorganization of the amygdaloid complex and an emphasis on functions processed in the lateral nucleus. This may reflect the primary connective relationship between the lateral nucleus and the temporal lobe (Stefanacci et al., 1996; Stefanacci and Amaral, 2002), which has also expanded over the course of evolution (Semendeferi and Damasio, 2000). The lateral nucleus also receives the majority of cortical sensory information directed to the amygdala (Stefanacci and Amaral, 2000, 2002; Ghashghaei and Barbas, 2002; Barbas et al., 2011), and it has been suggested that its expansion in humans may represent a heightened need to process more expansive and complex social stimuli and interactions (Barger et al., 2012). In addition, it has been argued that several features that set human cultures apart from behavioral traditions of non-human primates include socially shared regulation of behavior and emotional reinforcement of cultural rules (Hill et al., 2009), both of which may emphasize processing in central executive cortical regions as well as in the amygdala.

The neurons in the amygdala are morphologically suited to provide the foundation for their functional connectivity with numerous other brain regions. The morphology of neurons in the adult amygdala was described through Golgi studies dating back to 1928 (Gurdjian, studies in the rat). Spiny, pyramidal-like neurons and spine-sparse stellate neurons were first described by Hall (1972) in the cat and Braak and Braak (1983) carried out the first Golgi study in the human amygdala. The morphology of neurons in the basolateral complex (lateral, basal, and accessory basal nuclei) has been especially well described. In the adult amygdala, spiny, pyramidal-type neurons, and spine-sparse or aspiny stellate neurons have been identified in the basolateral complex of all species studied to date, including rats, cats, monkeys, and humans (for review see McDonald, 1992). These neurons are very similar to their counterparts in the cerebral cortex. Each of the other amygdaloid nuclei also contain at least one type of projection neuron that is spine dense and one type of spine-sparse neuron that appears to be a local circuit neuron (McDonald, 1992).

Most of the spiny neurons in the basolateral complex have a pyramid-shaped soma with a main dendrite that is longer than the other basal processes, like cortical pyramidal neurons. Unlike cortical pyramidal neurons, however, the basolateral neurons do not exhibit a preferential orientation. The soma and proximal part of the dendrites are smooth while more distal regions are characterized by pedunculated spines. The dendrites generally do not extend beyond nuclear boundaries or into the adjacent white matter, but axons have been observed to cross nuclear boundaries to join fiber bundles. This suggests that these represent projection neurons. An effective marker that can be used to identify pyramidal neurons in the basolateral complex is calcium/calmodulin-dependent protein kinase II (CaMKII), which has a critical role in long-term potentiation. When CaMKII was analyzed for neuronal localization in the basolateral nucleus of rats, virtually every pyramidal neuron appeared to be CaMKII-positive while non-pyramidal neurons were unstained (McDonald et al., 2002). Indeed, decades of studies in rats have demonstrated the importance of long-term potentiation in the amygdala for emotional learning and memory (Clugnet and LeDoux, 1990; Maren, 1999). Thus, the neurons in the basolateral complex of the amygdala are equipped to mediate the need for behavioral modifications encountered throughout life.

DENDRITIC ASYMMETRIES IN THE HUMAN CORTEX

Cerebral hemispheres in humans, more so than the hemispheres of other primates, are specialized for different types of information processing (Gazzaniga, 2000; Sun and Walsh, 2006). Although communication between the hemispheres still remains important in humans (Gazzaniga, 2000), certain functions are preferentially processed in one hemisphere over the other. In processing of spatial and face recognition, the right hemisphere exerts dominance over the left hemisphere, whereas language processing tends to be subserved by the areas located in the left hemisphere (Geschwind, 1978; Geschwind and Miller, 2001). Asymmetries observed at the gross level in the human cortex represent structural correlates of functional lateralization: adult humans display right frontal/left occipital asymmetries (Geschwind and Miller, 2001) forming an example of predictable, species-level cortical organization unique to humans that can be traced in the hominin lineage, as documented in the fossil record (see discussion below).

An important feature of cortical asymmetries is that they represent essentially a developmental phenomenon. Asymmetries can be observed in perisylvian regions and the planum temporale prenatally (30 gestational weeks; Chi et al., 1977a), and differences in gene expression between the two hemispheres are observed even earlier in the development (12–14 gestational weeks; Sun et al., 2005). During development, the right hemisphere may exhibit a faster tempo of development compared to the left hemisphere (Chi et al., 1977b; Sun et al., 2005) and the pattern of asymmetries seen in adults is either absent or reversed in infants and children. The typical adult-like pattern of asymmetry emerges during adolescence (Shaw et al., 2009). At the same time, structural asymmetries are either absent or reversed in several disorders – including dyslexia (Geschwind and Galaburda, 1985), autism, and developmental language disorder (Herbert et al., 2005). Changes in functional hemispheric dominance were reported in individuals with brain injuries (Joseph, 1986) and following corpus callosotomy (Gazzaniga et al., 1984). Taken together, these observations suggest that although development of asymmetries tends to be predictable in

humans and may be primarily under genetic control, environment processing demands appear to influence the establishment of proper functional circuitry underlying functional lateralizations in humans.

Analyses of morphology of pyramidal neurons in cortical areas associated with lateralized behaviors suggest that the lateralization observed in gross anatomical studies find their equivalent at the cellular level. In language areas, the so-called "dendritic laterality" has been reported in Broca's area, Wernicke's area, and Rolandic motor areas (Scheibel et al., 1985; Jacobs and Scheibel, 1993). The Wernicke's area equivalent in the right hemisphere was characterized by less neurophil, greater overlap among columns, and greater variability in orientation of pyramidal neurons. In the dominant (left) hemisphere, layer III pyramidal neurons were longer, more branched, and more spinous compared to the neurons in the right hemisphere. The hemispheric pattern changed with aging; in individuals older than 50 years, pyramidal neurons in the left hemisphere became more prone to degradation compared to the ones in the right hemisphere, resulting in the reversal of the dominance pattern. Unlike in younger individuals, the pyramidal cells in the left hemisphere of older individuals were shorter and less spinous than the cells in the right hemisphere (Jacobs and Scheibel, 1993). Pyramidal neurons in the language areas in the frontal lobe display a less clear pattern of hemispheric dominance. Scheibel et al. (1985) reported that the total dendritic length in Broca's area was comparable to the length of dendrites in the homologous area on the right hemisphere; the same pattern holds for Rolandic areas. The differences, however, were noted at more subtle elements of neuronal structure: pyramidal neurons in the left hemisphere were more branched and displayed greater number of high-order segments, i.e., fourth, fifth, and sixth order segments from the cell body. In the right hemisphere, pyramidal neurons in both areas displayed more lower order segments (first, second, third order) compared to the neurons in the left hemisphere. The pattern was consistent in right-handed subjects, and the hemispheric specificities was reversed in left-handed subjects (Scheibel et al., 1985). The authors suggested that the observed pattern, namely different modification of segments relative to the proximity to the cell body, reflected segment-specific developmental timing.

The segments closer to the cell body are formed during development prior to the higher-order segments, thus before the emergence of complex, lateralized behaviors. The appearance of more branched higher order segments coincides with functional maturation of the left hemisphere as the dominant hemisphere. Alternatively, as the authors suggested, higher order segments may be more plastic, and greater branching of high order segments in the left hemisphere might represent a response to higher demands of the behaviors processed in the left hemisphere (Scheibel et al., 1985).

The study by Scheibel et al. (1985) highlights an important point in examining the variability of pyramidal neurons in humans: in their adult phenotype, pyramidal neurons reflect cell-autonomous influences, as well as computational responses imposed upon them based on the area they occupy. Different parts of a pyramidal neuron may not respond in the same way to environmental influences: the parts of pyramidal neurons maturing at the time of environmental input may be more responsive in modifying their morphology, while developmentally earlier parts may remain more stable.

DEVELOPMENTAL PLASTICITY IN PYRAMIDAL NEURONS

The emergence of pyramidal neurons and their differentiation and establishment of proper synaptic connections represents the first step in the formation of cortical connectivity. In primates, cortical neurogenesis is limited to the first half of gestation. At embryonic day 40 (E40) in macaques and E43 in humans (Rakic, 1982), neuronal progenitor cells exit the cell cycle and migrate along radial glia toward their position in the developing cortical plate. Earlier born neurons are destined to occupy subgranular cortical layers (layers V/VI), whereas later born neurons migrate into supragranular layers (layers II/III; Rakic, 1982). In humans at 17 gestational weeks (gw), a set of neurons in the cortical plate starts displaying morphology typical of pyramidal neurons – large somata, three to five basal dendrites with developed secondary branches, and a distinct apical dendrite directed toward the marginal zone (Mrzljak et al., 1988). With the appearance of lamination in the cortical plate, it becomes possible to distinguish pyramidal neurons in the developing layer III from those in layer V: pyramidal cells in the developing supragranular layers appear less branched and less spinous compared to their layer V counterparts, displaying overall less mature morphology (Mrzljak et al., 1988). Despite being based on a small sample of prenatal human tissue, these studies show that already at this developmental stage layer III neurons are marked by variations – the neurons in the upper part of the layer III are less branched and shorter than their counterparts in the deeper portions of layer III (Marin-Padilla, 1970; Mrzljak et al., 1988). The differences in the morphology of pyramidal neurons based on their laminar affiliations will persist throughout development and into adulthood (Petanjek et al., 2008). Layer-specific developmental differences appear particularly prominent during the perinatal period, that is, the period marked by initial neuronal response to direct environmental stimuli (Bourgeois, 1997).

It is of particular interest that layer III pyramidal neurons in human PFC, i.e., the subset of neurons characterized by the most elaborate dendritic morphology and highest number of synaptic inputs in adulthood, are the least developed neurons at birth (Petanjek et al., 2008). The early post-natal period is marked by their extensive elaboration; by the end of the first year of life, layer III pyramidal neurons in PFC appear as developed as layer V pyramidal cells, and by the end of third year of life, they emerge as most complex neurons in the human cortex (Petanjek et al., 2008). The morphological development of pyramidal neurons tends to parallel cognitive maturation, with an increase in language abilities, working memory, and symbolic thought in human infants during the same period (Goldman-Rakic, 1987). Interestingly, further elaboration in the morphology of pyramidal neurons, although at a smaller scale, continues into adulthood (Petanjek et al., 2008), thus spanning the period of continued cognitive and behavioral maturation in humans. As environment plays a crucial role in establishing proper cortical circuitry, the immaturity of layer III pyramidal cells at birth, rapid modification in the first few post-natal years, coupled with a continued modification

until adulthood, allows for establishment of basic circuitry while enabling further individuation (*sensu* Bourgeois, 2001), depending on individual experiences and the needs of a particular social environment.

Significant changes during the post-natal period in the developing amygdala suggest that environmental inputs play an important role in specifying its morphology. It has been demonstrated both in humans (Joseph, 1999) and macaques (Harlow and Harlow, 1969) that lack of interaction with conspecifics and the inability to form attachments during the first year of life results in social and emotional abnormalities that persist throughout adulthood, possibly underlined by improper initial inputs into the amygdala from the social surrounding of an infant. As an example, humans infants suffering from neglect soon after birth tend to develop severe emotional non-responsiveness and fear of strangers, whereas those deprived of care after 6 months of age display increased need for attention, but remain unable to develop proper social adhesion (Joseph, 1999). In macaques, changes in social behavior and increased anxiety in adults are related to early life stress such as maternal separation. In turn, neonatal amygdala dysfunction has been shown to underlie non-adaptive responses to environmental and social stimuli. This suggests that alterations in amygdala development are linked with external changes in the environment. Monkeys with neonatal lesions demonstrate increased fear behavior in social interactions compared to control monkeys (Thompson et al., 1969; Prather et al., 2001). In contrast, monkeys with lesions produced in adulthood engage in greater amounts of affiliative social interactions than controls, suggesting a lack of social fear (Emery et al., 2001).

Structurally, the amygdala primodium first appears during the embryonic period in humans as a thickening in the wall of the interventricular foramen at the time that the hemispheres begin to evaginate. It is contiguous with the hippocampus and closely related to the striatum. The amygdala nuclei form by the migration of neuroblasts from the germinal layer of the striatal ridge, or ventricular eminence (also referred to as ganglionic eminence, Humphrey, 1968; Ulfig et al., 2003; Muller and O'Rahilly, 2006). At first, three main subdivisions emerge: the anterior amygdaloid area, the corticomedial complex, and the basolateral complex. The anterior amygdaloid area is identifiable first, followed shortly by the corticomedial complex (the cortical, medial, and central nuclei) and then the basolateral complex. Before the end of the embryonic period fiber connections develop between the amygdaloid nuclei and the septal, hippocampal, and diencephalic regions (Muller and O'Rahilly, 2006).

In the fifth gestational month in humans, aggregations of cell columns extend from the ventricular eminence into the basolateral complex. The presence of radial glia (demonstrated by vimentin immunoreactivity) between the columns suggests that these aggregations represent early migratory systems. In the sixth and seventh gestational months the cell columns begin to lose their connections with the ventricular eminence and fibers are no longer found between the cell columns. Finally, in the eighth and ninth month the aggregates of cell columns are no longer present and the lateral nucleus appears distinctly separate from the ventricular eminence (Ulfig et al., 2003). In parallel with this development, punctate immunolabeling of GAP-43, which is correlated with synaptogenesis (McGuire et al., 1988), appears in the fifth gestational month in the corticomedial complex and in the seventh month in the basolateral complex. By the ninth month there is no longer evidence of GAP-43 in the amygdala (Ulfig et al., 2003).

The amygdala in primates is immature at birth and its development thus depends on incoming stimuli from the environment. Differentiation of individual amygdala nuclei continues from the embryonic period through the fetal period and on into the post-natal period. Many nuclei exhibit distinct developmental profiles. For example, post-natally in macaque monkeys, the nuclei of the basolateral complex demonstrate a dramatic enlargement in volume between birth and 3 months of age, with slower growth continuing beyond 1 year. In contrast, the medial nucleus is near adult size at birth, while the volume of the central nucleus is half the adult value at birth and exhibits slow but significant growth even after 1 year of age (Chareyron et al., 2012). At a cellular level, early pyramidal neurons can be distinguished in the human amygdala by the eighth and ninth gestational months. Similarly to the pyramidal neurons in the neocortex, these early pyramidal neurons are characterized by medium diameter dendrites that emerge from pyramidal-shaped soma, a stout branching dendrite emerging from opposite pole of the soma, and an axon emerging from the base of the pyramids. The onset of synaptogenesis is delayed in the basolateral complex relative to the corticomedial complex (Ulfig et al., 2003). Since the lateral nucleus is characterized as derived in its organization in humans (Barger et al., 2007, 2012) and functions as an important part of the network processing of social and emotional stimuli, it remains possible that a prolonged period of maturation enables establishment of social and emotional bonds extending beyond the mother; a feature in particular important in humans species, where sharing offspring care represents an evolutionary strategy for increasing reproductive success (Hrdy, 2005). Compared to humans, infant care is less extensively shared among group members in great apes and most Old World monkeys, and the nature of alloparenting thus differs between humans and other primates.

Among the Efé of Central Africa, for example, by 18 weeks of age infants spend more than half a day with caregivers other than their mothers, averaging about 14 caretakers including both related and unrelated individuals (Hrdy, 2005). In comparison, a systematic study of alloparental episodes among the chimpanzees in Mahale Mountains, Tanzania, suggests that only certain members of the troop (e.g., nulliparous females) tend to display interest into handling infants, whereas parous females remain indifferent to the offspring of other females (Nishida, 1983). A similar pattern was observed among Japanese macaques (*Macaca fuscata*; Hiraiwa, 1981). Even among the species where infant sharing is quite common, such as Barbary macaques (*M. sylvanus*; Small, 1990), the mother remains the primary caretaker of the infant, and alloparenting never reaches the extent seen in humans. Similarly, the development of 'stranger distress' is delayed in human infants compared to other primates, appearing at approximately 7 months in humans, 4 months in chimpanzees, and 3 months in macaques (reviewed in LaFreniere, 2005). Although the appearance of fear reaction to strangers doubtlessly depends on other cognitive (e.g., development of the concept of the caregiver; LaFreniere, 2005)

and neural changes (e.g., neocortical maturation; Goldman-Rakic, 1987), developmental changes in the amygdala nevertheless underlie the emergent fear response in primates during the first year of life.

EPIGENETIC AND MOLECULAR ASPECTS OF HUMAN BRAIN EVOLUTION

It has been proposed that the environment mediates the establishment of neuronal morphology by two mechanisms of plasticity: experience-expectant plasticity, preparing neuronal circuits for ubiquitous environmental inputs, and experience-dependent plasticity, responsive to the circumstances unique to each individual (Greenough et al., 1987). Experience-expectant plasticity likely reflects evolutionary mechanisms emphasizing a particular type of sensory processing shared by all members of a species (Greenough et al., 1987). This is manifested by overproduction of synapses during the perinatal period in cortical areas subserving the sensory system in question, followed by a rapid pruning of synapses at the end of the period. Experience-dependent plasticity, on the other hand, is less predictable, characterized either by prolonging the period of synapse overproduction or delaying the offset of synaptic pruning (Bourgeois, 1997). Synaptogenesis in the primate visual cortex represents a typical example of experience-expectant plasticity. In rhesus macaques, rapid production of synapses in primary visual cortex (V1) begins 2 months before term, becomes intensified around birth, and ends at post-natal day 61 (P61; Bourgeois, 1997). The rate of synapse production remains stable even if the monkeys are delivered before term – thus exposed to light prematurely compared to the full-term controls – although the maturation rate of synapses appears to proceed faster in pre-term macaques (Bourgeois et al., 1989). It has been proposed (Joseph, 1999) that development of the amygdala and associated cortical regions involved in processing emotional and social stimuli represent another example of experience-expectant maturation (Harlow and Harlow, 1969; Joseph, 1999).

Experience-expectant plasticity is often associated with critical periods in development (Greenough et al., 1987) and it is in particular prominent in the maturation of sensory systems. In contrast, the basic premise of experience-dependent plasticity proposes that the opportunity to acquire complex behaviors varies across individuals and that the nature of the acquired information will differ from one animal to the next (Greenough et al., 1987). This type of plasticity underlies acquisition of multifaceted behaviors, including navigating one's social and ecological surroundings, language acquisition, and ability to acquire new technical and behavioral skills. Rather than providing a developmental window in which stimuli are necessary to establish functional circuitry, experience-dependent modifications are possible in late-maturing regions, depending on individual circumstances (Greenough et al., 1987). In macaques, rapid development of synapses proceeds uniformly in both V1 and PFC, although the two areas harbor two rudimentary different types of processing (Bourgeois et al., 1994). In humans, on the other hand, development of synaptic densities is postponed in PFC compared to other cortical regions (Huttenlocher and Dabholkar, 1997), suggesting that maturation of executive control in humans may be postponed compared to macaques, allowing for a prolonged period of modifications. Dendritic systems of pyramidal neurons in human PFC continue to mature longer than PFC neurons in macaques (Cupp and Uemura, 1980; Petanjek et al., 2008), with elaboration of dendritic branching continuing until adolescence (Petanjek et al., 2008) and maturation of spines proceeding until the third decade of life (Petanjek et al., 2011). The prolonged period of maturation of cortical microcircuitry in PFC thus encompasses two developmental stages unique to humans: childhood and adolescence (Bogin and Smith, 1996; Bogin, 1997). The additional period of cognitive plasticity in humans enables the acquisition of baseline skills necessary for successfully navigating social and ecological environments (Leigh and Park, 1998; Flinn, 2005), forming the basis for their elaboration in later life (Geary, 2005). It is important to note, however, that modifications in cortical microcircuitry continue throughout life, even without obvious pathologies or physical traumas (Jacobs and Scheibel, 2002), enabling modifications of behavioral responses to newly encountered circumstances.

A discussion about plasticity inevitably introduces the question of cell-intrinsic and epigenetic influences on the development, and the relative importance of each in influencing a particular aspect of neuronal morphology. The development of new comparative genomics, epigenetic analyses, and gene expression tools has catapulted interest in the molecular aspects of human brain evolution. Variability selection posits the importance of regulatory mechanisms of gene expression in lineages subjected to variability selection (Potts, 1998), with the activity especially prominent during development; comparative studies across primates have suggested differences in timing, increased importance of non-coding sequences, and accelerated rates of evolution of development-related genes in humans (Dorus et al., 2004; Prabhakar et al., 2006; Liu et al., 2012).

At the genomic level, several reported molecular events illustrate the complexity of human evolution. On one side, humans can acquire new genetic information. For example, KLK8 (also known as neuropsin) is a secreted-type serine protease that is involved in synaptogenesis, neurite outgrowth, and plasticity in the hippocampus and the neocortex (Mitsui et al., 1999). A human-specific point mutation gave rise to a novel functional isoform (type II) that is only expressed in humans during development in the embryo brain, suggesting a potential role in early CNS formation (Lu et al., 2007, 2009). On the other side, a loss of function is observed in the human genome, affecting a specific biochemical pathway. For example, the human deficiency of Neu5Gc is explained by the fixations of an inactivating mutation in the gene encoding CMP-*N*-acetylneuraminic acid hydroxylase, the rate-limiting enzyme in generating Neu5Gc in cells of other mammals. The mutation occurred after the split from our last common ancestor (Chou et al., 2002). Fixation in the ancestral population occurred at an unknown time thereafter and happens to be one of the first known genetic differences between humans and other hominids with an obvious biochemical readout. Together, these data are consistent with the presence of human-specific genomic alterations.

Alteration in gene expression is a common mode of evolutionary change and can result from multiple changes in the genome, affecting regulatory regions such as promoters and enhancers.

These alterations may affect gene dosage, timing and localization. Some studies suggested several differences that seem human specific: the majority of genes showing expression differences between humans and chimpanzees are upregulated in the human cortex (Cáceres et al., 2003) and show a species-specific pattern of expression (Enard et al., 2002). Gene expressions in regions involved in complex cognitive tasks tend to resemble one another, differing from the expression profiles in primary processing areas (Khaitovich et al., 2004). At the same time, comparative studies of gene expression between humans and chimpanzees suggest that the overall pattern of gene activity during the post-natal period is shared between these two species. However, compared to chimpanzees, about half of genes specific to a particular developmental stage are expressed at different levels in humans. Moreover, the difference between the two species increases over time, with the greatest difference occurring at 10 years of age (Somel et al., 2009). Several functional groups of genes involved into synaptogenesis and neuronal function display prolonged expression in humans compared to chimpanzees and macaques; in humans, their levels remain high during the first 5 years of life whereas in chimpanzees their levels decline early in the post-natal period. As a comparison, the same set of genes is elevated prenatally in macaques (Liu et al., 2012). Overall, the comparative molecular analyses of brain development suggest a tendency toward heterochrony – with a prolonged period of expression in humans compared to other primates – an increased role of regulatory mechanisms, and regional differences in gene expression across distinct brain regions.

Throughout the life of an individual, the brain faces two opposable needs: on one side, maintenance of the established functional circuitry and on the other, remodeling of the circuits in response to newly imposed computational needs (Abrous et al., 2005). Different parts of the brain may have solved this dilemma differently: regions characterized by continuous neurogenesis (e.g., hippocampus) through the addition of new neurons and the establishment of new circuitry (van Praag et al., 2002), while the non-neurogenic regions (e.g., the neocortex) through modifications in morphology of the existing neurons (Abrous et al., 2005). Morphological changes of pyramidal neurons – length, branching, and the number and distribution of dendritic spines – have been reported in the cortex of human subjects following physical (Jacobs et al., 2003) and chemical (Glantz and Lewis, 2000) changes, or behavioral manipulations in laboratory animals (Bock et al., 2005; Cerqueira et al., 2007). In a study of macaques raised in a cage without enrichment and with only visual contact with conspecifics, Bryan and Riesen (1989) reported decrease in density of spines on apical dendrites in V1 pyramidal neurons, but no reduction in their overall branching complexity. The same conditions resulted in decreased length, arborization, and density of spines on apical dendrites in primary motor cortex (M1; Bryan and Riesen, 1989), suggesting that the effects of deprivation affected neurons in different cortical regions differently, and that some parts of pyramidal morphology (e.g., spines) appear more prone to environmental influence than the others. These findings tend to be supported by gene expression analyses: expression of the immediate early genes (IEGs) in the cortex has been associated with learning and memory (Kaufmann and Worley, 1999), and electrical activity in neurons appears to mediate the effects of brain-derived neurotrophic factors (BDNF) in the developing cortex (McAllister et al., 1996). Expression of some of IEGs seems to be focused specifically on dendrites (McAllister et al., 1996) and on dendritic spines (Schratt et al., 2006), facilitating rapid morphological modifications of the neurons.

An example of changes in neuronal morphology reported by Jacobs et al. (2003) suggests that the human cortex may respond to the same stressor differently than the cortex of other mammals. Several decades after undergoing corpus callosotomy, pyramidal neurons in layer III developed unusually long, branched, and spinous basal dendrites, which descended deep into subgranular layers. These 'tap root' dendrites were in particular common in Broca's area (Jacobs et al., 2003), which shares connections with its homolog in the right hemisphere and receives numerous interhemispheric afferents from the right inferior temporal cortex (Di Virgilio and Clarke, 1997). The unusually developed basal dendrite, as the authors suggested, may represent an attempt by the neurons to maintain their function after losing cross-callosal inputs by increasing the area available for connections within the same hemisphere. In rabbits, callosotomy resulted in the decrease of spine number on oblique branches of apical dendrites in the parietal cortex, while at the same time the morphology of basal dendrites remained largely unaffected (Globus and Scheibel, 1967). These findings suggest that several factors – including the highly lateralized function of Broca's area and an increased reliance on regulatory mechanisms modulating the relationship between cell structure and neuronal activity – may underline the observed differences in the modifications of neuronal morphology between the two species. The study thus reinforces conclusions implicit to numerous comparative studies – that the cortex of each species is a product of its evolutionary history, favoring a particular way of processing or, in morphological terms, a particular pattern of cortical connectivity that is layer-, area-, and likely species-specific. While it is reasonable to expect that the neurons with the same biophysical properties will respond to the stimulus in a similar way, regardless of the species or the area they occupy, functional demands imposed upon the neurons likely differ, and their morphology will change in response to the epigenetic factors differently, depending on nature of the network they form.

THE DIRECT EVIDENCE OF HUMAN BRAIN EVOLUTION: THE FOSSIL RECORD

Fossil hominin endocasts can provide important clues to identify modifications of the human brain during evolution. An endocranial cast, or endocast, is a cast of the inner table of the cranial bones. Fossil endocasts are either naturally formed via filling and consolidation of sediment inside the braincase during the fossilization process, or artificially human-made. Endocasts of fossil specimens are the only available remnants of the morphology of their brains; as such, fossil hominin endocasts represent the only direct evidence of human brain evolution.

Endocasts preserve only some gross morphological characteristics of the brain's outer surface, as pia mater, arachoid tisue, and dura mater form a buffer preventing the brain from leaving imprints in the inner cranium. Typically, estimates of cranial capacity can be reliably extrapolated based on the endocasts,

whereas finer aspects of cerebral organization, such as gyral and sulcal pattern, remain more problematic and debatable (Holloway et al., 2004). Correlating microanatomical information with endocasts is a multistep process bridging microanatomy obtained from post-mortem histological sections with gross brain anatomy obtained from MRI. Such attempts have been made recently (e.g., Schenker et al., 2010; Annese, 2012; Yang et al., 2012), opening a promising field for future research. The second step is to evaluate the relationships between gross external neuroanatomy and endocranial morphology. Complex interactions throughout head ontogeny involve the brain, meninges, cranial vault, basicranium, face, mandible, and masticatory muscles (e.g., Moss and Young, 1960; Moss, 1968; Lieberman et al., 2000; Bastir et al., 2004; Bruner, 2004; Richtsmeier et al., 2006; Mitteroecker and Bookstein, 2008; Neubauer et al., 2009). Despite these interactions the shape of the cranial inner table (i.e., the shape of the endocast) reflects the shape of the brain until brain growth completion and throughout adulthood until incipience of brain tissue shrinkage (Courchesne et al., 2000; Resnick et al., 2003; Scahill et al., 2003; Kruggel, 2006; Sherwood et al., 2011; Ventrice, 2011). For this reason, endocranial volume and shape are used as proxies for brain size and shape.

The endocranial fossil record has been extensively reviewed (e.g., Bruner, 2003; Holloway et al., 2004; Falk, 2007, 2012). The ongoing study of the virtually reconstructed endocast of *Sahelanthropus tchadensis* (Brunet et al., 2002; Bienvenu et al., 2013), dated to 7 Ma (Mega Annum, a period of one million years) will open a unique window on the earliest stages of hominin brain evolution. Indeed, apart from this specimen, the earliest known hominin endocasts belong to australopiths dated around 3 Ma from South Africa and East Africa. They are formally separated into gracile (genus *Australopithecus*) and robust (genus *Paranthropus*) forms. Origins of the genus *Homo* are thought to be nested within genus *Australopithecus*, while robust australopiths are generally considered as side branches. The earliest *Homo* endocasts come from East Africa and date to less than 2 Ma. *Homo erectus sensu lato* is the earliest species known out of Africa around 1.8 Ma, found in Caucasus and Indonesia. *H. heidelbergensis* encompasses African and European fossils from the middle Pleistocene (between about 0.8 and 0.1 Ma). African *H. heidelbergensis* specimens may be ancestral to *H. sapiens*, while European specimens may be ancestral to *H. neanderthalensis*, Eurasian late archaic *Homo* ranging in age from about 0.2 Ma to 30,000 years ago. Australopiths are characterized by great ape-sized brains. When brain size began to increase in hominins is debated: increase in brain size began either gradually from around 3 Ma (Falk et al., 2000) or suddenly from around 2 Ma (Carlson et al., 2011; **Table 1**).

EVOLUTION OF HUMAN BRAIN ONTOGENY

The evolution of hominin brain ontogeny is attracting increasing interest (Zollikofer and Ponce de León, 2010, 2013; Leigh, 2012; Neubauer and Hublin, 2012) and deserves special attention here. Ontogeny includes growth (increase in size with age) and development (modifications in shape with age). From the growth perspective, the brain of modern humans is already bigger at birth compared to newborn chimpanzees (400 versus 145 cc; Zollikofer and Ponce de León, 2013) and it experiences a growth spurt during the first two post-natal years. This rapid initial growth does not occur in chimpanzees (Sakai et al., 2013) and it may account for our large adult brains, three to four times bigger than the brains of chimpanzees (1350 versus 385 cc; Zollikofer and Ponce de León, 2013). Brain growth slows down after the growth spurt, and brain size approaches that of adults after eruption of the first molar. From the developmental perspective, endocasts of humans and chimpanzees already have distinct shapes at birth, reflecting different prenatal ontogenies: notably, human neonates have squared-off frontal lobes (Zollikofer and Ponce de León, 2013). During early post-natal development, the human brain undergoes an extensive period of growth and there are modifications of the endocranium, including expansion in the parietal area and widening of the post-erior temporal parts (Neubauer et al., 2010). This change results in a more globular shape of the human cranium compared to both chimpanzees and late archaic *Homo* (i.e., *H. heidelbergensis* and Neanderthals; Lieberman et al., 2002; Neubauer et al., 2010; Gunz et al., 2012, but see also Ponce de León et al., 2013 for shared patterns among hominids). Although each extant ape species evolved its own ontogenetic trajectory, as exemplified by the differences between chimpanzees and bonobos (Lieberman et al., 2007; Durrleman et al., 2012), the early post-natal growth spurt and the associated "globularization phase" appear to be developmental features unique to anatomically modern humans and are either absent, or undetectable, in the developing great ape crania.

An important topic in paleoneurological studies is dating the transition from a more ape-like pattern of brain growth and development to a modern human pattern. There is some support for the idea that fossil hominin maternal pelvic dimensions can be used as an indirect source of information for neonatal brain size as in modern humans (Tague and Lovejoy, 1986), but it has also been argued that australopith female pelvic dimensions are larger than neonatal neurocranial dimensions, and obstetrical constraints were absent in australopiths as in extant great apes (Leutenegger, 1987). Moreover, taxonomic attribution of some important pelvic remains is also debated (Simpson et al., 2008; Ruff, 2010). For these reasons, we will only review the evidence coming directly from the endocasts of juvenile fossil hominins, in a chronological order.

Australopith brain ontogeny is documented mainly by the endocasts from Dikika and Taung. The Dikika child (*Australopithecus afarensis*), dated to 3.3 Ma, has an estimated age at death of approximately 3 years and an estimated endocranial volume between 275 and 330 cc (Alemseged et al., 2006). The Taung child (*A. africanus*; Dart, 1925), dated to 2.6–2.8 Ma (McKee, 1993), has an estimated age at death between 3.5 and 4 years (Lacruz et al., 2005) and an estimated endocranial volume of 405 cc (Neubauer et al., 2012). Brain ontogeny in early *H. erectus* is documented by one specimen, the 1-year-old Mojokerto child, dated to 1.8 Ma and with an estimated endocranial volume of 663 cc (Coqueugniot et al., 2004). In *H. neanderthalensis*, one specimen of special interest is the 1 to 2-week-old infant from Mezmaiskaya, Russia (Golovanova et al., 1999), dated to 0.073–0.063 Ma, with an endocranial volume estimated between 414 and 436 cc (Ponce de León et al., 2008; Gunz et al., 2012). *H. neanderthalensis* is probably the best known fossil hominin species concerning brain ontogeny, the whole range of individual ages

Table 1 | Endocranial asymmetries in selected fossil hominins.

Specimen	Species	Age	Location	Petalias	Broca's cap
Sterkfontein type 2	*Australopithecus africanus*	2.5 Ma	South Africa	No frontal petalia, occipital not preserved	Nascent?
MH1	*Australopithecus sediba*	2 Ma	South Africa	Right frontal	Nascent?
KNM-WT 17000	*Paranthropus aethiopicus*	2.5 Ma	East Africa	Right frontal-left occipital	Absent
OH 5	*Paranthropus boisei*	1.8 Ma	East Africa	Right frontal-left occipital?	Not preserved
SK 1585	*Paranthropus robustus*	1.5 Ma	South Africa	Left occipital	Absent
KNM-ER 1813	*Homo habilis*	1.8–1.9 Ma	East Africa	?*	Nascent?
KNM-ER 1470	*Homo rudolfensis*	1.8–1.9 Ma	East Africa	Pronounced right frontal-left occipital	Present
Any	Subsequent *Homo*	from 1.8 Ma	Africa, Eurasia	Pronounced right frontal-left occipital**	Present

Sources: Holloway and de la Coste-Lareymondie (1982); Holloway et al. (2004), Falk (2007), Grimaud-Hervé and Lordkipanidze (2010), Carlson et al. (2011), and Balzeau et al. (2012).

**Not scored consistently throughout the literature.*

***Most common pattern.*

being sampled, from the neonate of Mezmaiskaya to the "old man" of La Chapelle-aux-Saints.

The endocranial volume of a juvenile fossil can be compared to the endocranial volume of humans and apes of the same age in absolute terms, as a proportion of the estimated adult brain size, or as a proportion of the estimated neonatal brain size (Zollikofer and Ponce de León, 2010). For a fossil hominin species, estimated adult brain size is calculated as the average of the endocranial volumes of the conspecific adult specimens of the same sex. Estimated neonatal brain size is predicted from the regression of adult brain size versus neonate brain size in extant anthropoids (DeSilva and Lesnik, 2008). These three modes of comparison (absolute brain size, percentage of adult brain size, percentage of neonate brain size) may lead to different conclusions (**Figure 2**). Absolute brain growth curve and growth trajectory expressed as a percentage of neonatal brain size prove to be more discriminatory and reveal whether a species experiences a brain growth spurt or not, independently from adult brain size.

The Dikika endocast has the expected volume for a chimpanzee of the same age. The average estimated endocranial volume for adult female *A. afarensis* is 375–425 cc (Alemseged et al., 2006). The endocranial volume of the Dikika child expressed as a percentage of this expected adult endocranial volume is in the overlapping ranges of chimpanzees, gorillas, and humans. As a proportion of its estimated neonatal brain size, the Dikika endocast falls within the variability range of chimpanzees (Zollikofer and Ponce de León, 2013). The Taung child is within the chimpanzee range of variation concerning the percentage of adult endocranial volume and neonatal endocranial volume (Zollikofer and Ponce de León, 2013). However, its absolute endocranial volume is slightly greater than expected for a chimpanzee of similar age (Zollikofer and Ponce de León, 2013). Estimates of australopith neonate brain size are slightly larger than for chimpanzees (180 cc versus 150 cc; DeSilva and Lesnik, 2008), implying that chimpanzees and australopiths displayed different prenatal growths. The partially fused metopic suture observed in the Taung endocast highlights this potential difference with chimpanzees (Falk et al., 2012). The Taung metopic suture may be correlated with an enlarged neonate brain size, rapid early post-natal brain growth, and squaring-off of the frontal lobes.

With *H. erectus*, the ontogenetic trajectory approaches the one for modern humans. The Mojokerto child has an estimated endocranial volume which falls at the lower end of the modern human range (Zollikofer and Ponce de León, 2013). The average adult endocranial volume in *H. erectus* is lower than in modern humans; consequently, the Mojokerto child has reached a high proportion of its expected adult brain size as is the case in chimpanzees (**Figure 2A**), which led Coqueugniot and colleagues (2004) to the conclusion that the growth pattern of *H. erectus* was similar to that of chimpanzees. However, the estimated neonatal brain size of *H. erectus* is clearly larger than that of chimpanzees, probably about twice as large (Leigh, 2006; DeSilva and Lesnik, 2008; Zollikofer and Ponce de León, 2013). When expressed as a percentage of the estimated neonatal endocranial volume, which yields better discrimination among taxa (Zollikofer and Ponce de León, 2010), the Mojokerto child falls well within the modern human range and out of the chimpanzee range (**Figure 2B**). From this, it appears that *H. erectus* experienced an early post-natal brain growth spurt, although for a shorter period than modern humans, which led to smaller adult brain sizes.

As evidenced by the Mezmaiskaya specimen, the neonate endocranial volume in Neanderthals was similar to modern humans, around 400 cc (Hüppi et al., 1998; Ponce de León et al., 2008; but see Coqueugniot and Hublin, 2012). The pattern of brain growth as a proportion of adult endocranial volume is similar in *H. neanderthalensis* and modern humans. As *H. neanderthalensis* reach a higher adult endocranial volume than modern humans, they express differences in absolute brain growth and in the pattern of brain growth as a percentage of neonate endocranial volume. Higher values are reached because of a more sustained post-natal brain growth spurt. The growth pattern of *H. neanderthalensis* may indeed be similar to that for ancient fossil *H. sapiens*, as a decrease in brain size has been reported in modern humans since about 0.03 Ma (Henneberg, 1998). While *H. neanderthalensis* and *H. sapiens* have similar endocranial shapes at birth (Gunz et al., 2012; but see Ponce de León et al., 2008; Zollikofer and Ponce de León, 2013), their adult endocasts have

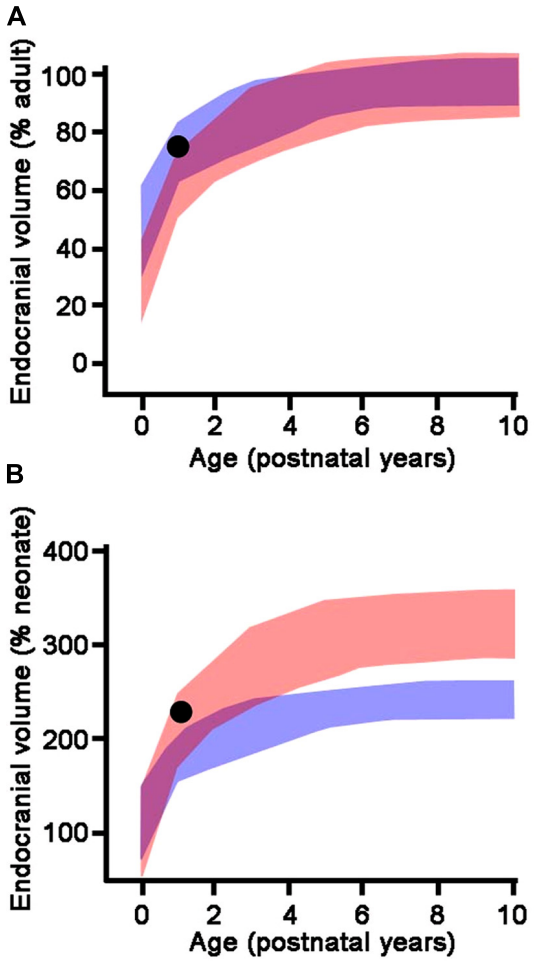

FIGURE 2 | Endocranial growth trajectories as a proportion of adult endocranial volume (A) and neonatal endocranial volume (B). Red areas represent modern human growth trajectories (mean ± 1 standard deviation). Blue areas represent growth trajectories for chimpanzees (mean ± 1 standard deviation). Purple areas represent overlap between human and chimpanzee growth trajectories. Black dot: *Homo erectus* (Mojokerto) infant dated at 1.8 Ma (average values for estimated age, expected adult endocranial volume, and predicted neonatal endocranial volume). As a percentage of its expected adult endocranial volume, the *Homo erectus* child follows a growth trajectory similar to chimpanzees, while as a percentage of its predicted neonatal endocranial volume, he falls within the modern human range of variation. This particular pattern accounts for the lower endocranial volume of *Homo erectus* compared to modern humans (high percentage of adult endocranial volume reached early in ontogeny), associated with an early postnatal brain growth spurt. Adapted from Zollikofer and Ponce de León (2010).

different shapes, and a recent study suggested differences in their brain organization (Pearce et al., 2013). Each species appears to reach similar brain size via distinct developmental pathways: the globularization phase occurring during the brain growth spurt is an autapomorphy (uniquely derived character state) of *H. sapiens* absent in Neanderthals (Lieberman et al., 2002; Gunz et al., 2012), which retain a similar developmental pattern to *H. erectus* (Bruner et al., 2003; but see also Ponce de León et al., 2013 for patterns present in great apes). Overall, the fossil record of juvenile endocasts suggests that the modern human brain growth pattern became established gradually from about 2 Ma in genus *Homo* (growth spurt), or even already in australopiths between 2 and 3 Ma (larger neonatal brain size). Conversely, the globularization phase typical of modern human brain development has so far not been established in the archaic *Homo*.

As discussed earlier, human cerebral hemispheres are highly specialized for different types of information processing (Gazzaniga, 2000), and this functional lateralization has its structural correlates at a gross level. Petalias, the differential expansion of one of the frontal or occipital lobe compared to its contralateral homologous, leave an impression and can be traced on the inner surface of the cranium. Fronto-occipital petalias occur together with a distortion of the midsagittal plane known as Yakovlevian torque, in which right frontal and left occipital lobe protrude across the midline, changing the position of the interhemispheric fissure (Toga and Thompson, 2003). Most pre-adolescent humans are characterized by a left frontal-right occipital petalial pattern (Ventrice, 2011), which reverses at adolescence, so that the most widespread adult human pattern is an association of a right frontal petalia and left occipital petalia (LeMay, 1976), in correlation with right-handedness (Galaburda et al., 1978). This pattern is also dominant in great apes, but to a lesser degree (Balzeau and Gilissen, 2010; Balzeau et al., 2012). No australopith petalial pattern approaches the pronounced right frontal-left occipital petalias observed in modern humans. Such marked petalias appear in early *Homo* around 1.8–1.9 Ma ago (**Table 1**). Taken together, the insights from the fossil endocasts suggest that structural lateralization typical of our species first appeared with the emergence of the earliest *Homo*. The petalias observed in fossil *Homo* may reflect the emphasis on preferential processing of certain tasks in one hemisphere over another, supporting the view that cerebra of the early members of our genus, in addition to an increase in size, were characterized by changes in organization and in the patterns of information processing compared to australopiths.

CHALLENGES FOR THE FUTURE

Bringing together information on the structure of the human brain, its evolution, and development from endocasts through neural systems, neuronal morphology, and epigenetic control of cortical development is a multistep task. It involves the study of the relationship between endocranial morphology and gross external neuroanatomy (**Figure 3**), as well as the relationship between gross external neuroanatomy and microanatomy (**Figure 1**). This task also goes beyond developmental influences on the establishment of adult morphology and encompasses instead the full spectrum of the human condition, including aging, cortical modifications in cognitive and neurodegenerative disorders, and comparison with closely related species. With respect to the fossil record, analyses of endocast to brain relationships remain scarce (Connolly, 1950; Fournier et al., 2011; Ventrice, 2011). From a methodological point of view, more of such studies are needed, as they are crucial in forming inferences about brain anatomy of fossil hominids based from the imprints they left on the endocranium. Notably in the context of brain aging the brain tissue shrinks from adolescence onward in humans, while the volume occupied

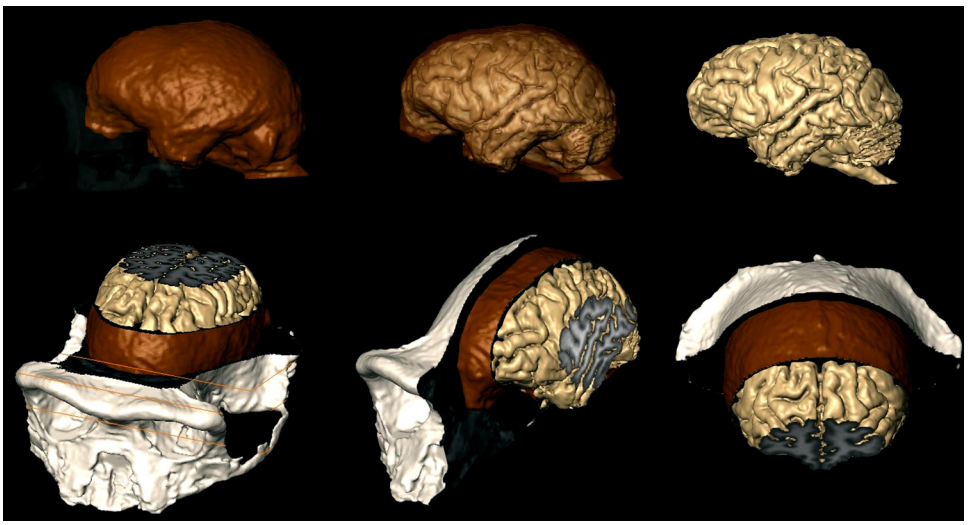

FIGURE 3 | MRI techniques used to study the brains of chimpanzees (Semendeferi et al., 2002), can now investigate the relationship between the brain and the endocast as shown here. Brain is beige; endocast is brown; exocranium is white. Top row: exocranium (left) and endocast (middle) are shown transparent. Bottom row: MRI slices reveal internal structures of the brain, meninges, and bone.

by cerebrospinal fluid and ventricles increases (Courchesne et al., 2000; Wanifuchi et al., 2002; Resnick et al., 2003; Scahill et al., 2003; Kruggel, 2006; Sherwood et al., 2011; Ventrice, 2011). Endocranial volume reaches a plateau at brain growth completion and, contrary to the brain, it is not significantly modified with aging (Courchesne et al., 2000; Scahill et al., 2003; Kruggel, 2006; but see Royle et al., 2013). It is reasonable to assume that neural tissue shrinkage within the solid, non-shrinking neurocranium, results in an increased gap between the brain and its case, filled with cerebrospinal fluid. This increase in the distance between the pial and endocranial surface with aging may explain why the endocranial impressions left by the growing brain become smoother in aging human individuals (Connolly, 1950; Grgurević et al., 2004; Zollikofer and Ponce de León, 2013). In addition, aged brain shrinkage is accompanied by a thickening of the inner cranial table (Royle et al., 2013), likely resulting in the osteoblastic filling of the endocranial gyral impressions (Tobias, 2006). The brain does not shrink significantly in aging chimpanzees (Sherwood et al., 2011) or in rhesus monkeys (Herndon et al., 1998), except in the most geriatric specimens (Herndon et al., 1999; Shamy et al., 2011). The smoothing of endocranial imprints from young adulthood in apes (Connolly, 1950) is more likely due to the continued expansion of the endocranial cavity after the completion of brain growth (Zollikofer and Ponce de León, 2013). The increased magnitude of brain shrinkage in humans may be a consequence of an extended lifespan (Sherwood et al., 2011) as increased longevity is a recent acquisition of modern humans (Caspari and Lee, 2004; Trinkaus, 2011). In this context, a study of the correlation between the level of endocranial gyral and sulcal details and age across hominin species would enable us to assess whether brain shrinkage only occurs in modern humans, or also happened in extinct human species with shorter lifespans.

Beyond endocasts, the study of the relationship between gross external neuroanatomy and microanatomy of the brain tissue is of special importance to the field of human neuroscience as a whole (e.g., Amunts et al., 1999; Schenker et al., 2010; Annese, 2012; Yang et al., 2012), and we expect that as such information becomes increasingly available, it will also assist in the meaningful interpretation of hominin endocasts in the years to come. Bridging different levels of analysis is a challenge and one good example of the types of complexities involved is provided by attempts to reconstruct the evolution of Broca's area.

Broca's area is defined cytoarchitectonically as the combination of Brodmann's areas (BA) 44 and 45. Macroanatomically, Broca's area roughly corresponds to a region in the inferior frontal lobe including the pars opercularis and the pars triangularis, bounded by specific sulci. However, the correspondence between sulcal pattern and cytoarchitectonic areas is loose in humans (Amunts et al., 1999). Broca's area is larger on the left hemisphere than its contralateral homologous area in modern humans, according to both macroanatomical MRI-based studies (Foundas et al., 1998) and histological analyses (Uylings et al., 2006). These asymmetries are reflected in human endocasts, and lateralizations in the anterior language area were traditionally scored based on the appearance of Broca's cap, i.e., the lateral and inferior bulging on the third inferior frontal convolution on the left hemisphere which corresponds to the anterior portions of Broca's area (BA 45 and BA 47; Falk, 1987; Holloway et al., 2004). The presence of the asymmetries is typically determined by comparing the measurements for width of the left and the right frontal lobe measured at the level of the cap. Even subtle differences in the measurements, coupled with qualitative observations, are indicative of differences in the extent of Broca's cap between the hemispheres (e.g., Broadfield et al., 2001). Broca's cap appears in early *Homo* around 1.8–1.9 Ma ago (**Table 1**) and great ape and australopith endocasts do not have a Broca's cap as modern humans do (Falk, 1987). Even though Broca's cap is absent in apes, an MRI-based quantification of the macroanatomical features of Broca's area homolog in African ape

brains shows a significant leftward asymmetry based on ape typical sulcal patterns for the inferior frontal lobe (Cantalupo and Hopkins, 2001; but see also Sherwood et al., 2003b). At the same time, even though Broca's area can be cytoarchitectonically defined in both humans and chimpanzees (Schenker et al., 2008), cytoarchitectonic asymmetry appears to be uniquely human (Schenker et al., 2010), suggesting that the insights gained from the three levels of evidence – endocasts, soft tissue analyses, and cytoarchitectonics – are still in need of better integration. Future studies should investigate possible asymmetries in the morphology of pyramidal neurons between the two hemispheres in additional species in primates, and ultimately asymmetric expression of genes. As discussed previously (Scheibel et al., 1985), the differences in dendritic morphology of pyramidal neurons between two hemispheres are often subtle and it remains to be seen whether morphological analysis of neurons in other hominids will shed additional light at the discrepancy between macroscopic (Cantalupo and Hopkins, 2001) and cytoarchitectonic (Schenker et al., 2010) findings. Moreover, a major challenge will be to disentangle the functional attributes of these different structural levels. Finally, a comprehensive understanding of Broca's area structure and function also needs increased sample sizes, boundaries of regions of interest consistently defined across levels to allow comparisons among different studies, and developmental insights.

Reconstructing the evolutionary emergence of the neurobiological phenotype that underlies the unique human cognitive and behavioral specializations in development and adulthood is a multistep, multifield endeavor that requires contributions from molecular, neuroanatomical, and paleontological perspectives. Although some of our focus here has been on neocortical pyramidal neurons, we attempted to demonstrate how the insights gained from different fields can be combined to construct an evolutionary history of the human brain at several levels. We focused specifically on three aspects of human brain anatomy – asymmetries, development, and age-related changes – as those provide a fertile ground for combining different perspectives in creating testable scenarios about human brain evolution. Compared to other primates, the human brain displays specificities in the morphology of excitatory neurons in the neocortex, differences in macroscopic organization, unique patterns of post-natal development, and responds to the same environmental influences differently compared to the brains of other mammals. All of these features may have been facilitated by an expanded period for establishing cortical circuitry in humans. At the same time, rapid modifications can be achieved throughout lifetime, thus providing a neural substrate for behavioral and cognitive capacities unique to our species.

Over recent decades, the number of fossil specimens has greatly expanded, and so has our knowledge of the genetic and molecular variations across primates. Long-term studies in the field have yielded additional insights into behavioral variations, adaptations, and cognitive potentials of non-human primates. The analyses of post-mortem brain material have begun to examine variation across primates – including the great apes – focusing on the organization of the brain typical of each species in the context of its behavioral, ecological, and cognitive adaptations. To understand the evolutionary history of the human brain, human behavioral specificities and the neural circuitry enabling their appearance must be placed within the larger context of similar behaviors and structures in other primates. At the same time, these characteristics must also be placed within the context of other human adaptations, exemplified by social and cognitive aspects unique to our species. While it is challenging to fully integrate the three lines of evidence discussed in this paper into a comprehensive analysis of human brain evolution, we hope to have opened a discussion across disciplines and to have provided opportunities for further studies surpassing the limitations of each individual field.

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Evolutionary appearance of von Economo's neurons in the mammalian cerebral cortex

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von Economo's neurons (VENs) are large, spindle-shaped projection neurons in layer V of the frontoinsular (FI) cortex, and the anterior cingulate cortex. During human ontogenesis, the VENs can first be differentiated at late stages of gestation, and increase in number during the first eight postnatal months. VENs have been identified in humans, chimpanzee, bonobos, gorillas, orangutan and, more recently, in the macaque. Their distribution in great apes seems to correlate with human-like social cognitive abilities and self-awareness. VENs are also found in whales, in a number of different cetaceans, and in the elephant. This phylogenetic distribution may suggest a correlation among the VENs, brain size and the "social brain." VENs may be involved in the pathogenesis of specific neurological and psychiatric diseases, such as autism, callosal agenesis and schizophrenia. VENs are selectively affected in a behavioral variant of frontotemporal dementia in which empathy, social awareness and self-control are seriously compromised, thus associating VENs with the social brain. However, the presence of VENs has also been related to special functions such as mirror self-recognition. Areas containing VENs have been related to motor awareness or sense-of-knowing, discrimination between self and other, and between self and the external environment. Along this line, VENs have been related to the "global Workspace" architecture: in accordance the VENs have been correlated to emotional and interoceptive signals by providing fast connections (large axons = fast communication) between salience-related insular and cingulate and other widely separated brain areas. Nevertheless, the lack of a characterization of their physiology and anatomical connectivity allowed only to infer their functional role based on their location and on the functional magnetic resonance imaging data. The recent finding of VENs in the anterior insula of the macaque opens the way to new insights and experimental investigations.

Keywords: insula, cingulate cortex, salience network, self-awareness, prediction, development

THE ANATOMY OF von ECONOMO'S NEURONS: AREAL AND LAMINAR DISTRIBUTION, MORPHOLOGY, CYTOCHEMICAL CHARACTERIZATION, AND CONNECTIVITY

Large spindle-shaped neurons have been described in layer V of cingulate cortex by Betz (1881) and of frontal cortex by Hammarberg (1895), and later confirmed by Ramón y Cajal (1901-1902, 1904) who first put in evidence their specific belonging to the cingulate and insular cortex. Such cells were occasionally reported in cingular and insular cortex by several authors in the first half of the 20th century, as reviewed by Butti et al. (2013).

Nevertheless, it was only von Economo and Koskinas (1925), von Economo (1926, 1927) who described in detail their morphology and distribution through the human cortex. For this reason spindle-shaped neurons were named von Economo's (VENs) thereafter (Allman et al., 2005). VENs were described by von Economo and Koskinas (1925) as large stick-, rod-like or spindle-bipolar/corkscrew-shaped neurons located in layer V of the frontoinsular (FI) cortex, and the anterior cingulate cortex (ACC; Brodmann area BA 24; Nimchinsky et al., 1995; Seeley et al., 2012). Later, VENs have been described in other areas of the limbic system, such as the subiculum and the entorhinal cortex (Ngowyang, 1936), and in the superior frontal cortex (area 9, Nimchinsky et al., 1999). The distribution of VENs in the ACC decreases rostrocaudally (Nimchinsky et al., 1995) in the subdomains of area 24 (24b > 24a > 24c; Vogt et al., 1995), and is more abundant in the FI of the right hemisphere (Allman et al., 2010; **Figure 1**).

The morphology and connectivity of VENs have been analyzed more deeply recently. VENs express neurofilament (Nimchinsky et al., 1995), the peptides neuromedin B (NMB), gastrin-releasing peptide (GRP; Allman et al., 2010) and activating-transcription factor 3 (ATF3), interleukin 4 receptor (IL4Ra), and NMB (Stimpson et al., 2011). VENs also express receptors for vasopressin 1a, dopamine D3 and serotonin 2b receptors (Allman et al., 2005). And finally, VENs express high levels of disrupted in schizophrenia SZ-1 (DISC1) (Allman et al., 2010), which is implicated in neuronal migration during development (Tomita et al., 2011), and are typically disrupted in schizophrenia (Allman et al., 2010). Their size is larger than those of layer V pyramids and layer VI fusiform neurons (Nimchinsky et al., 1995, 1999). Compared to layer V pyramidal neurons, VENs have a

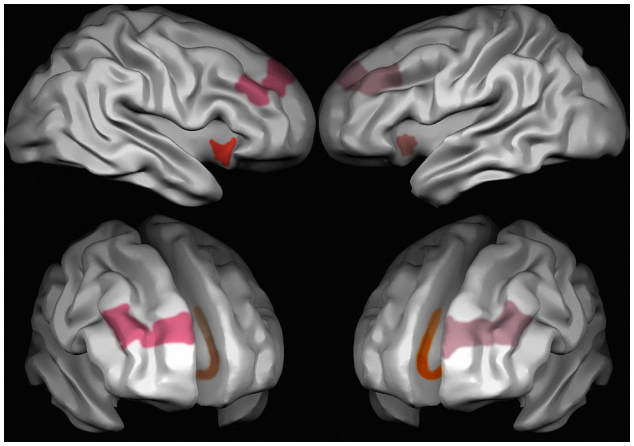

FIGURE 1 | Areas characterized by the presence of VENs in the human brain. Red, the anterior insula; pink, area 9 frontal cortex and brown, area 24 anterior cingulate cortex. Different intensities in the colors stand for different densities of VENs, which are more frequent on the right than on the left side in area 9 and in the anterior insula, and in cingulate area 24a > 24b > 24c.

vertically oriented basal dendrite, a very limited horizontal extension, and display a low number of dendritic spines (Watson et al., 2006). The vertical orientation of VENs and the narrow lateral extent of their dendritic arbors suggests that they may relay the output of cortical minicolumns (Mountcastle, 1997; Watson et al., 2006; Innocenti and Vercelli, 2010). VENs can be retrogradely labeled in fixed tissue by lipophylic dyes inserted in the white matter of the cingulum bundle (Nimchinsky et al., 1995). For this reason, and since VENs are positive for non-phosphorilated neurofilaments similarly to pyramidal neurons but not to markers of cortical interneurons such as parvalbumin, calretinin, and calcitonin (Nimchinsky et al., 1995), they have been considered as projection neurons (Golgi type I neurons).

The ontogenesis of VENs in humans is difficult to be investigated, due to the lack of specific markers. Actually, the only studies (Allman et al., 2002, 2010) report an increase in the number of VENs in late fetal period (35 weeks of gestation) with a postnatal peak at 8 months, with a decrease in some areas to reach the adult number at 4 years. It is unclear whether this is due to a late differentiation or migration of VENs, whereas layer V should be one of the first layers to form (Rakic, 1974; Zilles et al., 1986). It would also be interesting to investigate the pathway of migration of VENs, i.e., either vertical or tangential, and their origin, either from the subventricular zone or from the ganglionic eminence.

VENs express the peptides NMB and GRP, both of which are involved in the regulation of appetite. Together with the aforementioned expression of high levels of ATF3, interleukin-4 receptor a chain (IL4Ra), NMB, and GRP, proteins involved in gastrointestinal regulation and immune function, this findings led some authors (Allman et al., 2010) to infer that these cells originated in a phylogenetically ancient population of neurons in the insular cortex that are involved in the control of appetite, immune modulation and in the interoception of one's own homeostatic condition (Stimpson et al., 2011).

FUNCTIONAL CONNECTIVITY OF THE AREAS CONTAINING HIGH DENSITIES OF VENs

We have recently investigated the functional connectivity of areas containing VENs. At first, analysis on the functional connectivity of the three ROIs with the highest density of VENs [anterior insula (AI) and ACC] shows that they are part of a frontoparietal network (Vincent et al., 2008; Spreng et al., 2010), including most of the areas of the "saliency detection network" (Seeley et al., 2007a), part of the "control network" (Fox et al., 2006; Seeley et al., 2007a) and part of the network encompassing the posterior insula (Cauda et al., 2011; **Figure 2**). This finding is in line with previous studies that relate the activity of VENs to error monitoring (Dehaene and Cohen, 1994; Seeley et al., 2007a), evaluation of unexpected stimuli, and homeostatic functions (Allman et al., 2010; see Greicius et al., 2003 for a review). Indeed, the AI, one of the areas with a high density of VENs, has been repeatedly found to be active

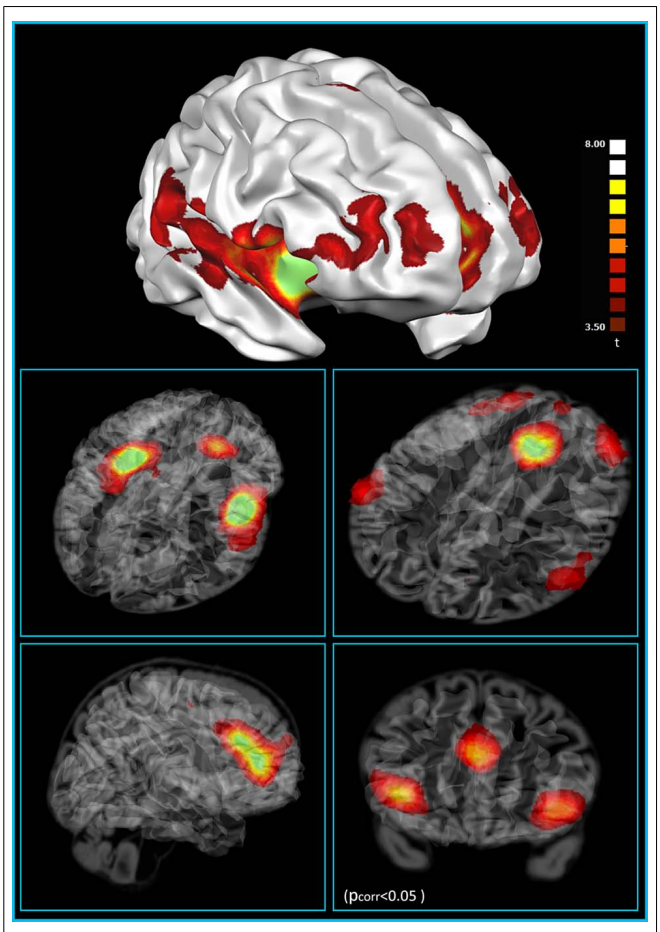

FIGURE 2 | Resting state functional connectivity of the VEN-containing areas (one sample *t*-test, corrections for multiple comparisons performed at the cluster level using a Monte Carlo simulation; $p < 0.05$), leading to a cluster threshold $k > 22$ voxels in the native resolution; maps are projected on a 3D average brain with use of the Brainvoyager QX surface tool (from Cauda et al., 2012).

in highly uncertain situations (Seeley et al., 2007a) and saliency evaluation (Menon and Uddin, 2010). VENs are also associated with basic functions of homeostatic regulation (e.g., in the regulation of hunger), and to the homeostasis of social interpersonal relationships. Related to this, it has be noted that VENs are found in species with a highly developed social life (Allman et al., 2010). Our findings on functional connectivity push further the results of the phenotype maps that show that the group of terms that involve salience, theory of mind and social brain are often found together, even though less frequently linked with VENs. The term that is most often used in association with VENs was "social brain" followed by "theory of mind" and "gut." Moreover, it is interesting, from an evolutionary point of view, to note that the circuits involving areas in which VENs are located comprise ventralmost areas in the frontal and parietal lobes and the insula, which are particularly developed in humans, even compared to great apes (Preuss, 2011).

A recent theory published by Craig (2009, 2010), posit the involvement of the ACC in a plurality of activities such as the evaluation of the emotional aspects of pain, empathy for pain, metabolic stress, hunger, pleasant touch, viewing faces of loved ones or allies, and social rejection (Seeley et al., 2007a). In this view this involvement can be explained if we consider the AI to be a site of convergence for the proprioceptive, interoceptive, emotional, cognitive, homeostatic, and environmental information originating in the posterior insula (Menon and Uddin, 2010). The AI would therefore build a coherent representation of the self in space and time, and the circuit that encompasses the AI would greatly contribute to the awareness of homeostatic changes, either stimulus-driven or stimulus-independent (Craig, 2009, 2010). This and other recent theories relate the activity of the insula to different kinds of awareness (Corbetta and Shulman, 2002; Craig, 2010; Menon and Uddin, 2010), such as motor awareness or sense-of-knowing (Kikyo et al., 2002). Recently Allman et al. (2005), Nelson et al. (2010) implicated VENs in the rapid intuition that relies on an immediate awareness, without the engagement of deliberative processes. These authors therefore specifically relate the VENs, not just to the areas wherein they are frequent observed, but to awareness. Such ability for "insight" is greatly reduced in patients affected by autism (Ben Shalom et al., 2006) and frontotemporal dementia (Day et al., 2013). On the other hand, an hyperconnectivity in the salience network (SN), involving the AI, has been observed in children with autism spectrum disorder (Uddin et al., 2013). Importantly, in the brains of individuals with these disorders, a pathological reduction of VENs has been proposed (Seeley et al., 2006; Santos et al., 2011), perhaps explaining their impaired discrimination between self and other, and between self and the external environment.

Our results (Cauda et al., 2013) also show that functional connectivity between areas with a high density of VENs is not limited to the "saliency-detection" system, but involves other areas of the frontoparietal control network. Recently, Sridharan et al. (2008) demonstrated that the activity of the right AI precedes and causally influences the activity of other areas that belong to saliency and control networks, determining the subsequent state of these two anti-correlated systems. A new theory proposed by Mesmoudi et al. (2013) and based upon some recent functional parcellation papers (Doucet et al., 2011; Cauda et al., 2012; Lee et al., 2012; to cite some), suggest a "dual intertwined rings" architecture of the brain. In this view the resting state brain networks are organized in two families. One with input–output sensorimotor family that includes visual, somatic, and auditory areas and one elaborative and association group that involve default mode, attentional and SNs. Our data on functional connectivity of VEN-rich areas suggest that these areas participate to the second "associative" network.

INVOLVEMENT OF VENs IN PATHOLOGY

Some data suggest that VENs may be involved in the pathogenesis of specific neurological and psychiatric diseases. VENs are selectively affected (69% reduction in number) in a behavioral variant of frontotemporal dementia in which empathy, social awareness and self-control are seriously compromised (Seeley et al., 2006, 2007a; Seeley, 2008). This reduction in number is specific for this disease, since it does not occur in Alzheimer's disease (AD; Kim et al., 2012 cerebral cortex). On the contrary, other authors reported a 60% loss of VENs in the ACC also in end-stage AD (Nimchinsky et al., 1995), possibly due to the different stage considered. From a functional point of view, the involvement of VENs could be correlated with apathy when occurring in the ACC.

A reduction in the number of VENs is associated with agenesis of the corpus callosum (CC; Kaufman et al., 2008), while ischemic lesions of the CC do not affect the number of VENs (Allman et al., 2010). The reduction in VEN number correlates with the extent of callosal agenesis, being almost totally absent in the total agenesis of the CC (Kaufman et al., 2008). Further studies would be needed to investigate whether this reduced number of VENs is due to a failure in development or migration, or to increased developmentally regulated apoptosis. The finding that stroke in the CC does not affect VENs supports the idea that their reduced number in CC agenesis is mostly due to developmental defects. Actually, whereas patients with callosal agenesis show, among other symptoms, emotional immaturity, lack of introspection, impaired social competence, general deficits in social judgment and planning, and poor communication of emotions together with diminished self-awareness (Paul et al., 2007), patients in which stroke affects the CC do not. Some of the behavioral deficits observed in callosal agenesis overlap with those reported in autism and schizophrenia.

A decrease in the number of VENs has been implicated in autism as well (Simms et al., 2009); studying a group of autistic patients compared to normal controls, in three out of nine cases an increase in the number of VEN and in six cases a decrease have been reported, and also the dorsocaudal decrease in VEN distribution was altered. This finding is disputed by Santos et al. (2011), who instead reports just an increase in this cell type and by Kennedy et al. (2007) that find no differences in FI VENs between the pathologic and the control group. In any case autism is such a multifarious disorder that might well be compatible with different phenotypes relatively to VENs (Uddin et al., 2013).

Also studies on schizophrenia led to contradictory results. In fact, stereological quantitative studies on the number of VENs in the ACC of patients affected by schizophrenia did not show significant differences between the schizophrenic and the control groups (Brüne et al., 2010). On the other hand, an early onset subgroup displayed a lateralized decrease in VEN number in the right ACC: the protein DISC1, involved in schizophrenia, is preferentially expressed in VENs, and the younger the age of onset of schizophrenia, the lower is the density of VENs in the right ACC (Brüne et al., 2010). This result is in line to the recent demonstration of an aberrant interaction of two large scale brain networks: the executive system, anchored in the dorsolateral prefrontal cortex and the saliency detection system, anchored principally in the right anterior insular cortex in schizophrenic patients (Palaniyappan et al., 2013). Changes in VEN number have been also associated to suicide behavior (Brüne et al., 2011): here VENs are increased in the right ACC, suggesting that an excess of interoception, emotional awareness and self-analysis might be involved in their suicidal behavior.

The finding that VEN's number is altered in FTD, autism and schizophrenia, developmental and degenerative diseases in which the social brain is affected, further supports a role of VENs in mammals in which the social brain has acquired a specific relevance living in large and socially complex groups (Dunbar, 1998).

AN EVOLUTIONARY PERSPECTIVE FOR VENs

VENs have been identified in the ACC of the great apes, including bonobos (*Pan paniscus*), common chimpanzees (*Pan troglodytes*), gorillas (*Gorilla gorilla*), and orangutans (*Pongo pygmaeus* and *Pongo abelii*; Nimchinsky et al., 1999). The previous finding of spindle-shaped, VEN-putative neurons in the ring-tailed lemur (*Lemur catta*) and in the chimpanzee (Rose, 1927, 1928) was not confirmed by more recent studies (Nimchinsky et al., 1999). VENs are also found in whales (Hof and Van der Gucht, 2007), and in a number of different cetaceans (with different brain sizes) including the bottlenose dolphin (*Tursiops truncatus*), Risso's dolphin (*Grampus griseus*), the beluga whale (*Delphinapterus leucas*), and humpback whale (*Megaptera novaeangliae*; Hof and Van der Gucht, 2007; Butti and Hof, 2010); they have also been observed in the brain of the elephant (*Loxodonta africana*, *Elephas maximus*; Hakeem et al., 2009). Their number decreases, as percentage of layer pyramidal neurons in primates, elephants and cetaceans (for a review, see Butti et al., 2013). Of interest is the occurrence of frequent VENs in all cortical areas in the pygmy hippopotamus, a close relative of cetaceans (Butti and Hof, 2010), whereas they are rare in the neocortex of the manatee, a close relative of elephants (Hakeem et al., 2009; Butti and Hof, 2010).

An evolutionary perspective on the involvement of VENs neurons in saliency detection tasks is supported by the finding that the cells are found mostly in animals with a large brain (>300 *g*), but their density is not correlated with relative brain size and encephalization (Allman et al., 2010). In fact, the increase in brain size could causes a conduction delay, i.e., longer time required for the transmission of information, due to the increased distance between connected cell groups. Large VENs, with large diameter axons and high conduction speed, could allow rapid information flow, and would represent an adaptive response to the brain enlargement. Therefore, VENs could provide long-range axons for conveying information as part of a saliency network that may have emerged as a consequence of a larger brain size (Allman et al., 2010). An extension of this hypothesis is that the VENs in FI cortex serve to rapidly relay information to other parts of the brain (Allman et al., 2011). Indeed VENs seem to be especially tailored to convey such information within restricted cortical domains (Buxhoeveden and Casanova, 2002).

This phylogenetic distribution (**Figure 3**) has led to the minimalist hypothesis that the presence of VENs is correlated to brain size; however, others have argued that the presence of VENs is related to special functions such as mirror self-recognition. Additionally, a higher proportion of VENs in human brains are immunoreactive for ATF3, IL4Ra, and NMB compared to the brains of other apes: no other neuron type in layer V of the ACC displays such a significant species difference in the percentage of immunoreactive neurons (Stimpson et al., 2011).

Based on their restricted location and on their specific morphology, VENs would represent the upper motor neurons of the interoceptive system, as well as Betz cells for the motor system and the Meynert cells for the visual cortex.

On the other hand, it has also been proposed that VENs characterize species with common adaptive pressures notwithstanding their divergent evolutionary histories, and which share social, cognitive, and emotional circuits of VEN-containing regions processing fundamental functions for social survival such as strategic communication and the appearance of social hierarchy among members (Hof and Van der Gucht, 2007; Butti and Hof, 2010).

The hypothesis that VENs in humans are implicated in the conscious perception of bodily states and in its integration in conscious decisional processing was initially evoked by Allman et al. (2005). This immediate and complex form of cognition can be also defined as "intuition" or "gut feeling." The strong labeling of VENs by dopamine D3 and serotonin 2b receptors, involved in signaling the expectation of reward and punishment, respectively (Daw et al., 2002; Sokoloff and Schwartz, 2002), and the strong expression of serotonin 2b receptors in VENs, which can also be found in gastrointestinal cells, was used to support this hypothesis (Baumgarten and Göthert, 1997). The expression in VENs of high levels of bombesin-like peptides, namely NMB and GRP, involved in the peripheral control of digestion and also known to participate in the conscious awareness of bodily states (Allman et al., 2010, 2011; Stimpson et al., 2011), further support this view. The role of the right AI in self-awareness (for review see Craig, 2009) together with the recent findings of Kim et al. (2012) showing that a loss of VENs in the right FI is correlated with symptom severity in bvFTD, indicates that VENs may play a role in interoceptive awareness.

Nevertheless, the increasing evidence for VENs through different species, some of which not closely related to humans, has somewhat challenged to idea of VENs as "the neurons which makes us human" suggesting that they could subserve a more

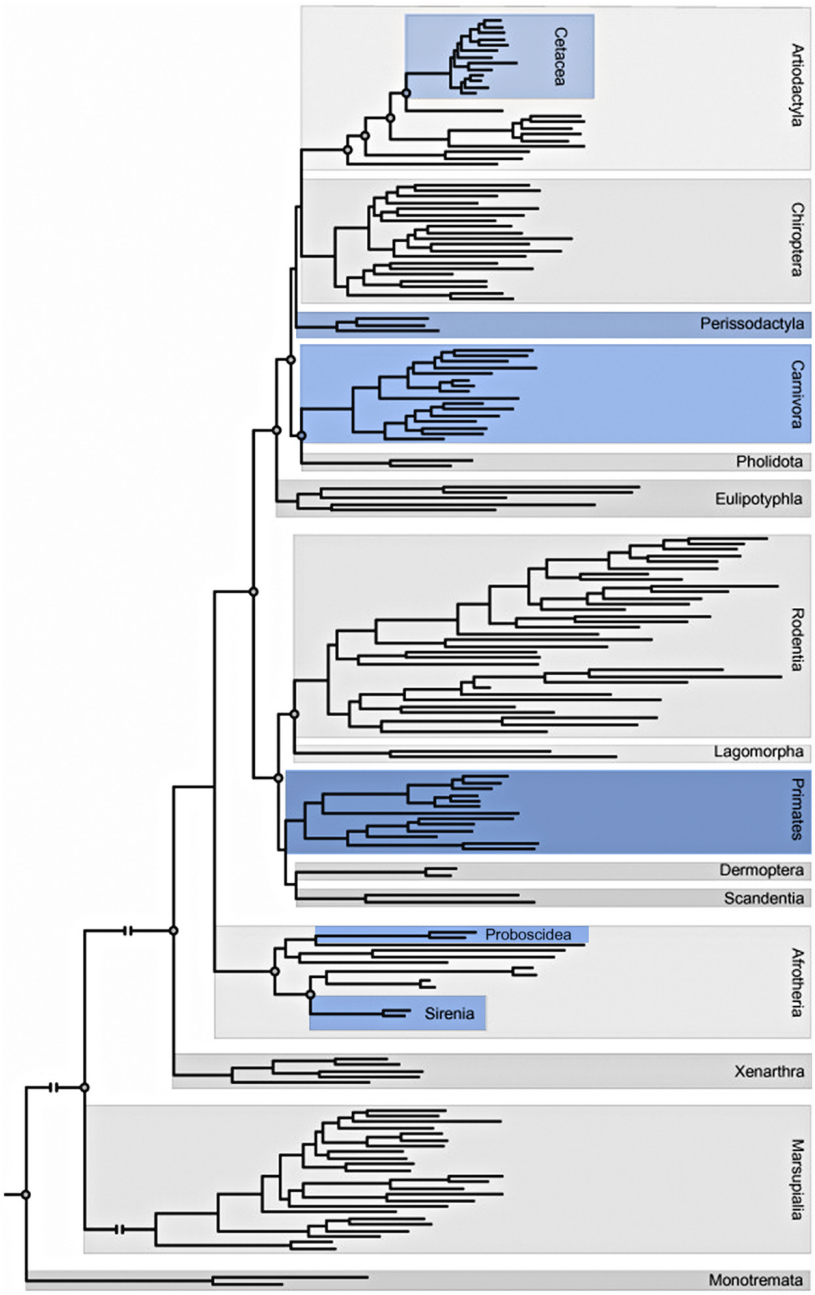

FIGURE 3 | Adaptation of the phylogeny of placental mammals including Orders and Superorders (Butti et al., 2013; Gatesy et al., 2013). Blue indicates orders that contain at least one species in which VENs have been described.

basic role in the networks in which FI and ACC are involved. In fact, recent and very accurate studies reported the occurrence of VENs in the ventral AI of two species of macaque monkeys, rhesus, and cynomolgus (Evrard et al., 2012). This backdates the emergence of VENs in primates from hominids (15 million years ago) to 25 million years ago, at the time of divergence between cercopithecids and hominids (Fabre et al., 2009). The ventral AI of the monkey has been related to both motor and sensory visceral functions (Kaada et al., 1949), which reminds of the visceral activity of the human insula (Craig, 2005). It has been hypothesized that VENs might project to visceral autonomic nuclei, such as the periaqueductal gray and the parabrachial nucleus which are involved in interoception (Craig, 2002; Allman et al., 2005; Seeley, 2008; Butti et al., 2009).

On the other hand, the finding of VENs in the macaque monkeys does not contradict their candidate role in self-awareness and social behavior, as suggested above, even though monkey

are probably less aware of the self than hominids (Anderson and Gallup, 2011). Nevertheless, these could be new functions taken up by VENs in addition to their interoceptive, autonomic role during phylogenesis. The occurrence of VENs in macaques will allow to investigate the anatomical connectivity of these neurons by tract tracing *in vivo* (Critchley and Seth, 2012; Evrard et al., 2012). Moreover, this finding should stimulate further studies in other species allowing experimental manipulations (Critchley and Seth, 2012), in parallel with the possibility to investigate their anatomical connectivity in humans with tractography (Jbabdi et al., 2013).

SUB-NETWORKS IN THE FUNCTIONAL CONNECTIVITY AND LATERALIZATION OF AREAS CONTAINING VENs

Recent findings underscore the hierarchical structural organization of cerebral networks, and suggest that the majority of cerebral networks may be further divided into sub-clusters (Bassett et al., 2008; Ferrarini et al., 2009; He et al., 2009; Meunier et al., 2009). This fact is well known to Researchers that perform tract tracing, indeed most cortical areas contain a massive and tight intermingling of neurons projecting to very different brain regions (Zhong and Rockland, 2003; Kennedy et al., 2013; Van Essen and Ugurbil, 2013). In our studies (Cauda et al., 2012), we analyzed the presence of sub-networks in the pattern of functional connectivity of areas with a high density of VEN's VENs'. By applying fuzzy clustering (Cauda et al., 2013) techniques we divided the network encompassing the AI and the ACC into four sub-networks: the main sub-network was composed of areas of the saliency system (**Figures 4** and **5**), and showed a right lateralization, consistent with the finding of a higher density of VENs in the right insula and cingulate cortex (Allman et al., 2011), and with the report that these cortical areas are thicker in the right hemisphere of normal subjects. Such asymmetry may be explained by Craig's theory on the asymmetry of the autonomic nervous system (Craig, 2005). In this theory Craig put in evidence that the right hemisphere is more related to sympathetic activation, whereas the left hemisphere is more related to parasympathetic activation; such asymmetry is also consistent with the right lateralization of the saliency detection function that evaluates the potential dangerousness of a stimulus for the survival of the organism (Craig, 2005). The right FI would also play a role in mapping internal arousal and conscious emotional awareness as explained in some recent papers by Craig (2002, 2003, 2009), Critchley (2004). The other three clusters were in part pertaining to the frontoparietal control network, but also of default mode network (Raichle and Snyder, 2007), control network (Menon and Uddin, 2010), altogether these clusters constitute a cognitive ensemble called parieto-temporal-frontal (PTF) ring that is related to attention, language, working memory, motivation and biological regulation and rhythms. The last cluster (Cauda et al., 2011) or auditory-visual, visual-somatic and auditory-somatic (VSA) ring is related to sensorimotor and visual areas (Mesmoudi et al., 2013). These two rings have been recently demonstrated to support a "dual integrative process" were the VSA sensorimotor areas perform fast real-time multimodal integration and PTF areas perform a cognitive multimodal integration (Mesmoudi et al., 2013). In fact, the brain networks constantly communicate with each other and have partially correlated activities (Jafri et al., 2008; Deshpande et al., 2011). Some areas exert a causal influence on the communication between networks, as does AI and central executive network (CEN) on the control and default mode networks (Sridharan et al., 2008; Chen et al., 2013). This causal influence have been recently demonstrated to be modified in patient suffering from schizophrenia (Palaniyappan et al., 2013). It has been suggested that the communication between brain networks may happen through "hubs" (Sporns et al., 2007; Buckner et al., 2009; Zamora-Lopez et al., 2010), areas that are common to two or more networks and that facilitate the transport of information.

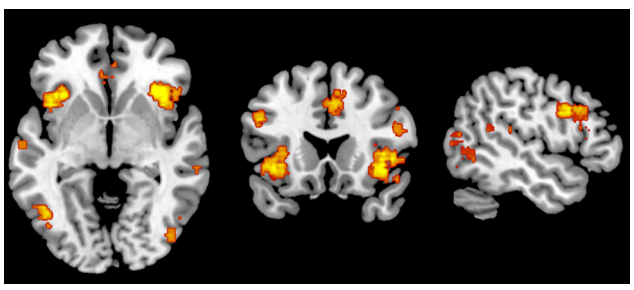

FIGURE 4 | Metaanalytic representation of the salience network (www.neurosynth.org).

Behavioral networks that more frequently activate cortical areas that have VENs are those associated with memory, emotions, attention, interoception, pain and action execution. All of these domains are coherent with the salience processing function and with subsequent activation of effector circuits related to the insula and dorsal cingulate cortex. We found an activation of the AI and of the ACC (Cauda et al., 2012). Indeed, AI and ACC are major components of the system for the flexible control of goal-directed behavior, as recently suggested by Dosenbach et al. (2006). In fact, all studies with functional magnetic resonance imaging (fMRI) paradigm require high attention from the subject. This network for goal-directed behavior is therefore necessarily activated during an activity such as fMRI task that requires sustained attention. It should be mentioned, that although our results cannot be taken as specific for VENs neurons, as the areas under exam present an intermix of different types of neuron, however, in this study we demonstrate that the VEN rich areas have a specific connectivity and probably a hierarchical sub-network structure.

Our data are in agreement with those of other authors, who described an anatomical and functional lateralization in cortical areas containing VENs, already during perinatal development (Allman et al., 2002, 2010).

PREDICTION, THE INSULA AND VENs

The term "prediction," as well as "preparation, anticipation, prospection, or expectations," refers to "any type of processing which incorporates or generates not just information about the past and the present, but also future states of the body and of the environment" (Bubic et al., 2010). These terms do not forcedly bear the same meaning, but they can be hardly differentiated.

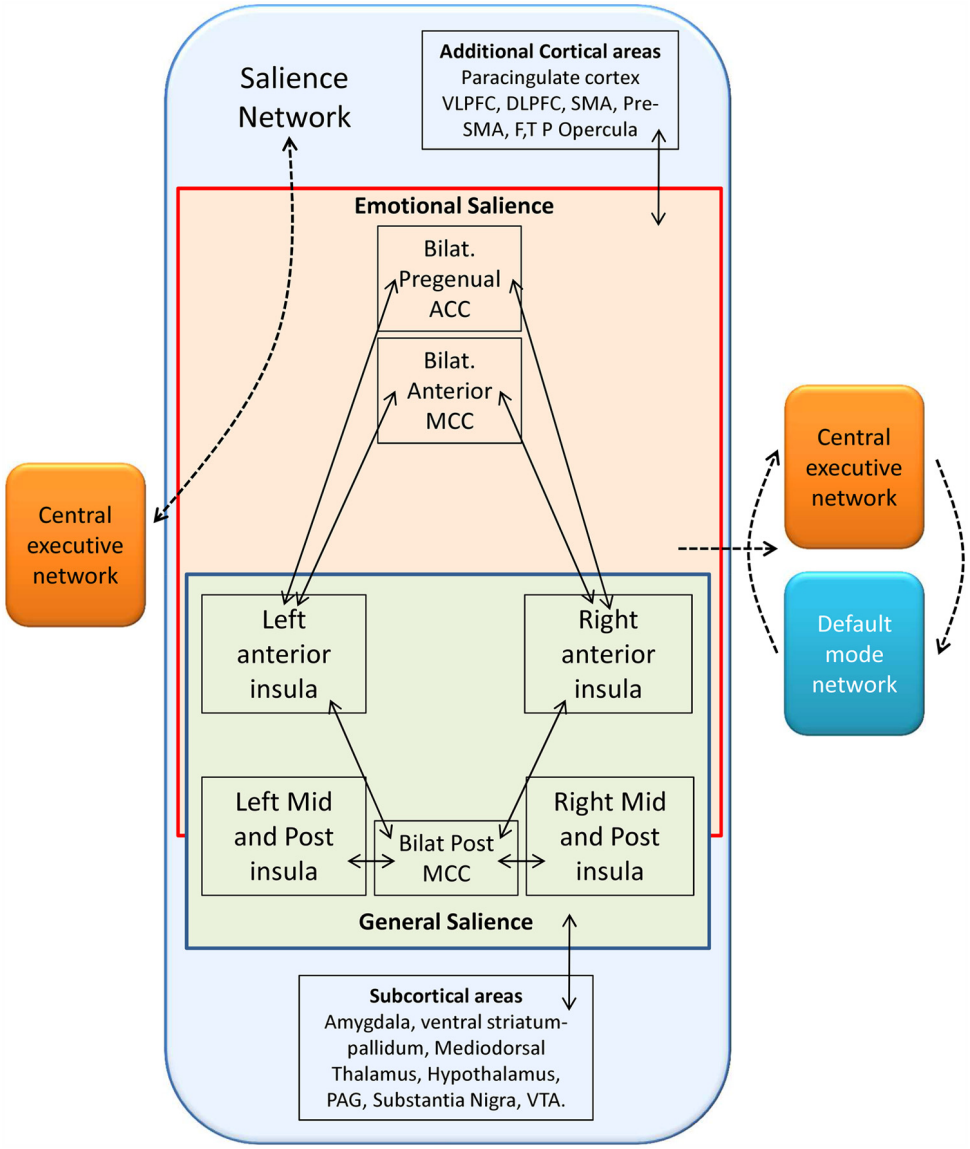

FIGURE 5 | Schematic representation of functional connectivity in the salience network following Seeley et al. (2007b), Taylor et al. (2009). The solid lines represent cortical areas found to be functionally connected in fMRI studies (Seeley et al., 2007b; Taylor et al., 2009). The dashed lines represent distinct functional networks and their proposed interactions among these regions. The salience network, characterized by the presence of VENs, can be subdivided in one emotional and one general salience networks both conveying in the anterior insula, whose function as a possible switch node between salience and executive control networks on the left (Seeley et al., 2007a), and as a switch among salience, central executive, and default mode functional networks on the right (Seeley et al., 2007b; Sridharan et al., 2008; Taylor et al., 2009). F, frontal; MCC, midcingulate cortex; P, parietal; SMA, supplementary motor area; T, temporal; VLPFC, ventrolateral prefrontal cortex. Redrawn from Butti et al. (2013).

Anyway, all of them underscore the relevance of top-down processing and of how previous knowledge drives and guides present event processing, either of sensory, motor or emotional nature (**Figure 6**).

Interoceptive aspects of emotion led to the theories of the "sentient self" (Craig, 2002, 2009), the "interoceptive awareness" (Critchley et al., 2004) and of the interoceptive predictive model in all of which the insula plays a key role (Critchley and Seth, 2012; Seth et al., 2012; Seth and Critchley, 2013). Some recent works (Ploran et al., 2007; Craig, 2010; Nelson et al., 2010) directly suggest that the insular cortex may be involved in awareness. This hypothesis was initially suggested by Kikyo et al. (2002) who inspected the neural correlates of the "feel of knowing" finding an involvement of the anterior insular cortex. The AI have been proposed to participate in intuition, insight and interoceptive predictive coding (Aziz-Zadeh et al., 2009; Allman et al., 2011). This interoception-related predictive activity is performed by comparing predicted to actual interoceptive signals (Paulus and Stein, 2006; Seth et al., 2012; Seth and Critchley, 2013). Indeed the anterior insular cortex may constitute a possible locus

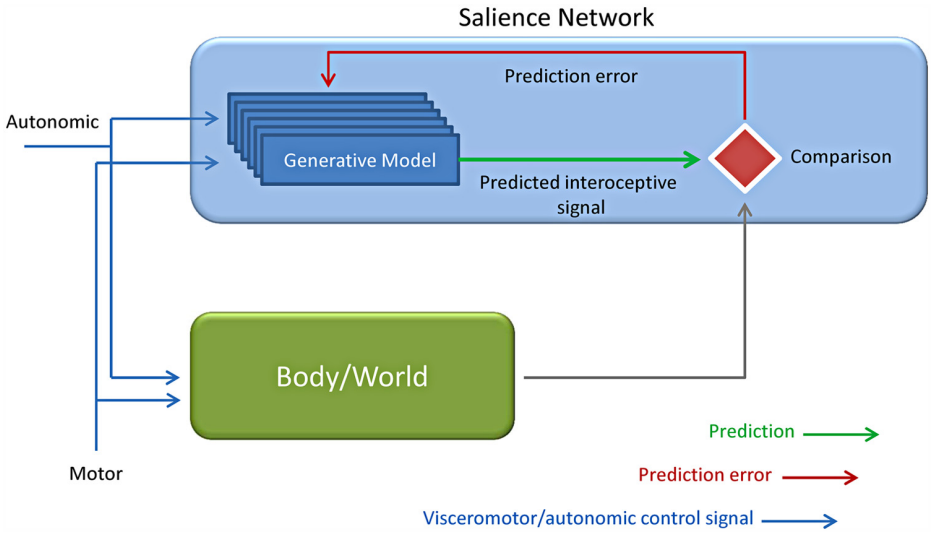

FIGURE 6 | Predictive coding applied to interoception. Based on the motor and autonomic control signals, a generative model is evoked together with interoceptive responses from the autonomic control (Body) and the environment (World). The interoceptive predicted (intero pred) responses by the generative model are finally compared to the incoming input by the body /world and used for predicting the consequences of one's own actions (Adapted from Bubic et al., 2010; Critchley and Seth, 2012; Seth et al., 2012).

for comparator mechanisms that underly interoceptive predictive coding. This evidence is confirmed by the demonstrated relevance of anterior insular cortex for interoceptive representation and observations reward-related prediction error signals as suggested by findings obtained in different contexts (Singer et al., 2009; Palaniyappan and Liddle, 2012; Seth et al., 2012). Fast connections within the salience detection system and with anterior cingulate and visceromotor systems are preconditions that allow a prompt updating of generative models (Critchley and Seth, 2012; Palaniyappan and Liddle, 2012; Seth et al., 2012). Given the large size of VEN axons these neurons have been hypothesized to provide fast communication between VEN-rich areas and other areas brain (Allman et al., 2011).This hypothesis, although mostly speculative, received an interesting confirmation in a recent study by Chen et al. (2013). In this experiment they demonstrated a directional causal relationship by which a dorsolateral prefrontal node situated within the CEN/SN compound inhibits CEN/SN connectivity with the MPFC portion of the DMN.

Similarly, VENs have been related to the "global Workspace" architecture: according to this hypothesis the VENs are strongly related to emotional and interoceptive signals by providing fast connections between salience-related insular and cingulate and other widely separated brain areas (Dehaene and Changeux, 2011).

AUTHOR CONTRIBUTIONS

Alessandro Vercelli wrote the manuscript together with Franco Cauda, who also prepared the figures. Giuliano Carlo Geminiani supervised the work and revised the manuscript.

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Evolution and development of interhemispheric connections in the vertebrate forebrain

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Axonal connections between the left and right sides of the brain are crucial for bilateral integration of lateralized sensory, motor, and associative functions. Throughout vertebrate species, forebrain commissures share a conserved developmental plan, a similar position relative to each other within the brain and similar patterns of connectivity. However, major events in the evolution of the vertebrate brain, such as the expansion of the telencephalon in tetrapods and the origin of the six-layered isocortex in mammals, resulted in the emergence and diversification of new commissural routes. These new interhemispheric connections include the pallial commissure, which appeared in the ancestors of tetrapods and connects the left and right sides of the medial pallium (hippocampus in mammals), and the corpus callosum, which is exclusive to eutherian (placental) mammals and connects both isocortical hemispheres. A comparative analysis of commissural systems in vertebrates reveals that the emergence of new commissural routes may have involved co-option of developmental mechanisms and anatomical substrates of preexistent commissural pathways. One of the embryonic regions of interest for studying these processes is the commissural plate, a portion of the early telencephalic midline that provides molecular specification and a cellular scaffold for the development of commissural axons. Further investigations into these embryonic processes in carefully selected species will provide insights not only into the mechanisms driving commissural evolution, but also regarding more general biological problems such as the role of developmental plasticity in evolutionary change.

Keywords: anterior commissure, axon guidance, commissural plate, comparative neuroanatomy, corpus callosum, hippocampal commissure

INTRODUCTION

In animals with bilateral symmetry, integration between the left and right sides of the body is crucial for processing lateralized sensory-motor functions. This is accomplished by axonal connections between the two sides of the nervous system, known as commissures. Commissural systems are present throughout vertebrate and invertebrate species (Arendt et al., 2008; Semmler et al., 2010), and similar mechanisms of axon guidance across the midline suggest the conservation of these developmental processes from a common bilaterian ancestor (Brose et al., 1999; Hirth and Reichert, 2007; Round and Stein, 2007; Evans and Bashaw, 2012).

During vertebrate evolution, several brain developmental events have been conserved from lampreys to humans, possibly explaining the broad anatomical similarity of adult forebrain commissures across species. However, diversification of the telencephalic commissures in mammals, including new axonal routes in diprotodont marsupials and the origin of the corpus callosum in eutherian (placental) mammals, illustrate natural examples of diversity in the developmental mechanisms involved in commissure formation.

Development of commissures entails a sequence of events involving morphogenic area patterning, cell-type specification, neuron-glia interactions, production and reception of guidance cues, axonal growth and navigation, and activity-dependent establishment of contralateral connections. In humans, disorders affecting these events at any stage can prevent the normal formation of the commissures, resulting in mild to severe sensory-motor and cognitive conditions (for specific review, see Paul et al., 2007). Therefore, understanding the fundamental processes directing commissure formation remains an important challenge for neuroscientists. One way to address this includes adopting an evolutionary-developmental perspective, i.e., to compare experimental data on commissure development and function from different species while considering the phylogenetic relationships between them. This allows the categorization of developmental processes as conserved or derived within lineages, thus outlining critical features of normal brain development. Using this approach, here we examine anatomical and developmental features of forebrain commissures in vertebrates to gain insights into the development and evolution of the corpus callosum, the largest axonal tract in the human brain.

CONSERVATION OF A DEVELOPMENTAL PLAN IN THE VERTEBRATE BRAIN

The origin and diversification of forebrain commissures in vertebrates is likely to be related to a general developmental plan

upon which evolution may act. Such is the case of the early molecular determination of midline forebrain territories, which is strikingly similar across vertebrate species. It involves the patterned expression of morphogens in defined regions that, through their interaction in three-dimensional space, specify cellular fate and commissure formation. After closure of the neural tube, patterning centers at the dorsal and ventral midline establish gradient territories through the expression of the diffusible morphogens Wnt/BMP and sonic hedgehog (Shh), respectively. At the rostral tip of the prosencephalon, fibroblast growth factor (Fgf) proteins are expressed in a region known as the anterior neural ridge, which then becomes the commissural plate, a structure through which the telencephalic commissures cross the midline (**Figure 1A**). Fgfs are also expressed more caudally along the dorsal midline, at the border between the presumptive prethalamus and dorsal thalamus, in a patterning region known as the *zona limitans intrathalamica*, which is characterized by a narrow band of Shh expression that forms a continuum with ventral Shh expression in the prechordal plate. The isthmic organizer, another patterning center widely conserved in vertebrates, is located at the border between the midbrain and hindbrain and is characterized by a narrow ring of Fgf and Wnt/Bmp expression extending dorsoventrally (**Figure 1A**). This general organization is largely maintained across vertebrate taxa from lampreys to mammals (Walshe and Mason, 2003; Buckles et al., 2004; Wilson and Houart, 2004; Tole et al., 2006; O'Leary et al., 2007; Rétaux and Kano, 2010; Rash and Grove, 2011; Sugahara et al., 2013), and therefore represents an important landmark in brain development. Moreover, the relative positions and expression profiles of these patterning centers are similarly present in some non-vertebrate lineages, such as the hemichordate acorn worm, suggesting the ancient conservation of a morphogenic program since early deuterostomes (Pani et al., 2012). Notably, these early systems of protein gradient production not only instruct overall brain area patterning (Shimogori and Grove, 2005; O'Leary et al., 2007; Assimacopoulos et al., 2012), but also serve as guidance cues for growing axons (Charron et al., 2003; Walshe and Mason, 2003; Tole et al., 2006; Zou and Lyuksyutova, 2007; Toyama et al., 2013). Similarly, as described in more detail below, the spatial locations of these organizing centers broadly coincide with regions of commissural axon crossing, such as the post-optic commissure and posterior commissure, which are the first commissures to form during vertebrate development (**Figure 1B**; Herrick, 1937; Kuratani et al., 1998; Doldan et al., 2000; Barreiro-Iglesias et al., 2008). Thus, the conservation of these early mechanisms of forebrain development across vertebrate species suggest that area patterning and cell-specification functions may have been co-opted for axon guidance and commissural circuit formation. Therefore, the emergence of non-disruptive variations in these processes may underlie the evolution of commissural diversity.

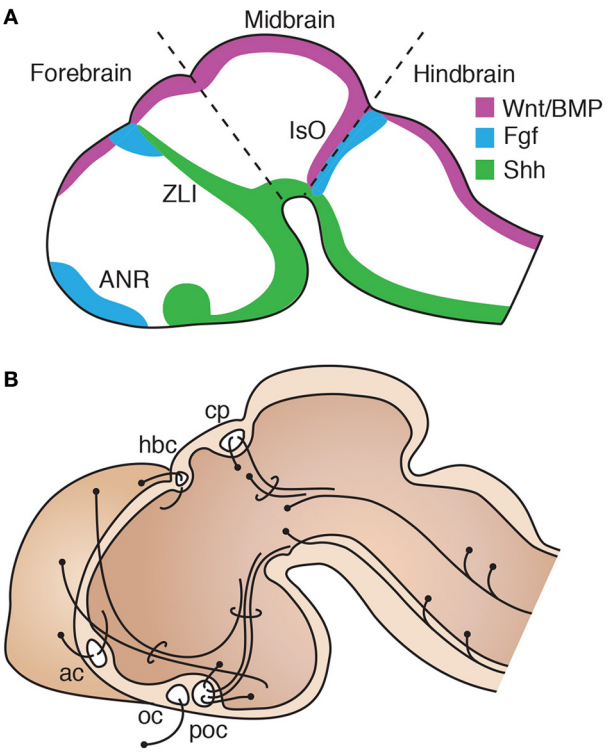

FIGURE 1 | Conservation of a general organization of vertebrate brain development. (A) Diagram of an early stage of brain development in a model vertebrate, equivalent to mouse E11, showing the principal regions of morphogen expression. Rostral expression of Fgf defines the anterior neural ridge (ANR). The *zona limitans intrathalamica* (ZLI) is defined by a narrow band of Shh expression, with Fgf and BMP/Wnt coexpression dorsally at the border between the presumptive telencephalon and diencephalon. Caudally, the isthmic organizer (IsO) marks the boundary between the midbrain and hindbrain territories. **(B)** Midsagittal schematic of a model vertebrate brain at a later stage, equivalent to mouse E14, showing the position of the first axon bundles that form during development, including the posterior commissure (cp) and post-optic commissure (poc), followed by the anterior commissure (ac), habenular commissure (hbc) and optic chiasm (oc). Dorsal is to the top and rostral to the left.

CONSERVED COMMISSURAL PATHWAYS IN EARLY VERTEBRATES

To examine commissural diversity and evolution, we will first refer to the anatomical organization of forebrain commissures in early-branched vertebrates. A gross comparison of the brain of the jawless hagfish and lampreys, cartilaginous sharks, and teleost fish, reveals overall similarities in the relative position of commissural connections within the brain (**Figure 2A**). Briefly, at the caudal-most extent of the forebrain lies the posterior commissure (cp; **Figure 2A**, yellow), which connects dorsal regions of the diencephalon (i.e., dorsal thalamus) and mesencephalon (i.e., pretectum and optic tectum) (Nieuwenhuys and Nicholson, 1998; Wicht and Nieuwenhuys, 1998). In the basal diencephalon, two regions of midline axon crossing are found throughout vertebrates: the postoptic commissure (poc; **Figure 2**, light green), and optic chiasm (oc; **Figure 2**, gray). The postoptic commissure carries axons bilaterally connecting the preoptic area and the hypothalamus, as well as telencephalic and thalamic fibers projecting to the hypothalamic region (Nieuwenhuys and Nicholson, 1998; Smeets, 1998; Wicht and Nieuwenhuys, 1998). In all vertebrates, axons from retinal ganglion cells decussate, at least partially, at the optic chiasm to terminate in contralateral diencephalic (lateral thalamus, hypothalamus) and mesencephalic

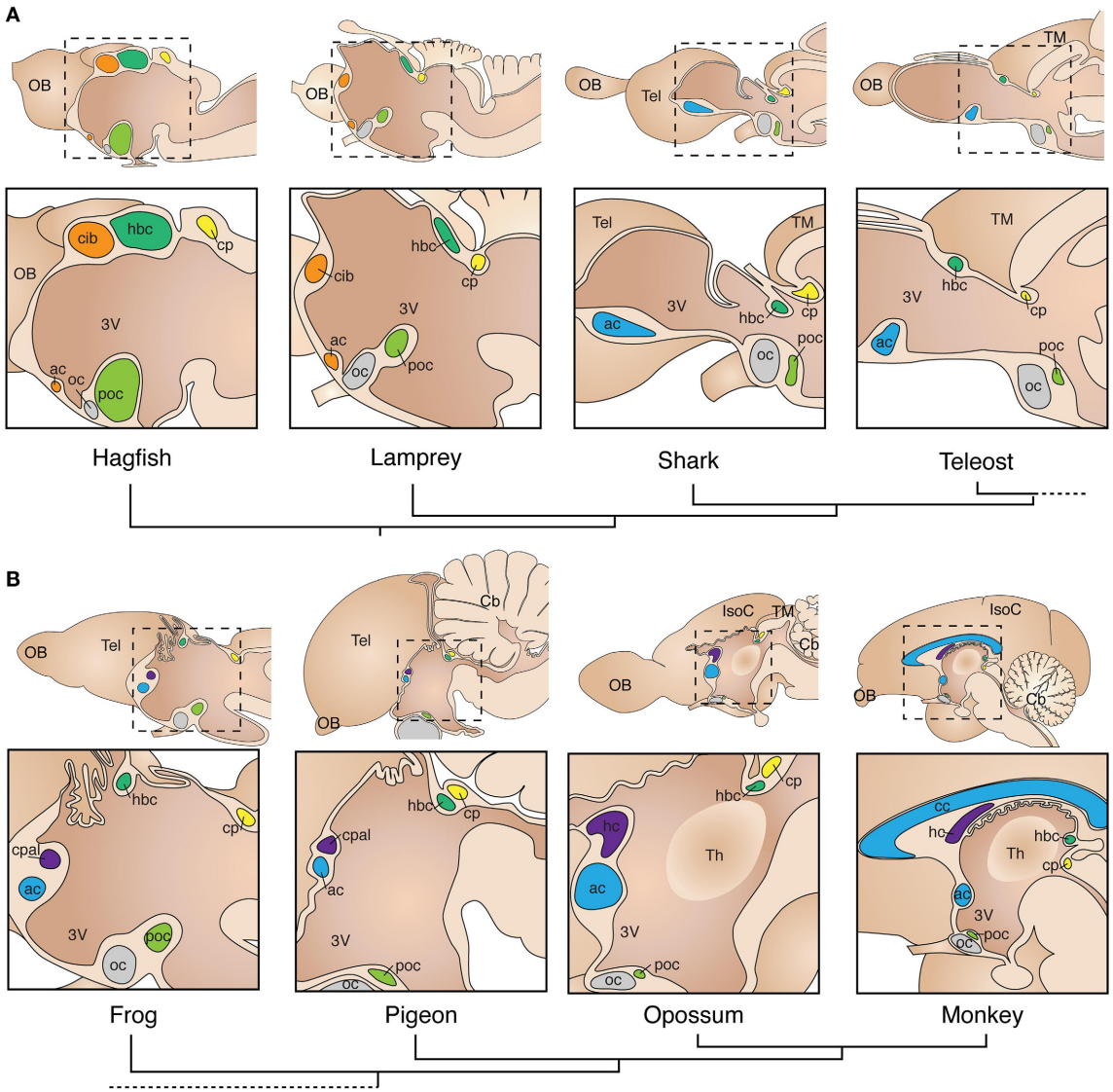

FIGURE 2 | Conservation of commissural systems across adult vertebrate species. (A) Commissures in non-tetrapod species. Note the conserved position of commissures relative to each other within and between species, commissures are color-coded according to homology hypotheses. The *commissura interbulbaris* (cib) and anterior commissure (ac) of lampreys and hagfish are depicted here with a unique color (orange) to indicate the uncertainty of definitive homology with other vertebrates. **(B)** Tetrapods are characterized by the evolution of a distinct pallial commissure (cpal) in close dorsal proximity with the anterior commissure. The mammalian homolog of the pallial commissure is known as hippocampal commissure (hc). The corpus callosum (cc) is an evolutionary innovation of placental mammals, located dorsal to the hippocampal commissure. Phylogenetic relationships between species are depicted with dendrograms below species name. 3V, third ventricle; Cb, cerebellum; cp, posterior commissure; hbc, habenular commissure; IsoC, isocortex; OB, olfactory bulb; oc, optic chiasm; poc, post-optic commissure; Tel, telencephalon; Th, thalamus; TM, tectum mesencephali.

(pretectum, tectum) targets. However, as axons forming the optic tract decussate *en route* to their central targets, without reciprocally connecting bilateral regions, the optic chiasm is not considered a proper commissure. Along the roof of the midline, immediately rostral to the posterior commissure, lies the habenular commissure (hbc; **Figure 2A**, green), which is prominent in agnathans as compared to other vertebrates (Wicht and Northcutt, 1992). The habenular commissure connects the epithalamus bilaterally, and also contains axons originating from the olfactory bulbs and medial pallium (*olfacto-habenularis* tract) that terminate contralaterally in pallial, subpallial and diencephalic targets (Northcutt and Puzdrowski, 1988; Polenova and Vesselkin, 1993). The largest commissure in the telencephalon of agnathans is the *commissura interbulbaris* (cib, **Figure 2A**, orange). It carries fibers from the olfactory bulbs and pallium, thus resembling the rostral component of the habenular commissure. In fact, the *commissura interbulbaris* and habenular commissure are located in close proximity to each other in hagfish, and it is hard to distinguish fibers crossing through one or the other commissure (Wicht and Northcutt, 1992, 1998;

Wicht and Nieuwenhuys, 1998). In contrast, lampreys have a relatively smaller *commissura interbulbaris*, located more rostral to the habenular commissure than hagfishes (**Figure 1A**; Northcutt and Puzdrowski, 1988; Polenova and Vesselkin, 1993; Nieuwenhuys and Nicholson, 1998; Pombal et al., 2009). This difference may relate to the fact that while hagfish undergo direct development with olfactory-guided swimming occurring throughout ontogeny, lampreys spend several years as a sessile larva buried in mud, with olfactory behaviors becoming active only during their brief adulthood. Thus, the seemingly derived behavioral and neuroanatomical features of extant agnathans makes it difficult to formulate hypotheses regarding homology of their telencephalic commissural circuits with those of other vertebrates (see **Table 1**).

At the rostral-most extent of the midline lies the anterior commissure, which in agnathans connect mostly the olfactory bulbs and septum with their contralateral homotopic structures, as well as with hypothalamic targets (Nieuwenhuys and Nicholson, 1998; Wicht and Nieuwenhuys, 1998). Similarly, in cartilaginous fish such as sharks and rays, the anterior commissure carries axons connecting the olfactory bulbs bilaterally, as well as with the septum and striatum (Smeets, 1983, 1998; Yáñez et al., 2011). Interestingly, secondary olfactory axons of cartilaginous and bony fish decussate not only through the anterior commissure, but also through the habenular and postoptic commissures (Smeets, 1998; Northcutt, 2011; Yáñez et al., 2011), suggesting that decussating axons from a single region may cross the midline using more than one commissural route. Whether the medial pallium of sharks and rays connects to contralateral homotopic regions through any of these commissures is not fully established. However, a general pattern of telencephalic connections through the anterior commissure linking olfactory, pallial and subpallial structures is also observed in ray-finned bony fish (**Table 1**; Folgueira et al., 2004; Northcutt, 2006, 2011). Ray-finned fish are characterized by a developmental eversion of the telencephalon, which contrasts with the evagination of the telencephalic vesicles observed in all other vertebrates, where the homologs of the medial pallium develop into the lateral-most part of the telencephalon (for specific reviews, see Meek and Nieuwenhuys, 1998; Northcutt, 2008; Nieuwenhuys, 2009). This telencephalic arrangement may have prevented the evolution of a defined pallial commissure (which connects the medial pallium in tetrapods, see below) at the dorsal midline in this group. However, in goldfish, axons arising from the homolog of the medial pallium (ventro-lateral portion of the *area dorsalis*), cross the midline at more dorsal territories within the anterior commissure than axons from the olfactory pallium (medial portion of the *area dorsalis*), which decussate more ventrally within the anterior commissure (Northcutt, 2006). Notably, this dorso-ventral parcellation of fibers according to the location of their cell bodies is a feature also present in the telencephalic commissures of tetrapods (see next section). Thus, a topographical arrangement of commissural fibers seems to predate the segregation and emergence of new discrete commissures. In summary, a basic configuration of commissural systems has been conserved since early vertebrates, including the coexistence of homotopic and heterotopic connections within commissural tracts, as well as a spatially segregated arrangement of axons according to their site of origin. Both anatomical features are further evident in the telencephalic commissures of tetrapods.

ORIGIN AND DIVERSIFICATION OF PALLIAL COMMISSURES

A crucial milestone in vertebrate evolution that resulted in several behavioral and anatomical adaptations, including a significant increase in brain complexity, was the colonization of terrestrial niches by the ancestors of modern tetrapods. In particular, the telencephalic pallium underwent considerable increase in size and number of connections, acquiring further complexity in mammals with the evolution of the six-layered isocortex. Consequently, the telencephalon of tetrapods evolved additional commissures that provide interhemispheric connections between pallial regions. Early neuroanatomists described a distinct commissure in the telencephalon of reptiles, termed the pallial commissure (cpal; **Figure 2B**, purple; Herrick, 1910; Johnston, 1913). This structure connects mainly the left and right portions of the medial pallium, which in mammals gives rise to the hippocampal formation (**Table 1**; Voneida and Ebbesson, 1969; Butler, 1976; Kokoros and Northcutt, 1977; Martínez-García et al., 1990; Atoji et al., 2002; Northcutt and Westhoff, 2011). The oldest indication of a distinct pallial commissure in vertebrates comes from the spotted African lungfish, a basal member of the lineage of lobe-finned fish that includes all tetrapods and their common ancestor (Sarcopterygii). In lungfish, the pallial commissure is located immediately rostro-dorsal to the anterior commissure. It differs from the anterior commissure by its medial pallial, as compared to subpallial, bilateral connections (Northcutt and Westhoff, 2011). Similarly, the telencephalic commissures of amphibians include bilateral connections from subpallial and olfactory-recipient nuclei through the anterior commissure, and medial pallial connections through the dorsally-located pallial commissure (**Figure 3**; Kokoros and Northcutt, 1977; Hofmann and Meyer, 1989; Northcutt and Ronan, 1992). This fiber topography in lungfish and amphibians, along with the axonal parcellation of the anterior commissure of teleost fish, suggest that the evolution of the pallial commissure likely involved a transition from dorsally-fasciculated medial pallial axons within the anterior commissure, to a more defined dorsal segregation of fibers within the rostral tip of the *lamina terminalis* (see **Figures 2B**, **3**). Accordingly, both commissures arise from the same embryonic territory, the commissural plate (see next section).

Sensory adaptations may also have influenced the evolution and diversification of telencephalic connections, including commissural systems. Colonization of land involved the evolution of aerial respiration and the emergence of an accessory olfactory system specialized in pheromone detection (for a review, see Suárez et al., 2012). In non-mammalian sarcopterygians, efferents from the main and accessory olfactory bulbs decussate through different commissural routes, i.e., the habenular and anterior commissure, respectively (Halpern, 1976; Ulinski and Peterson, 1981; Martinez-Garcia et al., 1991; Scalia et al., 1991; Lohman and Smeets, 1993; Lanuza and Halpern, 1997; Moreno et al., 2005; Patzke et al., 2011; Northcutt and Rink, 2012; Atoji and Wild, 2014), suggesting that the diversification of decussated sensory input to the telencephalon may have also affected the rearrangement of commissural systems.

Table 1 | Comparison of interhemispheric connections through telencephalic commissures in vertebrates.

	Agnatha (Jawless vertebrates; e.g., hagfish and lampreys)	**Gnathostomata (Jawed vertebrates)**						
		Chondrichthyes (cartilaginous fish; e.g., sharks and rays)	**Teleosts (ray-finned fish; zebrafish and goldfish)**	**Sarcopterygii (lobe-finned vertebrates)**				
				Lungfish	**Reptiles**	**Birds**	**Mammals**	
							Marsupials	**Eutherians**
Anterior commissure	Olfactory recipient nuclei and septum to contralateral homotopic regions and hypothalamus[1,2].	Olfactory bulbs to contralateral retrobulbar area, septum and striatum[5,6].	Olfactory bulbs, pallial and subpallial areas to contralateral homotopic regions[7,8].	Olfactory recipient and subpallial septum to contralateral homotopic regions[9].	Olfactory recipient and basal telencephalon to homotopic regions[10,11].	Olfactory recipient and basal telencephalon to homotopic regions[14].	Olfactory recipient, basal telencephalic, piriform cortex and isocortex to homotopic regions[16].	Olfactory recipient, basal telencephalic, piriform cortex and temporal isocortex to homotopic regions[18,19].
Commissura interbulbaris/pallial commissure/ Hippocampal commissure	(*Commissura interbulbaris*) Olfactory bulbs and pallium to contralateral homotopic, subpallial and diencephalic targets[1,3,4].	–/?	–/?	(Pallial commissure) Medial pallium to contralateral medial and dorsal pallium[9].	(Pallial commissure) Medial and dorsal pallium to contralateral homotopic regions[11,12,13].	(Pallial commissure) Medial pallium to contralateral homotopic regions[15].	(Hippocampal commissure) Hippocampus to contralateral homotopic regions[17].	(Hippocampal commissure) Hippocampus to contralateral homotopic regions and entorhinal cortex[20,21].
Corpus callosum	–	–	–	–	–	–	–	Cingulate cortex and most of isocortex to contralateral homotopic regions[21].

References: [1] *Nieuwenhuys and Nicholson, 1998;* [2] *Wicht and Nieuwenhuys, 1998;* [3] *Northcutt and Puzdrowski, 1988;* [4] *Polenova and Vesselkin, 1993;* [5] *Smeets, 1983;* [6] *Yáñez et al., 2011;* [7] *Folgueira et al., 2004;* [8] *Northcutt, 2006;* [9] *Northcutt and Westhoff, 2011;* [10] *Lanuza and Halpern, 1997;* [11] *Butler, 1976;* [12] *Voneida and Ebbesson, 1969;* [13] *Martínez-García et al., 1990;* [14] *Zeier and Karten, 1973;* [15] *Atoji et al., 2002;* [16] *Ashwell et al., 1996a;* [17] *Smith, 1937;* [18] *Ramón y Cajal, 1904;* [19] *Van Alphen, 1969;* [20] *Wyss et al., 1980;* [21] *Yorke and Caviness, 1975.*

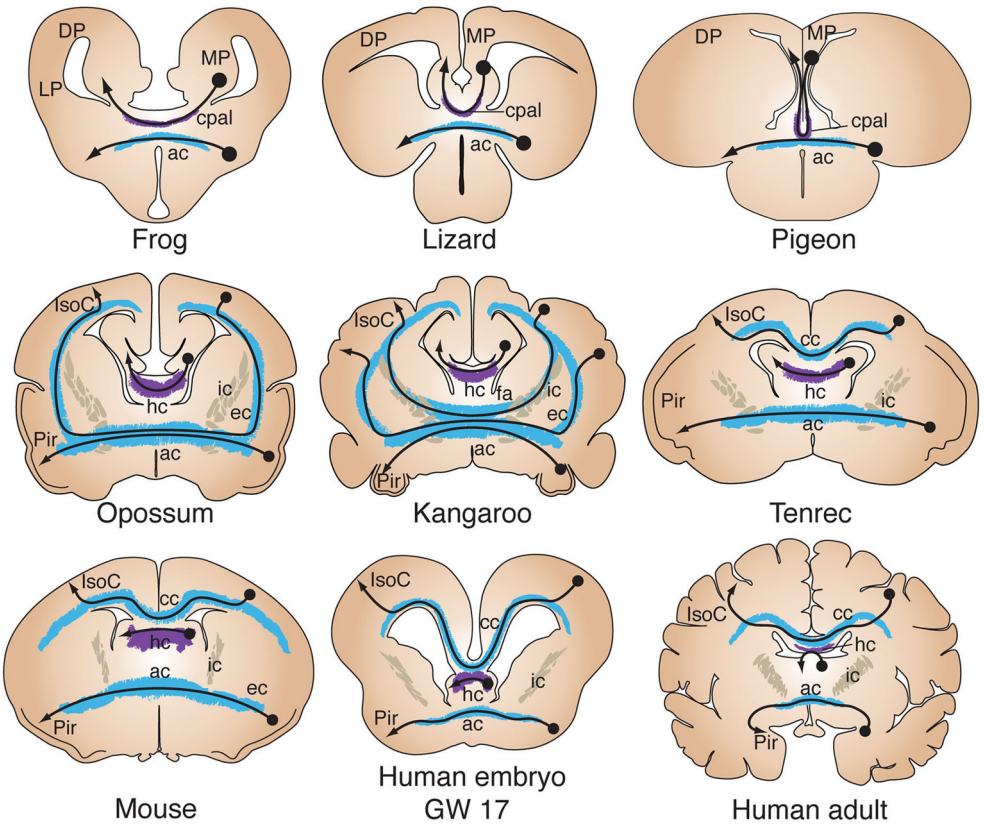

FIGURE 3 | Evolution of telencephalic commissures in tetrapods. Coronal schematics of tetrapod brains show the close association between the pallial commissure (cpal) and the anterior commissure (ac), bilaterally connecting the medial pallium (MP) and olfactory recipient structures, respectively. In the opossum all isocortical (IsoC) and piriform (Pir) commissural projections cross through the anterior commissure (ac) after coursing through the external capsule (ec). In the kangaroo, as in other diprotodont marsupials, axons from more dorsal regions of the isocortex course through the internal capsule (ic) toward the anterior commissure, forming the *fasciculum aberrans* (fa). Hippocampal neurons decussate through the hippocampal commissure (hc). In tenrecs, as in other basal placentals with a small IsoC/Pir ratio, the corpus callosum (cc) is a small structure located immediately above the hippocampal commissure. Developmental studies in mice and humans have shown that all three commissures arise from the commissural plate, forming a single plane of morphogenic patterning. GW, gestational week; DP, dorsal pallium; LP, lateral pallium.

Similar connectivity patterns are found in amniotes, such as reptiles and birds, where the anterior commissure connects mostly subpallial and olfactory-recipient regions from both hemispheres (Zeier and Karten, 1973; Butler, 1976; Lanuza and Halpern, 1997), whereas the pallial commissure carries axons connecting mostly the dorsal septum and topographically arranged fibers of the hippocampus (**Table 1**; Voneida and Ebbesson, 1969; Butler, 1976; Martínez-García et al., 1990; Atoji et al., 2002). Accordingly, since its discovery the pallial commissure has been considered homologous to the hippocampal commissure of mammals (**Figures 2B**, **3**; Herrick, 1910; Johnston, 1913). In mammals, the pallial commissure has received the names of hippocampal commissure, psalterium and crus (or decussation) of the fornix. It connects mostly homotopic regions of the hippocampus *cornu ammonis* between hemispheres, as well as heterotopic fibers connecting the hippocampus with the entorhinal cortex (Steward, 1976; Wyss et al., 1980; Voneida et al., 1981; Cui et al., 2013). The evolution of the six-layered isocortex in mammals correlates with a further increase in size and complexity of telencephalic commissures. For example, the corpus callosum, the largest axon tract in the human brain, is a relatively recent evolutionary innovation exclusive to placental mammals. Richard Owen, a prominent anatomist contemporary to Darwin, provided the first comparative study of telencephalic commissures in mammals. He discovered that marsupials lack a corpus callosum, and that their telencephalic commissures include exclusively the hippocampal and anterior commissures, referring to the commissural system of marsupials as "*... a structure of brain which is intermediate of that between placental Mammalia and Birds*" (Owen, 1837; p. 92). In monotremes and non-diprotodont marsupials all interhemispheric isocortical connections reach the anterior commissure via the external capsule, whereas diprotodont marsupials, such as koalas and kangaroos, possess an additional axonal tract, termed the *fasciculus aberrans*, that joins the dorsal aspect of the anterior commissure through the internal capsule (**Figure 3**; Flower, 1865; Smith, 1897, 1902, 1937; Johnston, 1913; Abbie, 1939; Ashwell et al., 1996a). Again, this topographic arrangement of commissural fibers may reflect a common feature of commissural systems. Interestingly, the evolution of the corpus callosum as the main pathway for

isocortical and cingulate commissural connections in eutherians resulted in the anterior commissure reverting to its ancestral state, i.e., connecting mostly olfactory recipient and subpallial nuclei. Still, some axons from lateral portions of the temporal isocortex decussate via the anterior commissure (Ramón y Cajal, 1904; Horel and Stelzner, 1981; Jouandet and Hartenstein, 1983; Tomasi et al., 2012).

The events that led to the evolution of the mammalian isocortex in general, and eutherian corpus callosum in particular, cannot be fully understood from the fossil record and therefore require comparative developmental and molecular approaches. However, fossil skull endocasts of early ancestors of modern mammals suggest that the primitive mammalian brain was dominated by olfactory structures, including a large piriform cortex, and a small isocortex (Rowe et al., 2011). In modern placental mammals with a small isocortex/piriform cortex ratio, such as hedgehogs (Eulipotyphla), bats (Chiroptera) or tenrecs (Afrosoricida), the corpus callosum is very a small structure located just above the hippocampal commissure (**Figure 3**), possibly resembling a primitive state of early eutherians (Flower, 1865; Smith, 1897; Abbie, 1939; Krubitzer et al., 1997). Consequently, a larger corpus callosum is found in species with a higher isocortex/piriform cortex ratio, such as rodents and primates (**Figures 2B**, **3**), suggesting that isocortical expansion explains the increase of corpus callosum size. The developmental time course of midline crossing of commissural axons in different species may also shed light on the evolution of commissures. For example, in wallabies, the anterior commissure forms first, followed by the *fasciculus aberrans* and finally the hippocampal commissure, whereas in placental mammals the anterior commissure forms first, followed by the hippocampal commissure and then the corpus callosum (Ashwell et al., 1996b). These developmental sequences suggest that the evolution of the corpus callosum involved a rerouting of dorsal cortical axons, from crossing through the anterior commissure to employing the same embryonic substrate as the hippocampal commissure. Although the developmental events that led to the evolution of the corpus callosum in placental mammals remain largely unknown, the formation of all three commissures in these species depends on the development of the commissural plate (Smith, 1897; Rakic and Yakovlev, 1968; Moldrich et al., 2010). This embryonic structure has been studied in mice and humans (**Figures 3**, **4**), and the molecular and cellular events that characterize its development are discussed below.

MOLECULAR SPECIFICATION OF THE COMMISSURAL PLATE

As discussed previously, patterning of the telencephalic midline in mouse embryos, including the establishment of dorsoventral territories of commissure formation, is directed by the spatially defined expression of a conserved set of morphogens. The medial pallium/cortical hem expresses Wnt/BMPs, the basal prechordal plate expresses Shh, and the anterior neural ridge, or presumptive commissural plate, expresses Fgfs (**Figure 4A**; Rubenstein et al., 1998; Campbell, 2003; Hebert and Fishell, 2008; Borello and Pierani, 2010). These morphogens interact via gradients of protein expression, whereby the relative concentration of each morphogen differs at each point of the extracellular space, resulting in either activation or suppression of intracellular effector pathways (**Figures 4A,B**). In particular, the precise patterning of dorso-ventral domains at the telencephalic midline is critical for the formation of all three telencephalic commissures. Formation of the commissural plate involves the thickening of the *lamina terminalis*, whereby providing a substrate for convergence and decussation of commissural axons (**Figures 4C–F**; Rakic and Yakovlev, 1968; Moldrich et al., 2010). From dorsal to ventral, the earliest subdivisions of the commissural plate include the cortical hem/medial pallium, the septum, and the preoptic area, where Wnt/Bmp, Fgf and Shh signaling, respectively, induce formation of these tissues in a concentration-dependent manner (**Figure 4D**; see for review Rubenstein et al., 1998; Campbell, 2003; Puelles and Rubenstein, 2003; Hebert, 2005; Fernandes and Hebert, 2008; Hebert and Fishell, 2008). The formation of borders within this primordial tissue is primarily controlled by either repressive or inductive mechanisms between individual morphogen signals. For example, studies in mice and chickens have described reciprocal repression between the Bmp/Wnt and Fgf signaling pathways, and between the Bmp/Wnt and Shh signaling pathways (**Figure 4E**; Lee et al., 2000; Ohkubo et al., 2002; Shimogori et al., 2004; Storm et al., 2006). In contrast, Fgf8 and Shh regulate the expression of one another to maintain normal expression levels, suggesting that a reciprocal inductive mechanism is in place between the septum and preoptic areas (Ohkubo et al., 2002; Storm et al., 2006). This reciprocity between Fgf8 and Shh signaling may be integrated by the transcription factor Six3, as it can directly bind and activate a forebrain-specific *Shh* enhancer, and can also regulate the expression of Fgf8 prior to telencephalic midline formation (Lagutin et al., 2003; Geng et al., 2008; Jeong et al., 2008). Moreover, following initial telencephalic midline formation, expression of Shh and Fgf8 in the subpallium maintains Six3 expression in the septum and preoptic area (**Figure 4E**; Storm et al., 2006; Geng et al., 2008). Once morphogenic patterning of the commissural plate has been established, tissue-specific transcription factors further affect cell fate identity, demarcating all three dorso-ventral domains (**Figure 4E**). First, the medial pallium is defined by expression of transcription factors such as Emx1 and Emx2 (regulated by Wnt signaling), as well as Msx1 and Msx2 (regulated by BMP signaling) (Lee et al., 2000; Hebert et al., 2002, 2003; Shimogori et al., 2004; Fernandes et al., 2007; Caronia et al., 2010). The subpallial septum is defined by the transcription factors Zic2, Vax1, and Lhx5, where ectopic Fgf8 signaling is sufficient to induce their expression, even in the absence of Shh (Okada et al., 2008). Finally, the preoptic area expresses Six3 and Nkx2.1 under control of Shh signaling, which is essential for the formation of the entire subpallium (**Figure 4E**; Patten and Placzek, 2000; Ohkubo et al., 2002; Corbin et al., 2003; Gunhaga et al., 2003; Nery et al., 2003; Xu et al., 2005, 2008; Gulacsi and Anderson, 2006; Fogarty et al., 2007; Butt et al., 2008; Garcia-Lopez et al., 2008; Geng et al., 2008; Lavado et al., 2008; Gelman et al., 2009; Hirata et al., 2009; Flandin et al., 2011). Finally, another transcription factor, Gli3, has also been shown to regulate cell-type patterning within the commissural plate (Magnani et al., 2012; Amaniti et al., 2013). Loss of Gli3 affects the expression of BMP/Wnt and Fgf8 at the midline, as well as the expression

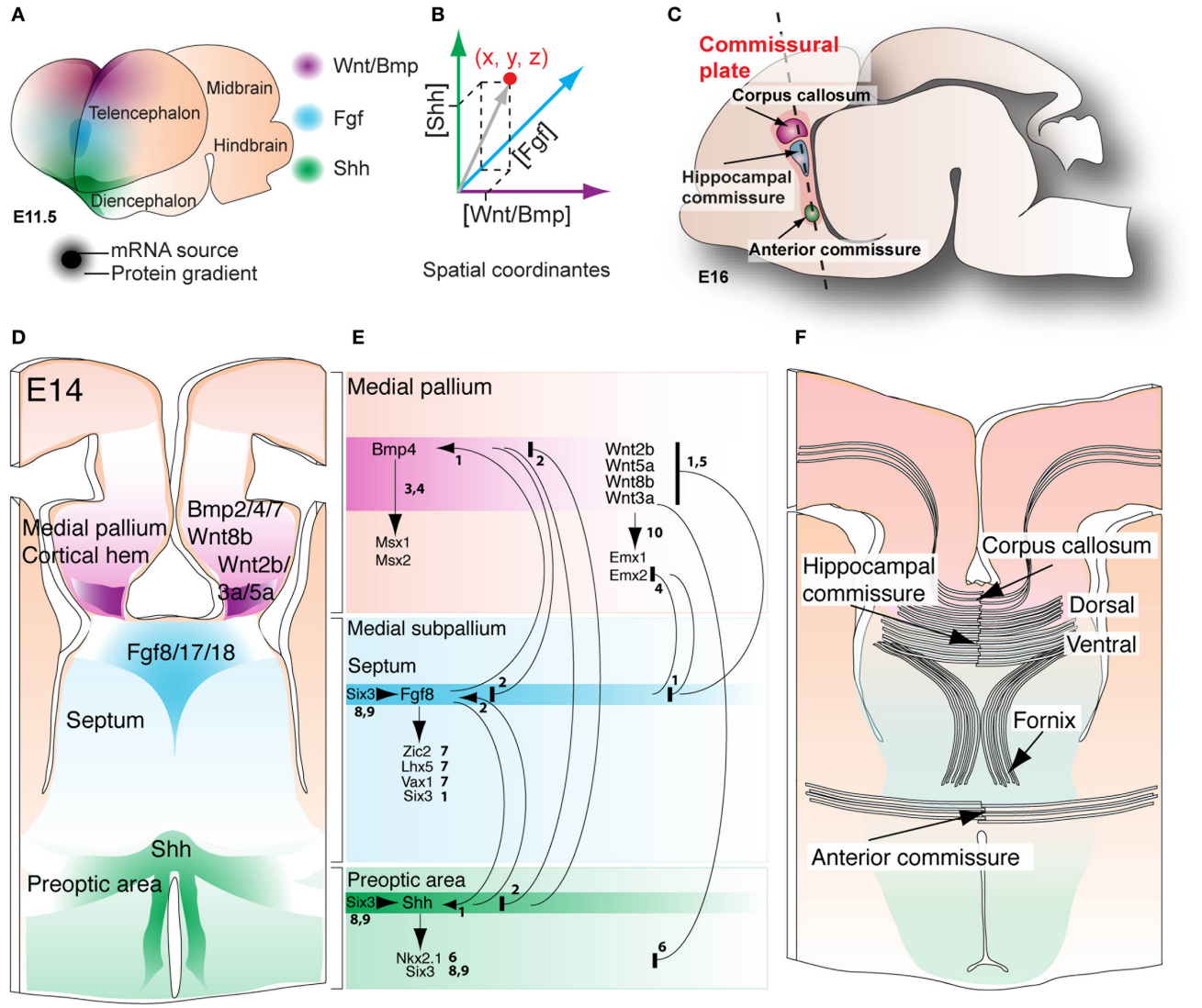

FIGURE 4 | Morphogenic patterning at the commissural plate. **(A)** Discrete regions of the early telencephalic midline of mice at E 11.5 express diffusible Wnt/Bmp, Fgf, and Shh proteins, as revealed by mRNA expression studies. **(B)** The differential concentration of each morphogen at any point in space results in distinct intracellular signaling outcomes, generating different cell fates. **(C)** A midsagittal schematic of the embryonic mouse brain showing the plane of section **(D,F)** defined by telencephalic commissures, known as the commissural plate. **(D)** Transverse section through the presumptive commissural plate at E14 shows the spatial extent of morphogen expression, mostly defining pallial, septal, and preoptic domains. **(E)** In general, morphogen interactions are reciprocally repressive between the pallial and subpallial regions; numbers denote references providing evidence for each interaction (see below for reference key). Further definition of the medial pallium, septum and preoptic areas is achieved by the induction of transcription factors such as Msx1/2, Emx1/2 (pallial), Zic2, Lhx5, Vax1 (septal), Six3 and Nkx2.1 (preoptic). **(F)** Dorso-ventral patterning domains also define the dorso-ventral level at which the three telencephalic commissures will cross within the caudal telencephalic midline. References: [1]Storm et al., 2006; [2]Ohkubo et al., 2002; [3]Fernandes et al., 2007; [4]Hebert et al., 2003; [5]Shimogori et al., 2004; [6]Gunhaga et al., 2003; [7]Okada et al., 2008; [8]Geng et al., 2008; [9]Jeong et al., 2008; [10]Lee et al., 2000.

of their downstream effectors, including Emx1 and Emx2 (Theil et al., 1999; Kuschel et al., 2003; Magnani et al., 2012). Although Gli3 is a known downstream effector of Shh signaling, its precise role in the integration of multiple morphogenic signals remains unclear.

Collectively, these genetic patterning studies suggest that initial formation of the commissural plate involves the morphogenic activity of BMP/Wnt and Shh to establish pallial and subpallial territories, respectively, and that the subpallium is then further refined into septal and preoptic regions through Fgf8 signaling. Thus, the specific location through which commissural axons cross the midline depends on the early molecular patterning of the commissural plate, whereby pioneer axons of the corpus callosum cross through the same pallial domain of the dorsal hippocampal commissure, while the ventral hippocampal and anterior commissures form at the septal and preoptic domains, respectively (**Figure 4F**; Moldrich et al., 2010). Taken together, comparative and molecular data suggest that evolution

of the corpus callosum involved a rerouting of commissural axons through a preexistent pallial commissural course.

COMMISSURAL AXON GUIDANCE AND CONTRALATERAL TARGETING

Another important aspect of commissure development that could also account for evolutionary events that led to commissure diversification involves axon guidance and targeting. Following the induction and patterning of the telencephalic midline, growing commissural axons are channeled toward and across the midline by a number of glial cell populations present throughout mammal species (Silver et al., 1982; Cummings et al., 1997; Pires-Neto et al., 1998; Lent et al., 2005). For example, the indusium griseum glia (IGG) and the glial wedge form dorsomedial and ventrolateral boundaries for growing callosal axons, respectively, while the midline zipper glia (MZG) demarcate a ventromedial boundary (**Figure 5**; Silver et al., 1993; Shu and Richards, 2001; Shu et al., 2003). In mice, glial wedge cells are born around embryonic day (E) 13 and, while retaining their cell bodies in the medial aspect of the lateral ventricle, they extend processes that cluster into a wedge shape that coincides with the boundary between pallial and subpallial domains (cortico-septal boundary, **Figure 5A**). This cell population, together with the IGG, guide growing axons by expressing chemorepellent molecules such as Slit2, Wnt5a, and Draxin, thus preventing callosal axons from coursing ventrally into septal territory (Shu and Richards, 2001; Keeble et al., 2006; Islam et al., 2009; Unni et al., 2012). By E15, pioneer axons from the cingulate cortex first cross the midline (Koester and O'Leary, 1994; Rash and Richards, 2001), followed by isocortical axons, which fasciculate with them to cross the midline approximately 1 day later (**Figures 5A,B**). Another cell population that participates in the guidance of callosal axons at the midline is the subcallosal sling (**Figure 5C**), also referred to as the callosal corridor, a transient neuronal population that lies at the ventral border of the corpus callosum (Silver et al., 1982, 1993; Silver and Ogawa, 1983; Hankin et al., 1988; Shu et al., 2003; Niquille et al., 2009; Benadiba et al., 2012). These cells express Sema3c, which acts as an attractant of pioneer axons from the cingulate cortex through interaction with its receptor Nrp1 (Niquille et al., 2009; Piper et al., 2009).

After crossing the midline, callosal axons grow into the contralateral hemisphere and innervate homotopic (Yorke and Caviness, 1975; Krubitzer et al., 1998; Rash and Richards, 2001; Hofer and Frahm, 2006), and heterotopic regions of the cortex (Boyd et al., 1971; Kretz and Rager, 1990; Aboitiz and Montiel, 2003). Histological studies in mice have revealed a dorso-ventral segregation of callosal axons according to the medio-lateral position of their cell-bodies within the cortex (Richards et al., 2004; Zhou et al., 2013). A similar situation has been described in humans using magnetic resonance imaging, where callosal fibers originating at different medio-lateral positions retain a dorso-ventral parcellation within the rostro-caudal axis (Abe et al., 2004; Tovar-Moll et al., 2007; Chao et al., 2009; Fabri et al., 2011; Fabri and Polonara, 2013). Thus, a highly refined topographic organization of axons at the midline is a shared feature of commissural systems. The primary somatosensory and visual cortices of rodents send callosal projections to homotopic and heterotopic regions, with a distinct axonal arborization at the border between primary and secondary corresponding areas in the contralateral hemisphere (Wise and Jones, 1976; Ivy and Killackey, 1981; Koralek and Killackey, 1990; Mizuno et al., 2007; Wang et al.,

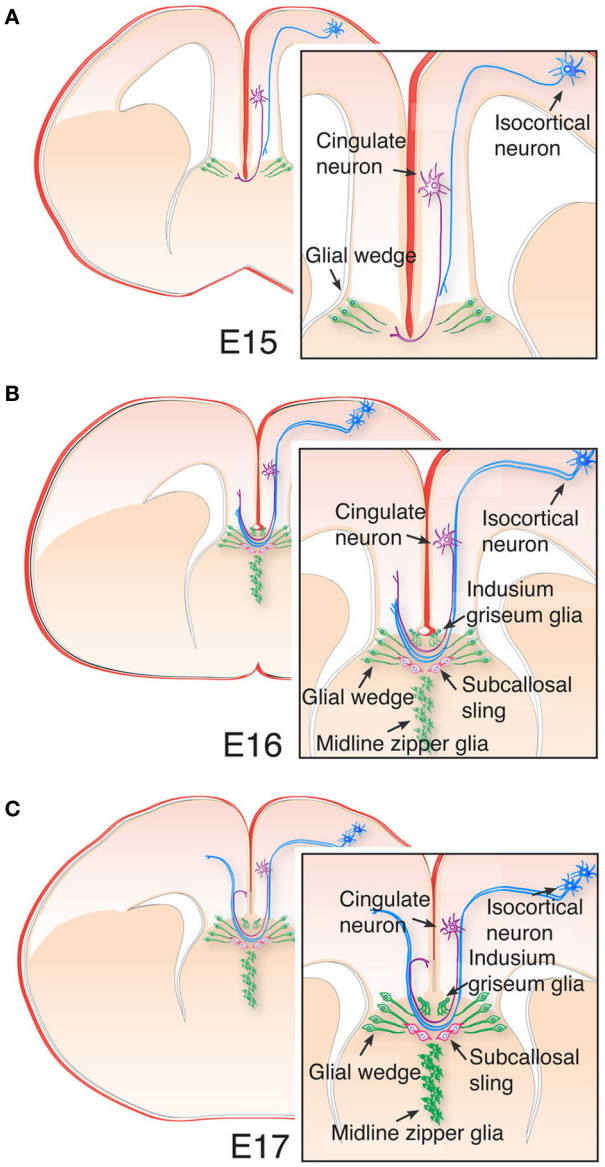

FIGURE 5 | Cellular architecture of the telencephalic midline and callosal development. (A) The ventral-most boundary of the corpus callosum is established by glial wedge cells, as cingulate pioneering axons first cross the midline at E15, while the more laterally located isocortical axons grow toward the midline following cingulate axons. **(B)** At E16, a small number of isocortical axons have crossed the midline, and the indusium griseum glia and midline zipper glia are now detectable with Gfap immunohistochemistry. The indusium griseum glia provide the dorsal boundary of the corpus callosum. In addition, cells of the subcallosal sling begin to migrate toward the midline, just beneath the corpus callosum. **(C)** By E17, isocortical axons have started crossing the midline, and cingulate pioneering axons are projecting to homotopic targets in the contralateral hemisphere. Midline crossing of callosal axons continues during early postnatal stages in mice.

2007). Formation of these contralateral projections occurs mostly during postnatal stages (Wise and Jones, 1976; Wang et al., 2007; Mizuno et al., 2010), and depends on sensory-evoked and spontaneous neural activity during a critical period. Early deprivation of the sensory periphery or thalamic lesions during the first postnatal week in rodents prevents normal development of callosal projections (Innocenti and Frost, 1979; Olavarria et al., 1987; Koralek and Killackey, 1990; Innocenti and Price, 2005). Similarly, disruption of electrical activity directly in callosal neurons results in disrupted contralateral projections (Mizuno et al., 2007, 2010; Wang et al., 2007), suggesting that early experience plays an instructive role in the precise targeting of contralateral axons (Huang et al., 2013; Suárez et al., 2014). Thus, additional developmental processes that may have influenced the origin and diversification of mammalian commissures include precise temporal and spatial interactions between glial cells and neurons, production of axon guidance ligands and expression of receptors, and early spontaneous and sensory-evoked neuronal activity.

CONCLUSION

In the context of evolution and development of forebrain commissures, a number of brain features can be distinguished as highly conserved throughout vertebrates, the first being a requirement for interhemispheric communication of the two halves of the CNS. The presence of commissural systems throughout bilaterians reflects a computational requirement of interhemispheric coordination for normal behavior. Second, the conservation in vertebrates of a defined set morphogen expression at the telencephalic midline indicates an important developmental event that directs both the identity patterning of brain areas and wiring of commissural axons. Third, another feature of commissural systems shared by vertebrates is the co-occurrence of decussating fibers that project to heterotopic regions with commissural fibers connecting homotopic regions between hemispheres. Moreover, the presence of profuse heterotopic projections in forebrain commissural pathways of early-branched vertebrates suggests that homotopic projections arose as a refinement of the former kind. Finally, a topographical arrangement of axons within the commissural tracts according the place of origin of their cell bodies can also be recognized as a general feature of commissural systems. Moreover, the origin of new commissures, such as the pallial commissure in early tetrapods and the corpus callosum in eutherian mammals, seems to involve the rerouting of a specific population of topographically arranged axons through preexistent commissural substrates. Such examples of axonal rearrangement can be found in congenital cases of callosal malformations in humans (Tovar-Moll et al., 2007, 2014; Wahl et al., 2009).

Although there is currently little evidence to allow speculation about the precise mechanisms that led to the evolution of the corpus callosum in eutherian mammals, an evolutionary developmental approach integrating current gene manipulation techniques in carefully selected animal models may shed light on this fascinating topic.

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The significance of the subplate for evolution and developmental plasticity of the human brain

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The human life-history is characterized by long development and introduction of new developmental stages, such as childhood and adolescence. The developing brain had important role in these life-history changes because it is expensive tissue which uses up to 80% of resting metabolic rate (RMR) in the newborn and continues to use almost 50% of it during the first 5 postnatal years. Our hominid ancestors managed to lift-up metabolic constraints to increase in brain size by several interrelated ecological, behavioral and social adaptations, such as dietary change, invention of cooking, creation of family-bonded reproductive units, and life-history changes. This opened new vistas for the developing brain, because it became possible to metabolically support transient patterns of brain organization as well as developmental brain plasticity for much longer period and with much greater number of neurons and connectivity combinations in comparison to apes. This included the shaping of cortical connections through the interaction with infant's social environment, which probably enhanced typically human evolution of language, cognition and self-awareness. In this review, we propose that the transient subplate zone and its postnatal remnant (interstitial neurons of the gyral white matter) probably served as the main playground for evolution of these developmental shifts, and describe various features that makes human subplate uniquely positioned to have such a role in comparison with other primates.

Keywords: cerebral cortex, neuron number, life-history, metabolic cost, subplate zone

INTRODUCTION

We humans have large brains, and flatter ourselves to be smart. Accordingly, we are prone to think that "bigger is better" and to assume that larger (i.e., more encephalized) brains should have larger computational and cognitive abilities (for a comprehensive and historical review, see Herculano-Houzel, 2009, 2011a,b, 2012a). Some recent versions of this notion assume that improved cognition does not depend on relative brain size (i.e., the level of encephalization), but simply correlates with absolute brain size (Deaner et al., 2007) or with absolute numbers of cortical neurons and their connections and synapses (Roth and Dicke, 2005). However, if advantages of higher encephalization or increased brain size are so obvious, why big brains are so rare (Parker, 1990)? To answer this paradox, one should obtain more detailed knowledge on neural scaling rules in various mammalian orders (Herculano-Houzel, 2011a,b), as well as ask what the costs of encephalization are and how they can be afforded (Foley and Lee, 1991).

TOTAL NUMBER OF NEURONS IS MORE IMPORTANT THAN BRAIN SIZE *per se*

In a series of recent studies, starting with invention of new quantitative method for comparative analysis of cell and neuron numbers (Herculano-Houzel and Lent, 2005), it was clearly revealed that neural scaling rules evolved differently in different mammalian orders, such as rodents and lagomorphs (Herculano-Houzel et al., 2006, 2011; Herculano-Houzel, 2007), insectivores (Sarko et al., 2009), and primates (Herculano-Houzel et al., 2007; Gabi et al., 2010) including great apes (Herculano-Houzel and Kaas, 2011) and humans (Azevedo et al., 2009; Herculano-Houzel, 2009). These studies pointed out that, in terms of neuronal numbers, the human brain is linearly scaled-up primate brain and that our superior cognitive abilities might simply reflect the largest total number of neurons in the human brain (Herculano-Houzel, 2009, 2012a,b). It seems that basic primate advantage consists in packing more neurons in the same brain volume, thus avoiding prohibitively large increase in brain size (Herculano-Houzel, 2012a,b). In addition, human brains have ∼3 times more brain neurons than gorillas and orangutans (Herculano-Houzel and Kaas, 2011). Another important finding concerns the coordinate increase in numbers of neurons in the cerebral cortex and cerebellum and the fact that the vast majority of all brain neurons are found in these two structures (Herculano-Houzel, 2009, 2010, 2011b, 2012a), thus supporting previous findings on cerebral-cerebellar co-evolution (Whiting and Barton, 2003; Ramnani, 2006; Ramnani et al., 2006; Balsters et al., 2010). Therefore, it has been proposed that "the larger the number of neurons in excess of that required to operate the body, the more complex and flexible the behavior of an animal can be expected to be, and thus the larger its cognitive abilities" (Herculano-Houzel, 2012a, p. 336).

THE BRAIN IS EXPENSIVE TISSUE, AND ONLY MOTHERS AND INFANTS OF A "CHOSEN PRIMATE" CAN AFFORD TO GROW IT BEYOND ORDINARY EXPECTATIONS

How much of the resting metabolic rate (RMR) is spend to maintain the adult brain? While most mammals expend 3–4% of RMR on brain metabolism (Mink et al., 1981; Armstrong, 1983, 1990), anthropoid primates spend about 8% of RMR to maintain their brains (Armstrong, 1983, 1990; Hofman, 1983a,b; Martin, 1983; Leonard and Robertson, 1992; Genoud, 2002). While the large brain-body-mass ratio of humans (the adult human brain is 2% of the body's mass) is not associated with elevations in RMR (Leonard and Robertson, 1992, 1994), adult humans nevertheless expend two to three times more energy on brain metabolism than other primates, that is 20–25% of RMR (Passmore and Durnin, 1955; Kety, 1957; Holliday, 1986; Aiello and Wheeler, 1995; Leonard et al., 1996; Rolfe and Brown, 1997; Genoud, 2002). These human brain costs are even more impressive during childhood, because the brain consumes roughly 87% of RMR in the newborn, and 44% in a 5 year old child (Holliday, 1986). In comparison to the neonate chimpanzee, the cost of the human neonate brain is significantly greater, and by the age of 5 years these costs are 3 times as great (Foley and Lee, 1991). Such energetic costs seem also to exert a selective pressure toward metabolically efficient neural morphology, that is, metabolically efficient patterning of dendritic arborizations (Wen and Chklovskii, 2008), neural codes (Levy and Baxter, 1996; Balasubramanian et al., 2001), and brain wiring patterns (Chen et al., 2006).

Positive pleiotropic gene effects on relative brain and body growth occur during prenatal and early postnatal periods, because genes affecting both traits generally do so during fetal and early postnatal growth, when both brain and body size are growing rapidly (Riska and Atchley, 1985).The fetal brain at any stage of development constitutes a markedly larger proportion of total fetal weight in primates than in other mammals (Sacher, 1982), and this difference is still observable in neonates (Martin, 1983). However, this difference is no longer clear in comparisons among adults, due to differential postnatal changes in different mammals (Martin, 1983). This points to the crucial importance of brain development (Martin, 1996). For example, evolutionary shifts in brain development lead to differences in development of social behavior and cognition even between such closely related species such as chimpanzees and bonobos (Wobber et al., 2010).

The growth of the brain significantly depends upon energetic and hence ecological conditions (Martin, 1983; Foley and Lee, 1991); as succintly stated by Foley and Lee (1991, p. 223): "whatever selective pressures there may be driving the size of the brain up, these are satisfied only in the context of there being sufficient energy." Having a large brain imposes additional energetic costs on both the infant and the mother; the mother can derive that energy either from the incorporation of higher quality food, from feeding for longer each day, or from maintaining lactation over a longer period (Foley and Lee, 1991). Thus, the evolution of a large brain requires that energetic constraints are lifted (Armstrong, 1983; Hofman, 1983a,b, 1993; Martin, 1983, 1996; Foley and Lee, 1991; Leonard and Robertson, 1992, 1994; Aiello and Wheeler, 1995; Leonard et al., 2003; Isler and van Schaik, 2006a,b, 2009).

Some recent evidence suggests that the metabolic cost may be an even more limiting factor to brain expansion than previously suspected (Herculano-Houzel, 2012b). Namely, the estimated glucose use per neuron is remarkably constant, varying only by 40% across the six species of rodents and primates, including humans (Herculano-Houzel, 2011c). Thus, it seems that the brain energy budget per neuron is fixed across species and brain sizes and that the total metabolic cost of a brain is a simple, direct function of its number of neurons (Herculano-Houzel, 2011c). These findings clearly suggest that neuronal metabolism imposes a series of constraints upon brain structure, function, and evolution (Herculano-Houzel, 2011c, 2012b; Fonseca-Azevedo and Herculano-Houzel, 2012). The metabolic constraints upon brain scaling in evolution are imposed by absolute number of neurons, because adding neurons to the brain comes at a sizable cost of 6 kcal/d per billion neurons (Herculano-Houzel, 2011c).

Three major hypotheses have been proposed to explain how larger brains are afforded among mammalian species (see Jones and MacLarnon, 2004, for a comprehensive review): direct metabolic constraint hypothesis (Armstrong, 1983; Hofman, 1983a,b); the expensive tissue hypothesis (Aiello and Wheeler, 1995); and the maternal energy hypothesis (Martin, 1981, 1983, 1996, 2007; Martin et al., 2005). None of these hypotheses has the general applicability in multiple mammalian clades with different evolutionary histories (Jones and MacLarnon, 2004), and there are several strategies for meeting the energetic demands of encephalization which can be manifested differentially across taxa (Barrickman and Lin, 2010). However, at least in the case of large-brained apes and humans, the maternal energy hypothesis seems to be well supported by the available evidence (Martin, 1996; Isler and van Schaik, 2006a,b, 2009; Isler et al., 2008). This hypothesis proposes that the brain size is constrained by the amount of energy that a mother can provide during the early stages of her offspring's ontogeny (Martin, 1996, 2007). It should be noted that such a primary link between the mother's metabolic capacity and the developing brain of her offspring allows other variables to influence ultimate adult brain size (Martin, 1996). In addition, there may be no very tight relationship between relative brain size and specific behavioral capacities, and an increase in brain size may be advantageous in a diffuse fashion, i.e., may have some kind of permissive or promotive influence with respect to the evolution of cognition (Martin, 1996).

The encephalization is also associated with prolonged duration of most life-history stages, especially in primates (Sacher and Staffeldt, 1974; Harvey and Clutton-Brock, 1985; Barton, 1999; Kappeler and Pereira, 2003; Leigh, 2004; Barrickman et al., 2008) including humans (Bogin, 1997, 1999, 2009; Leigh, 2001). At least three changes in developmental timing occurred during the evolution of human encephalization: extended brain growth, retarded postnatal body growth, and a derived brain growth allometry (Vinicius, 2005). The human brain achieves its final size more by lengthening the time of growth than by adopting an unusual rate of growth (Passingham, 1985). The prolonged period of growth in humans may be partly an adaptation to limit the already high total and brain energy requirements during childhood (Leonard and Robertson, 1992). Others have suggested that selection has acted to decrease human somatic growth rates

during childhood and juvenility (in comparison to chimpanzees), to help fuel the energy-expensive brain and to allow more time for increased cognitive development with lower body-maintenance costs (Walker et al., 2006).

So, how our evolving ancestors have solved the above mentioned energetic challenges? Obviously, there were a number of step-wise changes, stretching perhaps over last 2 million years, i.e., during the evolution of the genus *Homo*. One part of the solution seems to be a significant change in dietary and foraging habits, as humans have a much higher quality diet than expected for their size or their resting metabolic needs (Leonard and Robertson, 1994, 1997; Fish and Lockwood, 2003). Turning to animal source foods, such as meat, as a routine dietary component probably represented an important step (Milton, 1999, 2003). However, it seems that a diet relying solely on consumption of raw food was not sufficient to remove this metabolic constraint on the increase of brain size—as documented in a recent study, the largest great apes cannot afford both a large body and a larger number of brain neurons (Fonseca-Azevedo and Herculano-Houzel, 2012). The use of fire and the invention of cooking might have a substantial role, because the cooking increases enormously the energy yield of foods and the speed with which they are consumed (Carmody and Wrangham, 2009; Carmody et al., 2011). While raw meat increased the caloric content of the diet of early hominids (Milton, 1999), the cooked meat is easier to chew and has a higher caloric yield (Carmody et al., 2011). In fact, as the metabolic cost is limiting enough to impose tradeoffs in brain evolution (Fonseca-Azevedo and Herculano-Houzel, 2012), the invention of cooking food was probably necessary to overcome such a metabolic limitation in the human lineage (Wrangham et al., 1999; Wobber et al., 2008; Carmody and Wrangham, 2009; Carmody et al., 2011). It should be also noted that there is evidence of up-regulation of genes related to energy metabolism in human evolution (Grossman et al., 2001; Cáceres et al., 2003; Uddin et al., 2004).

Another part of the solution seems to be represented by profound changes in the human life-history (Bogin, 1997, 1999, 2001, 2009; Hawkes et al., 1998; Kaplan et al., 2000; Crews, 2003; Leigh, 2004; Gurven and Walker, 2006; Walker et al., 2006). There are several hypotheses on the evolution of human life-history, such as the grandmother hypothesis (Hawkes et al., 1998), the embodied capital hypothesis (Kaplan et al., 2000), the reserve capacity hypothesis (Crews, 2003; Larke and Crews, 2006), and the reproductive fitness hypothesis (Bogin, 1997, 1999, 2009). Briefly, primates and other social mammals have three postnatal life history stages: infancy, juvenile and adult (Pereira and Fairbanks, 1993). However, human life history is characterized by the addition of childhood, adolescence, and grandmotherhood (postmenopausal stage) as biologically, behaviorally, and mathematically definable stages of the life cycle (Bogin, 1997, 1999; Hawkes et al., 1998). The transition from infancy (birth to 30–36 months) to childhood is characterized by weaning and the completion of deciduous tooth eruption (Bogin, 1999, 2001). During the childhood, older members of the social group acquire, prepare, and provision foods to children, and this style of cooperative care represents a major evolutionary invention in the human life-history (Bogin, 1999, 2009). The adolescence includes the years of postpubertal growth (10–18 years for girls, 12–21 years for boys) (Bogin, 1999, 2001).

It is important to note that the childhood and adolescence stages of human life history evolved due to the selective advantages for increased fertility and reproductive fitness of mothers (Bogin, 1999, 2001, 2009), while the benefits of these stages for increased brain growth and learning are important, but secondary, outcomes (Bogin, 2009). In summary, the human species has more life stages than any other mammal and more time for growth and development than any primate (Bogin, 2009). Another important evolutionary novelty in human life-history is that human food provisioning and care to children and their mothers goes beyond the cooperative breeding of other mammals—humans use biological relationships and also marriage, systems of economic exchange, political power structure, and gender-role construction (Bogin, 2009). In other words, human life-history is culturally patterned (Bogin, 2001, 2009; Crews, 2003). Such investments of energy and care from prenatal to early adult life stages build a greater level of reserve capacity than found in any other primate (Crews, 2003; Larke and Crews, 2006; Bogin, 2009).

THE SUBPLATE IS CRITICALLY INVOLVED IN THE ONTOGENESIS OF THE HUMAN CEREBRAL CORTEX

The data reviewed above clearly suggest that the developing brain played significant role in the evolution of the human life-history. As the telencephalon and the cerebral cortex represent by far the largest part of the human brain, we here focus on the potential evolutionary role of the transient subplate zone, because it is critically involved in the development of the primate and human cerebral cortex (Bystron et al., 2008) and it reached a peak of its evolutionary prominence in the human brain (Kostovic and Rakic, 1990; Molnár et al., 2006; Rakic, 2006; Bystron et al., 2008). The role of the subplate in the development and plasticity of the cerebral cortex has been already well described in a number of excellent reviews (Allendoerfer and Shatz, 1994; Kostović and Judaš, 2002, 2006, 2007, 2010; Kanold and Shatz, 2006; Molnár et al., 2006; Rakic, 2006, 2009; Bystron et al., 2008; Kanold and Luhmann, 2010; Clowry et al., 2010; Judaš, 2011). Therefore, we will here only briefly review those aspects of the human subplate which are directly relevant for understanding of our present thesis. As the subplate development in the human brain has also been extensively illustrated in our previous publications (Kostovic and Rakic, 1980, 1990; Kostović and Judaš, 2002, 2006, 2007, 2010; Judaš, 2011), we here provide only a few figures aimed to enhance the understanding of our main argument.

The subplate zone was first described in the human fetal brain (Kostović and Molliver, 1974; Judaš et al., 2010a; see, for a comprehensive historical review). The subplate is the largest transient compartment of the fetal neocortical anlage (see Judaš, 2011, for a comprehensive review). The human subplate develops between 13 and 15 postconceptional weeks (PCW), remains the largest compartment of the neocortical anlage between 15 and 30 PCW, and begins slowly to disappear toward the end of gestation and during the early postnatal period (**Figure 1**). The developmental peak of the subplate is reached during midgestation, when it is about four times thicker than the cortical plate (**Figure 2**). It

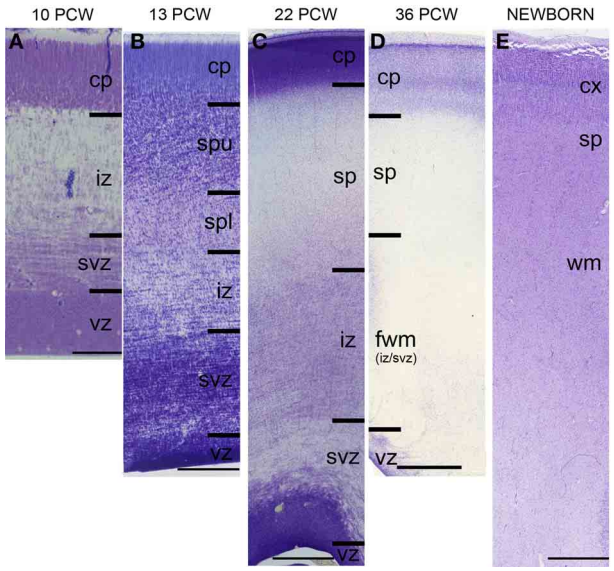

FIGURE 1 | Laminar development of human telencephalon from 10 postconceptional weeks (PCW) to newborn. The layers are transient and their appearance changes with changes in neurogenetic events. The subplate starts to develop around 13 PCW, reaches the peak of its development between 22 and 24 PCW, and starts to resolve around 34 PCW. In the newborn brain, the subplate remains during the first year, when the subplate disappears as a zone but its neurons become incorporated into the subcortical white matter as so-called interstitial neurons. cp, cortical plate; sp, subplate zone; iz, intermediate zone; svz, subventricular zone; vz, ventricular zone. Bar = 100 μm **(A)**, 250 μm **(B)**, 1 mm **(C–E)**.

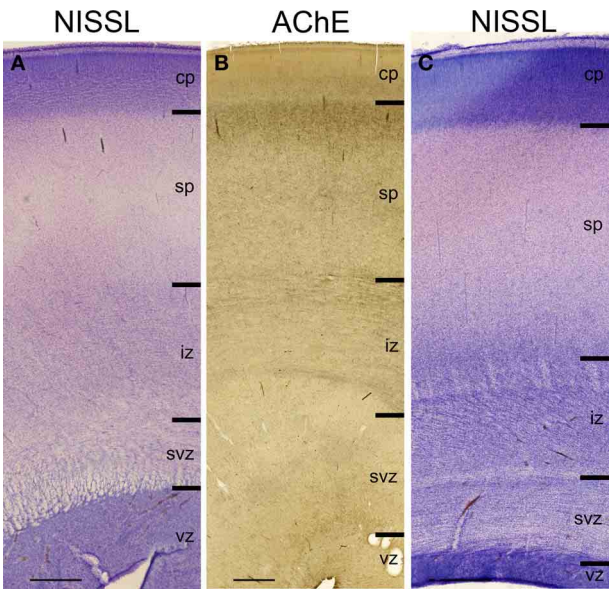

FIGURE 2 | Lamination of frontal (A), mid-central (B) and occipital (C) region of human telencephalon at the peak of subplate development (22–24 PCW), as revealed by Nissl staining and acetylcholinesterase (AChE) histochemistry. At the peak of subplate development (22–24 PCW), subplate zone is the largest compartment of the human telencephalon. It is the place of intense synaptic activity and "waiting" compartment for the thalamocortical fibers (dark band below cp). Note that there are regional differences in the lamination between frontal and occipital region. cp, cortical plate; sp, subplate zone; iz, intermediate zone; svz, subventricular zone; vz, ventricular zone. Bar = 1 mm.

should be noted that the subplate is still present in the newborn brain during the period when various corticocortical connections continue to develop (**Figure 3**). Finally, many subplate neurons survive postnatally and eventually transform into interstitial neurons of the subcortical (gyral) white matter of the adolescent and adult brain (**Figures 4**, **5**) (Kostovic and Rakic, 1980, 1990; Judaš et al., 2010b). While the dissolution of subplate begins during the last third of gestation, it remains present (as recognizable architectonic compartment) under the prefrontal and other association cortices up to 6 postnatal months (Kostovic and Rakic, 1990). It should be noted with a great regret that there are no data available on the subplate of great apes; in fact, there are no histological data on any aspect of prenatal cortical development in great apes.

The subplate contains numerous neurons of various morphological types (Mrzljak et al., 1988, 1990, 1992) and molecular phenotypes, including differentiated projection (glutamatergic) neurons and local (GABA and peptidergic) interneurons (Judaš et al., 1999, 2010b; Judaš, 2011). It also serves as a waiting compartment for growing cortical afferents (Rakic, 1977; Kostovic and Rakic, 1990). Various afferent fibers sequentially grow into the subplate, establish temporary synaptic circuits, and "wait" in the subplate for several months before relocating into their final target, the cortical plate (Kostović and Goldman-Rakic, 1983; Krmpotić-Nemanić et al., 1983; Kostovic and Rakic, 1984, 1990; Kostović, 1986). After 28 PCW, waiting associative and commissural pathways are major constituents of the subplate (Kostovic and Rakic, 1990; Kostović et al., 2008; Kostović and Judaš, 2009). While long corticocortical pathways begin to develop in the early fetal period (Vasung et al., 2010), the development of short corticocortical connections is very protracted and lasts for at least 1 year after birth (Kostović et al., 2012). It should be noted that cortical pyramidal neurons also require about 3 years of postnatal development in order to attain their adult-like size of dendritic arborization (Petanjek et al., 2008).

The subplate is also the major site of synaptogenesis in the midfetal brain (Molliver et al., 1973; Kostovic and Rakic, 1990) and contains diverse and transient neuronal circuits which represent a neurobiological basis for transient electrophysiological and behavioral phenomena in fetuses and early preterm infants (Kostović and Judaš, 2002, 2006, 2007, 2010). Although the onset of cortical synaptogenesis is an early fetal event (Molliver et al., 1973; Kostovic and Rakic, 1990), it should be noted that cortical synaptogenesis is predominantly postnatal process and that synaptic overproduction and developmental plasticity in the human cortex continue for at least 20 years (Petanjek et al., 2011).

The transformation of the fetal white matter occurs gradually and in parallel with gradual dissolution of the subplate, and continues postnatally (Judaš, 2011). The period spanning the last prenatal month and at least the first postnatal year is characterized by significant fiber-architectonic reorganization at the cortical/white matter interface (Kostović et al., 2012). This reorganization is

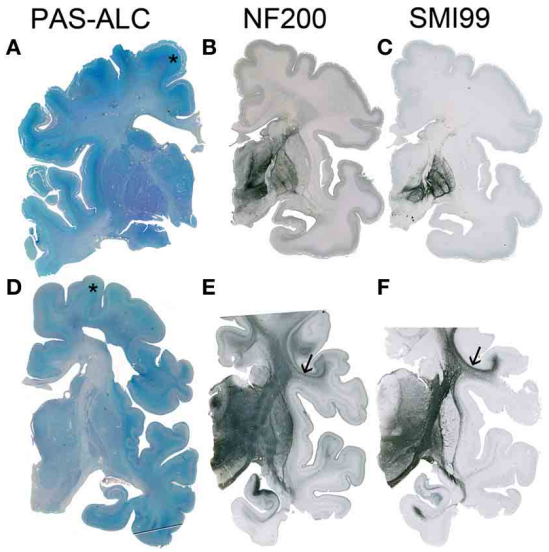

FIGURE 3 | Although the resolution of the subplate zone starts after 34 PCW, the subplate remains visible as a major component of the telecephalic wall (asterisk in A,D). In the human telencephalon, cortico-cortical connections are still not developed **(B)** or myelinated **(C)** at 33 PCW, while at 40 PCW substantial development and myelination of cortico-cortical fiber can be observed (arrow in **E,F**). **A–C** 34 PCW, **D–F** 40 PCW.

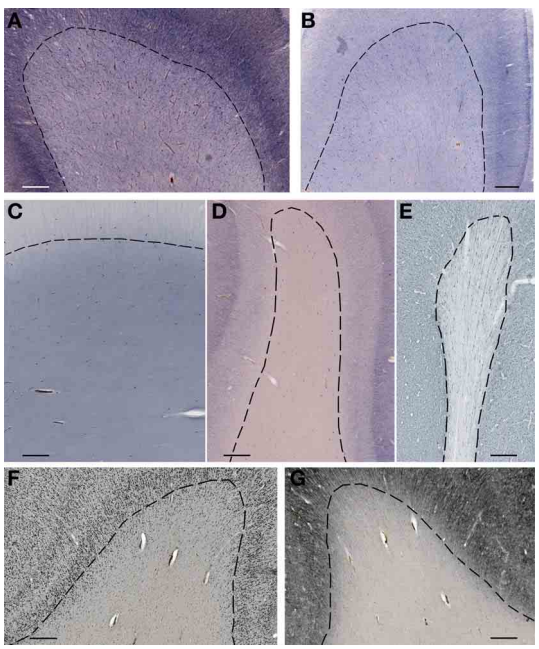

FIGURE 4 | Subplate and white matter interstitial neurons stained for NOS (NADPH-diaphorase-stained neurons in A–D), MAP2 (E,G) and NeuN (F) are visible throughout the subplate (A,B) and the white matter (C–G). Note that subplate/white matter interstitial neurons are numerous even after the first year of life, when subplate zone disappears. **(A)**, 37 PCW; **(B)**, 13 days; **(C)**, 12 years; **(D)**, 57 years; **(E,G)**, 13 months; **(F)**, 51 years. Bar = 1 mm.

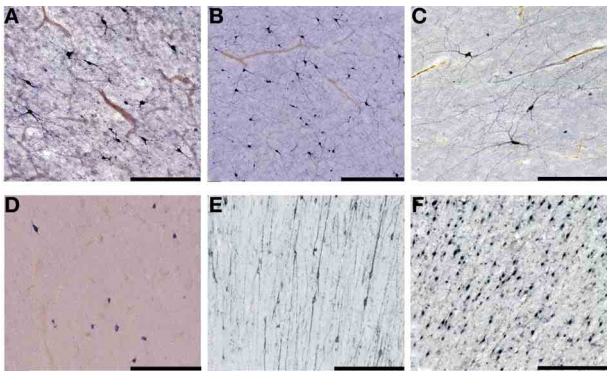

FIGURE 5 | Higher magnification view of subplate and white matter interstitial neurons displayed in panels A–F of the Figure 4 and stained for NOS (NADPH-diaphorase-stained neurons in A–D), MAP2 (E) and NeuN (F). Note that dendritic arborizations of subplate/interstitial neurons continue to grow and develop even after the disapearance of the subplate zone during the first year of life (compare (**A** and **B** with **C**). **(A)**, 37 PCW; **(B)**, 13 days; **(C)**, 12 years; **(D)**, 57 years; **(E)**, 13 months; **(F)**, 51 years. Bar = 0.5 mm.

related to the postnatal persistence of the subplate remnant, the onset of myelination, the appearance of tertiary gyri and sulci, development of short corticocortical connections (Kostović et al., 2012), and probably other factors, such as changes in microvascular network, changes in molecular profile of the extracellular matrix, development of white matter astrocytes, and so forth (Judaš, 2011).

Thus, histogenetic processes in the human fetal and perinatal brain are protracted and significantly overlap (Judaš, 2011), but the subplate represents a playground for the majority of important events during that developmental window. The functional significance of transient fetal circuitry and the pivotal role of the subplate have already been extensively reviewed in both experimental model animals (Allendoerfer and Shatz, 1994; Kanold and Luhmann, 2010) and in humans (Kostović and Judaš, 2006, 2007, 2010; Judaš, 2011). Therefore, it will suffice to point out that the human perinatal and early postnatal period is characterized by simultaneous existence of two separate (but interconnected) types of cortical circuitry organization: (a) transient fetal circuitry, centered at the subplate zone, and (b) immature but progressively developing permanent cortical circuitry, centered at the cortical plate (that is, developing cortical layers I-VI). Thus, the developing human cortex passes through three major early stages of functional development (Kostović and Judaš, 2006, 2007, 2010): (1) initial fetal circuitry which is endogeneously (spontaneously) driven, (2) perinatal dual circuitry (co-existence of endogeneously driven subplate-centered transient circuitry with developing cortical plate-centered permanent circuitry) and (3) postnatally established permanent (externally driven) cortical circuitry (Judaš, 2011).

THE SUBPLATE AS THE PLAYGROUND FOR EVOLUTION OF CORTICAL DEVELOPMENT

While the focus of this review is on putative (and relatively recent) evolutionary changes of the subplate in the primate and

hominid lineage, it is important to note that the subplate may have a much older phylogenetic origin. As pointed out in several recent studies (Montiel et al., 2011; Wang et al., 2011), there are currently three hypotheses about the phylogenetic origin of subplate neurons: (1) subplate neurons were all already present in the common ancestor of mammals and sauropsids (e.g., Marin-Padilla, 1978; Aboitiz et al., 2005); (2) subplate may be unique to mammals and represent an embryonic adaptation to support development of increasingly complex neocortex (Kostovic and Rakic, 1990; Supér and Uylings, 2001; Molnár et al., 2006); and (3) the subplate in mammals may represent a combination of new and ancestral cell populations (Aboitiz, 1999; Aboitiz et al., 2005; Wang et al., 2011; Montiel et al., 2011). The third hypothesis suggests that, although embryonic subplate cells were present in the common ancestor of both mammals and sauropsids, additional populations of subplate cells evolved in mammals as the neocortex became progressively larger and more complex (Montiel et al., 2011; Wang et al., 2011). As the evolution of the mammalian cortex required the modification of developmental programs, it seems probable that some of these started to rely on novel populations of subplate neurons possibly characterized by different targets of connectivity (Kostovic and Rakic, 1990; Montiel et al., 2011). Thus, it is important to determine if and how the subplate has been altered in distinct mammalian lineages and to perform comparative gene expression profiling studies of subplate neurons in different species (Osheroff and Hatten, 2009; Wang et al., 2010, 2011; Oeschger et al., 2012; Hoerder-Suabedissen et al., 2013). For example, species-specific differences in subplate markers have been described even between rat and mouse (Wang et al., 2011). In addition, in primates, in contrast to rodents, neurons are continuously added to the subplate throughout cortical neurogenesis (Smart et al., 2002; Lukaszewicz et al., 2005; Molnár et al., 2006). Finally, in addition to the increased number of neurons in the human subplate (Kostovic and Rakic, 1990; Smart et al., 2002; Bystron et al., 2008), there is both an increased complexity of subplate cell types (Kostovic and Rakic, 1990; Mrzljak et al., 1988, 1990, 1992; Wang et al., 2010) and subplate arrangements including the superficial vs. deep compartmentalization of human subplate neurons (Wang et al., 2010).

Thus, the available evidence suggests that human subplate contains an increased number of (ancestral and derived) subplate neurons as well as increased diversity of a derived population of subplate neurons. As these neurons are active and therefore metabolically expensive, the potential increase in number of subplate neurons was probably subject to a significant selective pressure due to above described metabolic constraints.

The lift-up of metabolic constraints by hominid ancestors opened new vistas for the developing brain, because it became possible to metabolically support transient patterns of brain organization as well as developmental brain plasticity for much longer period and with much greater number of neurons and connectivity combinations in comparison to apes. We propose that the transient subplate zone and its postnatal remnant (interstitial neurons of the gyral white matter) probably served as the main playground for evolution of these developmental shifts, for the following reasons.

First, as described above, the human brain contains about three times more neurons than the brain of apes. As monkey and human cortical neurons are all generated before birth (Rakic, 2006, 2009; Bystron et al., 2008), and newborn human brain is also significantly larger than that of newborn apes (ca. 350 vs. ca. 200 g), it is logical to conclude that brains of human newborns also contain greatly increased number of neurons in comparison to newborn apes. By extension, even if we assume that apes have proportionately equally developed subplate, humans would still have more numerous subplate neurons. Moreover, that huge number of subplate neurons is actively involved in shaping of cortical circuitry for at least 12 months (Judaš, 2011; Kostović et al., 2012), and large number of subplate neurons survives into adolescence and adulthood as subcortical interstitial neurons (Judaš et al., 2010b). Thus, significantly enlarged number of key players in developmental cortical plasticity is present and metabolically supported to play this game for much longer than in any other primate species.

Second, as also described above, the subplate serves as a "waiting" compartment for numerous contingents of ingrowing cortical afferents. The human subplate contains the largest amount of both subcortical and corticocortical waiting afferents, during the longest developmental period. The subplate is the major site of synaptogenesis and early circuit formation during the prenatal period. Its circuitry also coexists with initial adult-like circuitry during the perinatal period, and its neurons continue to be involved in the development of short corticocortical connections during the first postnatal year (Kostović et al., 2012). Thus, humans become able to sustain an extremely long period of cortical circuitry development, characterized by large overproduction of axonal and dendritic branches, synapses and reorganizational events in response to environmental influences. This includes the shaping of cortical connections through the interaction with infant's social environment, which probably enhanced typically human evolution of language, cognition and self-awareness.

In summary, we propose that life-history changes that enabled the metabolic sustainability of prolonged retention of the subplate also provided the playground for prolonged and more diverse perinatal and early postnatal plastic interactions between the increased number of subcortical and corticocortical afferents and increased number of cortical neurons (including the perinatal coexistence of fetal and adult-like cortical circuitry). This enabled the evolution of new types of modular, areal and connectional organization of the human cerebral cortex, subserving cognition and language. Our proposal is also in agreement with the reserve capacity hypothesis (Crews, 2003; Larke and Crews, 2006) and the reproductive fitness hypothesis (Bogin, 1997, 1999, 2001, 2009), because the increased reserve capacity of human species (in comparison to apes) clearly enables the longer development of the human brain, with significant consequences for learning and socialization as well as plasticity and recovery after brain lesions.

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Conical expansion of the outer subventricular zone and the role of neocortical folding in evolution and development

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There is a basic rule to mammalian neocortical expansion: as it expands, so does it fold. The degree to which it folds, however, cannot strictly be attributed to its expansion. Across species, cortical volume does not keep pace with cortical surface area, but rather folds appear more rapidly than expected. As a result, larger brains quickly become disproportionately more convoluted than smaller brains. Both the absence (lissencephaly) and presence (gyrencephaly) of cortical folds is observed in all mammalian orders and, while there is likely some phylogenetic signature to the evolutionary appearance of gyri and sulci, there are undoubtedly universal trends to the acquisition of folds in an expanding neocortex. Whether these trends are governed by conical expansion of neocortical germinal zones, the distribution of cortical connectivity, or a combination of growth- and connectivity-driven forces remains an open question. But the importance of cortical folding for evolution of the uniquely mammalian neocortex, as well as for the incidence of neuropathologies in humans, is undisputed. In this hypothesis and theory article, we will summarize the development of cortical folds in the neocortex, consider the relative influence of growth- vs. connectivity-driven forces for the acquisition of cortical folds between and within species, assess the genetic, cell-biological, and mechanistic implications for neocortical expansion, and discuss the significance of these implications for human evolution, development, and disease. We will argue that evolutionary increases in the density of neuron production, achieved via maintenance of a basal proliferative niche in the neocortical germinal zones, drive the conical migration of neurons toward the cortical surface and ultimately lead to the establishment of cortical folds in large-brained mammal species.

Keywords: neocortex, gyrencephaly, subventricular zone, neural progenitors, mammals, extracellular matrix, phylogenetics

1. INTRODUCTION

Cortical folding and brain development are tightly linked. The prenatal characterization of gyri and sulci may be used to identify functionally distinct cortical areas in many species and predict normal or pathological cerebral function at term. Close correlations between cortical morphology and behavioral function (or dysfunction) suggest that the early development of cortical folds constitutes an important step, either for normal development or as an indicator of normal development, in the construction of the human brain. Comparisons between normal and pathological human brains and between humans and other mammal species highlight important differences in progenitor cell-type abundances, cell-cycle dynamics, radial fiber organization, and gene expression profiles that account for gross phenotypic differences in neocortical morphology and function and even organismal behavior (Bayer and Altman, 1991; Beaulieu, 1993; Dehay et al., 1993; Polleux et al., 1997a,b; Lukaszewicz et al., 2005; Dubois et al., 2008; Toro et al., 2008; Clowry et al., 2010; Fietz et al., 2010, 2012; Hansen et al., 2010; Zilles et al., 2013).

2. THE CHRONOLOGY OF NEOCORTICAL FOLDING DURING DEVELOPMENT IS HIGHLY REGULATED AND CONSERVED ACROSS SPECIES

The emergence of neocortical gyri and sulci can be summarized in two stages: (1) the demarcation of primary gyri at human gestation weeks (GW) 23–31; and (2) the emergence of secondary gyri and the growth of sulcal length and depth between late stages of fetal development and early stages of postnatal life (**Figure 1**) (Chi et al., 1977; Armstrong et al., 1995; Mayhew et al., 1996). Stage 1, which follows the demarcation of cerebral lobes and limbic cortical gyri, is largely conserved between humans and other gyrencephalic primates. The correlative increase in cerebral volume and gyrification during this stage, including a dramatic increase in gyri in the occipital region, may in fact constitute the formation of a characteristic pattern of gyrencephaly common to all gyrencephalic primates. Work in Old World monkeys has shown that all neocortical gyri, with the exception of the superior temporal gyrus, emerge during Stage 1 and that both the chronology of emergence and rostrocaudal distribution of gyri are homologous in monkeys and humans (Zilles

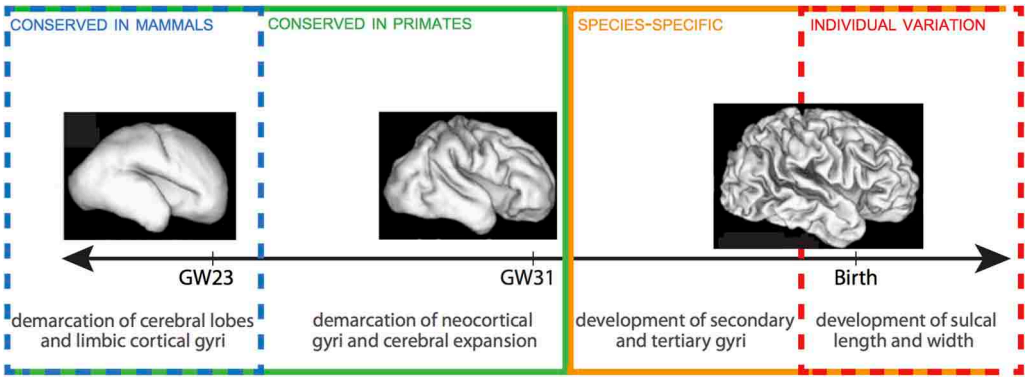

FIGURE 1 | Timeline of gyrification in human. Stages 1 and 2 are delineated by GW 31-32. There is a progressive lack of conservation in cortical folding patterns toward the final stages of gyrification, as minor developmental changes in gyri and sulci become increasingly specialized to species and, ultimately, susceptible to local environmental and experiential variations. 3D reconstructions of fetal human brains from Barnette et al. (2009). Figure follows Sawada et al. (2012b).

et al., 1988; Rilling and Insel, 1999; Sawada et al., 2012a,b). There is, despite this broad conservation, a delayed emergence of the parietoccipital gyri (e.g., cuneus, angular gyrus, supramarginal gyrus) in humans compared to monkeys, which, because these gyri are associated with Wernicke's area in humans but dorsal extrastriate cortex in monkeys (Sawada et al., 2012a,b), may indicate that heterochronic changes in gyri emergence reflect species-specific adaptations in particular cortical regions.

Across all mammal species, cortical folds accumulate non-linearly with increasing brain volume, such that, per gram, larger brains are more gyrencephalic than smaller brains (Zilles et al., 2013). Within species, gyrencephaly index (GI) shows high levels of heritability, but is negatively correlated with both cerebral volume and surface area (Rogers et al., 2010). The positive correlation between GI and cerebral volume and surface observed across species is, therefore, unlikely to come from a common set of genes. Certain human pathologies further demonstrate that genetic mutations affecting gyrencephaly may have limited effect on cerebral volume (e.g., lissencephaly, polymicrogyria) or cerebral volume on gyrencephaly (e.g., microcephaly, megalencephaly). The second stage of gyrification in humans is marked by the prenatal emergence of small sulci and dimples—generated independently of cerebral gyri and accompanied by a major increase in brain weight—and the postnatal growth of sulcal length and depth (Sawada et al., 2012a). Unlike Stage 1, this stage is not correlated with increases in cerebral volume. Rather, patterns in monkeys showing considerable increases in sulcal infolding in the occipital region and secondary and tertiary sulci formation in the frontoparietal region indicate that this period may define species-specific topography of gyri (Fukunishi et al., 2006; Kashima et al., 2008; Sawada et al., 2010, 2012a). For example, increased sulcal infolding in the frontal region of humans (Dubois et al., 2008) compared to macaques (Sawada et al., 2010) underscores the numerous human-specific adaptations to the prefrontal cortex (e.g., Sherwood et al., 2006; Bianchi et al., 2012); and disproportionate inter-indiviual variation in humans in the anterior prefrontal cortex further underscores the phylogenetic recentness and plasticity of this region (Huttner et al., 2005). The terminus of gyrencephaly, too, shows species-specificity: degree of gyrencephaly stabilizes in baboons around birth (Kochunov et al., 2010), while in macaques and humans it reaches a maximum around 1 year after birth (Sawada et al., 2012a). The wide-ranging conservation of gyrencephalic patterning, which cannot be explained simply as a physiological consequence of neocortical expansion, suggests that genetic mechanisms play an important—albeit likely indirect—role in the specification of cortical folding (Rakic, 1988). These genes may either programmatically shape the topology of germinal zones during cortical growth to anticipate gyral and sulcal formation (Smart and McSherry, 1986; Régis et al., 2005) or specify patterns of fiber connectivity to differentially effect tension at the developing cortex (Van Essen, 1997; Hilgetag and Barbas, 2006). The high heritability of early-forming gyri, as well as the species-specific distribution of late-forming sulci, support a scenario in which gyrencephalic tinkering may be accomplished through selection on axonal tension, but that establishment of primary gyri is determined by ventricular (VZ) and subventricular zone (SVZ) organization during cortical development.

3. SUBVENTRICULAR EXPANSION AND THE ESTABLISHMENT OF GYRI

The emergence of new structures is typically limited to selection on existing developmental pathways. Minor perturbations in timing or cell-type proportions may result in major phenotypic adaptations (e.g., delayed retinal neurogenesis in nocturnal vs. diurnal monkeys or the preponderance of basal or apical neurogenesis in larger- and smaller-brained species). Notwithstanding, there are quite divergent developmental pathways able to generate nearly identical phenotypes (e.g., gastrulation, neural crest formation, and germ cell formation). But in either case, we may assume that selection at the gross morphological level is complemented by adaptations in developmental processes. Therefore, any understanding of the appearance and distribution of cortical folds must be gleaned from a comparison of neural progenitors during development across taxa (**Figure 2**).

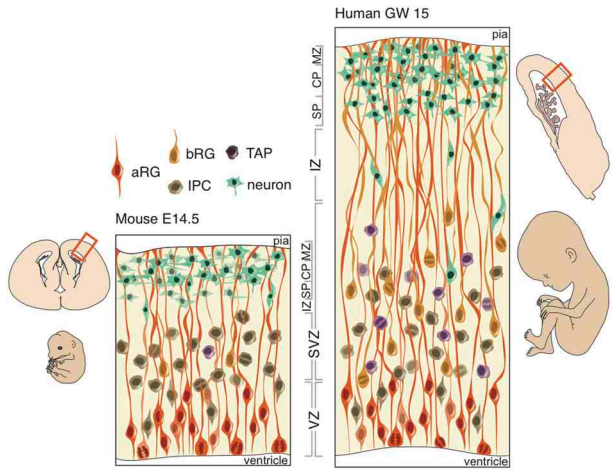

FIGURE 2 | Schematic of neural progenitors in the developing neocortex in mouse (left) and human (right). Polarized progenitors (bRG and aRG) are depicted with processes extending to the apical (bottom) and/or basal (top) surface. Non-polarized cells (IPCs and TAPs) divide exclusively in the SVZ in both mouse and human. The human SVZ is relatively expanded compared to the mouse and divided into an outer (OSVZ) and inner (ISVZ) region. CP, cortical plate; IZ, intermediate zone; MZ, marginal zone; SP, subplate.

At the onset of neurogenesis, neuroepithelial cells forming a pseudo-stratified epithelium divide rapidly and symmetrically, thus expanding the progenitor pool that will directly or indirectly generate all of the excitatory neurons in the neocortex. As neurogenesis proceeds and the epithelium thickens, neuroepithelial cells, while retaining their apical and basal contacts (Huttner and Brand, 1997; Farkas and Huttner, 2008), begin to express astroglia-specific markers (Campbell and Götz, 2002; Kriegstein and Alvarez-Buylla, 2009), lose their tight junctions and elongate (Kelava and Huttner, 2012). These apical radial glia (aRG) perform interkinetic nuclear migration (Taverna and Huttner, 2010), like neuroepithelial cells, and divide asymmetrically at the apical surface of the VZ (Götz and Huttner, 2005; Fietz and Huttner, 2011; Lui et al., 2011) in order to produce a neuron, intermediate progenitor (IP), or basal radial glia (bRG) (Miyata et al., 2001, 2004; Noctor et al., 2001, 2004; Haubensak et al., 2004; Fietz et al., 2010; Hansen et al., 2010; Reillo et al., 2011). IPs and bRG, like neurons, delaminate from the apical surface and translocate their nucleus to the basal region of the VZ to form the second germinal layer, the SVZ, where non-polar IPs self-consume to produce two neurons and unipolar bRGs generate neurons asymmetrically via IPs or transit-amplifying progenitors (TAPs) (Fietz and Huttner, 2011; Franco and Müller, 2013).

In gyrencephalic species, such as the human and ferret, an abundance of basal-oriented progenitors form not only the SVZ, but subdivide the SVZ into an outer (OSVZ) and inner (ISVZ) region (Smart et al., 2002), each with a distinct expression profile (Fietz et al., 2012). The presence of an OSVZ populated by bRG is thought to be necessary for gyrencephaly: lissencephalic species (e.g., mouse, rat, rabbit) lack this derived region, whereas gyrencephalic species (e.g., human, macaque, ferret) maintain this region. But neither the presence of bRG, which constitute a small minority of SVZ progenitors in the mouse (Shitamukai et al., 2011; Wang et al., 2011), nor an abundance of bRG, which exist in comparable proportions in the lissencephalic marmoset and gyrencephalic human (Kelava et al., 2012), is sufficient for developing a folded neocortex. Several lines of evidence and hypothetical modeling may evince which neurobiological features are both necessary and sufficient for development of a gyrencephalic neocortex.

4. AXONAL TENSION AND LATE-STAGE PLASTICITY IN CORTICAL FOLDING

The first cortico-cortical and cortico-subcortical tracts emerge during development of the preplate. As radial pathways across the cortical mantle gradually regress, the subplate forms and thalamo-cortical fibers advance into the cortical plate and cortico-cortical pathways emerge (Kostovic and Rakic, 1990; De Carlos and O'Leary, 1992; Kostović and Jovanov-Milosević, 2006; Kostović and Judas, 2010). In humans, both the radial organization of fiber tracts and establishment of pathways proceed along a posterodorsal→anteroventral gradient, with gyri formation beginning at the parieto-occipital and central sulci during GW24 (Takahashi et al., 2012). One of the earliest suggested and most widely debated hypotheses of a developmental cause for folding focuses on the mechanical tension of axons (Van Essen, 1997). The so-called tension-based hypothesis states that strong, tangentially organized cortico-cortical and weak, radially organized cortico-subcortical pathways, in an effort to minimize the distance between interconnected regions, cause the outward and inward folding of the cortex, respectively.

A recent extension of this hypothesis, which ascribes axonal tensions through the white matter the responsibility of pulling inward the cortical surface, proposes that cortical folding is a function of white matter connectivity (Mota and Herculano-Houzel, 2012). While the emergence of primary sulci with long associative fiber tracts is conserved in gyrencephalic species, as is the close correlation between white matter volume and gyrencephaly during development, no direct connection between gyrification and white matter myelination has been observed (Neil et al., 1998). More importantly, the crucial assumption in tension-based hypotheses—that axonal tension is directed across gyri – finds little evidence in its defense (**Figure 3**). Work in the ferret has shown that, while axons are under considerable tension in the developing brain, the tension is predominantly located in subcortical axon bundles, too deep to affect folding at the surface, and that there is no significant circumferential axonal tension in developing gyri (Xu et al., 2010). In humans, no relationship is observed between gyral formation and the establishment of cortico-cortical fiber pathways (Takahashi et al., 2012). Therefore, axonal tension is unlikely to causally affect cortical folding. However, radial tension within gyri, regulated by white matter connectivity, may limit expansion of the cortex and thereby mediate the shape of the cortical surface (Toro and Burnod, 2005).

Regional variations in axonal tension across the cortex have been suggested to affect cortical shape and influence local folding patterns (Hilgetag and Barbas, 2006; Toro et al., 2008), indicating

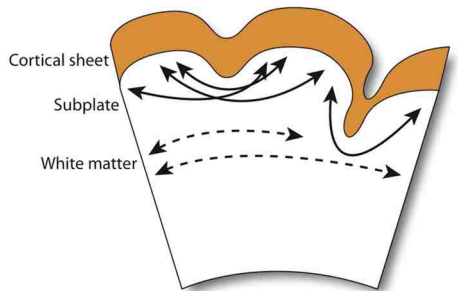

FIGURE 3 | Observed axonal tension across neocortical gyri. Axonal tension (arrows) is distributed circumferentially across the subcortical white matter (dashed arrows), but radially in the subplate and gyral folds (filled arrows). Contrary to the connectivty-driven hypothesis (see section 4), circumferential tension is not observed across neocortical gray matter (Xu et al., 2010).

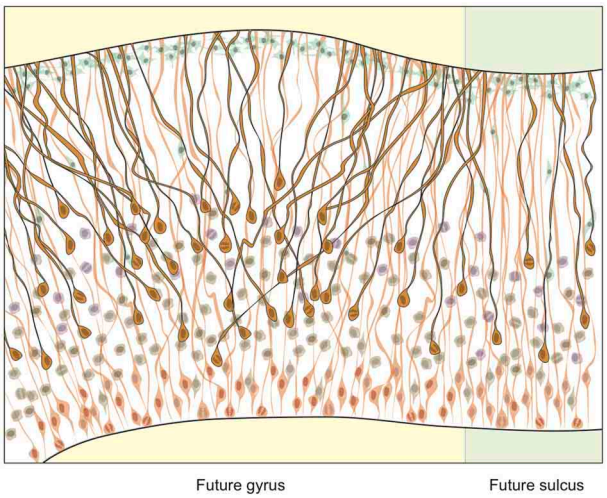

FIGURE 4 | Basal fibers extending to the cortex during development. The density of progenitors in the proliferative basal compartment is increased and the angle of migration of their fibers more oblique at sites of developing gyri compared to sulci. In lissencephalic species, the basal compartment is scarcely populated by proliferating progenitors and fibers migrate in parallel to the developing cortex.

that axonal tension is either the driving force behind late-stage increases in species-specific gyrification or that early-stage tension forces—too small to drive cortical folding by mechanical deformation—may, nonetheless, provide feedback signals that trigger patterns of differential growth in the germinal zone (see Beloussov, 1998). The coincident emergence of primary sulci with long associative fiber tracts lends support to the latter scenario, wherein the subplate zone plays host to interactions between developing fiber tracts and the production and migration of immature neurons (Kostovic and Rakic, 1990; Armstrong et al., 1995). On the other hand, axonal tension is not observed to induce morphological deformations (Knutsen et al., 2013); so, regional variation in cortical tension, proceeding from a topology of gyri and sulci established by differential gray matter (GM) growth, is more likely to only tinker with late-stage gyrencephaly. Minor intraspecific differences in gyri and sulcal formation, particularly in the late-forming prefrontal cortex, support this scenario (Toro et al., 2008).

5. EXPANSION OF THE OSVZ INCREASES CORTICAL SURFACE AREA

The fibers of polarized progenitors provide scaffolding to guide migrating neurons to the developing cortex. In the OSVZ, the scaffolding of bRG resembles a fan, which modifies the trajectory of migrating neurons by driving them to expand conically (**Figure 4**) (Fietz and Huttner, 2011; Lui et al., 2011; Borrell and Reillo, 2012). This, in turn, increases cortical surface area; and experimentally increasing or decreasing cortical surface area during development leads to the production or reduction of gyri, respectively (Reillo et al., 2011). While the caudal→rostral gradient of cortical folding tends to mirror the transverse gradient of neurogenesis (Smart and McSherry, 1986), no gyrencephalic species has a uniform distribution of gyri and sulci, but a pattern that reflects both functional specialization and phylogenetic inheritance. Therefore, the topology of gyri should be reflected in the distribution and mitotic activity of OSVZ progenitors in the developing neocortex. And so it is. In the cat, the density of OSVZ mitoses is three-fold higher in the prospective parietal compared to temporal cortex, reflecting the higher degree of folding and expanded surface area in the former compared to the latter region; in the ferret, the density of OSVZ mitoses is three-fold higher in the prospective splenial gyrus than lateral sulcus, reflecting the relative conical expansion and cortical folding of those regions; and in the human and monkey, OSVZ mitoses are most abundant in the highly folded parietal and temporal regions (Lukaszewicz et al., 2005; Reillo et al., 2011). The evidence suggests, therefore, that OSVZ progenitors accumulate and/or cycle faster in regions that will undergo the greatest cortical folding.

The degree of cissoidian radial fiber divergence, which drives 3D conical expansion of the cortical surface, increases exponentially during neurogenesis in prospective gyral regions, but remains mostly parallel in smooth regions, as it does in lissencephalic species (Lui et al., 2011; Borrell and Reillo, 2012). Importantly, it is not the production of neurons but the divergence of radial fibers (which may be an evolutionary response to increases in neuron production) that drives conical expansion. Enucleation studies in the ferret show how a reduction in the proliferation of bRG leads to a smaller, but no less gyrified, splenial gyrus (Reillo et al., 2011). The mechanistic, and likely genetic (see section 2), dissociation of neuron production and cortical folding is also clear in disease phenotypes. Pachygyria, for example, is characterized by a decrease in cortical surface area, but not neuron number (Ross and Walsh, 2001), whereas the decrease in neuron number in microcephaly is not accompanied by a commensurate loss in cortical folding (Bond et al., 2002). However, the dissociation of neuron production and cortical folding in development does not necessarily imply that these traits were subject to distinct selection pressures. On the contrary, the ubiquity of enlarged, gyrencephalic brains across the mammalian phylogeny, and the near absence of large-brained lissencephalic species, strongly suggests that neocortical expansion and folding evolved in concert.

6. GYRENCEPHALY AND CORTICAL THINNING AS MECHANISTIC RESPONSES TO EVOLUTIONARY INCREASES IN NEURON PRODUCTION

Given two brains of equal radial dimensions, the more folded specimen tends to have a thinner cortex (Hofman, 1985; Pillay and Manger, 2007). In humans, a thin and extensively folded neocortex is characteristic of polymicrogyria (Rakic, 1988; Chang et al., 2004) and may manifest in schizophrenia (Harrison, 1999; Palaniyappan and Liddle, 2012), Williams syndrome (Gaser et al., 2006), and autism (Jou et al., 2010). Across species, the most gyrencephalic taxa (cetartiodactyla) also have the thinnest cortices (Manger et al., 2012). Nonetheless, the relationships between brain volume, gyrencephaly, and GM cortical thickness, in development and evolution, remain elusive (**Figure 5**).

GM thickness and GI—like brain volume, cortical surface area, and gray matter volume—are heritable traits (Panizzon et al., 2009; Eyler et al., 2012). But while brain volume, cortical surface area, and gray matter volume show high levels of statistical and genetic correlation within a population, GM thickness and GI are lowly or negatively correlated with most neuroanatomical traits (Rogers et al., 2010; Winkler et al., 2010). In mammalian evolution, we also find a somewhat chaotic correlative pattern of GM thickness (**Figure 5**). Cetaceans are the most gyrencephalic mammals and exhibit a thin cortex (<1.75 mm) and low neuron density (<65,000 per mm^3) (Hof et al., 2005; Kern et al., 2011); but despite a magnitude of variation in brain volume across cetacean species, GI values remain nearly constant. Pinnipeds, the aquatic carnivores, likewise show very high levels of gyrencephaly (Manger et al., 2012). So perhaps adaptation to an aquatic environment releases a constraint on evolving increasingly folded cortices (see Butti et al., 2011). However, the manatee, the only other aquatic mammal, has a relatively large, lissencephalic brain and a thick cortex (∼3 mm) (Reep et al., 1989; Reep and O'Shea, 1990; Marshall and Reep, 1995). Among terrestrial mammals, artiodactyls have the highest GI values, as well as distinctly thin cortices and low neuron densities compared to primates and carnivores (Chow, 1950), whereas the relatively large-brained beaver, like the manatee, is lissencephalic (Pillay and Manger, 2007). A loose negative correlation between GI and relative (i.e., corrected for neocortical volume) ventricular volume [$F_{(1,\ 30)} = 3.834$, $P = 0.06$] may explain the large ventricles and smooth cortices of the beaver and manatee. Furthermore, our analyses find significant scaling relationships between GM thickness and both brain weight and neuron density (**Figure 6**) (Harrison et al., 2002). These data support the observed convergence of GM thinning in large-brained species, but not the lack of correlation between GM thickness and other neuroanatomical variables within human and other primate populations (see above). If the genes, and therefore selection pressures, mediating GM thickness and folding are independent of those mediating other brain variables, as our and previous analyses suggest, then we should consider a developmental scenario wherein cortical folding and thinning become advantageous to selection for increases in neuron number.

There is a 1000-fold difference in cortical neuron number between mouse and human, but only a 10-fold difference in the length of the neurogenic period. The increase in neuron number in human, therefore, means an exponential amplification of neuron generation. As discussed in section 3, neurons in the human and other large-brained species are generated primarily in the OSVZ, where immature neurons migrate to the cortical plate along fibers provided by bRG. It is the divergence of these fibers that drives conical expansion and ultimately gyrification of the neocortex (see section 5). However, the divergence of radial fibers exiting the OSVZ only organize the migration of neurons to the cortex, allowing them to fan out across an expanding surface rather than continue to populate an overcrowding cortical column (i.e., radial fiber divergence has adapted to accommodate selection for increased neuron generation). The ubiquity of gyrencephaly across mammalian orders, absent any genetic correlation between brain volume and GI (see above), suggests that the mechanistic ability for radial fibers in the OSVZ to diverge in response to rapid increases in neuron generation is either extremely adaptable or deeply homologous (i.e., the conical expansion of fibers is likely constrained by mechanistic limitations or by a conserved developmental toolbox that makes any other solution to the problem of increasing neuron generation deleteriously demanding). But in either case, cortical folding is simply a conserved, mechanistic response to selection for an increased generation of neurons per neurogenic period. In the next section, we will discuss how maintenance of a proliferative niche in the OSVZ may underpin such increases in neuron generation.

7. MAINTENANCE OF A BASAL PROLIFERATIVE NICHE DURING PEAK NEUROGENESIS

Conical expansion of the SVZ into outer and inner regions is a hallmark of increased neurogenic proliferative capacity (Smart et al., 2002). It is likely necessary—but not sufficient (Kelava et al., 2012)—to generate a gyrencephalic neocortex. In the human OSVZ, bRG cells may generate neurons via TAPs, progenitor cells capable of multiple rounds of proliferation (Hansen et al., 2010); and while TAPs are putatively present in other large-brained, highly gyrencephalic species, they have not been observed in significant numbers or with comparable proliferative capacity in lissencephalic species (Wang et al., 2011). Intrinsic factors, such as the expression level and inheritance of certain transcription factors (e.g., Pax6, Sox2) likely play a role in the proliferative capacity of bRG and TAPs, but there is accumulating evidence that extrinsic factors distinguish the behavior of progenitors in the basal compartment between lissencephalic and gyrencephalic species.

Extracellular matrix has been implicated in expansion of the SVZ (Barros et al., 2011; Fietz et al., 2012). For example, interference with integrin signaling, a major part of ECM-derived signaling, results in a reduced number of bRG without affecting the TAP/IP population (Fietz et al., 2010). This suggests that the proliferative capacity of bRGs, compared to TAPs/IPs, depends on integrin signaling maintained via the basal process. Furthermore, there is a denser invasion of incoming thalamic fibers in the SVZ of gyrencephalic compared to lissencephalic species. These fibers secrete proliferation-promoting factors (Kriegstein and Alvarez-Buylla, 2009; Dehay et al., 2001) and subdivide the SVZ into an outer and inner region in gyrencephalic species (Smart et al., 2002). Work in the mouse has shown that blood vessels in the SVZ, which have basal lamina, establish a proliferative niche

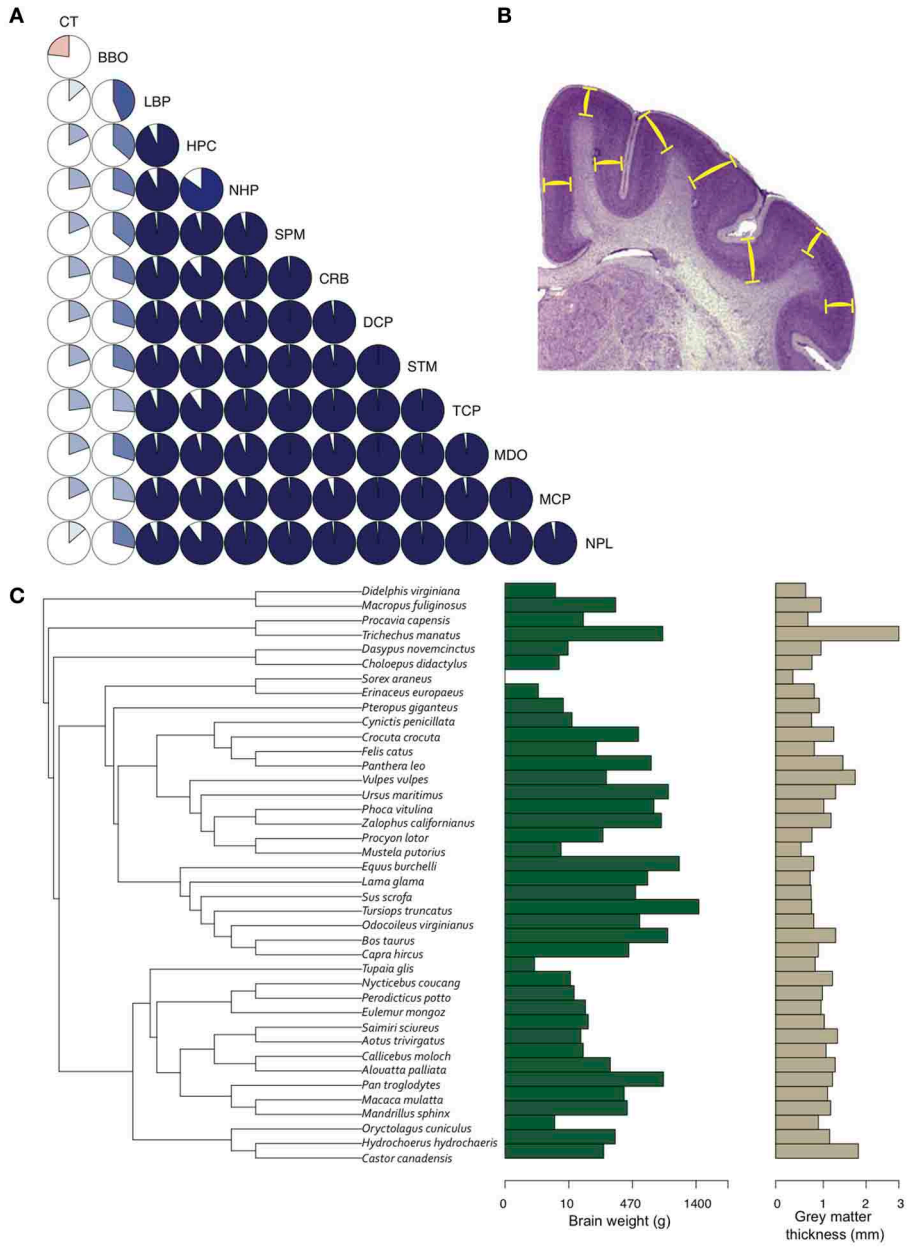

FIGURE 5 | Gray matter cortical thickness varies with brain regions and phylogeny. (A) Twelve brain region volumes and GM thickness presented in a pie-chart matrix of positive (blue gradient) and negative (red gradient) correlations. Note that all brain region volumes - except BBO, which is a developmentally and functionally separate region - show very high ($R^2 > 0.8$) positive correlations, whereas cortical thickness is lowly ($R^2 < 0.4$) correlated with all brain region volumes. BBO, olfactory bulb; CRB, cerebellum; CT, cortical thickness; DCP, diencephalon; HPC, hippocampus; LBP, piriform lobe; MCP, mesencephalon; MDO, medulla oblongata; NHP, neurohypophysis; NPL, neopallial; SPM, septum; STM, striatum; TCP, telencephalon. Volumetric data from Stephan et al. (1981). **(B)** GM thickness is measured as the average distance between layers I and VI (yellow bars) in a systematic random sample of the neocortex. **(C)** A phylogenetic tree of 40 mammal species (Bininda-Emonds et al. 2007) showing the distribution of brain weight (log10 + 1) and GM thickness (log10 + 1) across species. GM thickness in all species was measured with Fiji (Schindelin et al., 2012) on slides from brainmuseum.org. See Lewitus et al. (2013) and **Table A1** for neuroanatomical data in **(C)**.

in their vicinity (Javaherian and Kriegstein, 2009; Stubbs et al., 2009), so vascularization of the developing neocortex is also likely to be integral to the establishment and maintenance of a proliferative SVZ. While it remains unknown which factors are secreted by blood vessels, basal processes, and other ECM vehicles to determine the proliferative capacity of the basal compartment, transcriptome analyses of the developing neocortex in human and mouse have revealed an enrichment of ECM-related transcripts, not only in the OSVZ compared to the VZ, but also in the human OSVZ compared to the mouse SVZ (Arai et al., 2011; Fietz

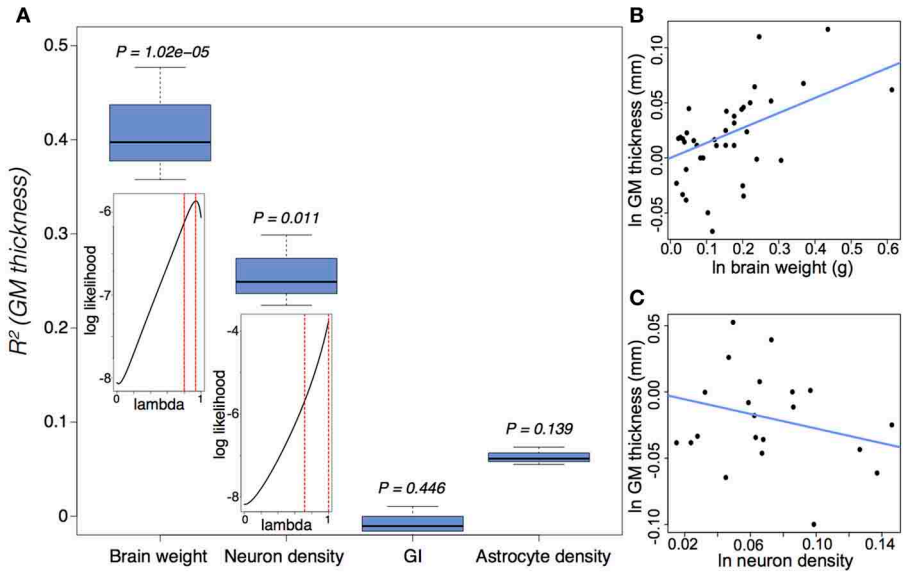

FIGURE 6 | Gray matter (GM) thickness is a function of brain weight and neuron density. (A) Variation in GM thickness can be significantly explained by brain weight [$F_{(2,\ 37)} = 22.58$, $P = 3.9 \times 10^{-7}$] and neuron density [$F_{(2,\ 20)} = 7.96$, $P = 0.003$], but not by either GI [$F_{(2,\ 38)} = 0.066$, $P = 0.936$] or astrocyte density [$F_{(2,\ 20)} = 2.37$, $P = 0.119$]. The insets suggest a strong phylogenetic signal (Pagel, 1999), tantamount to a random walk, in the scaling of GM thickness as a function of brain weight (lambda $= 0.89^{(+0.07)}_{(-0.09)}$) and neuron density (lambda $= 0.88^{(+0.12)}_{(-0.17)}$). **(B,C)** Ln-transformed phylogenetically independent contrasts with regression through the origin for GM thickness as a function of **(B)** brain weight and **(C)** neuron density. GM thickness scales positively as a function of brain weight ($e^{0.136 \pm 0.027}$) and negatively as a function of neuron density ($e^{-0.276 \pm 0.098}$). Cell densities pertain to gray matter counts in the visual cortex from Lewitus et al. (2012). See (Lewitus et al., 2013) and **Table A1** for neuroanatomical data.

et al., 2012), providing clear evidence for an interplay between ECM signaling, an expanded basal compartment, and a large, gyrencephalic neocortex.

8. CONCLUSION

Brain size is subject to significant heritability. As such, selection pressures directing brain evolution in humans have ranged from tool-making abilities to diet to long-distance running [reviewed in Healy and Rowe (2007)]. While none of these pressures is likely to be solely responsible for human neocortical expansion—nor can any of them be incorporated into a general theory of mammalian neocortical expansion—the fact remains: the neocortex has expanded many times in mammalian evolution; and the features underwriting that expansion may ultimately be traced back to neurogenic changes at the cellular level. What remains to be understood, however, is which features are highly constrained and which features have been repeatedly implicated in neocortical evolution.

Adult mammalian brains are not identical at the cellular level. Phylogenetic differences in the density of cortical columns and in the morphology and biochemistry of neurons have been identified in most orders (e.g., Beaulieu, 1993; Peters and Yilmaz, 1993; Nimchinsky et al., 1999; Preuss and Coleman, 2002; Hof and Van der Gucht, 2007; Herculano-Houzel, 2011). The configuration of structural and functional topographical maps that constitute the mammalian brain, too, has seen many evolutionary examples of proliferation, addition, and segregation [reviewed in Krubitzer and Seelke (2012)]. Therefore, universal modular architecture does not exist for the mammalian neocortex and neocortical size may not fairly be considered as an index of general functional capacity. Differential growth across the neocortex and between species, however, may tell us how variation in neocortical size is achieved, even if it will not necessarily inform us of the environmental selection pressures effecting that variation. Here, we have taken a reductionist approach by claiming that a gross neuroanatomical feature (neocortical folding) may signify differences in neurogenic programming both within an individual and across species. We have made this claim based on evidence that neocortical size is determined before any neuronal connections are established and on the assumption that the formation of neocortical gyri is the result of an interaction between selection pressures in cognitive or sensory behavior and the cell-biological properties of neural progenitors throughout neurogenesis. Neocortical size is determined by neurogenic programming (i.e., the distribution of progenitor-type populations and the differential regulation of those populations during neurogenesis). Some neocortical regions may have higher neuron numbers or densities requiring greater degrees of local modulation and control (Collins et al., 2010; Collins, 2011; Bianchi et al., 2012). In these regions, tremendous perinatal increases in astrocytes and oligodendrocytes will drive the morphological expansion of neocortical regions. Specializations in behavior are known to be complemented by cellular or molecular enhancements in the regions of the brain mediating those specializations (Krubitzer, 2007). The enlargement of Meynert cells in the visual cortex of monkeys compared to carnivores, for example, is thought to represent

the evolution of a cellular substrate for specialized sensorimotor capacities related to eye-hand movements that are highly developed in monkeys compared to carnivores (le Gros Clark, 1942; Sherwood et al., 2003). Similarly, the introduction of acoustic noise to rat pups has been shown to alter the cortical magnification of particular neuronal frequencies in the primary auditory cortex (Chang and Merzenich, 2003), showing that even within an individual behavioral and cellular adaptations are tightly linked. In the case of mammalian neocortical expansion, we observe increased vascularization of the neocortical germinal zone, subdivision of the SVZ into an outer and inner region, expansion of the OSVZ, upregulation of ECM signaling to abventricular progenitors, and increased proliferative capacities of non-polar progenitors in the basal compartment of large-brained, gyrencephalic species. We think that these features are correlated in both development and evolution and that any variation between individuals or species in neocortical morphology will not only be underwritten by changes in neurogenic programming but will also be constrained by limitations imposed by the mammalian neurogenic program.

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APPENDIX

Table A1 | Neuroanatomical parameters in 40 mammal species*.

Species	Brain weight (g)[a]	Neuron density (per mm^3)[b]	Astrocyte density (per mm^3)[b]	Gray matter thickness (mm)[c]	Ventricle (1 and 2) volume (mm^3)[a]	GI[d]
Castor canadensis	41.17	NA	NA	1.82	NA	1.02
Hydrochoerus h.	63.5	NA	NA	1.19	NA	1.3
Oryctolagus cuniculus	6.5	NA	NA	0.94	NA	1.15
Erythrocebus patas	105.65	416869	154882	NA	561	1.91
Miopithecus talapoin	39.1	NA	NA	NA	262	1.74
Mandrillus sphinx	NA	263027	138038	1.21	NA	2.14
Lophocebus albigena	103.38	NA	NA	NA	742	1.87
Macaca mulatta	89.22	422149	113783	1.14	834	1.79
Piliocolobus badius	76.75	NA	NA	NA	455	1.81
Pygathrix nemaeus	84.83	NA	NA	NA	911	1.64
Gorilla gorilla	477.44	144544	138038	NA	3608	2.26
Pan troglodytes	392.06	208930	123027	1.25	1899	2.46
Hylobates lar	101.52	NA	NA	NA	555	1.86
Alouatta palliata	52.75	176349	49168	1.31	NA	1.33
Lagothrix lagotricha	95.58	NA	NA	NA	1090	1.97
Callicebus moloch	19	467735	125893	1.11	NA	1.25
Aotus trivirgatus	17.4	410950	59930	1.36	105	1.31
Callimico goeldii	10.95	NA	NA	NA	48	1.26
Callithrix jacchus	7.61	NA	NA	NA	52	1.17
Saguinus midas	10.5	NA	NA	NA	251	1.2
Saimiri sciureus	22.98	478630	117490	1.07	299	1.46
Microcebus murinus	1.85	190546	112202	NA	11	1.1
Cheirogaleus major	6.43	NA	NA	NA	83	1.15
Cheirogaleus medius	3.01	186209	109648	NA	25	1.11
Avahi laniger	10.65	NA	NA	NA	172	1.26
Avahi occidentalis	9.69	NA	NA	NA	74	1.15
Propithecus verreauxi	26.9	NA	NA	NA	231	1.35
Indri indri	37.35	NA	NA	NA	330	1.46
Daubentonia m.	44.89	NA	NA	NA	392	1.25
Eulemur fulvus	28.1	NA	NA	NA	194	1.46
Eulemur mongoz	20.75	234423	138038	1	NA	1.33
Varecia variegata	49.83	NA	NA	NA	299	1.32
Lepilemur ruficaudatus	7.5	NA	NA	NA	77	1.14
Perodicticus potto	13.54	NA	NA	1.03	127	1.27
Loris tardigradus	6.63	NA	NA	NA	52	1.29
Nycticebus coucang	11.73	109648	53703	1.25	142	1.21
Galago senegalensis	4.8	338844	151356	NA	40	1.17
Otolemur crassicaudatus	10.6	NA	NA	NA	147	1.26
Galago demidoff	3.35	NA	NA	NA	30	1.21
Tupaia glis	3.03	131826	107152	0.87	NA	1.06
Capra hircus	106	NA	NA	0.94	NA	2.28
Bos taurus	462	NA	NA	1.32	NA	2.53
Odocoileus virginianus	160	NA	NA	0.84	NA	2.27
Tursiops truncatus	1489	147911	229087	0.79	NA	4.76
Sus scrofa	137.65	48978	70795	0.78	NA	2.16
Lama glama	216.77	NA	NA	0.76	NA	2.7
Equus caballus	712	NA	NA	0.84	NA	2.8
Mustela putorius	8.25	NA	NA	0.56	NA	1.75

(Continued)

Table A1 | Continued

Species	Brain weight (g)[a]	Neuron density (per mm^3)[b]	Astrocyte density (per mm^3)[b]	Gray matter thickness (mm)[c]	Ventricle (1 and 2) volume (mm^3)[a]	GI[d]
Procyon lotor	40.02	104713	83176	0.8	NA	1.85
Zalophus californianus	363	30903	57544	1.22	NA	2.52
Phoca vitulina	273.75	NA	NA	1.06	NA	2.38
Ursus maritimus	472.68	44668	95499	1.32	NA	2.04
Vulpes vulpes	45.63	81283	77625	1.75	NA	1.8
Panthera leo	247.21	NA	NA	1.48	NA	1.85
Felis catus	31.18	114815	22909	0.85	NA	1.5
Crocuta crocuta	153.27	63096	79433	1.28	NA	1.74
Cynictis penicillata	12.51	141254	123027	0.79	NA	1.35
Pteropus giganteus	9	NA	NA	0.96	NA	1.25
Erinaceus europaeus	3.5	194984	128825	0.85	NA	1
Sorex araneus	0.2	338844	295121	0.38	NA	1
Choloepus didactylus	7.7	NA	NA	0.8	NA	1.38
Dasypus novemcinctus	10.75	NA	NA	1	NA	1.07
Trichechus manatus	382	51286	97724	2.71	NA	1.02
Procavia capensis	19.17	NA	NA	0.71	NA	1.37
Macropus fuliginosus	64.8	NA	NA	1	NA	1.41
Didelphis virginiana	6.72	NA	NA	0.66	NA	1.12

**All data for adult.*

[a] *Stephan et al., 1981.*

[b] *Lewitus et al., 2012.*

[c] *See **Figure 5**.*

[d] *Lewitus et al., 2013.*

frontiers in
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Cortical plasticity within and across lifetimes: how can development inform us about phenotypic transformations?

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The neocortex is the part of the mammalian brain that is involved in perception, cognition, and volitional motor control. It is a highly dynamic structure that is dramatically altered within the lifetime of an animal and in different lineages throughout the course of evolution. These alterations account for the remarkable variations in behavior that species exhibit. Of particular interest is how these cortical phenotypes change within the lifetime of the individual and eventually evolve in species over time. Because we cannot study the evolution of the neocortex directly we use comparative analysis to appreciate the types of changes that have been made to the neocortex and the similarities that exist across taxa. Developmental studies inform us about how these phenotypic transitions may arise by alterations in developmental cascades or changes in the physical environment in which the brain develops. Both genes and the sensory environment contribute to aspects of the phenotype and similar features, such as the size of a cortical field, can be altered in a variety of ways. Although both genes and the laws of physics place constraints on the evolution of the neocortex, mammals have evolved a number of mechanisms that allow them to loosen these constraints and often alter the course of their own evolution.

Keywords: epigenetic, comparative neuroanatomy, cortical development, evolution, Evo-Devo

"We certainly need to remember that between the genotype and phenotype, and connecting them to each other, there lies a whole complex of developmental processes."

Waddington, 1942.

Evolution and development of the nervous system are inextricably intertwined. Studies that link these two biological processes have recently re-emerged from the older foundations of comparative neuroanatomy and descriptive neurodevelopment as the flashy new discipline often referred to as "Evo-Devo." This re-awakening was made possible by two events. First, descriptive neurodevelopment transformed into an experimental discipline with the advent of molecular and genetic techniques that allowed scientists to figuratively "poke the frog." The ability to make targeted changes, via genetic manipulations that differentially affect specific aspects of development, allowed us to appreciate the contingencies inherent in the developmental process and to understand the role these genetic cascades play in the construction of specific features of the nervous system. Importantly, it is becoming increasingly clear that the cortical field is not a static entity, but transforms continually at all stages of development. The second event was the emergence of new technologies in genetics that allowed scientists to decode and compare entire genomes of selected species. The prospect that this would ultimately uncover the fundamental differences between species propelled the somewhat aging field of evolutionary neurobiology to the forefront of neuroscience.

Our laboratory has long been interested in the evolution of the neocortex and has used comparative studies to formulate testable hypotheses regarding neurodevelopment. Specifically we are interested in the developmental mechanisms that give rise to aspects of neocortical organization that have changed significantly in species over the course of evolution. We focus on the neocortex for two important reasons. The first is that the neocortex is the portion of the brain involved in complex behaviors including perception, cognition, language, and temporal planning of events. Second, it is the portion of the brain that has changed most dramatically in mammals compared to other parts of the brain (Krubitzer, 2007). The neocortex has expanded tremendously in human and non-human primates, and has expanded independently in several other orders of mammals including cetaceans, proboscidea, and rodentia. However, it is not just an increase in the size that distinguishes some large-brained mammals from others, but also an increase in the number of functional subdivisions, and importantly, alterations in their patterns of connectivity. Studies of endocasts of the skulls of early mammals (Luo et al., 2001) as well as comparative studies (Meredith et al., 2011; O'Leary et al., 2013) suggest that the first mammals that roamed the earth some 200 million years ago had a small neocortex with perhaps 10–15 cortical fields, and a relatively large pyriform cortex and olfactory bulbs (Rowe et al., 2011; Dooley et al., 2013; see Kaas, 2011 for review). This early mammaliform and its descendants evolved to produce some extant species with a neocortex that dominates the rest of the nervous system and contains billions of cells with hundreds of cortical fields. The question is how did this occur, and what factors contribute to this increased complexity of form, function and behavior.

One obstacle in addressing this question is that cortical evolution in mammals cannot be studied directly. The types of changes that brains have evolved occur over multiple generations and often take tens of thousands to millions of years to emerge. However, there are two ways to circumvent this problem. The first is to examine the products of evolution, extant animal brains and bodies, to determine *what* changes have occurred. This comparative approach has been used to good effect to appreciate common features of the neocortex that all species share as well as derivations that have been made to the basic plan of organization. Unfortunately, comparative studies do not provide information on how phenotypic transformations occur, or the rate at which changes can happen. To appreciate how changes occurred we study the developmental mechanisms that are proposed to give rise to some aspect of cortical organization. Thus, it is critical to appreciate how processes such as neurogenesis, cell migration, neuronal differentiation, and axon guidance are altered in mammals with different cortical phenotypes. These alterations give rise to some feature of organization that we study in our comparative analysis such as cortical sheet size, cortical field size, and connectivity. For these reasons developmental studies tell us *how* phenotypic changes occur.

It is important to stress that any theory of brain evolution, cortical function or cortical plasticity should not consider the neocortex in isolation, but must recognize that the neocortex is only one component of the entire nervous system. Further, the nervous system is embedded in a body, which interacts with other organisms and the environment. This group of organisms and their environment generates a complex and highly dynamic "collective biomass" that itself has emergent properties which differ from, and in some instances exceed, the individual elements of which it is composed (Krubitzer, 2009). Further, it is critical to appreciate that the relationship between genes, the brain, the body, and the target of natural selection (behavior) is often highly convoluted and indirect (see Krubitzer and Seelke, 2012 for review).

In the following review we first provide an overview from comparative studies that outlines common features of cortical organization that have been identified in all species examined and how aspects of this common plan have been modified. Second, we address the question of how these phenotypic transformations have occurred, including a review of studies that examine how genes contribute to neurogenesis, cortical sheet size, and aspects of cortical arealization across development. We underscore the importance of examining not only genes intrinsic to the neocortex, but also genes that regulate the body plan and limb and effector morphology. Next, we discuss activity-driven alterations to the cortical phenotype. To appreciate the gene/environment interactions we look to natural examples of extreme morphological/behavioral specialization that is accompanied by exaggerated aspects of cortical organization, and describe our developmental studies in which we try to mimic these changes to the neocortex by radically altering sensory inputs. Finally, we describe more subtle examples in which animals of the same species, reared in different sensory environments, develop alterations to the cortical phenotype. We discuss potential epigenetic mechanisms that construct context dependent alterations to the phenotype.

WHAT IS THE PLAN AND HOW HAS IT CHANGED?

Comparative studies use multiple criteria to define a cortical field including functional techniques (e.g., electrophysiological recording, imaging, intracortical microstimulation), combined with architectonic and neuroanatomical techniques. In our experiments we survey a large extent of the neocortex by recording neural activity from hundreds of sites while successively presenting visual, auditory, and tactile stimulation to determine sensory domain allocation (the amount of cortex devoted to a particular sensory system). These techniques also allow us to determine the number and overall organization of different cortical fields within a sensory domain. These data can be combined with architectonic techniques in which the region of interest is stained for particular cell types, myelinated axons, enzymatic activity, or any number of other histochemical markers that illuminate cortical field boundaries, which are then directly related to functional techniques. Cortical regions can also be divided using neuroanatomical techniques to examine subcortical, cortical and interhemispheric connections of the field in question.

Using such techniques in a number of different species, our own and other laboratories have generated schemes of cortical organization composed of architectonically, connectionally, and functionally distinct maps of the sensory receptor arrays associated with visual, somatosensory, and auditory processing. These comparative studies indicate that there is a constellation of cortical fields that all mammals possess that can be defined using multiple criteria. These include primary visual, somatosensory, and auditory cortical fields (V1, S1, and A1 respectively) as well as one or two additional sensory areas (**Figure 1**; e.g., V2, S2/PV, R) (Dooley et al., 2013; see Kaas, 2011 for review).

Interestingly, these fields are present even in the absence of apparent use in animals showing extreme specialization such as blind mole rats (Cooper et al., 1993; Bronchti et al., 2002). Moreover, independently evolved modifications to this plan take a similar form in different lineages (Krubitzer and Kaas, 2005). Systems-level evolved changes in cortical organization include:

1. The absolute and relative size of the cortical sheet
2. Sensory domain allocation
3. Response properties and stimulus preference of neurons within a cortical field
4. Relative size of cortical fields
5. Magnification of behaviorally relevant body parts
6. Addition of modules to cortical fields
7. Number of cortical fields
8. Connections of cortical fields

The persistence of the shared cortical field plan across all mammals and the similarities in its modifications suggest that there are large constraints on how cortical fields evolve. For further discussion of constraints and variability see Krubitzer and Seelke, 2012.

WHAT FACTORS CONTRIBUTE TO THESE CHANGES?

As noted above, while comparative studies allow us to appreciate the types of changes that have been made to the neocortex, developmental studies provide insights into how these changes occur.

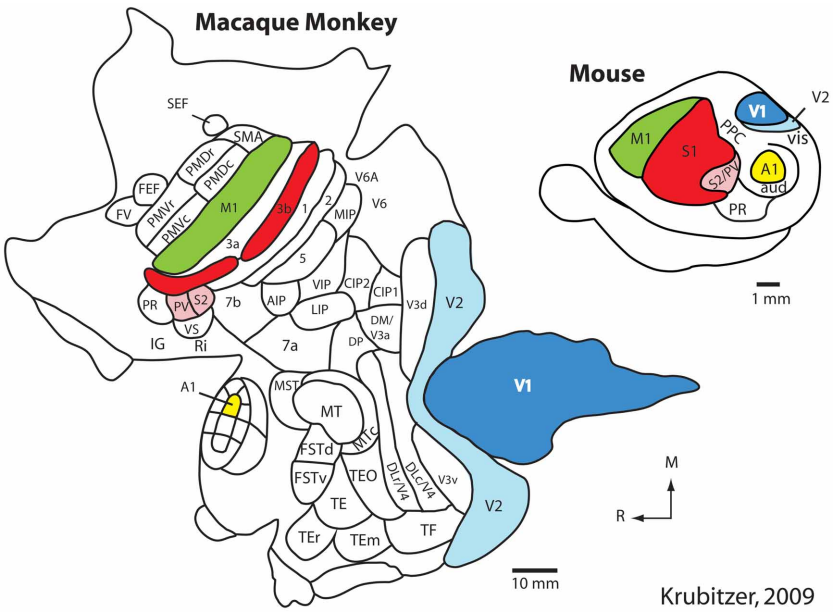

FIGURE 1 | The organization of the neocortex in the macaque monkey and mouse in cortex that has been peeled from the brainstem and thalamus and flattened. Homologous cortical fields include the primary somatosensory area (S1/3b; red), the second somatosensory area and the parietal ventral area (S2/PV; rose), the primary visual area (V1; dark blue), the second visual area (V2; light blue), the primary auditory area (A1; yellow) and motor cortex (M1; green). While this common plan of organization can be identified in these species, there are also notable differences. Specifically, in macaque monkeys the neocortex has greatly expanded and multiple additional cortical areas have been added. Further, the relative size of homologous cortical fields (as a percentage of overall cortical area) is different. While different investigators have proposed different schemes of cortical organization in the macaque and mouse, it is clear that macaque monkeys have many more cortical fields than does the mouse. Modified from Krubitzer (2009). See **Table 1** for abbreviations. All abbreviations for the macaque monkey are not provided; this figure simply demonstrates that the number of cortical fields has increased.

Thus, the next question that arises from our comparative analysis is what factors contribute to within-species variability of the features of cortical organization listed above. This is a question that has been posed for decades, commonly presented as a nature vs. nurture debate. Recently, advances in comparative genomics and epigenetics confirm the contributions of both genetic and context-dependent factors to different aspects of the cortical phenotype and within-species variability. Still contentious, however, is the extent to which each factor shapes or constructs any given phenotype.

Traditionally, context-dependent changes to cell phenotypes during development had been referred to as "epigenetic" (Waddington, 1942). Waddington coined the term epigenetics to explain how cells in the developing organism can have the same genotype, but gradually differentiate into different tissue. This phenomenon underscores that there is not a one-to-one correspondence between genotype and phenotype, and that there must be something beyond the genotype that generates this diversity. We now appreciate that this same ability to alter a cellular, systems, or behavioral phenotype occurs in mature, non-dividing cells in the central nervous system (Day and Sweatt, 2010), and this phenomenon has also been termed epigenetics. While early in development, context-dependent changes may be as simple as folic acid availability or location of a particular cell on a developing blastocyst, as development progresses, the context (and thus its potential for change) becomes more complicated. This is particularly true for the mammalian neocortex, where environmental context routinely molds the phenotype. A particular cortical phenotype may persist for multiple generations if the context in which it develops is static, but these features of cortical organization are not inherited and thus do not evolve. However, new studies, which we will discuss below, have overturned some assumptions about heritability and have begun to uncover the mechanisms that generate contextually dependent phenotypes that can be expressed in multiple generations, and in some instances become incorporated into the germ line and evolve.

CORTICAL SHEET SIZE

One of the well-defined systems-level changes to the brain has been an expansion of the cortical sheet. Throughout the course of mammalian evolution, this expansion has taken two different forms: (1) Absolute increase in size (direct scaling), and (2) Relative increases in size (non-linear scaling). Direct scaling consistently occurs with an increase in body size. The brain scales directly with the body, and every structure, including the neocortex and constituent fields, expand roughly equally. This is exemplified by the comparison of two closely-related rodents: The guinea pig (700 g) and the South American capybara, the largest rodent on earth which weighs up to 91 kg (200 lbs; **Figure 2**). The neocortex of the guinea pig is much smaller than that of the capybara, but relative to body size, the size of the neocortex and

Table 1 | Abbreviations used throughout the text.

A1—Primary auditory cortex
Emx2—Empty spiracles homeobox 2—transcription factor expressed in a caudal (high) rostral (low) gradient
FGF8—Fibroblast growth factor 8—morphogen important for generating the rostral-caudal axis
GR—Glucocorticoid receptor
HPA—Hypothalamic–pituitary–adrenal
IPC—Intermediate progenitor cells
ISVZ—Inner subventricular zone
LG—Licking and grooming
M1—Primary motor cortex
oRG—Outer radial glial cells
OSVZ—Outer subventricular zone
Pax6—Paired box protein 6—transcription factor expressed in a rostral (high) caudal (low) gradient
PV—Parietal ventral area
R—Rostral somatosensory field
RG—Radial glial cells
S1—Primary somatosensory cortex
S2—Second somatosensory area
SVZ—Subventricular zone
V1—Primary visual cortex
V2—Second visual area
VZ—Ventricular zone

the primary sensory fields are comparable (Campos and Welker, 1976).

The second type of increase in the size of the cortical sheet is non-linear and is related to a different type of cortical organization. The California ground squirrel is similar in overall body size to the guinea pig (700 g), but its neocortex is substantially larger both absolutely and relative to the body or rest of the brain (Campi and Krubitzer, 2010). This non-linear increase in the size of the cortical sheet is accompanied by a decrease in the overall percentage of neocortex occupied by primary sensory areas along with an increase in the absolute number of cortical fields on the cortical sheet (**Figure 2**), a pattern even better exemplified in non-human primates such as squirrel monkeys. Squirrel monkeys have about the same body mass as both California ground squirrels and guinea pigs (750 g), but have an extraordinarily large neocortex compared to the body and the rest of the brain, and a dramatic increase in the number of cortical fields. Thus, an absolute (linear) increase in the size of the neocortex is not sufficient to yield an increase in its complexity (i.e., more cortical fields/changes in connections). Conversely, a relative (non-linear) increase in the size of the neocortex does appear to be necessary to increase number of cortical fields, but may not be sufficient to induce this change.

Some questions that emerge are: (1) How is an increase in the size of the cortical sheet accomplished? (2) Are the underlying mechanisms of direct and non-linear scaling of the cortex different? (3) What is the link between changes in brain and body size? and (4) Are the underlying mechanisms that give rise to increases in cortical sheet size similar in species that have independently increased the size of the cortical sheet (e.g., primates and cetaceans)?

THE EVOLUTION OF NEUROGENESIS

Recent studies of neurogenesis have made important inroads into understanding, at least in some species, the mechanisms that contribute to tangential increases in the size of cortical sheet during development and how these mechanisms may be altered in different species to produce differences in the size of the cortical sheet. Historically, researchers investigating neurogenesis have hypothesized that animals with larger (usually gyrencephalic) brains have an increased duration of neurogenesis and modified cell cycle kinetics, and that such alterations are not present in small (lissencephalic) brained animals. This notion is supported by comparative studies in mice and macaque monkeys that demonstrate that more rounds of cell division occur over a longer period of time in the macaque compared to the mouse (Takahashi et al., 1995; Kornack and Rakic, 1998; Kornack, 2000). Subsequent studies described additional changes in neurogenesis that could account for an expanded cortical sheet in some lineages. One important alteration, first described in the macaque monkey, was the presence of an outer subventricular zone (OSVZ, Smart et al., 2002; **Figure 3**). Additionally, within the OSVZ are proliferative radial glia-like cells termed outer radial glial cells (oRG) that generate neurons that will compose the cerebral cortex (Fietz et al., 2010; Hansen et al., 2010; Reillo et al., 2011; Shitamukai et al., 2011; Wang et al., 2011; Martínez-Cerdeño et al., 2012). This large OSVZ and the oRG proliferative cells, at least in part, account for the exponential expansion of the cerebral cortex in some orders such as primates.

Initially, this expanded OSVZ and the corresponding oRG cells were considered an adaptation limited to large-brained, gyrencephalic mammals, but recently a much smaller OSVZ has been described in rats. This OSVZ shares many of the same features found in larger brained ferrets and macaques, such as the presence of oRG proliferative cells (Martínez-Cerdeño et al., 2012). There is also evidence for an OSVZ in the marmoset (a dwarfed, nearly lissencephalic primate) and the agouti (a gyrencephalic rodent; García-Moreno et al., 2012). Thus, small-brained mammals from multiple orders possess the basic ventricular compartments (OSVZ) and proliferative cells (oRG) that can generate expansions in the cortical sheet.

If not the presence of OSVZ and oRG, what differentiates large and small brains? It appears that large-brained animals have an increased generation of intermediate progenitor cells (Wang et al., 2011), a greater number of oRGs present across development (Hevner and Haydar, 2012), and a thicker OSVZ (Bystron et al., 2008; Martínez-Cerdeño et al., 2012), all of which can lead to a larger neocortex with a greater number of neurons (**Figure 3**). Additionally, while oRGs have been shown to produce neurons and intermediate progenitor cells in primates, which further divide into post-mitotic neurons (Hansen et al., 2010), in mice they have only been shown to divide directly into neurons (Wang et al., 2011), although this is not the case for all rodents (Martínez-Cerdeño et al., 2012). While more comparative studies need to be done, mounting evidence suggests that changes in the

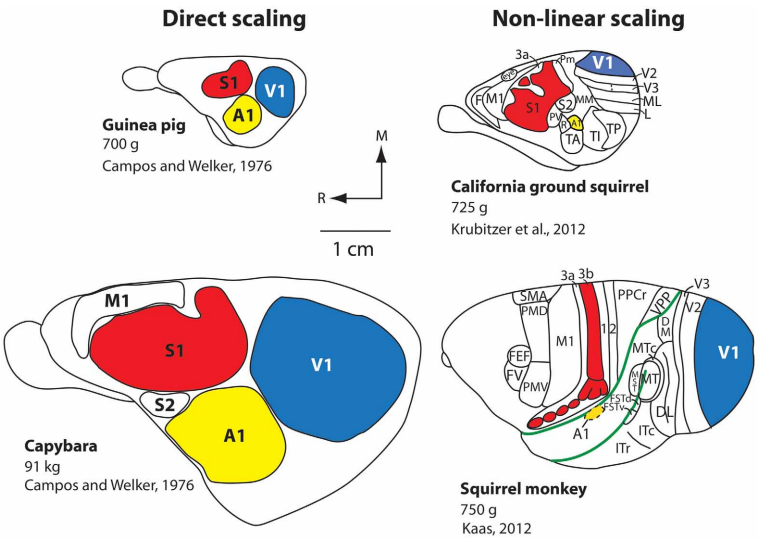

FIGURE 2 | Scaling of the neocortex in different mammals. Comparative studies demonstrate that the neocortex scales linearly or non-linearly. Capybaras can weigh up to 91 kg and have an enlarged brain and neocortex compared to the closely related guinea pig, which weighs 700 g. The more distantly related California ground squirrel has a similar body size to that of the guinea pig, but the scaling of the cortical sheet and cortical fields compared to the capybara is non-linear, and there is an increase in the number of cortical fields. An extreme example of a non-linear increase in the size of the cortical sheet is observed in squirrel monkeys. Although squirrel monkeys are of a similar weight (750 g) compared to the guinea pig and California ground squirrel, they have a relatively large neocortex (about the size of the capybara's), a relative decrease in the size of primary cortical fields (e.g., A1, S1, V1) as a percentage of overall cortical area, and the addition of cortical fields (note that not all known cortical fields in the squirrel monkey neocortex are shown; the blank areas contain additional cortical fields). All brains are drawn to scale. The work on the guinea pig and capybara is modified from Campos and Welker (1976); the divisions of the ground squirrel are redrawn from Krubitzer et al. (2011); divisions of the squirrel monkey are redrawn from Kaas (2012). Other conventions as in previous figure.

size of the cortical sheet are due to expansions of existing populations of cells and cell cycle kinetics, rather than the creation of novel mechanisms.

Exciting research published in the last year has identified proteins which appear to regulate the population of oRG cells (Trnp1; Stahl et al., 2013) and intermediate progenitor cells (BAF170; Tuoc et al., 2013), such that both over expression and under expression of these proteins in the neocortex alter the number of these progenitor cells and ultimately alter cortical sheet size. Further, research by Nonaka-Kinoshita et al. (2013) shows that increasing the pool of basal progenitors in the lissencephalic mouse increases the size of the neocortical sheet, but is not sufficient to induce gyrencephally; however, the same manipulation in the naturally gyrecephalic ferret both increased the size of the cortical sheet and induced additional cortical sulci. Thus, while increasing the number of progenitor cells invariably leads to a larger cortical sheet, existing data suggests that a sufficient population of oRG cells must also be present to create sulci and gyri in a naturally lissencephalic cortex (Stahl et al., 2013; Tuoc et al., 2013).

It is important to note that epigenetic events can also regulate the size of the cortical sheet. These context-dependent alterations in cortical sheet size appear to be caused by a variety of factors. For example, it has been well documented that folic acid (and cholate) regulates neurogenesis and apoptosis in the developing fetal brain, and differences in intake can alter the number of progenitor cells undergoing mitosis by 33–54% in the neocortex of mice (Craciunescu et al., 2004, 2010). Although a number of studies have demonstrated that domestication also has a profound impact on the size of the cortical sheet (see Kruska, 2005), it is difficult to disambiguate the contribution of genes vs. environment on cortical sheet size.

CORTICAL FIELD SIZE AND CONNECTIVITY

Like cortical sheet size, both genetic and epigenetic factors contribute to aspects of cortical field size and connectivity. A plethora of studies demonstrate that intrinsic factors contribute to a number of features of cortical organization including relative position on the cortical sheet, relative size of the cortical field, and cortical field connections (e.g., Bishop et al., 2000; O'Leary and Sahara, 2008; Assimacopoulos et al., 2012). For example, groundbreaking studies from a number of laboratories demonstrated that morphogens such as FGF8 generate a rostral cortical identity, and that these early signaling centers set up genetic cascades which regulate position, size, and connectivity of cortical fields. The importance of these early signaling centers is clearly demonstrated in recent studies in which *Fgf8* was electroporated into different regions of the developing mouse embryo and duplicate fields (with rostrocaudal axes) were observed (Assimacopoulos et al., 2012, **Figure 4**). Electroporating *Fgf8* into a caudal (aberrant) location results in an almost complete duplication of cortical maps with a mirror reversal of V1 and S1 at mid cortex, with two distinct "rostral" poles and a shared caudal pole boundary (**Figure 4B**). This compelling result presents a possible mechanism for mirror reversal organization of cortical fields (such as

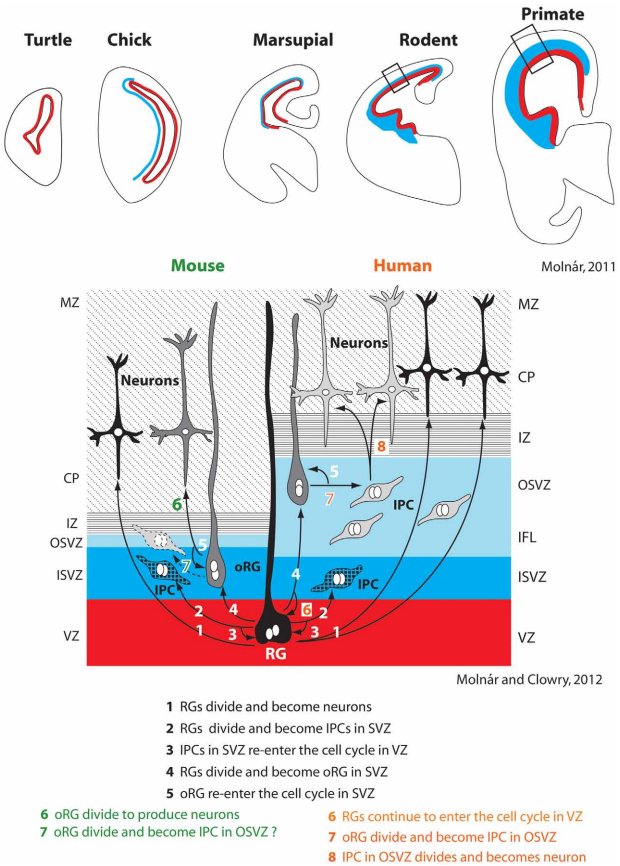

FIGURE 3 | Changes in the subventricular zone (SVZ; blue) in vertebrates (top row). Specific alterations in cell cycle kinetics, the overall thickness of the SVZ, the proportion of the SVZ corresponding to the inner and outer layers (ISVZ and OSVZ respectively), and the proportion of asymmetrical radial glial (RG) and outer radial glial (oRG) cell divisions producing intermediate progenitor cells account for expansion of the neocortex in some lineages, such as primates (right half of bottom panel). The SVZ and particularly the OSVZ is larger in primates than in many other species. While mammals with both a large and small neocortex share a number of aspects of neurogenesis (steps 1–5 bottom figure), several additional adaptations are observed in animals with a large neocortex such as primates. This includes increased thickness of particular layers (such as the OSVZ), additional rounds of division for RGs that re-enter the cell cycle in the ventricular zone (VZ) (6), division of oRGs into intermediate progenitor cells (IPC) in the OSVZ (7), which ultimately divide again to produce neurons (8). Whether oRGs also divide to produce IPCs in rodents is still contentious (dotted line on left side, 7). These figures have been modified from Molnár (2011) and Molnár and Clowry (2012). Abbreviations in **Table 1**.

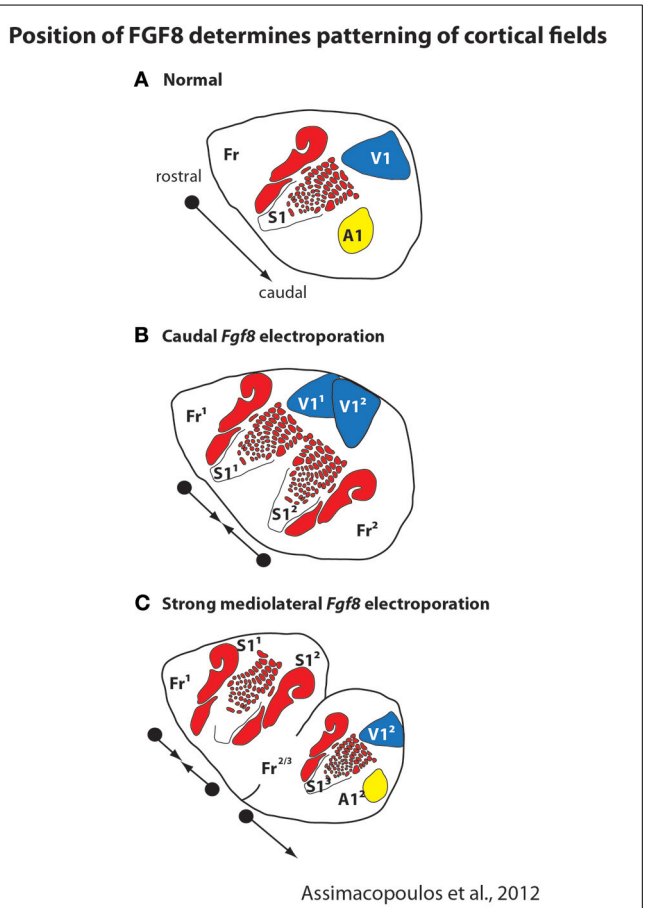

FIGURE 4 | Early in development the position and strength of morphogens, such as FGF8, determines the location and patterning of cortical fields on the cortical sheet. In normal mice **(A)**, FGF8 is expressed early in development in the rostromedial neocortical primordium and forms a rostro-caudal gradient that regulates subsequent rostrocaudal patterns of gene expression. Studies in which *Fgf8* is electroporated at differing levels and in different locations in the embryonic mouse (E10.5) demonstrate its importance as an early cortical map organizer. Ectopic placement can result in the duplication of a cortical field (**B**; $S1^1$ and $S1^2$) or multiple cortical fields arranged along variant rostro-caudal axes **(C)**. These new duplicated fields are also functionally distinct and form topographic maps, as in normal animals. Modified from Assimacopoulos et al. (2012).

in anterior parietal fields 3a, 3b, 1 and 2 in primates). These naturally occurring duplicate somatotopic maps could have originated as an alteration in location and strength of these early signaling centers in parietal cortex. While the connectivity of duplicated cortical maps is not known, they do appear to be functionally responsive and topographically organized (Assimacopoulos et al., 2012).

Generation of this rostral-caudal axis by FGF8 influences downstream transcription factors expressed early in development, such as *Pax6* and *Emx2*, which themselves appear to be critical for establishing appropriate expression patterns of cell adhesion molecules (Bishop et al., 2000, 2002; Hamasaki et al., 2004; O'Leary and Sahara, 2008; **Figure 5**). These molecules in turn regulate a number of aspects of the cortical phenotype including the relative size of cortical fields and their connectivity (Suzuki et al., 1997; Inoue et al., 1998; Bishop et al., 2002; Terakawa et al., 2013). For example, over or under expression of *Emx2* in the early developing mouse neocortex has been shown to alter expression of cell adhesion molecules (Stoykova et al., 1997; Bishop et al., 2000, 2002; Andrews and Mastick, 2003), ultimately resulting in an increase or decrease (respectively) in the size of cortical fields on the caudal pole of the neocortex including V1, and alterations in thalamocortical connections (Bishop et al., 2000; Hamasaki et al., 2004; **Figure 5**). Importantly, in the

absence of thalamocortical afferents, the expression patterns of some of these early transcription factors and genes are maintained (Nakagawa et al., 1999) indicating that activity is not requisite for their expression and thus certain aspects of cortical organization are immutable, regardless of context.

GENES EXTRINSIC TO THE DEVELOPING NEOCORTEX CONTRIBUTE TO CORTICAL ORGANIZATION AND CONNECTIVITY

Most studies of cortical development focus almost exclusively on genes that are intrinsic to the developing neocortex. However, as noted in our introduction, brains do not develop or evolve in isolation, but in the context of the body, behavior, and a rich sensory environment generated by biological and non-biological sources. An excellent example of the interaction between genes that regulate body morphology and the effect of this on the brain and behavior comes from comparisons of limb development in species that have radically different forelimb phenotypes, such as the mouse and the short-tailed fruit bat (**Figure 6**). The early development of the mouse and bat forelimb is remarkably similar. However, at mid stages of limb development, the interdigit membranes in the mouse undergo apoptosis, which results in a separation of individual digits of the forepaw (Cretekos et al., 2008). Conversely, at this stage of limb development in the bat apoptosis does not occur. In addition, in the bat there is a lengthening of the forelimb and elongation of the digit phalanges. Together these alterations generate much of the phenotypic differences in these species, which in turn are related to radical differences in the use of the forelimb. Comparative studies of gene expression during

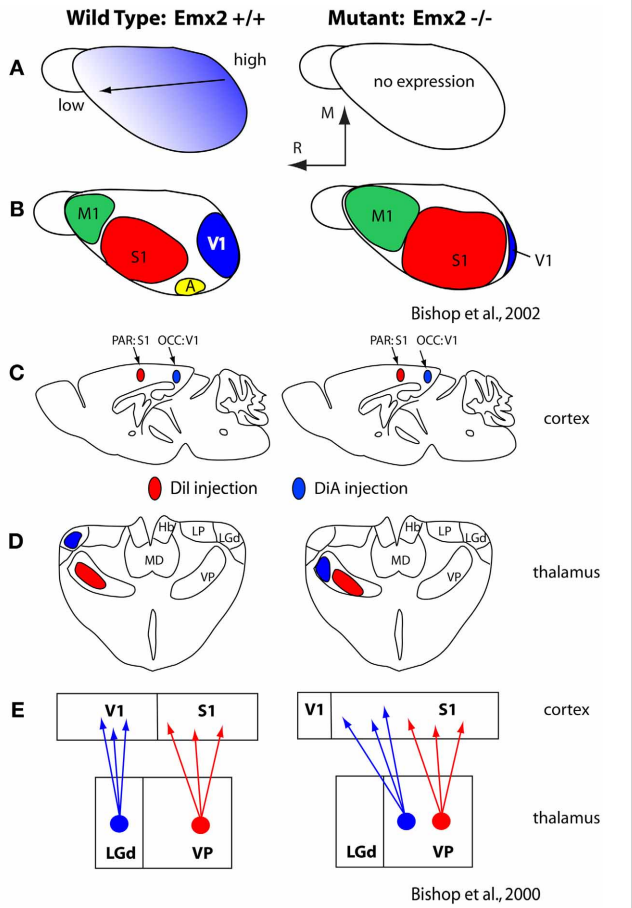

FIGURE 5 | (A) Graded expression of *Emx2* in the normal (left) and mutant (right) mice. Normal expression generates normal patterns of cortical fields (**B**; left) and absence of *Emx2* generates altered patterns of organization such that caudal domains have decreased (V1 is small) and rostral domains have expanded into the caudal territories (**B**; right). **(C)** Injections into parietal cortex (what will become S1) and occipital cortex (what will become V1) demonstrated altered patterns of thalamocortical connections **(D)**. In mutants what would normally develop into visual cortex has projections from VP, normally associated with somatosensory processing. The schematic in **(E)** demonstrates normal thalamocortical connections of S1 and V1 (left) and the caudal shift of VP projections into what would normally be visual cortex (**E**; right). These figures are modified from Bishop et al. (2000, 2002). Conventions as in previous figures.

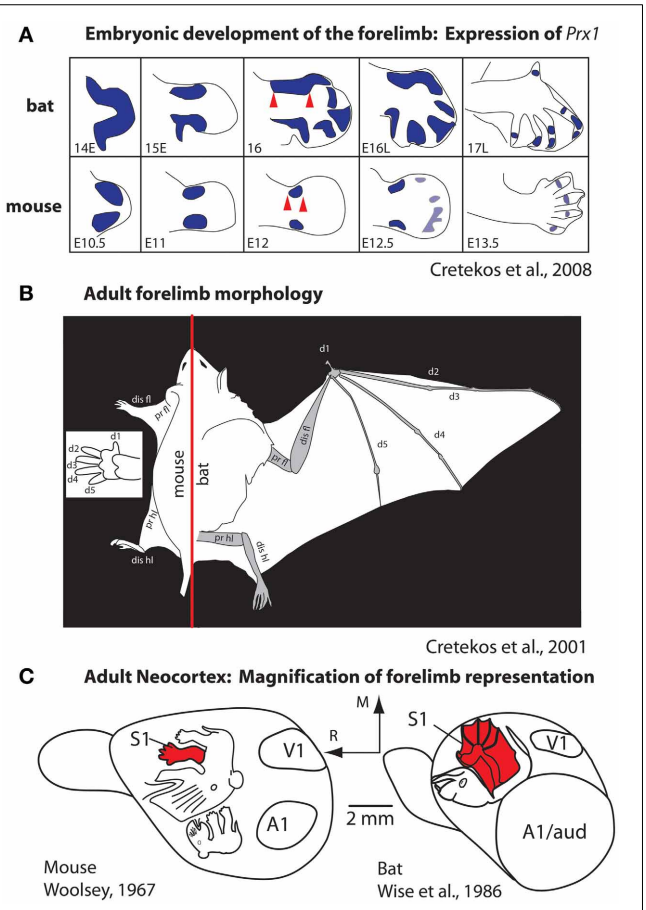

FIGURE 6 | Development (A) and morphology (B) of the forelimb, and the representation of the forelimb in somatosensory cortex (C) in mice and bats. (A) At middle stages of forelimb development the expression of *Prx1* (purple) is expanded in the distal forelimb (red arrows). This alteration, among a number of other molecular changes, accounts for the radical differences in the rat forepaw compared to the bat wing **(B)**. These morphological differences in the distal forelimb in addition to differential use of the paw vs. wing have likely contributed to the differences in size and internal organization of the forelimb representation in S1 **(C)**. Figures are modified from Cretekos et al. (2001, 2008); Woolsey (1967), and Wise et al. (1986). Other conventions as in previous figures.

limb development indicate that there are several key genetic alterations that account for these differences. In the bat, upregulation of *Prx1* results in a lengthening of the distal forelimb (Cretekos et al., 2008; Behringer et al., 2009; **Figure 6A**) and a posterior shift in *Hoxd13* expression reduces some skeletal elements. In the mouse, BMPs trigger apoptosis of interdigit membranes. In the bat BMPs are inhibited by *Gremlin* thus preserving interdigit membranes and this inhibition is accompanied by an increase in FGF8 in the apical ectodermal ridge, which extends the distal growth of the forelimb. Another important distinction of the bat forelimb is the presence of touch domes. These specialized receptor assemblies are found across the wing membranes and are beautifully sensitive to small changes in air pressure (Zook and Fowler, 1986; Sterbing-D'Angelo et al., 2011).

These changes to the forelimb are associated with differential use of the limb and the ability to make fine discriminations with the wing for self propelled flight and wing to mouth feeding behavior (Sterbing-D'Angelo et al., 2011). Studies of neocortical organization of the somatosensory cortex demonstrate an expansion of the forelimb and digit (wing) representation within S1 of the bat compared to the mouse (Woolsey, 1967; Wise et al., 1986; Cretekos et al., 2001, 2008, **Figure 6C**). Additionally differences in the interhemispheric connections of the forelimb in bats have been observed. In both large and small-brained mammals with discrete digits, the forepaw/hand representation within S1 is almost devoid of connections across hemispheres (for review, see Innocenti, 1986). These acallosal hand/paw representations in S1 and associated anterior parietal fields are particularly discrete in species like primates that use the glabrous digits as a major effector for object exploration. In bats digits 2–4 are fused by the wing membranes and tactile stimulation of the wings is used for fine control in self-propelled flight. The wing representation in primary somatosensory cortex and associated fields receives dense callosal inputs for rapid interhemispheric communication between centers that process incoming inputs and generate fine motor control of the wing during flight (Krubitzer et al., 1998).

There are numerous other model systems demonstrating the role peripheral body morphology can have on the development of the neocortex in the scientific literature. Perhaps the most extensively studied peripheral/central system is the vibrissae and their corresponding barrels in S1 (for review, see Erzurumlu and Gaspar, 2012). While a complete discussion of the experimentally-induced plasticity of this system is beyond the scope of this review, genetic manipulations have produced mice which possess additional whisker follicles (Welker and Van der Loos, 1986) or which lack several whisker follicles (North et al., 2010). Welker and Van der Loos generated six strains of mice with differing patterns of extra vibrissae and found that regardless of the peripheral patterns of vibrissae, all extra vibrissae were represented cortically with extra barrels (Welker and Van der Loos, 1986). Likewise, mice lacking particular vibrissae also lacked the corresponding barrels in S1, as the representations of these vibrissae in associated subcortical pathways (North et al., 2010).

It should be noted that environmental factors also contribute to features of body morphology and in turn brain organization. For instance, gravitational stress can affect craniomandibular morphology including bone density (Singh et al., 2005), and diet and associated mastication behavior affects craniofacial morphology (He, 2004; Koyabu and Endo, 2009). Environmental factors such as salinity, temperature and humidity also contribute to body morphology (Johnston and Gottlieb, 1990), and even sex determination (Matsumoto et al., 2013). Together these body morphology changes could radically affect a number of aspects of behavior including self-propelled flight and feeding, which in turn could alter aspects of sensorimotor cortex organization and connectivity.

What is not understood is the extent to which these changes to peripheral morphology and use can drive fundamental changes in cortical organization, connectivity, sensory mediated discriminations, perceptions, and higher level cognitive processes, and if or how these changes to the brain become genetically encoded and evolve.

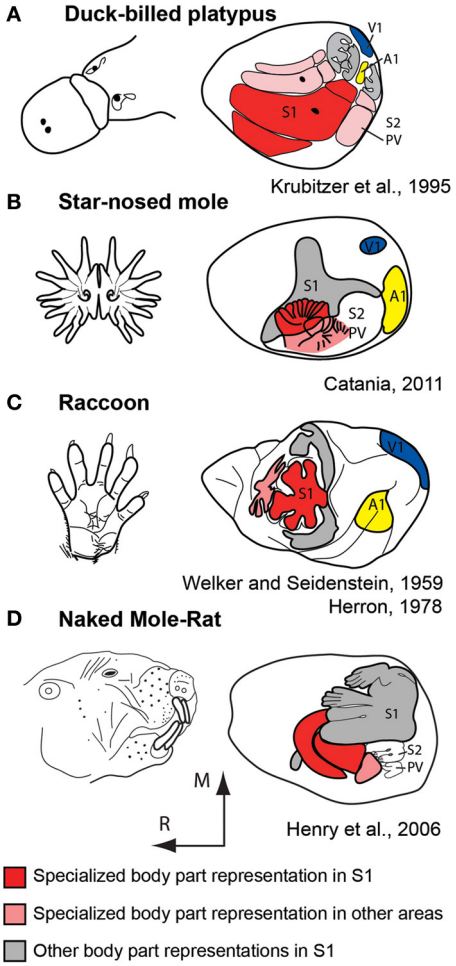

FIGURE 7 | Examples of extreme cortical magnification of behaviorally relevant effectors for somatosensory cortex of the duck-billed platypus (A), star-nosed mole (B), raccoon (C), and naked mole-rat (D). Although the specialized morphological structure and associated sensory receptor arrays are on different body parts, the same principle of magnification in the neocortex is observed. These figures are modified from Krubitzer et al. (1995) **(A)**; Catania (2011) **(B)**; Welker and Seidenstein (1959) and Herron (1978) **(C)**; Henry et al. (2006) **(D)**. Conventions as in previous figures.

OBSERVATIONS FROM THE NATURAL WORLD

For decades comparative neurobiologists have examined mammals that have evolved extreme specializations in an attempt to uncover general rules of construction as well as constraints imposed on the evolving nervous system. These types of observations highlight features that may be more difficult to uncover when only subtle differences exist in some aspect of brain organization in different species. One of the most extraordinary examples of this comes from studies of the duck-billed platypus (**Figure 7A**). The platypus has evolved electrosensory receptors that form anteroposterior rows on the bill that interdigitate with rows of mechanosensory receptors (Scheich et al., 1986; Gregory et al., 1987, 1988; Iggo et al., 1992). Most activities of the platypus are performed in the water during which time its eyes, ears and nose are closed. Thus, inputs from the bill, and to a limited extent the body, are the brain's source of information about the animal's immediate environment. Examination of the organization of the neocortex indicates an enormous expansion of the bill representation with clear territories devoted to processing electrosensory vs. mechanosensory inputs. There are three separate representations of the bill, which together occupy about 50% of the cortical sheet. In S1 alone, this magnification of a behaviorally relevant body part is enormous; the bill representation occupies 95% of S1 (Krubitzer et al., 1995).

Additional examples of extreme magnification have been observed in the primary somatosensory area of a number of mammals including the naked mole rat and star-nosed mole (**Figure 7**). This expansion of cortical territory related to effector specific inputs and active use is also observed in other sensory systems including an expansion of central vision in diurnal primates, and an expansion of ultrasonic frequency representations in echolocating bats (Suga et al., 1987). These alterations are due to changes in peripheral morphology, use, and the physical environment in which the animal develops and ultimately lives.

To determine the extent to which sensory receptor arrays, as well as inputs from multiple sensory systems, contribute to aspects of the cortical phenotype, our lab bilaterally enucleated short-tailed opossums very early in development, before thalamocortical afferents reached the cortex and before retinal ganglion cell axons reached the thalamus (Taylor and Guillery, 1994; Molnár et al., 1998). We found that loss of visual input results in a massive reallocation of sensory cortex (cortical domain changes) in that "visual cortex" is functionally taken over by the auditory and somatosensory systems (Kahn and Krubitzer, 2002; **Figure 8A**). This early loss of visual input resulted in a decrease in the size of architectonically defined V1 as well as an increase in the size of S1 (Karlen and Krubitzer, 2009). Further, cortex in the expected location of V1 received aberrant inputs from somatosensory and auditory structures of the cortex and thalamus (Karlen et al., 2006; **Figure 8B**). Studies in anophthalmic mice have also demonstrated alterations in subcortical connections and large changes in functional organization of "visual cortex" (Godement et al., 1979; Chabot et al., 2007), and studies of congenitally deaf mice show that auditory cortex is taken over by the visual and somatosensory systems (Hunt et al., 2006). Work in experimentally deafened cats supports these data. Cats that are deafened early have superior peripheral visual localization and motion detection abilities, and these abilities can be abolished when

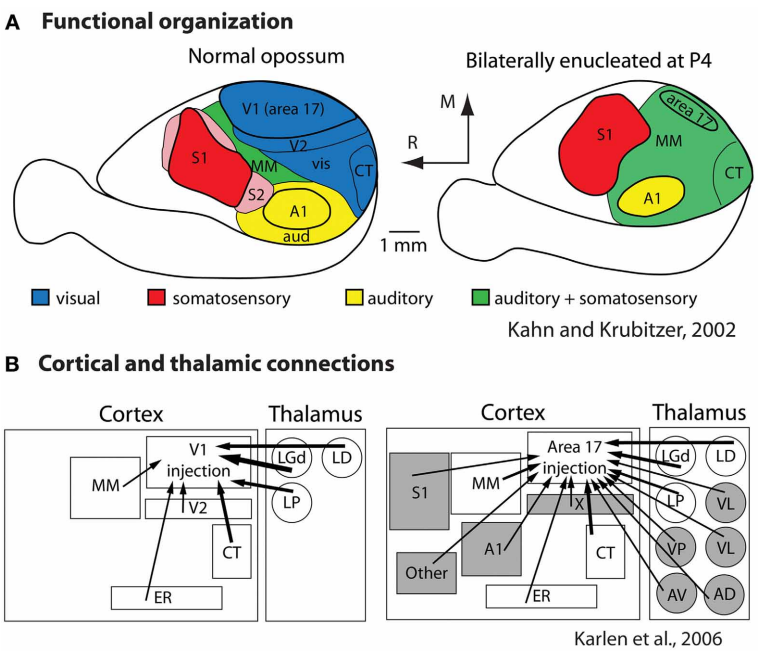

FIGURE 8 | Alterations in the functional organization (A) and connectivity (B) in bilaterally enucleated opossums. In normal animals (left) much of cortex is devoted to visual processing. With early and complete loss of vision (right) all of what would normally develop into visual cortex is taken over by the spared sensory systems. This functional reorganization is accompanied by alterations in thalamocortical and corticocortical connections **(B)**. Modified from Kahn and Krubitzer (2002) **(A)**; Karlen et al. (2006) **(B)**. Conventions as in previous figures.

specific areas of auditory cortex are deactivated (the posterior auditory field and the dorsal zone, respectively; Lomber et al., 2010). Recently it was shown that projections from extrastriate visual areas to the dorsal zone of auditory cortex provides the anatomical substrate for this behavioral plasticity (Kok et al., 2013).

Armed with knowledge of the types of alterations that occur with extreme changes in receptor array and major loss of sensory input, scientists can determine if these same types of alterations occur with changes in environmental context in which the animal develops. There are numerous examples in the auditory, visual, and somatosensory systems that demonstrate physical rearing conditions produce changes to the cortical phenotype. For example dark-rearing or stripe-rearing in cats and ferrets leads to a decrease in neural responses to visual stimuli in orientations in which the manipulated animals lack experience (e.g., Blasdel et al., 1977; Sengpiel et al., 1999; Li et al., 2006) and recent studies in rodents have corroborated these results, demonstrating that diverse visual experience is necessary for normal visual development (O'Hashi et al., 2007; Kreile et al., 2011). Similar findings have been found in the auditory system, in which repeated presentation of specific auditory stimuli early in development produces an expansion of the cortical representation of the tones presented (Zhang et al., 2001). Finally, an increase in the amount of cortex devoted to representing particular regions of the body have been generated either through extensive use of the animal's optimal effector (Recanzone et al., 1992), or in some cases, training using the non-optimal effector (Tennant et al., 2012).

Recently we examined the effects of lifestyle and exposure to radically different sensory environments on the size and cellular composition of cortical fields in different rodents for different sensory systems. First, we quantified relative cortical field size in diurnal vs. nocturnal rodents and terrestrial vs. arboreal rodents (**Figure 9A**). We found differential expansions and contractions of visual, auditory and somatosensory cortex that were related to lifestyle. For example, diurnal squirrels had a relatively larger V1 while nocturnal rats had a relatively larger S1 and A1 (expressed as a percentage of the entire cortical sheet, Campi and Krubitzer, 2010). Furthermore, arboreal squirrels, which live in a visually demanding environment, had a larger V1 and showed an expansion of visual cortex compared to terrestrial squirrels.

We also quantified and compared differences in cortical field size and cellular composition of primary visual cortex between wild-caught Norway rats and Norway rats reared in the laboratory. Obviously the sensory experience, motor demands and sensory mediated behaviors in a natural (and pervasive) environment are more dynamic and complex than the more limited demands of the laboratory environment. We found that there were significant differences in the size of primary sensory areas with laboratory rats having larger a S1 and A1 compared to wild caught animals (Campi and Krubitzer, 2010; **Figure 9A**). Conversely, V1 in wild caught rats had a larger percentage of neurons and a greater density of neurons compared to laboratory rats (Campi et al., 2011; **Figures 9B,C**). These studies indicate that the fundamental structure of neocortex can be modified through experience.

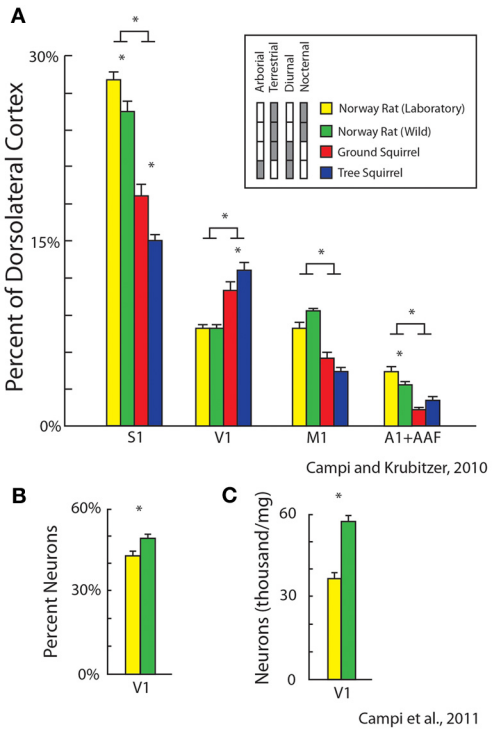

FIGURE 9 | Alterations in the relative size of primary cortical areas (A) and cellular composition (B,C) between different populations of rodents. These features of organization are related to lifestyle (diurnal vs. nocturnal; arboreal vs. terrestrial) and rearing condition (laboratory, yellow vs. wild-caught, green). Bars represent mean ± standard error, asterisks represent statistical significance. Modified from Campi and Krubitzer (2010) **(A)**; Campi et al. (2011) **(B,C)**.

WHAT ARE THE MECHANISMS THAT GENERATE EPIGENETIC ALTERATIONS TO THE NEOCORTEX?

Decades of studies on developmental and adult plasticity of the neocortex demonstrate that sensory experience can profoundly transform features of cortical organization that are known to be altered throughout the course of evolution, such as cortical field size, organization, cellular composition, neural response properties, and connectivity. Rather than a simple and small refinement of parameters initiated by genes, experience plays a critical role in the construction of the neocortex. This should not be surprising since the role of the neocortex appears to be that of a comparative predictor for the generation of adaptive behavior, and behavior is the target of natural selection. These behaviors are often tightly temporally correlated with the stimulus, or temporally uncorrelated in which a substantial amount of time may have elapsed between the stimulus and behavior. In any case, the predictive precision of the neocortex is built by accurate representations of the physical context or collective biomass in which the animal develops and behaves. Thus, it is not surprising that there are mechanisms that allow the animal, and the brain, which generates its behavior, to change substantially within a lifetime.

Although the field of epigenetics has had a recent resurgence, as noted above, the notion that a number of processes occur

between the genotype and the ultimate phenotype has been appreciated since the last half of the previous century (Holliday, 2006 for review). The current review has attempted to provide a number of concrete examples in which aspects of the cortical phenotype can vary based on a number of different genetic and experience dependent factors. While describing the details of epigenetic mechanisms is beyond the scope of our laboratory's purview, it would be remiss not to discuss how environmental signals program the operation of the genome, and the mechanisms by which these effects endure beyond the period of exposure during development (Kappeler and Meaney, 2010).

Some of the best examples of these interactions come from studies of mother–offspring interactions in rats. Maternal licking and grooming (LG) of pups is a variable trait in Long-Evans rats (Champagne et al., 2003), and the frequency of the maternal LG is dictated by environmental factors such as stress levels and light/dark cycles (Champagne and Meaney, 2006; Toki et al., 2007). For example, natural variations in LG of pups during the early postnatal period affect the development of the hypothalamic–pituitary–adrenal (HPA) axis (Liu et al., 1997; Caldji et al., 1998; Menard et al., 2004). In adulthood, offspring of high LG mothers have lower circulating adrenocorticotropic hormone levels during stress. This blunted stress response is associated with changes in glucocorticoid receptor (GR) mRNA and protein expression in the hippocampus, which regulates glucocorticoid feedback sensitivity (Weaver et al., 2004). Importantly, these behavioral effects and changes in gene expression that regulate the HPA in adults are initiated by mother-infant interactions during the early postpartum period. It is proposed that during the early postnatal period variations in tactile stimulation during LG induce epigenetic modifications in the promoter region of the GR gene resulting in alterations of GR expression in the hippocampus that persist throughout life. Increased tactile stimulation received by offspring of high LG mothers results in an increase in neurotransmitter binding and subsequent intracellular signaling in the hippocampus, which activates GR gene transcription. Importantly, the pattern of increased GR transcription persists into adulthood because of a reduction in methylation of the GR gene. DNA methylation is typically associated with a repression of gene expression (Miranda and Jones, 2007; see Kappeler and Meaney, 2010 for review), therefore a reduction in methylation of the promoter region of the GR gene is associated with increased GR gene expression (Meaney and Szyf, 2005). This modification of the genome and the behaviors ultimately generated by these changes can be transmitted to the second generation offspring, but are reversed with cross-fostering (rearing low LG pups with high LG parents).

There are also examples of epigenetic mechanisms operating directly on the nervous system. Work by Putignano et al. (2007) demonstrates that during visual critical periods, sensory inputs can directly turn on and off regulatory factors which alter the accessibility of gene promoters. When these genes are made experimentally accessible in adulthood, much of the ocular dominance plasticity that is observed early in development is reinstated (Putignano et al., 2007). Further studies have identified a specific histone deacetylase (HDAC9) which has been shown to translocate from the nucleus to the cytoplasm following neural activity early in development. When HDAC9 was experimentally prevented from translocating, manipulated cells showed decreased dendritic branches, while knockdown of HDAC9 increased dendritic growth (Sugo et al., 2010).

Despite the constraints imposed by genes and the contingencies of genetic cascades, and the laws of physics that govern all forms of matter and energy, biological organisms have evolved mechanisms that allow them to loosen these constraints and dynamically adapt both within a lifetime and across generations. In a sense, the strength of this evolvability (Earl and Deem, 2004) and the evolution of a large, malleable comparative predictor (neocortex), rather than specific genes or gene products, may be one of the fundamental differences that distinguish humans from other animals.

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Brains, innovations, tools and cultural transmission in birds, non-human primates, and fossil hominins

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Recent work on birds and non-human primates has shown that taxonomic differences in field measures of innovation, tool use and social learning are associated with size of the mammalian cortex and avian mesopallium and nidopallium, as well as ecological traits like colonization success. Here, I review this literature and suggest that many of its findings are relevant to hominin intelligence. In particular, our large brains and increased intelligence may be partly independent of our ape phylogeny and the result of convergent processes similar to those that have molded avian and platyrrhine intelligence. Tool use, innovativeness and cultural transmission might be linked over our past and in our brains as operations of domain-general intelligence. Finally, colonization of new areas may have accompanied increases in both brain size and innovativeness in hominins as they have in other mammals and in birds, potentially accelerating hominin evolution via behavioral drive.

Keywords: brain, innovation, tool, cultural transmission, bird, non-human primate, hominin

Neuroscientists and paleoanthropologists use very different approaches to study the relationship between intelligence and the brain. While neuroscientists study variance between contemporary individuals and species, drawing on techniques like brain imaging, intelligence tests and comparative analyses, paleoanthropologists focus mostly on variation over time and space in fossils and artifacts, in particular tools. This emphasis gives paleoanthropologists a unique insight into three key features of human intelligence: *innovation*, the first appearance of a novel technique or behavior, *tool* use and manufacture, and *cultural transmission*, the diffusion of innovations over space and time.

Studies of tools, innovations and cultural transmission in relation to avian and non-human primate brains have become more numerous in recent years. In this chapter, I review these studies and argue they are relevant to the neuroscience of hominin[1] evolution. More specifically, the studies suggest that (1) large brains and increased intelligence in hominins may be partly independent of our ape phylogeny: convergence with avian and platyrrhine cognition, not just ape cognition, may be relevant to understanding our own; (2) tool use, innovativeness and cultural transmission might be linked over our past and (3) in our brains; (4) colonization of new areas may have accompanied increases in both brain size and innovativeness in hominins as they have in other mammals and in birds, potentially accelerating hominin evolution via behavioral drive.

VARIATION IN INNOVATION RATE IS HIGHLY SKEWED TOWARD A FEW PHYLOGENETICALLY INDEPENDENT TAXA

If, in archeology, cultures carry the name of the first site where they were discovered, Swaythling and Koshima should feature prominently in the terminology of non-human cultures. In 1921, blue tits in Swaythling, a town near Southampton, were first seen to open milk bottles on doorsteps and drink the cream accumulating at the top. By 1949, the behavior had been noted in hundreds of localities throughout England, Wales, and Ireland (Fisher and Hinde, 1949). In the 1950's, a young female macaque on the Japanese island of Koshima innovated two food-washing techniques (potato washing in 1953 and wheat placer mining in 1956) that were later seen in several members of her troop (Kawai, 1965).

For decades, the main preoccupation of researchers was whether or not the "Swaythling bottle opening culture" and the "Koshima food washing culture" were truly cultures, i.e., whether social learning was behind the increase in the behaviors over time. Critical discussions (Hinde and Fisher, 1951, 1972; Galef, 1992; Ingram, 2001; de Waal, 2003), experiments on captive animals (Sherry and Galef, 1984, 1990; Kothbauer-Hellmann, 1990; Visalberghi and Fragaszy, 1990; Aplin et al., 2013) and statistical models of diffusion over space and time (Lefebvre, 1995a,b) were all concerned with transmission, but no one really asked why the innovations occurred in tits and macaques in the first place. When, decades later, innovation rates were calculated in birds and primates, tits and macaques were among the top genera: the genus *Macaca* is surpassed only by *Pan*, *Pongo*, and *Cebus* in Simon Reader's primate database (Reader and Laland, 2002; Reader et al., 2011), while the tit genus (formerly *Parus,* now split into *Parus, Poecile*, and *Cyanistes*) is eighth out of 362 genera with at least one innovation in the avian database collated by my lab (see supplement in Overington et al., 2009, 2011).

Overall, the primate and avian data sets show two clear and similar trends: first, some species have much higher innovation rates than others, and second, high innovation species are found in distant parts of the phylogenetic tree of their class or order. In primates, 60% of all innovations occur in a single species,

[1]The term "hominin" describes current humans and their immediate ancestors, while the terms "hominoid" and "hominid" include respectively apes and great apes.

the common chimpanzee. When the innovations of orang-utans and gorillas are added to the chimpanzee total (bonobos do not appear in the Reader database because they are so difficult to study in the field), the proportion of innovations that occur in great apes goes up to 75%. The genera *Cebus*, *Papio*, and *Macaca* together contribute another 20%. If baboons and macaques are not very distant in terms of molecular phylogeny (tribe *Papionini*), the group they belong to, the *Cercopithecinae*, is clearly very distant from the lineages that led respectively to *Cebus* and the great apes (see Figure 1B in Reader et al., 2011).

Simple counts of innovation frequency might not be the best way to compare taxa because they are probably biased by many factors. Species that are more populous than others or on which more research is conducted might yield more cases of innovative behavior. Up to now, thirteen such biases (often correlated with each other) have been shown to occur in studies of avian and primate innovation, but they are easily corrected by including the most important ones as confounding variables in multivariate analyses (Lefebvre et al., 2001; Lefebvre, 2011). When the main bias, research effort, is taken into account, the same primate genera as before yield the highest residual innovation rates, except for *Macaca*. Chimpanzees and orang-utans show standardized residuals that are clear outliers, respectively, 4 and 3.5 standard deviations above the primate average. High innovativeness thus seems to have evolved three or four times independently in primates: in the great ape lineage, the capuchin lineage and the baboon and macaque lineage (see Figure 1B in Reader et al., 2011). The capuchin lineage has been evolving separately from that of *Hominidae* and *Papionini* for more than 40 million years.

In birds, the distribution of innovations is also skewed toward some taxa. The families *Corvidae*, *Accipitridae* and *Laridae* rank at the top with over 200 innovations each, but none dominates the way great apes do in primates (Lefebvre et al., 1997; Overington et al., 2009). In birds, the ten genera with the highest innovation frequencies make up only 30% of the more than 2300 cases recorded. The taxonomic distribution of innovation rate is a bit more skewed at higher levels, but again less so than in primates. At four standard deviations above the avian mean, the *Corvoidea* superfamily (crows, shrikes, magpies, drongos, jays) is the clear outlier in birds when innovation rate is expressed as a residual of research effort, but even then, its innovation frequency represents only 15% of the avian total. Within this parvorder, the genus *Corvus* (ravens and crows) is an outlier at over eight standard deviations above the avian mean, by far the highest of all genera. Other avian clades with large residual innovation rates are raptors, woodpeckers, hornbills, gulls, kingfishers, roadrunners, and herons. Estimates of phylogenetic distances between these groups have changed drastically over the past 25 years, but innovation trends have proven robust (Overington et al., 2009) to major revisions, e.g., from the Sibley and Ahlquist (1990) phylogeny to the one published by Hackett et al. (2008).

In birds, variation in innovativeness has only been studied at the species level and higher, but in primates, Reader and Laland (2001) have also examined potential differences between males and females, as well as differences between juveniles and adults and high- vs. low-ranking individuals. Imo, the most famous primate innovator, was a high-ranking juvenile female when she invented potato and wheat washing, but trends in primates as a whole and in chimpanzees in particular do not confirm the picture seen at Koshima. In primates in general and in chimps in particular, males innovate significantly more than females when we take into account the sex ratio of the populations, which is often female biased; when sex ratio is not included in the analysis, males and females innovate at rates that are not significantly different. Across all primates, adults innovate more often than juveniles; in chimps, however, there is no significant difference between the two age classes. In chimps, as well as in primates in general, low ranking individuals innovate more frequently than mid- or high-ranking individuals.

The data on non-humans thus suggest two possibilities behind the high innovation rate of *Homo*: a trait that is phylogenetically shared with our hominid cousins, but also a trait that might have been influenced by convergent, independent evolution under pressures similar to those that favored innovativeness in *Cebidae*, *Corvidae*, and other taxa.

INNOVATION, TOOL USE AND SOCIAL LEARNING: CO-EVOLVED COGNITIVE MODULES OR GENERAL INTELLIGENCE?

In archeology, the study of tools, innovations and cultural transmission often go together. Recent analyses (Lycett and von Cramon-Taubadel, 2008; Lycett and Norton, 2010) on geographic distributions of lithic technologies, for example, focus on different modes of tool making, dates and loci of innovations (e.g., first appearance in Africa) and models of cultural transmission from the African areas of innovation to the farthest points of diffusion east of the Movius line. The study of tool use, innovation and cultural transmission also go together in quantitative counts of cognition in birds and primates. Using the same method to gather case studies on tool use and social learning (the mechanism that allows cultural transmission) as they did on innovations, Reader and Laland (2002) found significant positive correlations between the taxonomic distributions of the three measures. As with innovations, the great majority of tool use cases are found in *Pan*, *Pongo*, and *Cebus*; the three genera together make up 96% of recorded cases. The trends are maintained after correction for research effort: *Pan*, *Pongo*, and *Cebus* have corrected tool use rates that are 2–5 standard deviations above the average primate line.

This strong skew in the taxonomic distribution of primate tool use is also reflected in the avian database. Seventy-two percent of cases in the feeding domain (Lefebvre et al., 2002) and 87.5% of cases in all tool use domains (Bentley-Condit and Smith, 2010) are found in songbirds, the suborder *Passeri*. The genus *Corvus* once again stands out: fifteen species in this genus feature at least one tool use technique, with the New Caledonian species *Corvus moneduloides* showing the most sophisticated forms of use, manufacture and invention, as well as a causal understanding of tools, meta-tools and proto-tools (Taylor et al., 2009).

Quantitative counts of social learning in primates follow the same trends as do innovations and tool use. Again, chimpanzees and orang-utans clearly dominate, making up 68% of cases between the two of them and reaching 3–4 standard deviations

above the mean primate line when corrected for research effort. *Cebus* scores a bit lower on this measure than it does on innovation and tool use, while *Macaca* (especially *M. fuscata*, the Japanese macaque on which extensive social learning research has been done) scores slightly higher with over 10% of primate cases. In birds, there are surprisingly few recorded cases of social learning of foraging behavior in the field. In primates, reports of innovation and social learning are about equally frequent, but in birds, there are less than 100 social learning reports (vocalizations excluded from this measure) for over 2300 innovation reports (Lefebvre and Bouchard, 2003); most are concentrated in the songbird suborder *Passeri*.

Taxonomic counts of tool use and innovation are positively correlated in both birds (Lefebvre et al., 2002) and primates (Reader and Laland, 2002; Lefebvre et al., 2004). This could be an artifact of a common bias in the collection method for the measures, as both are based on systematic surveys of the anecdotal literature. However, the fact that the measures also correlate with experimental results from captive animals argues against this possibility. In birds, differences in reversal learning errors between species from seven families correlate with both innovation rate and size of the mesopallium (Timmermans et al., 2000), while differences in problem-solving between five species of West Indian birds correlate with differences in innovation frequency (Webster and Lefebvre, 2001; Lefebvre and Bolhuis, 2003). In primates, differences in innovation rate also correlate with differences in reversal learning in six species [(Lefebvre et al., 2004); based on Riddell and Corl (1977) and Reader and Laland (2002)], and in nine types of cognitive tasks in 24 genera (Deaner et al., 2006; Reader et al., 2011).

Reader et al. (2011) have explored the idea of general intelligence with a principal components analysis that included five measures of cognition, adding Byrne and Whiten's (1987) tactical deception and Parker and Gibson's (1979; Gibson, 1986) extractive foraging to innovation, tool use and social learning, as well as three lifestyle or socio-ecological measures (diet breadth, percent frugivory, and group size). All five cognitive variables clustered together on the first PC, while the three lifestyle measures clustered on a second, independent, PC. This suggests that some form of general intelligence (abbreviated as *g* in the literature, e.g., Colom et al., 2006) might underlie the evolution of the different cognitive measures. Interestingly, the idea that animal intelligence includes distinct social and non-social domains was not supported in Reader et al.'s analysis: instead of a split between social variables (social learning, tactical deception, group size) and non-social ones (tool use, extractive foraging, and diet), the PCA revealed independent lifestyle and cognitive factors, whether social or not. Deaner et al. (2006) came to the same conclusion as Reader et al. (2011): a common general intelligence factor seems to underlie the co-variation in performance over the nine types of cognitive tasks they analyzed in 24 primate genera (see, however, Amici et al., 2012).

The implication for hominins are that cognitive traits such as innovativeness, tool use, social learning, tactical deception and reversal learning might all have evolved together. For many years, the dominant view in evolutionary psychology has been that cognition is best understood as a mental tool kit that includes several independent modules, each specialized for a particular purpose (Samuels, 2000; Shettleworth, 2010). While some cognitive features in non-humans seem to be modular (e.g., specialized, domain-specific and based on a dedicated neural substrate, such as filial imprinting, song, and spatial memory), other cognitive abilities could be better understood as domain-general processes. The positive correlations across species suggest that there are few trade-offs and that a species that ranks high on one cognitive measure can rank high on others. Chiappe and MacDonald (2005) have argued that selection for modular specializations depends on repeated encounters with situations that select for them (e.g., repeated winters killing birds that do not store food efficiently). By definition, this cannot be the case for innovation, which constantly deals with new problems rather than repetitions of the same one. Resource defense and game theory further predict that the spatial and temporal unpredictability of food should drive social and ecological intelligence in similar directions (Overington et al., 2008), which argues for concerted selection on multiple cognitive domains rather than strict modular specialization. If we add to this evidence from brain imaging (Colom et al., 2006; Barbey et al., 2012), genetics and intelligence test research in contemporary humans (Plomin and Spinath, 2002) and non-humans (Galsworthy et al., 2002), it is plausible that changes in *g* might lie behind many cognitive innovations found in our hominin past. Recent papers by Deaner et al. (2006), Byrne and Bates (2007) and van Schaik et al. (2012) have underlined this new interest in general vs. modular processes for the evolution of intelligence. It should be noted here that acknowledging the existence of *g* in no way implies that it accounts for all (or even most) of the variance in performance over different tasks across clades. In humans and other mammals, the proportion of variance explained by the first PC on a battery of cognitive tests is usually around 40% (Chabris, 2007), leaving a majority of the variance unexplained or associated with task- or domain-specific effects.

BIG BRAINED BIRDS AND PRIMATES HAVE HIGHER RATES OF INNOVATION, TOOL USE, AND SOCIAL LEARNING

Several neural measures are used in comparative studies of non-human cognition. The measures vary in the neuroanatomical level they focus on and the extent to which body size allometry is controlled for. In birds, innovation and tool use rates are positively correlated with allometrically corrected size of the whole brain, of the telencephalon and of the mesopallium and nidopallium, two areas that show convergent evolution with association areas of the mammalian cortex (Timmermans et al., 2000; Mehlhorn et al., 2010; Güntürkün, 2012). They are not correlated with absolute size of the brain, due to the presence of very large-bodied groups with poor cognitive skills such as ostriches, emus, bustards, and turkeys. Neither the anatomical level used (whole brain, telencephalon, or mesopallium and nidopallium) nor the method used to correct for body size (residuals, EQ or executive brain ratio) have an effect on the magnitude of the relationship between innovation rate and neural substrate (Lefebvre and Sol, 2008). In primates, innovation and tool use also co-vary, as well as correlate positively with absolute and allometrically corrected size of the isocortex. Taxonomic differences in social learning also

correlate with isocortex size, as well as with rates of tool use and innovation (Reader and Laland, 2002).

One caveat is that these correlations, despite being highly significant, do not account for a large proportion of variance. In birds, residual brain size at the family level explains only 13.4% of the variance in diversity of technical innovations, the best measure of innovativeness in Overington et al. (2009) re-analysis of the avian database. In primates, the magnitude of the relationship between brain size and cognitive measures accounts for 13–18% of the variance when phylogenetic relatedness between taxa is taken out of the analysis (Reader and Laland, 2002). What this implies is that enlarged brains might be a necessary, but not a sufficient, factor in explaining innovativeness, tool use and social learning, whether this is in non-humans or in hominins. Other factors, be they environmental (e.g., spatially and temporally unpredictable resources) or behavioral (e.g., boldness, low neophobia) need to be considered.

In non-human primates, up to 26 different measures have been used to document lifestyle, cognitive, life history and evolutionary predictors of encephalization [reviewed in Lefebvre (2012)]. These range from log absolute mass of the whole brain, to the ratio of non-visual cortex volume divided by volume of the rest of the brain minus the cerebellum, to residuals of isocortex volume regressed against brainstem volume. Eighteen of the 26 measures use some measure of isocortex volume, removing or not the visual areas and adding or not the volume of the striatum. Structures used in allometric corrections of isocortex volume include the whole brain, the medulla, the brainstem (mesencephalon plus medulla oblongata), and the brain minus the isocortex (usually termed "rest of brain").

In hominins, fossil data are almost always limited to estimates of endocranial volume, often inferred from incomplete crania (note that shape can also be analysed in some cases, e.g., Bruner, 2004; Gordon et al., 2004). We thus cannot do largescale analyses on hominins using the most popular structure for non-human primates, the isocortex, nor correct for allometry with intra-brain measures like the brainstem or the "rest of brain." Largescale tests on hominins can only be done on whole brain size and allometric corrections done with body size, which can be selected naturally or sexually independently of brain size and vary more than the brain as a consequence of nutrition and disease. These limitations must be kept in mind when comparing variation in hominin brain size with that of non-human primates.

Henneberg and colleagues (Mathers and Henneberg, 1996; Henneberg, 1998; de Miguel and Henneberg, 1999, 2001; Henneberg and de Miguel, 2004) have collated the available data for brain and body size in hominins from 3.2 million to 10,000 years BP. Absolute values from their database are plotted in **Figures 1A,B**, excluding robust species *Paranthropus*, *Australopithecus boisei*, and *A. robustus*. Brain size is plotted as absolute volume, to emphasize the constant increase over time, while body size is plotted as log transformed kg, to emphasize the variation, both within and between time periods that is much larger than that of brain size. Some of the values (blue triangles) on the body size graph are so large that they represent outliers, possibly very large males in periods of high sexual dimorphism. The absence of similar outliers in the brain size graph is typical of dimorphism trends in non-human primates, where large sex differences in body size are often accompanied by small differences in brain size.

Henneberg and de Miguel (2004; see their Figure 1) point out the continuous nature of the parallel trends in brain and body size over time. If we were working with birds or non-human primates, however, we would examine actual allometrically corrected encephalization measures, using either residuals of log brain size regressed against log body size or ratios, which can be calculated as simple brain mass divided by body mass or as EQ, the ratio of

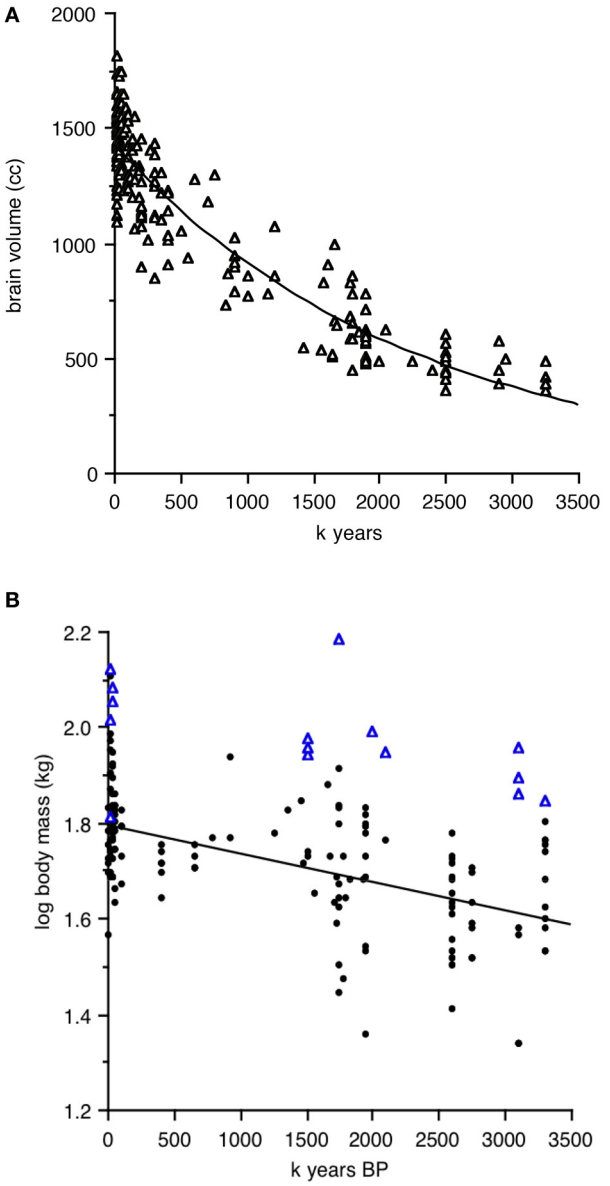

FIGURE 1 | Hominin brain and body size as a function of time from 3.2 million to 10,000 years BP. Data from Henneberg and colleagues, excluding robust species and data points for which species identity is uncertain. **(A)** Absolute brain size in cc. **(B)** Log transformed body size in kg; triangles in **(B)** represent very large individuals.

observed brain mass divided by the mass expected for the average member of body size × in a given taxonomic group. Brain and body estimates in such cases are normally taken from the same individuals; alternatively, brain mass is measured from fresh tissue or endocrania, and body mass taken from a standard source of species-typical mass, for example Dunning (2008) for birds. For hominins, the problem is that fossils used for brain and body size estimates are rarely from the same individual. We thus cannot simply match an individual brain size data point with its matching body size in the Henneberg database.

One solution is to use the gaps in the fossil record and the divisions in hominin clades to calculate a series of average brain and body masses for particular time periods. **Table 1** presents one way of dividing the fossil record into time periods. It separates the clades recognized in Henneberg's database (*Australopithecus afarensis, A. africanus, Homo habilis, H. erectus*, archaic *Homo sapiens, Neanderthal*, and modern *H. sapiens*), eliminating cases where species identification is uncertain [e.g., entries 114–123 in de Miguel and Henneberg (1999)]. Given the long history of *H. erectus* and the large amount of body size variation seen in this clade, the table separates this species into four time periods.

Figures 2, **3** illustrate the changes over time in the averaged data. **Figure 2** shows averaged absolute brain and body size over the clades and periods. The validity of the divisions in **Table 1** is supported by the small standard errors of the mean for time periods and brain size; in line with the large amount of body size variation obvious in **Figure 1B**, SEM's in **Figure 2B** are quite large on the y-axis. **Figure 3** shows averaged allometrically corrected brain size according to four methods: brain/body ratio, EQ according to Jerison's (1973) formula, EQ according to Martin's (1981) formula and residuals of log brain regressed against log body size. In the last case, a reference group is required to yield the regression line with respect to which a hominin data point is to be compared. Here, I use brain and body size for contemporary Catarhines (apes and Old World monkeys), the clade that hominins belong to, adding to this data set the hominin data point for a given period and repeating the regression for each time and/or clade division in **Table 1**.

The striking thing about **Figures 2**, **3** is that all methods yield the same qualitative trends: the periods of maximum increase in both absolute or allometrically corrected brain size are the same: from 1.83 to 1.65, 0.88 to 0.63, and 0.36 to 0.05 My BP. This suggests that different ways of calculating hominin encephalization produce similar results, at least for the temporal and taxonomic divisions used here. Other ways of splitting the hominin data might yield different results, but the exercise attempted here at least supports the idea that the method used to calculate hominin

Table 1 | Brain and body size averaged for time periods and clades (data based on Henneberg and colleagues).

Clade	Time span (*k* years BP)	Mean time (*k* years BP)	Mean br (cc)	Mean body (kg)
af	3200–3246	3223	425.83	43.13
aa	2585–2622	2603	477.24	43.20
hh	1803–1855	1829	635.98	51.44
he	1612–1682	1647	882.11	49.50
he	1137–1250	1193	890.37	60.00
he	877–884	881	883.32	68.30
ahs	612–650	631	1224.66	52.80
he	323–400	362	1066.53	51.66
n	47–51	49	1496.50	60.00
hs	38–40	39	1471.22	66.25

Abbreviations: af, Australopithecus afarensis; aa, Australopithecus africanus; hh, Homo habilis; he, Homo erectus; ahs, archaic Homo sapiens; n, Neanderthal; hs, Homo sapiens.

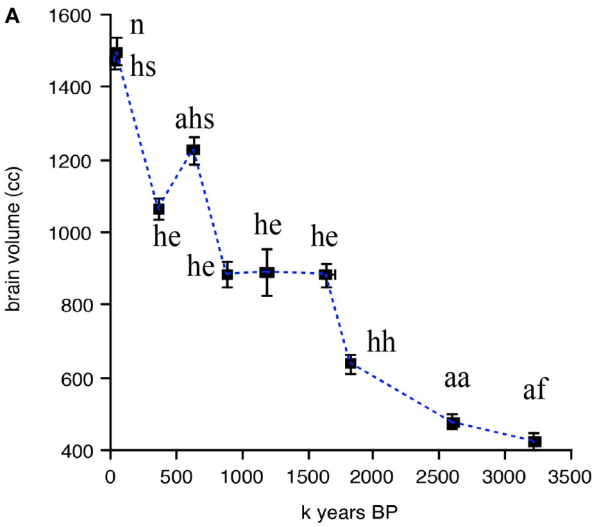

FIGURE 2 | Changes over time in absolute brain and body size averaged for periods and clades. (A) Absolute brain volume (in cc). **(B)** absolute body mass (in kg) over time. Data from Henneberg and colleagues; errors bars on the x and y axes represent SEM's. Abbreviations above each data point in **(A)** correspond to the ten clades in **Table 1**; data points in **(B)** as in **(A)**.

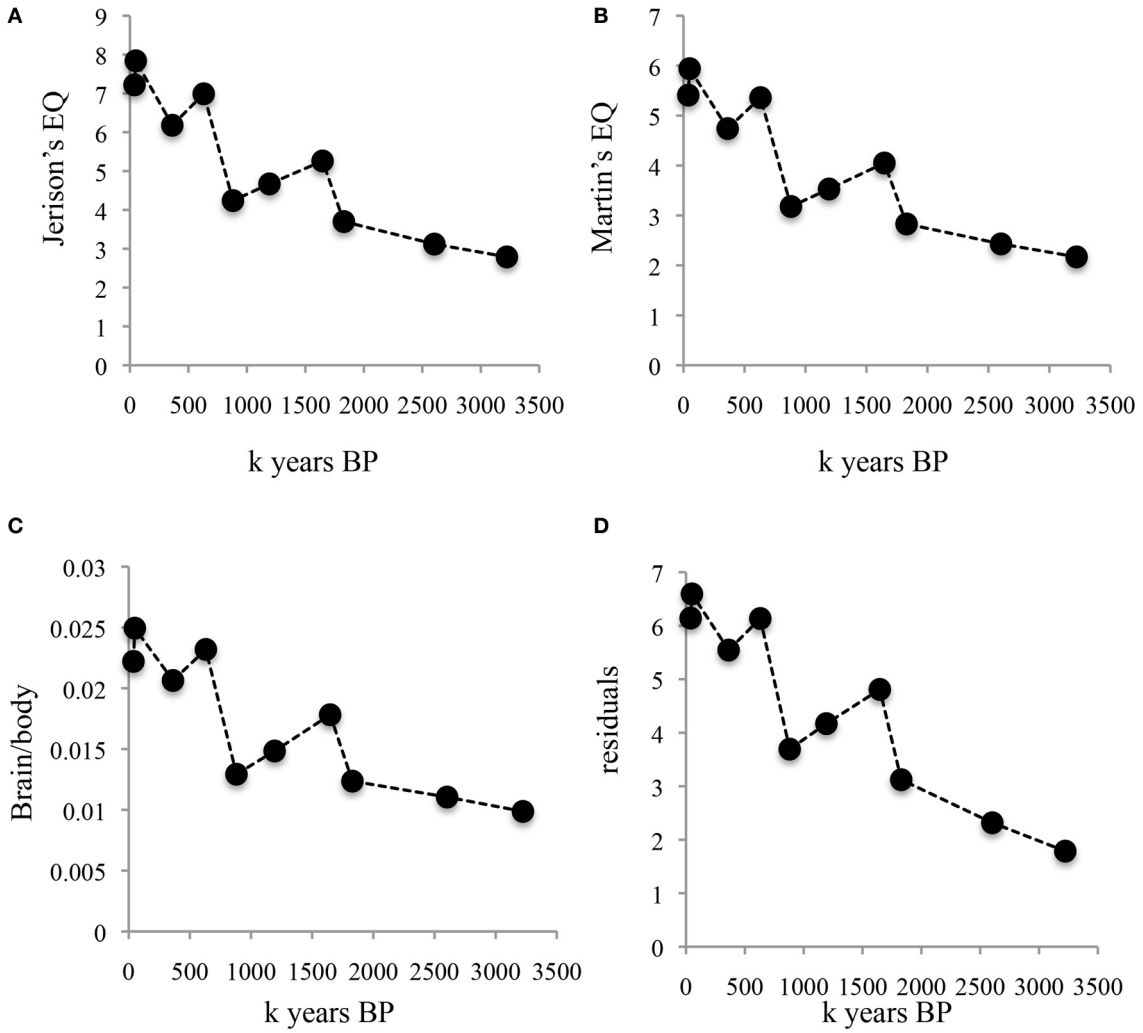

FIGURE 3 | Changes over time in allometrically corrected brain and body size averaged for periods and clades. (A) Brain size corrected for body size according to Jerison's EQ. **(B)** Brain size corrected for body size according to Martin's EQ. **(C)** brain/body ratio. **(D)** Studentized residuals of log brain size regressed against log body size. Data points as in **Figure 2**.

encephalization trends does not have a strong effect on conclusions. The exercise also suggests that absolute hominin brain size yields similar temporal trends to those obtained with allometric corrections.

Two of the cognitive measures known to correlate with encephalization in birds and non-human primates, innovation and tool use, can be compared to the temporal trends in hominin brain size. Stout (2011) has proposed an ordinal scale of complexity changes over time for hominin tool innovations. The measures of complexity are based on archeological data, on inferences concerning mental operations, as well as observations and brain imaging of skilled contemporary stone toolmakers (Stout and Cheminade, 2007, 2009, 2012; Stout et al., 2011). The scale, albeit ordinal on the y-axis, fits remarkably well with Henneberg's continuous data on absolute brain size changes over time (**Figure 4**).

The overall message here is that hominin encephalization trends over time appear to be robust to the method used to estimate them, and that the relationship between tool use, innovations and brain size that shows convergent co-evolution in birds and non-human primates [see Figure 2 in Lefebvre et al. (2004)] might also apply to hominins.

COLONIZATION AND BEHAVIORAL DRIVE

In the early 1980's, Wilson and colleagues (Wyles et al., 1983; Wilson, 1985) proposed that the combination of innovatiness, social learning and large brains might have an accelerating effect on the pace of evolution. The example they used was that of the Swaythling bottle opening culture mentioned in the first part of this article. Birds do not digest the carbohydrates in milk, only the lipids. However, if a mutation in digestive enzymes were to occur that gave its avian bearer the equivalent of mammalian lactase, this mutation would easily become fixed in bottle opening birds, but not in birds that do not face a situation where the mutation provides an advantage. Once

the lactase equivalent mutation results in a survival and reproductive advantage for the bearer and its descendants, several consequences may follow. First, any other trait that facilitates the one first selected might also be selected. Secondly, the new lines of lactose-digesting bottle openers might start diverging from their ancestral population, if only by the increased advantage they derive from urban and suburban habitats. The implication is that both the rate of evolution of different traits and the rate of divergence of populations may increase as a result of what Wilson and colleagues call "behavioral drive." Mayr's (1965) idea that behaviorally flexible species might succeed better than conservative ones at invading new habitats complements Wilson's ideas quite well and leads to the prediction that innovative clades should be better colonizers and show a greater species and subspecies diversity than less innovative ones. Sol and colleagues have shown, for birds introduced to New Zealand (Sol and Lefebvre, 2000) and in other areas of the world (Sol et al., 2002, 2005a) that colonization success can be predicted by brain size and by innovation rate in the country of origin. Several species from the genus *Corvus*, the most innovative avian genus, have a very high colonization success and are considered pests, e.g., *Corvus splendens* in Africa, Singapore and the Arabian peninsula, *C. macrorhynchos* in Japan, *C. corax* in the American southwest. Successful mammal colonizers also have larger brains than unsuccessful ones (Sol et al., 2008), as do amphibians and reptiles (Amiel et al., 2011), but not fish (Drake, 2007).

The genus *Homo*, which Wells and Stock (2007) call "the colonizing ape," has succeeded in invading almost every habitat on the surface of the earth, from the coldest to the hottest, from the driest to the wettest. Templeton (2002, 2005) has analyzed evolutionary trees of human haplotypes and pinpointed three major historical events that led to gene flow out of Africa, dated at approximately 1.9 million, 650,000, and 130,000 years ago. How do these dates compare to the temporal trends in brain size plotted in **Figures 1**, **2**, **3**? Repeated "out-of-Africa" events are reasonably close in time to the peaks in brain size, allometrically corrected or not, that characterize the averaged data per clade and time period. **Figure 5A** shows the three major "out-of-Africa" emigration events identified by Templeton's (2002, 2005) analyses

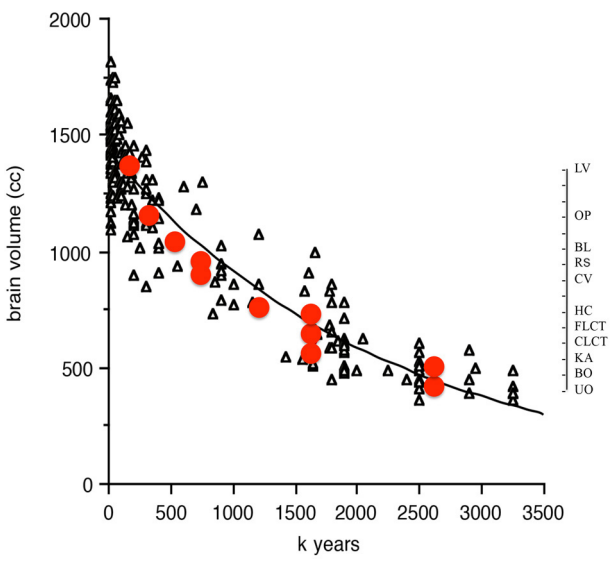

FIGURE 4 | Ordinal tool complexity scale (red circles) from Stout (2011) plotted over absolute brain size (in cc) as a function of time from 3.2 million to 10,000 years BP. Scale on right indicates ordinal increases in tool complexity. Abbreviations refer to categories in Stout (2011) **Figure 2**. UO, unifacial Oldowan; BO, bifacial Oldowan; KA, karari; CLCT, core LCT; FLCT, flake LCT; HC, hierarchical centripetal; CV, cleaver variants; RS, refined shaping; BL, blades; OP, other predetermined; LV, Levallois variants.

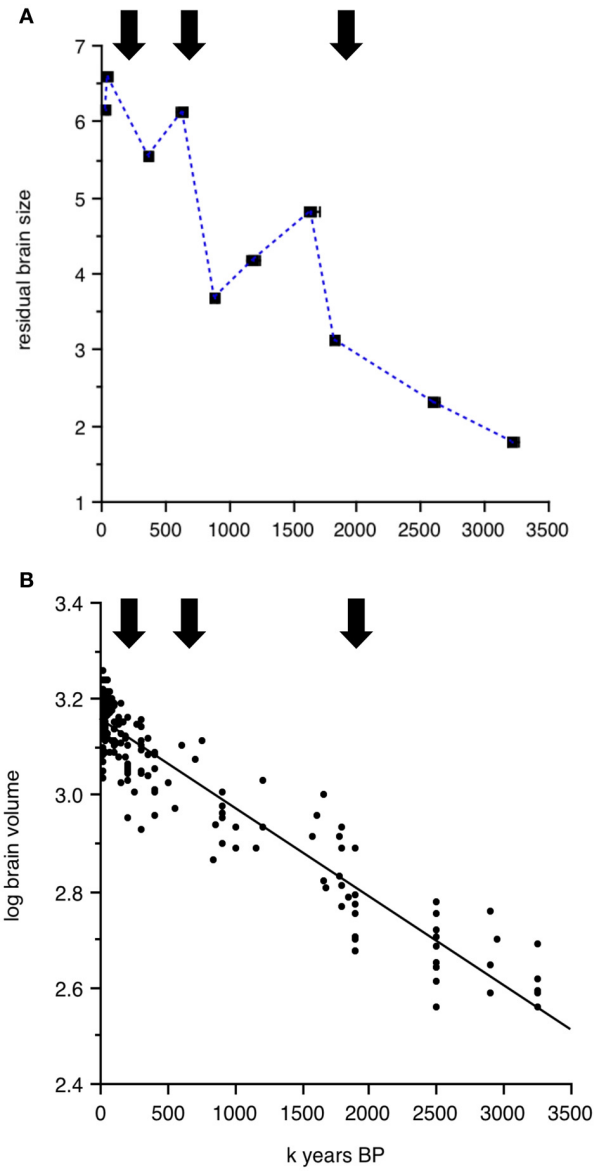

FIGURE 5 | Dates of major hominin emigration events out of Africa (arrows) according to Templeton's (2002, 2005) plotted against (A) studentized residuals of log brain size regressed against log body size averaged for the time periods and clades presented in Table 1. (B) Continuous change of log absolute brain size as a function of time from 3.2 million to 10,000 years BP.

plotted against residual brain size. The coincidence of these emigration events with continuous changes in absolute brain size over time is more difficult to see (**Figure 5B**).

One important factor behind Wilson's interest in behavioral drive was the possibility that evolutionary rates might vary between clades. Wilson was one of the pioneers of molecular clocks (Wilson et al., 1987) and famously proposed the "Mitochondrial Eve" hypothesis (Cann et al., 1987) as well as the 4–5 million years divergence date between the chimpanzee and hominin lineages (Wilson and Sarich, 1969). One prediction of behavioral drive is that large-brained, innovative taxa should show accelerated rates of evolution. Recent molecular analyses (Curnoe et al., 2006) suggest that speciation times for hominoids (0.66 My) were much faster than those that characterize other primates (1.1 My), as well as mammals in general (2.2 My, Avise et al., 1998). Accelerated speciation times, combined with the increased potential for separation of populations due to greater colonization success, might also lead to a higher diversification rate. In birds, the number of species (Nicolakakis et al., 2003) and subspecies (Sol et al., 2005b) per clade correlates with innovation rate and brain size. It is difficult to ascertain the number of species and subspecies in the hominin clade, but estimates based on fossils range from 5 species to 23, with a median of 14 (Curnoe and Thorne, 2003). Probability estimates also vary greatly from 8 to 27 species (Bokma et al., 2012). The possibility that several species and subspecies of hominins may have evolved and gone extinct over a relatively short timeline, as well as within overlapping periods, would be a logical extension of the behavioral drive hypothesis.

CONCLUSION

This article attempts to summarize convergent trends in innovation, tool use, cultural transmission, and brain size in birds and non-human primates, and then see if the trends are useful in thinking about hominin evolution. Phylogenetic influences on hominin evolution have been the focus of much work, based on important field and captive studies of great apes, in particular chimpanzees and orangutans. Recent work on innovation and tool use in corvids (Hunt and Gray, 2003) and capuchins (Fragaszy et al., 2004) should remind us, however, that we have much to learn from thinking about hominin intelligence in terms of convergent, multiple independent evolutionary events. To understand the intelligence of *Homo*, the most invasive and opportunistic primate genus, an invasive and opportunistic avian genus like *Corvus* might be as useful as the currently dwindling and geographically limited populations of our closest sister taxa *Pan*, *Gorilla*, and *Pongo*.

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From imitation to meaning: circuit plasticity and the acquisition of a conventionalized semantics

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The capacity for language is arguably the most remarkable innovation of the human brain. A relatively recent interpretation prescribes that part of the language-related circuits were co-opted from circuitry involved in hand control—the mirror neuron system (MNS), involved both in the perception and in the execution of voluntary grasping actions. A less radical view is that in early humans, communication was opportunistic and multimodal, using signs, vocalizations or whatever means available to transmit social information. However, one point that is not yet clear under either perspective is how learned communication acquired a semantic property thereby allowing us to name objects and eventually describe our surrounding environment. Here we suggest a scenario involving both manual gestures and learned vocalizations that led to the development of a primitive form of conventionalized reference. This proposal is based on comparative evidence gathered from other species and on neurolinguistic evidence in humans, which points to a crucial role for vocal learning in the early development of language. Firstly, the capacity to direct the attention of others to a common object may have been crucial for developing a consensual referential system. Pointing, which is a ritualized grasping gesture, may have been crucial to this end. Vocalizations also served to generate joint attention among conversants, especially when combined with gaze direction. Another contributing element was the development of pantomimic actions resembling events or animals. In conjunction with this mimicry, the development of plastic neural circuits that support complex, learned vocalizations was probably a significant factor in the evolution of conventionalized semantics in our species. Thus, vocal imitations of sounds, as in onomatopoeias (words whose sound resembles their meaning), are possibly supported by mirror system circuits, and may have been relevant in the acquisition of early meanings.

Keywords: imitation, language, circuit plasticity, onomatopoeia, pantomime, semantics

INTRODUCTION

In the last decade the evolution of human language has been a topic of increasing interest. This has focused on the evolutionary and neurocognitive foundations of human communication, and a wealth of comparative studies involving human and primate brains has intended to find a phylogenetic continuity between the structural networks subserving human language and neural circuits present in the primate brain. Other lines of research that consider other species of mammals, especially songbirds, have contributed to enlarge this complex theoretical framework. As a consequence, the comparison between humans, non-human primates, vocal learning birds and other species has favored the emergence of several theories, some involving the motor systems and others invoking cognitive processes. However, all of them have addressed auditory-vocal integration as a critical element for human language acquisition (Petkov and Jarvis, 2012).

In this paper, we discuss those aspects associated with the origin of a primitive form of learned semantics in the human lineage, understood as a rudimentary conventionalized system of symbols representing objects or events in the world. This is different from the innate referential vocalizations of some vocal non-learning primates, in which calls may signal the presence of specific predators (Seyfarth and Cheney, 2003a,b; see below). For this purpose, we propose the consideration of three major issues in order to place our discussion in an evolutionary context: first, a general approach to different theories seeking to explain the similarities and differences of vocal learning in a broad range of species including humans, non-human primates and other animals. Thus, we place the emergence of conventionalized semantics in a phylogenetic framework encompassing both behavioral and neurobiological foundations. In our view, vocal learning is a critical point in the origin of spoken language and meaning. Second, we discuss the structural homologies between the human brain networks associated to language and the premotor and temporo-parietal connections that are present in the primate brain. Two lines of evidence can be identified in this

domain of research, making emphasis on different aspects with regard to the critical elements in the acquisition of language: one underlines the emergence of auditory-premotor circuits in the macaque brain as a pivotal step in language origins (Aboitiz and García, 1997; Aboitiz et al., 2006), and another claims that human language evolution is rooted in the development of the hand and gesture motor system (Arbib, 2005, 2011). In a third section, we will extend this conceptual framework by including a discussion about the likely processes leading to the emergence of primitive meaning in human communication. Here, we will consider putative contributing factors like pantomimes and onomatopoeias, neural plasticity associated to vocal learning, the social control of attentional resources and finally the development of a plastic phonological sensorimotor circuit featuring a strong auditory working memory capacity as a critical factor supporting the establishment of an increasingly complex referential semantic framework.

VOCAL LEARNING SPECIES

Vocal learning is a key topic for the evolution of human language. This makes reference to the ability to acquire vocalizations through imitation rather than by instinct (Jarvis, 2004). This skill is found in some species of mammals (humans, bats, and cetaceans) and birds (parrots, hummingbirds and songbirds). Petkov and Jarvis (2012) recently reviewed motor and other neurobiological theories previously proposed for language evolution. In their review, the authors distinguished between vocal learning and auditory learning, and described the distribution of these traits among different species. They argue that auditory learning is widespread in higher vertebrates, while vocal learning capacity is restricted to some lineages. Furthermore, vocal learning is not an all-or-none ability, as there are varying degrees of vocal learning capacity in different species.

Considering that mammalian and avian vocal learning species are distantly related, it has been proposed that vocal learning evolved independently from vocal non-learner ancestors, either in the three vocal learning groups of mammals or in the taxa of the three aforementioned vocal-learning birds. The foundations for this hypothesis come from avian neuroanatomical evidence specifying a dedicated vocal-learning circuit specific for songbirds. In fact, Jarvis (2004) claims that the three groups of vocal learning birds have seven similar, but not identical, vocal cerebral nuclei distributed within two vocal pathways: one anterior and the other posterior. While the anterior vocal nuclei are part of an anterior forebrain pathway loop connecting pallial, striatal and thalamic regions and participate in song learning and sequencing, the posterior nuclei are connected to vocal motor neurons of the brainstem and control song production (see Jarvis, 2004 for a detailed description). In the posterior vocal pathway, there is a projection from the robust nucleus of the arcopallium (RA) to motor neurons in the XII nerve nucleus that control the muscles of the syrinx. Interestingly, the vocal learning pathways described above have not been found in vocal non-learning birds such as chickens and pigeons (Jarvis, 2004). Finally, Jarvis (2004) identifies an auditory pathway that is highly conserved among songbirds and other bird species.

In humans, a similar subdivision of anterior/posterior vocal pathways was proposed by Jarvis (2004) with an anterior vocal pathway, which connects the premotor cortex (including Broca's area) and surrounding regions with the anterior basal ganglia and anterior thalamus; and a posterior vocal pathway that extends from the face motor cortex to the brainstem. This latter pathway sends direct projections from the face area in BA 4 (from a region called laryngeal motor cortex, LMC), to the nucleus ambiguus in the brainstem. The LMC is linked to the production of vocalizations when stimulated (Simonyan and Horwitz, 2011). Thus, the posterior vocal pathway takes control of speech, whereas the anterior pathway is proposed to participate in speech learning.

It is interesting to note that recent research has revealed that adult male mice possess some basic skills which allow them to modify and maintain the spectral contents of their ultrasonic vocalizations (Arriaga and Jarvis, 2013). Furthermore, mouse ultrasonic vocalizations are represented in cortical regions including the motor cortex (perhaps analogous to the LMC in humans) and in striatal regions, and there is a projection from vocal motor cortex to the brainstem vocal motor nucleus ambiguus (Arriaga and Jarvis, 2013). Interestingly, the insertion of a human variant of the language-related FoxP2 gene in mice results in shifts and modulation of pup ultrasonic vocalizations and in local architectural changes in the striatum (Fischer and Hammerschmidt, 2011).

No homolog of the LMC has been yet described in non-human primates, although further research is needed to confirm this. Based on these findings, some researchers have claimed that the evolution of spoken language in humans is associated with the development of a direct projection from LMC to nucleus ambiguus (Jarvis, 2004; Simonyan and Horwitz, 2011). In support of this sort of evidence, some motor theories about the origin of vocal learning have been recently proposed, which will be discussed in the next section.

MOTOR THEORIES ABOUT VOCAL LEARNING

A theory about vocal learning across species has been proposed by Feenders et al. (2008), who describe a general motor system in both vocal-learning and non-vocal learning birds that is located adjacent to the vocal motor pathway of vocal learners. These areas display expression of some immediate early genes (IEG) with body movements, while the same genes become expressed in vocal learning nuclei of songbirds when they sing (Jarvis et al., 2000). Furthermore, in songbirds, these body-movement associated areas appear to be organized in anterior and posterior pathways, in paralell with the adjacent vocal motor nuclei. Based on these findings, Feenders et al. (2008) propose that brain systems dedicated to vocal learning in distantly-related bird species evolved as specializations of preexisting motor systems inherited from a common ancestor, and are involved in vocal movement control and probably in motor learning. Feenders et al.'s (2008) theory prescribes that the three lineages of vocal learning birds evolved independently similar cerebral systems, but these were derived from a somatic motor network inherited from a common ancestor. Moreover, they claim that this proposal may be extended to mammals, and in particular, to humans: the main vocal learners. Additional evidence has shown

that in zebra finches, some vocal learning nuclei like HVC and RA activate both in song production and in a learned food aversion task, while other nuclei important for vocal plasticity like LMAN and Area X activate only during singing (Tokarev et al., 2011). The authors claim that these findings indicate that some vocal control nuclei participate in non-vocal learning, thus existing some overlap between vocal learning and non-vocal learning nuclei. Furthermore, this is consistent with the notion that parts of the brain circuitry for song learning originated from networks related to feeding. With regards to anatomy, these suggestions agree with our original interpretation that part of the language-related Broca's region and its homolog in other primates (area 44), derive from the ventral premotor cortex (Aboitiz and García, 1997). From a behavioral perspective, Feenders et al. (2008) likened their proposal to the gestural theory for the origin of spoken language alongside the mirror neuron hypothesis, to argue that gestural behavior in humans and non-human primates is a precursor for the acquisition of speech and language (Arbib, 2005, 2011; Gentilucci and Corballis, 2006).

CONNECTIVITY OF THE HUMAN LANGUAGE AREAS

In the human, Broca's area is located in the inferior frontal gyrus (IFG) and includes the pars opercularis (most posterior region), the pars triangularis (anterior) and the pars orbitalis (ventral). These subdivisions include Brodmann's areas 44, 45 and 47, which fit the definition of the macaque ventrolateral prefrontal cortex (VLPFC). In the auditory region of the posterior temporal lobe, auditory area Tpt in the superior temporal gyrus (STG) has been associated with Wernickes area by some authors. This area is conceived as a multimodal cortical region receiving afferents from somatosensory and auditory regions (Galaburda and Sanides, 1980; Preuss and Goldman-Rakic, 1991).

Over the last few years, the use of MRI tractography has been fundamental in describing the structural connectivity of the language circuits in the human brain (Catani and ffytche, 2005; Parker et al., 2005; Friederici et al., 2006; Anwander et al., 2007; Frey et al., 2008; Glasser and Rilling, 2008; Friederici, 2009). Consistent with other studies, Frey et al. (2008) described an arcuate fasciculus (AF) that connects the posterior STG (Wernicke's region) to area 44 (posterior Broca's region; **Figure 1**). However, these authors have also emphasized a robust projection from the inferior parietal lobe (IPL) and anterior temporal lobe to the VLPFC: there is a large projection from area PFG (anterior area 39, posterior supramarginal gyrus) in the IPL, via the superior longitudinal fasciculus (SLF) to area 44, and another from area PG (posterior area 39, anterior angular gyrus) to area 45 (this is subdivided into areas 45A and 45B; see **Figure 1**). Noteworthy to point out is that the IPL receives connections from temporal lobe auditory areas through the middle and inferior longitudinal fasciculi, thereby closing a circuit to area 44 (see **Figure 1**). These two projections, a direct one via the AF and an indirect one via the middle longitudinal fasciculus and the SLF to the VLPFC, make up the dorsal pathway for audition and language. In addition, there is a ventral pathway from anterior temporal areas that courses through the external capsule and ends in areas 47 and 45 (**Figure 1**). The dorsal auditory pathway has been considered a participant in phonological working memory, verbal articulatory processes and complex syntactic processing, while the ventral pathway is thought to be involved in speech recognition, verbal retrieval and simple grammatical processing (Buchsbaum et al., 2005a,b; Hickok and Poeppel, 2007; Saur et al., 2008).

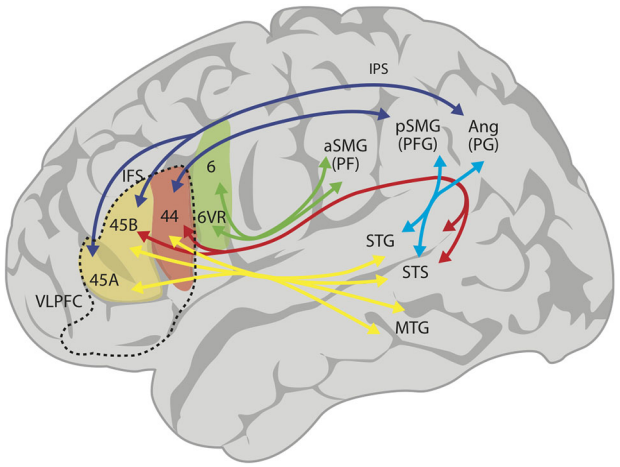

FIGURE 1 | Proposed schematic connectivity of the language-related regions in the human brain, based on Kelly et al. (2010). The superior longitudinal fasciculus (SLF) connects inferior parietal area PF (anterior supramarginal gyrus, aSMG) with premotor area 6v (green arrows), area PFG (posterior supramarginal gyrus) with area 44 and area PG (angular gyrus) with areas 45B and 45A (dark blue arrows). The arcuate fasciculus (AF; red arrows) connects the posterior superior temporal sulcus (STS) and gyrus (STG) with areas 44 and 45B. The middle longitudinal fasciculus connects STS and STG with PFG and PG (light blue arrows). Finally, there is a ventral projection via the extreme capsule (yellow arrows), connecting more anterior aspects of the STG, STS and middle temporal gyrus (MTG) with Broca's region (areas 44 and 45). In summary, connecting the anterior and posterior language areas, there is a dorsal pathway with (i) a direct component (AF, red arrow); (ii) an indirect component (middle longitudinal fasciculus and SLF, light blue and dark blue arrows); and (iii) a multimodal ventral pathway (yellow arrows). The ventrolateral prefrontal cortex (VLPFC) is the area inside the broken lines, and includes areas 44, 45A and 45B, and area 47 (not colored). 6VR, area 6 ventral-rostral.

Yet, the tractographic approach cannot precisely determine the specific areas of origin for the axonal connections in lateral temporal and inferior parietal cortices (Margulies and Petrides, 2013). Considering this, these authors implemented a resting-state functional connectivity analysis with the aim of unveiling the functional pattern of parieto-temporal-frontal connectivity. Their findings reveal that areas 45 and 44 display a distinct and unique profile, with area 45 functionally connected to the superior temporal sulcus (STS), the STG and middle temporal gyrus. In the inferior parietal cortex, area 45 was uniquely correlated with the angular gyrus (area PG in **Figure 1**), whereas area 44 was correlated with the supramarginal gyrus (area PFG in **Figure 1**). Interestingly, the ventral part of the precentral gyrus (area 6VR, see **Figure 1**), where the orofacial musculature is represented, is functionally linked to the rostral part of the supramarginal gyrus (area PF in **Figure 1**), while the primary motor cortex connects primarily with the postcentral gyrus (somatosensory cortex). Therefore, area 6VR is functionally

linked with the somatosensory cortex on the post central gyrus with no direct communication with Broca's area except indirectly through the premotor cortex. These results highlight the distinct patterns of connectivity in the two areas comprising Broca's region, area 45 and 44, and predict functional differences between these regions. In fact, functional neuroimaging studies suggest an involvement of Broca's region in the control of verbal fluency, with area 44 playing an important role in phonological fluency (Heim et al., 2008) and area 45 more involved in the control of retrieval of information from memory (Kostopoulos and Petrides, 2003).

HOMOLOGS TO HUMAN LANGUAGE CIRCUITS IN THE MONKEY

One of the most noticeable neuroanatomical findings in recent years is that brain regions, and circuits comparable to that of human vocal language-dedicated ones, have been confirmed in the monkey brain. These studies have revealed that the VLPFC of the macaque brain is structurally and functionally homologous to the IFG of the human brain (Romanski, 2012). In the macaque, the VLPFC occupies the inferior convexity of the prefrontal cortex and is subdivided similarly to the human frontal lobe: area 45, anterior to the inferior arcuate sulcus, area 12/47 just anterior to area 45 and ventral to area 46, and area 12 orbital in the most ventrolateral portion of the inferior convexity. Area 45 can be subdivided into areas 45A, extending rostrally in the adjacent inferior frontal convexity, and area 45B, lying caudally in the prearcuate bank (Petrides and Pandya, 2002; Petrides et al., 2005; Gerbella et al., 2010). These authors have also identified a dysgranular area 44 in the depth of the inferior arcuate sulcus, homologous to its homonym in the human.

Furthermore, recent evidence from neuroanatomical and imaging studies have contributed to clarify the understanding of temporo-parietal-frontal networks in primates. In the macaque, there is a double stream of auditory projections comparable to the organization of human language networks: a dorsal stream from auditory areas in the posterior superior temporal lobe that reaches dorsolateral frontal areas (8, 46) involved in eye movement control (Kaas and Hackett, 1999) and a ventral stream originating in anterior and middle areas of temporal lobe that sends visual and auditory inputs to areas 12 and 45 in the VLPFC (Romanski et al., 1999a,b). Interestingly, in areas 12 and 45 an auditory domain has been described in which neurons sensitive to vocalizations of conspecifics are intermingled with facial-sensitive neurons (O'Scalaidhe et al., 1997, 1999; Romanski and Goldman-Rakic, 2002; Romanski et al., 2005), suggesting an integration between vocalizations and orofacial gestures in the homolog of Broca's area in humans (Sugihara et al., 2006). There is also a projection from caudal auditory cortex to the dorsal prefrontal cortex and even light projections from caudal auditory cortex to caudal area 45. In addition, the STS has direct projections to the VLPFC (Romanski et al., 1999a). However, such posterior temporal projections to the Broca's area homolog have been considered to be weaker than in the human (see Aboitiz and García, 1997; Aboitiz, 2012).

Additionally, the IPL of the monkey has been shown to send a strong projection into the VLPFC. As in the human, the monkey IPL is subdivided into area PF, area PFG, area PG and finally, an area AIP in the intraparietal sulcus (Petrides and Pandya, 2009; see also Gerbella et al., 2011). Petrides and Pandya (2009) confirmed a projection originating in the inferior posterior parietal areas (PFG, PG) and arriving to areas 45 and 44 via the SLF. There is also a connection from the STS and posterior STG to the IPL that can potentially convey auditory information into the latter. As mentioned, connections from the ventral IPL and caudal STS running in the AF reach the VLPFC, but these are apparently much weaker in monkeys than in humans (Petrides and Pandya, 1999, 2002, 2009). In the ventral pathway, fibers via the extreme capsule and uncinate fasciculus that originate in the auditory and visual areas of the anterior and middle temporal lobes were found to end in areas 45, 47/12, and also in area 44 (Petrides and Pandya, 2009; see **Figure 1**). This is consistent with Webster et al.'s (1994) report that visual area TE in the anterior temporal lobe is connected with areas 8 and 45 in the inferior limb of the anterior bank of the arcuate sulcus and with area 12/47 in the inferior prefrontal convexity. Petrides and Pandya (2009) also suggested that the ventral projections to VLPFC are involved in memory retrieval, whereas the dorsal route (SLF and AF) suppports vocalization control only in humans.

Furthermore, using human resting-state technology, Neubert et al. (2014) report in macaque VLPFC regions a pattern of functional connectivity similar to areas in human ventrolateral frontal cortex largely associated with language. However, a noticeable species difference was found in how ventrolateral frontal areas coupled with posterior auditory association regions. Macaque auditory association areas in the superior temporal cortex correlated with regions in the anterior cingulate cortex (ACC), while human auditory association areas were strongly coupled with almost all ventrolateral frontal areas, confirming a human, species-specific enhanced auditory-motor vocal connectivity.

We must mention that overall, these findings in the human and in the macaque are anatomically consistent with, and confirm, our original hypothesis (Aboitiz and García, 1997), in which we claim a tripartite input into Broca's region and its monkey homolog: one direct from the posterior superior temporal lobe via the AF, another one, an indirect route via the IPL and the SLF, and a ventral projection via the anterior temporal lobe. Furthermore, we claimed that the dorsal pathway had undergone an important alteration throughout the course of human evolution, particularly by increasing the relative size of the AF. As will be seen below, our hypothesis was that these innovations were fundamental for the development of a sensorimotor auditory-vocal circuit supporting phonological working memory, which was a key event in the acquisition of human language.

THE PHONOLOGICAL LOOP, WORKING MEMORY AND A PRIMITIVE SYNTAX

In a series of reports, we've claimed that the acquisition of a sensorimotor phonological loop was a key innovation in human language evolution (Aboitiz and García, 1997; Aboitiz et al., 2010). In line with trend-setting findings by Baddeley and collaborators (see Baddeley, 2003), we originally claimed that an expansion of auditory working memory capacity was of critical importance in learning and processing complex phonological sequences and a key step in the acquisition of speech. According to

these claims, the development of a cortico-cortical auditory-vocal sensorimotor circuit was associated to the emergence of a functional phonological loop, which dramatically amplified the universe of possible vocalizations based on combinations of previously learned phenomena. Of note, this was also supported by the concomitant acquisition of voluntary control over the larynx and the supralaryngeal tract via a direct cortical projection to the brainstem vocal motor neurons.

In our view, the origin of this sensory motor circuit allowing for the rehearsal of newly learned phonological items in short-term memory, represents a cornerstone in human evolution because it made possible an inner speech skill that improved the elaboration of complex messages and the generation of new combinations of learned phonemes (Aboitiz, 2012). This circuit relies largely on the development of the dorsal pathway connecting Wernicke's and Broca's area, whereas the ventral pathway remains somewhat more conservative in evolution and, as in monkeys, was probably involved in vocalization processing and recognition in our ancestors (Romanski et al., 2005).

Consistent with this view, recent evidence has unveiled a limited capacity for auditory short-term memory in monkeys (Scott et al., 2012), which is in line with the concept that auditory working memory puts a limit to the complexity of vocal utterances. Nonetheless, although non-human primates are at best limited vocal learners (Hopkins et al., 2007; Snowdon, 2009; Petkov and Jarvis, 2012), research in auditory sequence learning capabilities has reported that non human primates are apparently capable of learning some simple artificial grammars. In fact, Wilson et al. (2013) have obtained evidence that Rhesus macaques can learn an auditory artificial grammar including branching relationships like those seen in the vocal production of songbirds (Hurford, 2012). We suggest that the increase in working memory capacity significantly amplified the ability to learn more complex sequences and to translate them into vocal motor patterns used in communication.

In this context, we have proposed that a phonological system provides a robust support for the emergence of an increasingly complex syntax based on distant dependencies between linguistic elements (Aboitiz et al., 2006; Aboitiz, 2012). From a neuroanatomical perspective, many imaging studies have shown Broca's area involved in working memory processes linked to syntax. Recent evidence points to area 44 as a critical node for processing syntactic working memory, especially in the superior part (Friederici, 2004), while the dorsal pathway connected to it is involved in the syntactical processing of structures organized in a hierarchical manner (Friederici et al., 2006; Anwander et al., 2007).

Although the IPL may contribute to verbal working memory, it apparently holds a supporting role rather than that of storage system. In fact, any role for the IPL as a phonological storage mechanism has been recently challenged, as the only areas showing sustained activation during verbal working memory tasks are the STS and an area termed Spt in the STG, but not the IPL (Hickok and Poeppel, 2007; Hickok, 2009; see also Aboitiz et al., 2006, 2010). Accordingly, area Spt is thought to be an interface between the sensory and motor representations when the phonological ítems are on line, and may be part of area Tpt described above, perhaps even contributing fibers to the AF (Buchsbaum and D'Esposito, 2008; Buchsbaum et al., 2011).

MIRROR NEURONS, THE HAND-MOTOR SYSTEM AND LANGUAGE

As mentioned previously, another line of research concerning language evolution has claimed the involvement of the motor system as a crucial step for human language development. This view has been strongly reinforced by the discovery of mirror neurons, a type of visuo-motor neuron associated with hand-grasping in monkeys. Mirror neurons were identified as being activated when an animal subject observed the experimenter or another animal making meaningful hand movements (di Pellegrino et al., 1992; Rizzolatti and Luppino, 2001; Rizzolatti and Craighero, 2004). These neurons are located in area F5 (BA 6v), a premotor area that is subdivided into regions Fa, Fb, Fc and Fd. Interestingly, Fa is adjacent to area 44, and has been conceived as an integration site for parietal sensory-motor signals with premotor and prefrontal information (Gerbella et al., 2011). Moreover, in the lateral aspect of Fa, face-selective mirror neurons have been detected whose activity increases when a monkey observes the communicative gestures of conspecifics (Ferrari et al., 2003; Rizzolatti and Craighero, 2004). Mirror neurons have also been detected in the rostral IPL where they are associated with both observation and execution of actions, and in the STS as a group of neurons responding to goal-directed hand movements (Perrett et al., 1990).

In humans, however, it has been difficult to search for mirror neurons for technical and ethical reasons. On the other hand, imaging and electroencephalographic tools have allowed for a visualization of the MNS related to observation of actions, imitation, and empathy (Rizzolatti and Craighero, 2004; Iacoboni and D'Apretto, 2006). The human MNS seems to be served by a wide network encompassing parietotemporal visual areas, the rostral IPL and inferior precentral and frontal gyri areas. Recently, a ventral pathway from the anterior temporal lobe has been suggested to support planning and decision making (Arbib, 2010) and the prediction of intentions and the goals of actions (Kilner, 2011). From a behavioral perspective, the MNS in humans is thought to be involved in the recognition of actions which is critical for decoding the other's intention (Rizzolatti and Craighero, 2004).

On the basis of this conceptual framework, Rizzolatti and Arbib (1998) and Arbib (2005, 2011) have proposed that language emerged from neural circuits evolved from mirror neurons originally implicated in imitation and gestural behavior. In this sense, Arbib (2005, 2011) has proposed a progressive and sequential scenario starting from an imitation grasping system followed by a gestural system including pantomime as a key element leading to the development of a referential system. Finally, a "protosign" stage based on hand symbols would have somehow facilitated the emergence of vocal plasticity, configuring a "protospeech" stage that would evolve into modern speech (Arbib, 2005). Furthermore, Arbib claims that the MNS contains a neural mechanism for understanding actions and that this served as a blueprint for the origin of a simple syntax. To this respect, the use and manufacturing of tools may have had an important role in decomposing

goal-directed actions in which the MNS participates. Tool use activates the inferior parietal and VLPFC and can be conceived of as a hierarchically-organized collection of body movements that might represent a rudimentary means of acquiring a nested and recursive syntactical structure (Stout and Chaminade, 2012).

Recently, Prather et al. (2008) observed a group of motor neurons in the swamp sparrow forebrain that fired along with the auditory note sequences in the sparrow's repertoire, and on a similar note, the song sequences of other birds. These authors interpret these findings as evidence for mirror neurons, although more studies may be needed to confirm this possibility. Moreover, these neurons innervate striatal structures critical for song learning and their auditory-vocal properties seem to parallel those found in the MNS in the primate brain (Mooney, 2014). Furthermore, oral mirror neurons, that activate with facial gestures like lip smacking and feeding behavior, have been detected in F5 of the monkey, near area 44 (Rizzolatti and Craighero, 2004). This has suggested to some authors that neural control of communicative vocal behavior partly evolved from feeding-related circuits, and is consistent with the finding of food-associated activation of vocal learning nuclei in songbirds (Tokarev et al., 2011). Therefore, it is possible that the circuit associated with the phonological loop in humans contains mirror neuron-like elements that participate in generating an auditory-motor sensory interface (see also Aboitiz et al., 2006; Arbib, 2011; Aboitiz, 2012).

A MULTI-MODAL COMMUNICATION SYSTEM

As we have discussed up until this point, two lines of research have intended to account for the neurobiology of human language evolution: one that features an auditory-vocal mechanism as a pivotal step, and another based on hand symbols supported by neuro-mechanistic scaffolding provided by the MNS. However, it is our view that a more integrative perspective is necessary. In the current proposal, communication has evolved as a multimodal, opportunistic process in both humans and monkeys, in which several possible mechanisms to convey socially relevant information are valid according to differing circumstances. In fact, functional and anatomical evidence indicates a confluence of facial and vocal information in the VLPFC (Sugihara et al., 2006) as well as the convergence of auditory, visual and somatosensory inputs in VLPFC (Romanski, 2012). More specifically, area 47/12 is a vocal-sensitive region with neurons responding to species-specific calls (Romanski and Goldman-Rakic, 2002; Romanski et al., 2005, reviewed in Romanski, 2007) and facial stimuli (O'Scalaidhe et al., 1997, 1999), whose activity has been confirmed more recently with fMRI (Tsao et al., 2008). Moreover, the body and hand representation in premotor area F5 of the monkey strongly suggests an integration of hand, face gestures and vocalization patterns (Aboitiz, 2012). Of interest in this context, a recent article reports that in the monkey, face-voice associations take place when the sender is a familiar individual but not for unfamiliar ones (Habbershon et al., 2013). Additional studies have shown that chimpanzees can match vocalizations with gesturing faces (Izumi and Kojima, 2004) and that the chimpanzee homolog of Broca's area reaches a maximal activation during simultaneous gestural and vocal communicative actions, particularly when gestures and vocalizations are oriented toward calling the other's attention (Taglialatela et al., 2008). In humans, area 44 has been found to be activated during mouth movements related to objects and in the imitation of gestures (di Pellegrino et al., 1992; Buccino et al., 2001). Another imaging evidence in humans has revealed that areas 44, 45 and 47 become activated when gestures and speech co-operate in communication (Willems et al., 2007; Gentilucci and Dalla Volta, 2008). Thus, in both humans and monkeys, a multimodal communication system makes use of overlapping neural circuits subserving both vocal and hand/body gestures (Aboitiz and García, 2009).

Finally in this section, recent studies have called attention to the voluntary control of the supralaryngeal tract in non-human primates, which is innervated by the hypoglossus and facial nuclei (Lameira et al., 2014). The supralaryngeal tract is required for the production of most consonants and may have contributed to learned vocal behavior long before the vocal folds in our ancestors. Furthermore, communicative lip smacking movements in monkeys are dissociated from throat movements and have a frequency close to five cycles-per-second, similar to lip movements during human speech and much more rapid than chewing (Ghazanfar et al., 2012; Morrill et al., 2012), which suggests a continuity between ancestral communicative facial gestures and modern human speech. Note again, that mirror neurons that activate with lip smacking have been described in the premotor cortex of monkeys (Rizzolatti and Craighero, 2004).

EMERGENCE OF CONVENTIONALIZED SEMANTICS IN HUMAN LANGUAGE EVOLUTION

Based on a multimodal perspective of communication, we will discuss the probable routes and mechanisms conducive to the capacity to utter learned, articulated sentences conveying meaning in a communicative context in human ancestors. This is a skill that characterizes our species but a rudimentary form of external reference can be found in other primates. In this section we will address evidence coming from both the hand/body gestures and the vocalization lines of research.

POINTING BEHAVIOR

Under the MNS paradigm/approach, gestures have been proposed to be critical for the origin of primitive meanings in humans. As Arbib (2011) claims, grasping activity and hand voluntary control play a fundamental role in motor actions demanding shared attention. This may have facilitated the development of pointing behavior as a derivation of hand-reaching, a simple behavior that allows making reference to the external world (Aboitiz, 2012). Pointing was possibly the impetus for other hand communicative gestures in an evolution from imitative behavior to simple, ritualized semantics (Aboitiz, 2012).

Pointing may be a non-communicative action when it incorporates only subject and object. Nonetheless, it becomes communicative in a three-way relationship including a subject who points, an object and an addressee (Cleret de Langavant et al., 2011). Fundamentally, pointing intends to share information about an object with another person, and in an evolutionary scenario it could represent a transition stage in the capacity of one to direct the other's attention to a common object allowing an interchange of a particular meaning in a natural context. Interestingly,

human infants and baboons share a right hand preference when they use pointing in a communicative task. In fact, the right hand preference was stronger for pointing tasks than for grasping objects, revealing left hemisphere dominance for communicative gestures (Meunier et al., 2012). Furthermore, communicative pointing seems widespread in non-human primates considering that pointing in the chimpanzee also conveys intentional and relational content (Leavens et al., 2004). Neural correlates of communicative pointing have implicated the right STS area at the temporoparietal junction (TPJ) in the IPL and right pre-supplementary motor area (pre-SMA), suggesting that pointing, as a communicative behavior, is involved in processes related to taking the other person's perspective (Cleret de Langavant et al., 2011). These findings have been supported by imaging and electroencephalography techniques in a task binding gaze, gestures and emotions. In this study, directional cues like gaze and pointing activated the right parietal and pre-SMA, showing that the dorsal pathway is involved (Conty et al., 2012). In sum, pointing may represent a primitive stage in the development of learned semantics present in some non-human primates and infants. Fundamentally, it allows conveying information about objects incorporating an addressee in shared attention and social interaction.

PANTOMIMES

A second aspect involved in the appearance of primitive semantics in language evolution regards pantomimic actions related to events and objects (Arbib, 2005). Pantomimes are gestures resembling the actions they represent, and evidence has revealed that in non-human primates these particular gestures are merely representations lacking abstraction, whereas in humans they involve abstract content and are related to a form of symbolic communication (Cartmill et al., 2012). Fundamentally, pantomimes are representational gestures and these kinds of motor actions are restricted to humans. In fact, primate gestures lack the representational nature of humans, although their gestures are used flexibly and intentionally (Cartmill et al., 2012). Among the types of human gestures—deictic like pointing, conventional and representational—the latter are critical for human communication and pantomimes are thought to represent a stage in the progression from manual action to meaningful spoken language (Cartmill et al., 2012). In this sense, the MNS hypothesis has been proposed to provide a neural basis for this transition (Arbib, 2005). Interestingly, using functional neuroimaging, Emmorey et al. (2010) reported that deaf signers displayed different patterns of brain activation when passively viewing pantomimes and ASL signs compared to hearing non-signers. Pantomimes strongly activated frontoparietal regions (MNS) in hearing non-signers, but only bilateral middle temporal regions in deaf signers. Presumably, life-long experience with hand/arm signs reduces or eliminates neural involvement of the MNS (Emmorey et al., 2010). Nonetheless, pantomiming, as a critical stage in language evolution, has been criticized because of evidence coming from chimpanzees. Experiments comparing children aged 2–4 years and chimpanzees in gesture imitation tasks revealed a restricted ability for chimpanzees in this type of imitative learning (Tomasello, 1996; Whiten et al., 1996). In our view, the particular relevance of pantomimes in the transition from gestural to vocal communication remains unclear. Probably, gestural pantomimes could be accompanied by the use of sounds making reference to the objects, opening, in this way, a stage where gestures and vocal activity co-occured. This could be relevant in the development of meaning in vocal behavior (Taglialatela et al., 2011; Aboitiz, 2012). Above, we have mentioned that Broca's region activates strongly when subjects use speech and hand gestures concomitantly (Willems et al., 2007; Gentilucci and Dalla Volta, 2008). Furthermore, using functional MRI, Xu et al. (2009) have reported that pantomimes and spoken stimuli activated the same left lateralized network of inferior frontal and posterior temporal cortex suggesting that this perisylvian network represents a modality independent of semiotic system that plays a broader role in human communication.

VOCALIZATIONS AND ONOMATOPOEIAS

From our perspective, vocalizations are a critical element in the acquisition of human language and meaning. Vocalizations could have enriched joint attention with others, especially combined with gaze direction. Related to this, the anterior cingulate cortex (ACC), a region involved in affect-related vocalizations in humans and monkeys (Yukie and Shibata, 2009), participates in the detection of incongruent stimuli or events that are contrary to expectations (Allman et al., 2001). Recall the aforementioned findings of Neubert et al. (2014), who found a strong, functional coupling between the VLPFC and the ACC in monkeys (and in humans). Hence, vocal behavior could make reference to socially salient situations or events that contradict predictions. In line with this, (Seyfarth and Cheney, 2003a,b) have found that vocalizations produced by vervet monkeys and baboons are not only emotional, but also referential, as the listener may extract external information from the calls, such as the presence of specific predators. However, as these authors assert, these vocalizations differ from human language in at least one aspect: the listener can acquire information from vocalizations, but the caller may not intend to provide it.

One step further, the capacity to produce onomatopoeia-like vocal imitations of sounds could have participated in the acquisition of early meanings in attentionally-demanding contexts (Assaneo et al., 2011). Exposure to onomatopoeias activate the left anterior STG, and bilaterally, the STS, the middle temporal gyrus and the IFG, areas implicated in the processing of verbal and non-verbal sounds (Hashimoto et al., 2006). It is tempting to propose that onomatopoeias may be supported by mirror neuron circuits on the basis of alleged temporal and frontal networks involved in the MNS of monkeys and, probably, humans as well (Arbib, 2005).

DISCUSSION

The evolution of human language and its underlying cerebral networks has been a matter of intense debate and discussion over the last few years. Although one approach has emphasized a predominantly "gestural" origin for language, and a second one has focused on the development of an auditory-vocal mechanism

leading to human language, we, however, have indicated that an alternative perspective exists. We postulate a multimodal and opportunistic system of communication using manual signs and vocalizations in natural contexts, which could be a more plausible model for explaining human language evolution (Aboitiz, 2012). In this proposal, both gestural and vocal information coincide in the emergence of conventionalized semantics, leading to object-naming and eventually to describing the environment surrounding us. In our view, a fundamental event in semantics acquisition has been the development of plastic neural circuits subserving both gestural and auditory-vocal networks allowing complex human communication. In this frame, gestural-based actions like pointing and pantomimes cooperate dynamically with learned vocalizations. Eventually, the latter became of critical importance during human evolution, reaching a predominant role. Moreover, recent evidence has revealed that human vocal activity has considerable functional flexibility allowing human infants to control affective expression through early vocalizations (protophones) (Oller et al., 2013). These data strongly suggest that this functional flexibility appearing early in the first year of human life could be critical for the development of vocal language. Until now, such flexible affective expression of vocalizations has not been reported for any non-human primates. Furthermore, although both gestural and vocal communication were important in the establishment of a learned referential semantics, we argue that the advent of vocal learning, and more importantly, the expansion of verbal working memory capacity, were crucial events in the amplification of communicative signals into modern language.

Finally, and to differ from MNS exponents, we consider less likely the possibility that vocal plasticity appeared directly to support transmission of novel meanings in the context of an "open-ended" gesture-based communication system (termed the "proto-sign" stage), as Arbib (2011) and others have proposed. This possibility would imply that a very complex vocal system became recruited at once and out of nearly nothing, developing plastic and combinatorial capacity, while at the same time involving a semantic component. We prefer the alternative that this was achieved gradually whereby vocal learning coevolved with gestural communication, as it happens in other animals (Lipkind et al., 2013). In early humans, vocal learning capacity was possibly acquired in the context of mother-child bonding, individual recognition, and some other social requirements. Subsequently, through imitation-based onomatopoeias combined with gestural pantomimes, these vocalizations began to assimilate some type of primitive meaning. Importantly, superior vocal tract sounds associated with facial gestures, like lip smacking and others, may have been present from very early stages of language evolution and are likely continuous with some lingual or facial movements used in modern speech (Lameira et al., 2014). In our view, the gesture-based "proto-sign" stage specified by Arbib (2011) as a sequential link between pantomimes first and proto-speech last, is largely hypothetical and apparently not well defined in terms of its specific structure or examples. Furthermore, we have found no evidence that in primitive humans, gestural communication went much beyond what is observed in typical, modern speech-based human communication, neither in child development nor in the adult.

Thus, we concur with exponents of the MNS in acknowledging an important role of gestures and pantomimes in the origin of linguistic meaning, but consider that this is only part of the full story in which learned vocalizations worked together with gestures and significantly contributed to transmit meaning, both by inducing shared attention and by imitating sounds of physical objects. In other words, while the MNS hypothesis emphatically prescribes a sequential process, first via signs and then vocalizations, we prefer a scenario in which gestures and vocalizations coevolved from very early stages, with vocalizations leaving gestures behind concomitant with the development of a robust, functional phonological loop supporting verbal working memory. From then on, complex vocal messages and a primitive syntax began to emerge, rapidly leading to modern human language.

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Allocating structure to function: the strong links between neuroplasticity and natural selection

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A central question in brain evolution is how species-typical behaviors, and the neural function-structure mappings supporting them, can be acquired and inherited. Advocates of brain modularity, in its different incarnations across scientific subfields, argue that natural selection must target domain-dedicated, separately modifiable neural subsystems, resulting in genetically-specified functional modules. In such modular systems, specification of neuron number and functional connectivity are necessarily linked. Mounting evidence, however, from allometric, developmental, comparative, systems-physiological, neuroimaging and neurological studies suggests that brain elements are used and reused in multiple functional systems. This variable allocation can be seen in short-term neuromodulation, in neuroplasticity over the lifespan and in response to damage. We argue that the same processes are evident in brain evolution. Natural selection must preserve behavioral functions that may co-locate in variable amounts with other functions. In genetics, the uses and problems of pleiotropy, the re-use of genes in multiple networks have been much discussed, but this issue has been sidestepped in neural systems by the invocation of modules. Here we highlight the interaction between evolutionary and developmental mechanisms to produce distributed and overlapping functional architectures in the brain. These adaptive mechanisms must be robust to perturbations that might disrupt critical information processing and action selection, but must also recognize useful new sources of information arising from internal genetic or environmental variability, when those appear. These contrasting properties of "robustness" and "evolvability" have been discussed for the basic organization of body plan and fundamental cell physiology. Here we extend them to the evolution and development, "evo-devo," of brain structure.

Keywords: cortex, modularity, evo-devo, visual system, neural re-use

Brain evolution is an ultimate expression of neuroplasticity. Neuroplasticity, in turn, should inform us about what brain architectures have been selected over evolutionary time. If any current computer users were informed that their personal computers, which heretofore had been used only for word processing, could also store and transform images, few would be amazed. If the same people, however, were informed that their parents' video cameras, by simply adding new input and output devices, could function as word processors, they would probably be incredulous, and undertake a re-analysis of their presumptions about video camera technology. In the same way, understanding of how brains can change and understanding of neural architecture should bootstrap each other. The multiple kinds of brain plasticity—evolutionary, developmental, damage-induced and normal individuation—should be joined together into a natural unit for this investigation.

To understand how brains evolve, a central goal must be to distinguish a brain modification resulting from a direct genetic change in a single brain location from the spreading, downstream reorganization produced by adaptive nature of the brain itself responding to that genetic change. For example, a genetic change might directly cause the enlargement of the precursor pool for a single brain region and increase its neuron numbers, or, cause those neurons to express a new neurotransmitter, or, increase their axonal branching. Following on any one of these changes, however, the regions to which a genetically-altered region connects might be reconfirmed in any number of ways through "standing" mechanisms of neural development and plasticity, about which we now have extensive knowledge. For example, loss or gain in neuron numbers in connecting structures could result via changes in trophic support in normal developmental cell death, or changes in the volume of axonal and dendritic arbors via new activity levels, or new connectivity at the neuron level via Hebbian synaptic sorting under changed parameters. These mechanisms are the environment in which genetic change must operate. Although neuroplasticity was first understood through observations of adaptive responses to damage or stress, for example, rerouting of axons to new targets when a target was lost, or upregulation of excitability in case of denervation, it can now be understood in a larger context. The developing domain of

"evo-devo," the study of the selection of developmental mechanisms in evolution (Kirschner and Gerhart, 2005), is the context to understand neuroplasticity more broadly as stabilized adaptive responses to genetic as well as environmental variation. A few uncontroversial examples of how selection might favor some classes of developmental mechanisms over others will illustrate this idea. Co-regulation of neurogenesis, gliogenesis and vascularization rather than independent specification of each could make an entire such assembly more robust to variation in any part. The existence of basic Hebbian circuity or directed re-use of existing circuitry could enable either new environmental sources of information, or new information introduced by genetic change (e.g., new receptor sensitivities) to be automatically employed without requiring committed recognition circuitry to be generated by random variation and selected at each processing stage in the brain, allowing evolvability. No impermissible precognition resides in such mechanisms, only the fact that the normal opportunities, variations and disasters of life on earth, small and large, external and external, will progressively filter all organisms for those containing the suite of mechanisms that allowed their ancestors' survival.

Before we discuss these aspects of neuroplasticity, we need to examine assumptions about basic brain architecture that have proliferated independently in the different groups of scientists who concern themselves with the brain. Developmental biologists, neuroethologists, geneticists, anthropologists, psychologists, neuroscientists and cognitive and computer scientists each bring their own explanatory taxonomies to the investigation, each grappling with the relationship of their taxonomy to the physical parts of the brain using the analytical tools and measurements each has at hand. In this review, we will examine the interaction of particular concepts of brain architecture with mechanisms of neural development and plasticity. Particularly, we will discuss the idea of a "module," a hypothesis about the relationship of species-typical behaviors (from escape behaviors in molluscs to language in humans) to single neurons or brain part. This hypothesis about function-structure relationships has different names and forms in different disciplines, such as "proper mass" or "mosaic evolution" in paleontology and comparative neuroanatomy, or "massive modularity" in psychology and cognitive science. Note that the sense of the word "module" as it is often used in neurobiology (e.g., Buxhoeveden and Casanova, 2002) to mean simply a unit or segment that can be iterated, like a cortical column, is not the sense of the term we are considering here. Our second focus is "evolvability" (Kirschner and Gerhart, 2005). Central to evo-devo is the resolution of the apparent paradox that existing developmental processes must have been selected both to be robust to perturbations and accidents, but not so robust as to not be "evolvable," and should be able to allow, or even facilitate useful evolutionary variation. The concepts of "module" and "evolvability" have found extensive empirical intersection in the general problem of how to allocate neuron number, volume, and metabolic energy to important brain functions in each species independently, and across species. Here we will offer some initial proposals regarding how conserved developmental mechanisms may channel neural reuse, and begin the process of identifying those neural mechanisms that must eventually resolve the brain's evo-devo paradox, shedding light on how the allocation and reallocation of neural resources is made on both individual and evolutionary scales.

In the immediately following historical overview, we will concentrate on work that has described resource assignment and allocation in the brain. In anthropology, comparative neuroanatomy and neuroscience, researchers generally address neural number and brain volume, and integration of information at the level of single neurons. In current neuroimaging and cognitive neuroscience, volume and amount of activation, as determined in current neuroimaging methods, are the central measures. These brief histories are not meant to be comprehensive, but to remind readers of several intellectual threads we hope to integrate. We will interleave some empirical work on the developmental specification and control of neuron number, brain volume and brain activation with discussion of brain architecture and with this history, but will follow with more detailed examples after candidate brain architectures as they are understood in several disciplines have been laid out.

THE CURRENT STATUS OF THE MODULARITY DEBATE

NEUROSCIENCE AND NEUROETHOLOGY

The reverse-engineering stance of the first electrophysiologists like Hubel and Wiesel (1962), Mountcastle et al. (1975) and Schiller et al. (1976), that much could be learned from investigating the responses of single neurons and inferring from their properties the mechanisms of perception and action, dominated the early years of central nervous system investigation. For these explicitly atheoretical, inductive approaches, the fact that single neuron responses in the cortex were reasonably interpretable by presenting simple stimuli to cats and monkeys produced an explosion of descriptive and systematic research. In due course these lines of work became subsumed under more analytically-driven work, such as the "single neuron doctrine" of Barlow (1972), and later by the more functionally driven "levels of analysis" approach of Marr (1982).

The idea of the brain as an evolved organ, however, was singularly absent from the work of all of these researchers. The idea that the brain is best viewed as a collection of functionally-committed circuits, each put in place by natural selection, rose in parallel, in opposition to the initial descriptive approach (Camhi, 1984). Neuroethologists concatenated a number of strategies and hypotheses together in their evolutionary approach: that the best kinds of behavior for study were those essential for survival, under strong, species-typical selection (e.g., mating calls or other species-typical communication, or prey capture and recognition); that these were best studied in "simpler" systems than large mammals; and that attention must be paid to the environment of each species and how every signal should be perceived or produced in relation to that context. Finally, it was assumed the nervous system ideally should be specialized for these specific adaptive ends throughout, from receptor to motor neuron. In essence, each piece of adaptive behavior was imagined to be supported by a committed, specialized module.

In the famous case of frog prey capture, the center-surround receptive fields were characterized as "fly detectors" (Lettvin et al., 1959); in the toad, "worm" and "anti-worm" signaling at the level

of the midbrain tectum was said to direct prey-strike or avoidance directly (Ewert, 1984). The frog auditory system bracketed in its two auditory end-organs the two essential croak frequencies, and the hunt was on to locate the and-gate for those two frequencies, a single-neuron "croak detector" somewhere in the frog brain (Frishkopf et al., 1968). For songbirds, the "song system" was designated within the bird brain and each component given its own song-specific nomenclature (Nottebohm et al., 1976). (This initial description virtually precluded understanding song in terms of the non-song circuitry it was embedded in and presumably derived from, now being redressed—e.g., Goldberg et al., 2012). In invertebrates, the useful feature of individually-identifiable, large neurons raised the prospect of a direct map of the circuitry of these large neurons to a short list of the behaviors these animals could produce (Camhi, 1984). As with reverse engineering, the neuroethological approach yielded an explosion of useful information. In due course, in virtually every case, realization began to arise that not every feature of adaptive behavior mapped directly to corresponding special adaptations in neurons and neuronal circuits, and that many features were vertebrate-(and invertebrate-) general. Some of these findings will be listed here, and we'll return to a more specific discussion of aspects of neuroplasticity in this domain later.

Across the board, it became apparent that peripheral receptors (at least in vertebrates) are rarely tuned narrowly to the frequency of a communication channel, or the color of a preferred food, but rather tend to be broadly tuned to extract information in the channel of interest, the entire visible spectrum, for example (Lythgoe and Partridge, 1989; Kocher, 2004; Spady et al., 2006; Osorio and Vorobyev, 2008). Often, it appeared that it was the signal rather than signal decoding that had undergone selection to be maximally apparent or attention-getting to a generic nervous system, termed "sensory exploitation." Systems as diverse as visual signaling in fish and anoles, mating croaks in frogs, and fruit identification in primates have this characteristic (Ryan, 1998; Persons et al., 1999). Specializations nested in broad channels, such as visual and auditory "foveas" are more common adaptations than commitment of all resources to a specialized bandwidth. In parallel, the computational complexity of the problems common to all vertebrates (or, in fact, all mobile life-forms) began to be better appreciated. General functions such as localization of items of interest in egocentric space, construction of topographic maps, learning the benefits and consequences of particular cues or environments, recognizing food or conspecifics as a category (as distinguished from recognition of one's own species), and motor control, all had to co-exist with any specialized circuitry. Generic "environments" exist as well: across niches, visual and acoustic environments on earth, "natural scenes," proved to have a specific, statistical structure that all nervous systems of any complexity must exploit (Field, 1994; Lewicki, 2002).

Even for the simplest system, considering cases of invertebrates with small numbers of neurons, and smaller-still numbers of discrete behaviors, where selection and adaptation might be presumed to produce the most direct linkage of behaviors to distinct, or encapsulated neuronal pools, modularity was rarely found. For example, the same set of neurons, in the presence of particular neuromodulators, could produce various functional rhythmic behaviors; in marine molluscs with several motor behaviors, single neurons might be engaged in multiple behaviors (Katz, 2011).

Detailed work with *C. elegans* demonstrates that single neurons can participate in generating multiple different behaviors, as a result of the modulation of the neuron's sensitivity, physical connections, and functional connectivity by various chemicals and genes. These findings do not at all discount the existence of functional differentiation between these neurons, but they do suggest that a more nuanced account of their functional complexity is called for. For instance, the olfactory neuron AWCON can direct both attraction and repulsion to the same odor, depending on the presence of specific neuromodulators (Tsunozaki et al., 2008); and the nocioceptive ASH neurons can cause both social aggregation and avoidance, depending on whether the gap junction with RMG neurons and the associated aggregation circuit has been decoupled by the expression of the *npr-1* gene, which encodes a g-protein coupled receptor (Bargmann, 2012). Bargmann writes:

> A profound violation of the one neuron-one behavior rule was uncovered by characterizing behaviors under different conditions. For example, avoidance of the repulsive odor octanol at particular concentrations can be generated by two different sets of sensory neurons. In well fed-animals, octanol avoidance is almost entirely mediated by the ASH nocioceptive neurons, but after an hour of starvation, octanol avoidance is distributed between ASH, AWB, and ADL nocioceptive neurons, revealing a change in circuit composition... Food changes the composition of a circuit for oxygen preference behavior (aerotaxis) as well... Aerotaxis is more robust in starved than in well-fed animals, due to the activity of multiple neuromodulators (Cheung et al., 2005; Chang et al., 2006; Rogers et al., 2006)... the *npr-1* neuropeptide receptor that affects aerotaxis also regulates a second behavior, the aggregation of animals into feeding groups. Aggregation is triggered by a number of sensory neurons including the nocioceptive ASH neurons and oxygen sensing URX neurons (de Bono et al., 2002; Coates and de Bono, 2002)... integrated by one pair of npr-1 expressing neurons called RMGs (Macosko et al., 2009)... npr-1 action in RMG uncouples the aggregation circuitry, but leaves the avoidance circuitry intact. This allows ASH to generate different behaviors in two neuromodulatory states. (Bargmann, 2012; pp. 460–461)

By now, the approaches of the descendants of original descriptive electrophysiologists and the neuroethologists have converged, each adding aspects of the initially opposing view, though the intellectual lineages of both can still be traced. Understanding of the complexity of natural scenes and the functions and motivations of perception and behavior came to be part of descriptive neurophysiological studies (Vinje and Gallant, 2000; Brady and Oliva, 2008; Adolphs, 2010). The question of how to embed specific adaptive behaviors in the larger contexts of organization is now being addressed with increasing specificity (Johnson, 2001, 2011).

PALEONTOLOGY, ANTHROPOLOGY AND COMPARATIVE ANATOMY

The resolution of the tools physical anthropologists and comparative anatomists are able to use to examine fossil brains, or (historically) could be used to describe primate brains is necessarily crude, but a version of the same local-global, modular-

vs. general purpose-circuitry has played out in these fields at a larger scale. The most available measurable entity is whole brain size, allowing taxon-level analysis of changes in the ratio of brain size to body size ("grade shifts"), coupled with analysis of behavioral changes associated with such changes, like homeothermy or carnivory (Jerison, 1973; Northcutt, 1981). Subsequently, primatologists and comparative anatomists attempted to link changes in particular brain parts (e.g., cerebellum; olfactory bulb, a particular cortical gyrus) to changes in behavior (e.g., motor ability, visual vs. olfactory specialists; language), usually after removing shared allometric variation across species. In general, this behavior-to-residual-structural-variation mapping is termed "mosaic" brain evolution. Initially, proponents of mosaic brain evolution pursued the same ends as neuroethologists, in this case attempting to equate species-specific adaptions with the relative sizes of particular brain parts. Overall, initial investigation of mosaic evolution produced rather few interesting generalities, since most behavioral functions are distributed over a number of regions, and allometric covariation of brain parts is extremely high, leaving only a few percentage points of residual anatomical variance to map behavioral variation onto (Stephan et al., 1986; Finlay and Darlington, 1995; Aboitiz, 1996; Finlay et al., 2001; Yopak et al., 2010). For example, in confronting this puzzle, Aboitiz conjectured if there were somehow two different kinds of "size" in the brain, the less-interesting shared variance related to general organismal processes, the remainder important for species-specific adaptations. As a definitional aside here, note that in the case of gross brain morphology, "visual cortex," for example, will mean anatomically-defined visual cortex to anatomists, and not "regions of brain activated by visual stimulation" as it will, on occasion, for neuroimaging researchers.

A second version of mosaic adaptation emerged, the simple identification of any structural components of variation independent of allometric variation, not necessarily predicted from behavioral specializations (Iwaniuk et al., 2004; Hager et al., 2012), to be considered as potential sources of evolutionary variation and change. Cross-brain-part covariation associated with cognitive and behavioral adaptation of residualized volumes is another way of attempting to locate species-specific adaptations in volume and number differences (de Winter and Oxnard, 2001; Sherwood et al., 2012; Smaers and Soligo, 2013).

For this version of mosaicism or modularity, resolution has not been rapid. Each element of the argument, the nature of the proposed adaptation (e.g., "planning" in humans), the brain part on which the adaptation is to depend ("frontal cortex"), and the survival or reproductive benefit of the adaptation typically remain conjectures. For example, the hypothesis that humans have been specially selected for unusual social competence via specific cortical enlargement, the "social brain hypothesis," has become quite popular (Dunbar, 1998, 2012). Note that it is the *linkage* of increased volume of particular regions of brain to social ability that is under debate, not whether social structure in humans is unusual. Residual excess cortical size, across all areas (Dunbar, 1993), or enlargement of a particular region involved in the processing of social information (Powell et al., 2012), or perhaps, the presence of a distinctive type of large neuron (Allman et al., 2010) have all been proposed and have not been explicitly resolved by the proponents of this approach. A similar enduring debate is whether the frontal cortex in humans has been the subject of special adaptation in relative size, subregions or neuronal phenotypes, variously associated with aspects of language, multiple behaviors associated with mirror neurons, cognitive control or planning capabilities. Analyses of old and new data for and against this claim have been made over a period of 40 years at this point (of many: Jerison, 1973; Semendeferi et al., 2002, 2011; Schoenemann, 2006; Barton and Venditti, 2013).

By contrast, the behavioral benefits associated with a relatively large brain are of obvious adaptive significance, directly measurable and correlate across taxonomic groups. Simple encephalization across birds, mammals generally, and primates correlates with field measures of behavioral innovation, the rate of success in invasion of new niches, laboratory measures of behavioral flexibility, and reduced mortality in the field (Lefebvre, 2013). Still, a reasonable criticism of the "concerted evolution" interpretation of brain scaling is that large brain divisions like "cerebellum" or frontal cortex" must reflect many of animal's specific behavioral capacities and would certainly contain multiple modules. Thus many important specializations carved out within overall ability might be overlooked. The changes in the neuroethological view of specialization, and the changing views in cognitive neuroscience about functional commitments, however, have come to intersect anthropology and gross comparative anatomy in level of analysis, and they inform each other. That is the reason for considering them together here.

COGNITIVE SCIENCE

Modularity (Fodor, 1983) is a venerable hypothesis in the understanding of the architecture of the mind and brain, arguably dating back to 18th century faculty psychology (Reid, 1785/2002) and its influence on phrenological accounts of brain organization (Gall, 1857). In its Fodorian incarnation, the modularity hypothesis was that (some of) the mind was constituted as a collection of specialized, encapsulated, communicating components—or modules—each dedicated to handling some well-defined aspect of the overall information-processing requirements of the organism. Insofar as this was so, Fodor argued, then each module should have some specific design features. For instance, it should be domain specific, in that it has access to (or at least responds only to) a narrow class of inputs, and transforms these according to some consistent and well-defined function to produce its output; it should be encapsulated, i.e., relatively isolated from influence by the operations of other modules; and it should be implemented in dedicated neural structures. From this perspective, it would also appear that the structures of the brain ought to have some of these same features. Insofar as neural structures are dedicated to particular modules, they will likewise be domain specific and encapsulated with respect to one another. Moreover, each of these design characteristics is mutually supporting in various ways. For instance, a module implemented in neural structures shared with other modules is less likely to be encapsulated relative to those modules; and if a neural structure serves the needs of more than one module, it would appear less likely to be domain specific.

A modular brain, then, would be a collection of domain dedicated, functionally specialized, relatively encapsulated neural structures that together served the information processing needs of the mind. Fodor himself argued that the only parts of the brain likely to be modular "to some interesting extent" (Fodor, 1983; p. 37) were "peripheral" structures dedicated to specialized sensory and motor processing. The probable non-modularity of "central" systems is a result of their hypothesized function of deriving true beliefs, and an argument to the effect that our beliefs are holistically related to one another in various ways—for instance, any belief, regardless of its ostensible domain (e.g., cell biology) could inferentially impact our acceptance of or the consequences we derive from any other belief (e.g., one about summer boat travel in Madagascar). Thus, such central inferential systems are not informationally encapsulated.

Whatever the merits of this Cartesian distinction between peripheral and central systems (cf. Dewey, 1896; pp. 357–358), it seems fair to characterize the current consensus as a rejection of Fodorian modularity as a research guiding idealization of brain architecture. The evidence gathered over the past 30 years overwhelmingly indicates that few parts of the brain or processes of mind appear to have the design characteristics hypothesized by this brand of modularity. Evidence (for instance) for top-down effects on visual processing; for cross-modal integration in perception; for the acute sensitivity of modules to developmental conditions; for cross-modal neural plasticity of many different sorts; and for the implementation of ostensibly distinct processes in overlapping neural structures, including the observation that even very small lesions of the brain typically induce multiple behavioral deficits, all point to a brain organized along rather different principles than those outlined by Fodor (see Barrett and Kurzban, 2006; Prinz, 2006; Anderson, 2010, for reviews).

In response to these critiques, and motivated as well by a desire to integrate psychology and neuroscience more fully with evolutionary biology, advocates of modularity have shifted the focus from the sort of *structurally defined* modularity advocated by Fodor toward a *functionalist* modularity positing a collection of functionally specialized, separately modifiable sub-systems, such that any specific design features of a given module are determined by individual functional requirements not necessarily shared by other modules (Tooby and Cosmides, 1992; Sperber, 2002, 2005; Barrett and Kurzban, 2006; Carruthers, 2006). On this view, sometimes called "massive modularity," there is no distinction between central and peripheral systems, and the focus is squarely on the evolution of modules that implement solutions to an organism's adaptive problems. This represents a step away from Fodor's Cartesian focus on central belief-fixing representational systems, and toward a more pragmatic, interactive account of the brain's central role in an organism's life. Interestingly, however, massive modularity retains the Fodorian focus on *computation,* and with it a focus on the algorithmic (or heuristic) efficiency of purported psychological solutions to adaptive problems such as food choice, mate selection, kin identification, and cheater detection. The claim is two-fold: that evolution will favor efficient solutions, and that the most efficient solutions will be specialized, domain specific, hence modular components. In many ways this view converges on the approach of the first neuroethologists, though these literatures are virtually independent. Consider the following from Barrett and Kurzban (2006); we quote at length as some of the details of the position will later become important:

> Our position, then, is that functionally specialized mechanisms with formally definable informational inputs are characteristic of human (and non-human) cognition and that these features should be identified as the signal properties of "modularity." By this we intend an explicitly evolutionary reading of the concepts of function and specialization: modules evolved through a process of descent with modification, due to the effects they had on organisms' fitness. …As a direct and inseparable result of this evolutionary process of specialization, modules will become *domain specific*: Because they handle information in specialized ways, they will have specific *input criteria*. …For example, systems specialized for assessing the numerosity of objects accept only representations previously parsed into distinct objects; systems specialized for speech perception process only transduced representations of sound waves; and systems specialized for making good food choices process only representations relevant to the nutritional value of different potential food items. (Barrett and Kurzban, 2006; p. 630)

As should be clear from the quote, it is a central part of massive modularity that each module should be separately modifiable, both in theory, and in the course of evolutionary development [see extensive discussion of this point in Carruthers (2006)]. Indeed, here functional specialization and domain specificity is a *result* of the fact that the modules are separately targeted by evolutionary pressures. Insofar as the focus is on the efficiency of individual computational solutions, as well as the collective efficiency of the system as a whole, a collection of separately modifiable modules that can operate largely in parallel, free of pleiotropy, can easily seem like an elegant design solution, and one to which the various demands of evolution might naturally converge.

And yet, as we have been seeing, the architectures of evolved nervous systems do not seem to reflect this particular solution. So, how should we reconceive the principles governing nervous system evolution? We begin to address this question in the next section.

FROM SIMPLE TO COMPLEX, SENSORIMOTOR TO INTEGRATIVE: MECHANISMS THAT CONTROL BRAIN SIZE NEURAL PLASTICITY AND NEURAL RE-USE

The large majority of the variation in evolution of vertebrate and mammalian central nervous system numbers can be described as concerted, and allometrically predictable (Stephan et al., 1986; Yopak et al., 2010). Important "grade shifts" in volume allocation often appear at taxonomic boundaries, for example, greater relative volume of the forebrain and cerebellum in mammals compared to reptiles and fish at comparable brain sizes, to which we will return later (Jerison, 1973; Northcutt, 1981; Yopak et al., 2010). In addition, developmental features associated with this conserved evolutionary outcome are being identified: the conserved segmental divisions common to all vertebrate brains (Puelles et al., 2013) coupled with a conserved pattern of neurogenesis whose property of "late equals large" automatically produces

disproportionate growth in the same regions (cerebellum, forebrain) in the largest brains across every vertebrate taxonomic group (Finlay et al., 1998). This identification of a developmental mechanism underlying allometric regularity in no way eliminates the requirement that an adaptive account be given of concerted scaling as much as for species-specific adaptation. The notion that a disadvantageous pattern of cell proliferation (appealing to "developmental constraint" as initially hypothesized by Gould, 1977) would be conserved over 450–500 MYA, particularly given the metabolic cost of the brain, is implausible in the extreme. A similar pattern of overwhelming conservation has been described in multiple domains, principally the vertebrate body plan and basic physiological circuits (Gerhart and Kirschner, 1997), and has required the same shift in explanatory style. Given all this conservation, however, species variations in behavior most definitely exist and must be accounted for, considering any collection you choose—catfish, catbirds and cats, for example. The need to explain these profound differences does not disappear if residual variation in brain structure volumes does a poor job in accounting for them. Fresh approaches to this problem will be the focus of this paper.

Considering the adaptive value of conserved scaling, and its niche-independent, brain-size-dependent features, a molar and a molecular account can both be given. The molar account has been discussed elsewhere, and concerns the benefits of this pattern of allometric scaling for a computational device (Finlay et al., 2011; Charvet and Finlay, 2012). Some kinds of computational architectures are simultaneously more amenable to addition or loss of components (such as memory resources) than others (Brooks, 1986; Hawes et al., 2007). Considering the cortex alone, the rostral-to-caudal gradient in length of cortical neurogenesis with its resulting rostral to caudal gradient in increasing neuron number per cortical column, which becomes more pronounced in increasingly larger brains, can be directly related to progressive reduction of dimensions and abstraction of information on that same axis (Charvet et al., 2013).

Here instead we will concentrate on the second problem of how adaptive specializations may be enacted within a generic architecture. First we will look in more detail at the claim that the relative numbers of neurons in or volumes of CNS structures are associated with or are a mechanism of species-specific adaptations. We will particularly underline the idea that many of the demonstrations of such effects, particularly in the case of volumes, may well be describing the downstream effects of the animal's extensive use of a particular sensory modality due to increased elaboration of the sensory periphery, activity changes or motivational state, resculpting the nervous system via its own activity. Changes in brain volumes may often be the result, not the cause of a behavioral change or an alteration in the sensorimotor periphery (Krubitzer and Seelke, 2012). We will also note that the assumption that increase in neuron number should result in improvements in function is often unjustified, particularly when the computational role of each nucleus and neuron class in a functional system is considered.

The potential, empirically well-described, developmental sources of changes in neuron numbers and volume are myriad, even considering only neocortex. These minimally include reassignment of embryonic boundaries (Alfano and Studer, 2013); rate and duration of neurogenesis (Charvet et al., 2011; Workman et al., 2013); respecification of neuronal type or redirection of migration (Letinic and Rakic, 2001); developmental cell death (Finlay and Slattery, 1983; Rehen et al., 2001), and activity-dependent increases in axonal and dendritic arbors produced by experience and resulting changes in cortical volumes (Greenough and Black, 1992; Krubitzer and Seelke, 2012). This list is long if we consider only neuroanatomically defined regions (like "striate cortex"), and even more extensive still if we consider methods, like reuse (Anderson, 2010), by which active inputs may claim processing space in the brain in multimodal or otherwise associative regions. Each developmental mechanism has a range of effect sizes, and developmental onset and offset that should be relevant to our understanding of brain evolution. To understand what kinds of evolution are possible we need to distinguish "primary" genetic changes from the downstream effects of the brain environment of neuroplasticity. Sometimes neuroplasticity might be expected to constrain the effects of undesirable changes, and other times amplify useful ones, and we will supply examples of both.

REGULATION OF NEURON NUMBER IN INDIVIDUAL BRAIN REGIONS

The idea of specialized, localized functional modules as targets of selection appeared to simplify the problem of selecting for behavioral adaptations by coupling two features both thought to be important in enhancements of brain function. First, special circuitry is often proposed as central to new functionality (from the control of jointed limbs to "grammar modules"). Second, it seems reasonable that more processing resources, neurons and connectivity both, should be committed to important, species-specific capabilities. If both changes could be realized in a single brain part, it would appear to be more efficient than a search of the evolutionary landscape of the entire brain for an optimal combination of dedicated neurons and altered circuitry. As such extreme discrete functional adaptations eventually became to seem unlikely, as discussed earlier under "massive modularity," a search for how single functional adaptations might be made to "cascade" through spatially separated regions of the developing nervous system was begun. This search produced unexpected results.

The observation that neurons are massively overproduced in early development and die as they establish connectivity (as do synapses) produced a first attempt at neural "evo-devo" (Oppenheim, 1991). The particular case of sexual differentiation of neuron number for sexual behavior in vertebrates is a reasonable entry point, as it involves control of different muscle mass, numbers of motorneurons in the spinal cord and control of the behavior at supraspinal levels. The rat spinal cord begins as uniform in neuron number, and early testosterone allows the survival of the motor neurons associated with the male reproductive apparatus by supporting muscle survival in the periphery; the neurons die in females without the trophic support supplied by the muscle fibers (Lubischer and Arnold, 1995; McCarthy and Arnold, 2011). This hypothesized method of generating system-wide individual differences was eagerly seized as a potential model to sculpt species differences by propagating a single genetic change through the developing nervous system:

perhaps a "generic" central nervous system might be generated, and a single specialization, for example, a larger eye, could cascade through multiple sites in the brain by rescuing neurons and synapses from developmental cell death (Finlay, 1992). The functional hypothesis in these series of experiments is similar to the "mosaic" idea of brain evolution: if an animal is specialized for a particular function, there would be benefit for it to amplify the number of neurons committed to that function wholesale throughout its brain.

As initially plausible as this idea might have been, it proved not to be the case, neither for sexual differentiation of individuals nor visual system evolution across species (Oppenheim, 1991; Finlay, 1992). As always, the empirical actuality proved ultimately more interesting than the first guess. Basically, interconnected groups of neurons do not respond with any degree of sensitivity to "match" their relative numbers to each other, but respond with measurable neuron loss only in cases of catastrophic loss of input or target. A single change in neuron numbers at one point in a circuit simply did not propagate past its immediate neighbor. For example, while embryonic complete loss of an eye might cause catastrophic neuron loss in the midbrain and thalamus, and propagate through to change the boundaries of visual cortex, the converse manipulation of introducing large increases in retinal input to the same structures, more relevant to evolutionary adaptations, had little effect, even though there was potentially a great deal of neuron loss and synaptic connectivity the extra tissue might "take up" (Finlay and Pallas, 1989).

The series of experiments of Sarah Pallas and colleagues (Pallas and Finlay, 1989; Huang and Pallas, 2001) on the physiological consequences to visual system organization of numerical imbalances in interconnecting structure provided a case where mechanisms of plasticity appear to work to counter the effects of localized increases in neuron number. These experiments redirected our interest from the idea that increased neuron number in a single structure might be a useful building block of brain evolution to instead, how sensorimotor systems insure the reliability of how they extract information, which we discuss at a little length to illustrate the point. Initially we imagined supplying supranormal retinal input to the midbrain might illuminate how the receptive fields of neurons in the superior colliculus were constructed: we imagined that the receptive field of each cell would have to be twice as large to accommodate the increased input. Nothing of the kind happened: the receptive field sizes of single neurons remained the same. Eventually it appeared that the mapping problem was solved not by reducing cell death in the supra-innervated colliculus, nor allowing increased convergence on single cells, but by increasing the spatial overlap or redundancy of midbrain cells' receptive fields. Activity-dependent mechanisms operating at the midbrain target "permitted" receptive fields only of a certain size, prohibiting plasticity in spatial convergence on single neurons. In hindsight, considering how a functioning visual system should best respond to unexpectedly large ratio variations in neuron number between brain structures, it now seems reasonable that an animal's visual acuity should *never* be dependent on the ratio relationship of its internal parts, but that hard-won peripheral acuity should be maintained over variations as much as possible. In this case, a plastic mechanism works to defend visual function and conserve receptive field properties, and preserve the animal's midbrain-dependent behaviors (Xiong and Finlay, 1996).

When specializations of sensorimotor or behavioral systems in particular species are obvious, what is genetically changed in those species? First, and predominantly, extreme differences can routinely be seen in the sensory and motor periphery. Across sensory systems, the details of peripheral topography will be found faithfully reproduced in the cortex (e.g., Silveira et al., 1989; Catania and Kaas, 1995; Krubitzer and Seelke, 2012; Meyer et al., 2013). An evo-devo account of the minimal number of alterations of neurogenesis to produce the very long list of changes of the eye of the nocturnal owl monkey compared to its diurnal forebears, concentrating on the enrichment of its population of rods and 4 other retinal neuron classes, has been made by one of the authors and her colleagues (Dyer et al., 2009) the point of this example is both to emphasize the multiple specializations for light capture of the nocturnal eye, and the mechanisms coordinating them. Close to the periphery, but definitely within the CNS, special computational devices can be seen, for example, the delay-line neurons of the superior olive that compute time-of-arrival differences for auditory input in the two ears (Carr and Konishi, 1988). Deeper in the CNS, adaptations for special processing that are specified independent of input become progressively more difficult to identify—for example, if there are genetically-specified special transmitters, receptors, or axon lengths in the striate cortex of particular advantage for vision, they have never been explicitly identified. The idea of a "canonical circuit" in the cortex spanning multiple modalities has come to dominate current discussion (Douglas and Martin, 2004; Harris and Mrsic-Flogel, 2013).

While a number of individual reports of selective structural increases of presumed adaptive significance have been made (to be reviewed below), it is worth recalling first that several extensive surveys of particular sensory and behavioral systems with the intention to describe number or volume differences have produced negative results (with the striking exception of the song system in passerine birds). This negative catalogue is rarely cited. For example, Glendenning and Masterton (1998) undertook an analysis of the volumes of 10 subcortical auditory nuclei in 53 diverse mammals, and found they were all highly correlated, and predicted from overall brain size. The three species that deviated most in increased size from the mean values were the little brown bat (other microbats were not unusual), the beaver and the laboratory mouse, the latter two not usually remarked for auditory specialization. Similarly, relative "dexterity," using a scale ranking animals from hooves to hands, was predicted better from absolute brain size than the relative size of somatosensory cortex (Nudo and Masterton, 1990). Across both birds and mammals, the idea that the relative demands on memory for scatter-hoarding vs. other methods of foraging should be associated with a larger hippocampus enjoyed an initial success (Sherry et al., 1989; Jacobs and Spencer, 1994; Healy and Krebs, 1996), which became progressively less clear as the details of the relationship of real-world foraging to memory, and the lability of hippocampal volume became better understood (Roth et al., 2010; Smulders et al., 2010). A series of studies of the neuron numbers and volumes of visual system structures in primates and mammals including

the retina and fovea (Franco et al., 2001; Finlay et al., 2008), lateral geniculate (Finlay et al., 2013), pulvinar (Chalfin et al., 2007), superior colliculus (Cheung, 2003), striate and extrastriate cortex (Kaskan et al., 2005), showed no niche-related effects unexplained by scaling but one (to be discussed) in central structures, major differences of multiple features of the eye and retina, and a substantial "grade shift" between midbrain and forebrain scaling in rodents vs. primates independent of niche. The bird "song system," however, stands out as a counterexample. Though the identification of the volume of a nucleus specifically with numbers of songs has undergone much elaboration and qualification since its original description (Nottebohm et al., 1981), numerous forebrain specializations have been demonstrated including relationships of neuron numbers to elaborations of capacity, relationship of the same to variation between species (Szekely et al., 1996), and heritability of such differences (Airey et al., 2000). What feature of the song system distinguishes it from the other systems we have reviewed is clearly of major interest. Overall, the point of this catalogue is not to engage the argument that genetically-specified increases in neuron numbers in CNS structures associated with species-specific adaptions have not or cannot ever occur, but that they are simply not as pervasive as an evolutionary mechanism as the list of isolated examples often offered would suggest. In fact, they appear to be rare.

It is worth recalling that while the allometric predictability of neural volumes is very high, the residual variation of individual structures (between and within species) is also high, due to the enormous range of brain sizes.

> …The enormous range of structure sizes across species is important for the following reason: In a moderate-sized sample, a normally distributed variable typically has a total sample range of about five times its standard deviation. In predicting the size of brain structures, as noted above, the standard deviation of predictive errors is 0.187 averaged across structures when variables are measured on logarithmic scales. This suggests that for a typical structure, two species identical on our two major factors may have structure sizes differing by as much as 5 X 0.187 or 0.935 on a logarithmic scale. Because exp(O.935) = 2.55, individual structures may differ by a factor of as much as 2.5 in size, even when the two species being compared are very similar on the two major factors. Inspection of the raw data confirms this conclusion. To the investigator seeking evidence for species-specific adaptation, a twofold difference in a structure's volume is striking, even if it is trivial in comparison to the total range of size of that structure and small in comparison to the range of structure size with body size held constant. (Finlay and Darlington, 1995), p. 1580.

So, for example, if a single comparison of the superior colliculus of the nocturnal laboratory rat is made to the diurnal ground squirrel, the two differ in volume by a factor of 10 though their overall brain size is fairly similar (Kaas and Collins, 2001). Unfortunately, however, it is also the case that in the rodent lineage across multiple species there is simply no significant relationship between nocturnal/diurnal niche and midbrain size demonstrable thus far, as laid out in the previous list of citations. Large variations between individuals within a species are often observed, as well. One of the first was the observation of Van Essen and colleagues of nearly four-fold variation in surface area in a small sample of macaque primary visual cortex area (1984). Recently, variation in attention to local vs. global orientation sensitivity has been linked to V1 size (Song et al., 2013) and increased Vernier acuity and decreased susceptibility to two optical illusions (Bakken et al., 2012). An adaptive purpose for these distinctions is not obvious, and no clinically important "small V1 syndrome" has ever emerged. Large ranges in number and volume between individuals within species in at every level of the visual system can be seen, variability characterized by a strong central trend with distinct outliers, but with no identification of the outliers with any obvious behavioral pathology (Franco et al., 2001; Kaskan et al., 2005). It will be interesting to attempt to make specific predictions in any of these cases, but the "rectifying" nature of the neuroplasticity environment discussed earlier for numerical imbalances should be taken into account (Pallas and Finlay, 1989) The case of dramatic "imbalances" in the red/green photoreceptor opsin array unaccompanied by perceptual differences will be discussed shortly (Williams et al., 1993).

Many reported volume increases in single structures linked to niche-specific variations are likely to be the outcome of a "generic" nervous system operating in an unusual niche: the effects of environmental deprivation and enrichment on primary visual cortex volumes, for example, range around 5–10% (Greenough and Black, 1992), and feral rats differ from laboratory rats in these approximate magnitudes (Krubitzer et al., 2011). Not all observations can be described this way: two species of squirrels appeared to have larger relative areas of visual compared to somatosensory cortex, which will be useful for further investigation of phylogenetic vs. developmental causes of this kind of specialization (Krubitzer and Seelke, 2012). Other examples of "coordinated" changes within functional systems seem likely to be developmental, if not tautological in origin: synaptically connected structures within functional systems literally contain volumetric components of each other in their axonal inputs (Barton and Harvey, 2000; Barton et al., 2003).

In the study of primate vision, contesting and conflicting accounts of the adaptive purpose of visual system features are ceaselessly argued. For example, considering the trichromacy of New and Old World primates [whose species comprise a majority of frugivores, but also insectivores, folivores, carnivores, tree-gum-specialists and omnivores like ourselves (Fleagle, 1999)], convincing evidence that trichromacy improves scene segmentation (Hansen and Gegenfurtner, 2009), distinction of shading from reflectance (Kingdom, 2003), social communication involving detection of blood oxygenation, (Changizi et al., 2006), foraging for fruits (Regan et al., 2001), or distinction of leaf age for folivory (Lucas et al., 1997) have all been offered; clearly it is likely that trichromacy contributes to all of them. But when we leave psychophysics and turn to the brain, details of what adaptation and what processing model best describe the primate visual system are left behind, using the assumption of "more is better" for every stage of visual system organization. For example, Barton argues that a statistically demonstrable increase in the P/M cell ratio of the lateral geniculate is a special adaptation for frugivory in diurnal primates. The ratio of parvocellular neurons (P cells, small cells, primarily representing the fovea, specialized

for high spatial acuity and one aspect of trichromacy) vs. magnocellular neurons (M cells; larger neurons, more evenly spread across the retina; higher temporal acuity and participating in dichromacy only) in the lateral geniculate increases with regular allometry with brain size and is slightly higher in diurnal primates than nocturnal ones (Barton, 1998, 2004). We were recently able to confirm and extend this observation (P/M ratio higher in diurnal primates) to more primate species (Finlay et al., 2013), but also show that the cause was likely to be the developmental cell death of the M neurons representing the visual periphery, competing unsuccessfully for synaptic space in primary visual cortex dominated by early arrival and topographic occupation of the cortex by the foveal representation, a hitherto unexplained developmental observation of Williams and Rakic (1988). The cause of the changed ratio, therefore, is not a genetic change directly producing greater P cell numbers, but a downstream effect of the developmentally "generic" mechanism of active and early-generated sensory specializations claiming greater synaptic space.

The differing computational role of number at different stages of sensory and cognitive analysis needs to be considered as well when considering allometric relationships—how much more is better? For example, in the primate retina, cones, because they are flooded with photons in high light levels, may sample a large visual angle selectively without loss in acuity without increase in number as the eye enlarges, while rods normally carpet the retina to maximize sensitivity. The allometric outcome is that rods increase rapidly in number with eye size while cone numbers change little, so that humans, the primate with the largest eye, have by far the most rods of the diurnal primates (Finlay et al., 2008). The optic nerve and primary visual thalamic nuclei, in concert with sensory thalamic nuclei in general, appear to be defended as a bottleneck, and do not increase rapidly with brain size. This phenomenon has several interesting candidate functions, such as production of an efficient compression or multiplexing of retinal input, or roughly equilibrating the information contributed by various sensory modalities to the cortex (Fetsch et al., 2013).

Overall, we argue, with the several empirical exceptions noted, that the evidence for structure-by-structure genetic selection on neuron number for particular adaptive ends is surprisingly poor, especially given the pervasive belief the phenomenon should exist. Most of the variance in neuron number is shared, and the simple existence of unshared variance by itself is not evidence for "mosaic" evolution. Marked individual local variations in number so far have not advertised their functional consequences, and in at least a few cases, appeared to be actively compensated rather than exploited. Within the visual system, and perhaps for sensory systems generally, a niche-independent computational role for the scaling of each cell group can often be identified. Several striking time points in vertebrate evolution exist where changes relative proliferation of brain parts accompanies a niche change, such as those associated with homeothermy, or becoming terrestrial. Interestingly, though, in those cases, the structures with the highest allometric slopes in the stem group are the same ones that are further amplified in the derived group. There is, however, at least one distributed, covarying and relatively independent system that can be discriminated within the brain, from the onset of vertebrate evolution. This is the "limbic" system, comprising olfactory bulb and cortices, hippocampus and various forebrain nuclei, which varies relatively independently from the rest of the brain (Jerison, 1973; Finlay and Darlington, 1995; Reep et al., 2007). Why this relative independence should have persisted for 450 MY, in tandem with the regular scaling of the rest of the brain, is a very intriguing question. Several distinctions can be made between these functions of these large systems, the first olfactory vs. visual specialization, but that does not exhaust all possibilities. Egocentric vs. allocentric spatial representations, and short-term vs. very long term memory storage distinguish these systems as well.

EXAMPLES OF MULTIFUNCTIONALITY IN NERVOUS SYSTEMS, FROM NEURONS TO REGIONS

In light of such increasingly common discoveries as those detailed above, a different perspective on functional brain evolution and organization has begun to emerge, that puts the focus not on the selective targeting of individual structures, but instead on overall efficiency in deployment of neural resources. According to these so-called neural reuse theories (Anderson, 2010), resource constraints and efficiency considerations dictate that, rather than developing new structures *de novo*, whenever possible neural, behavioral and environmental resources should have been reused and redeployed in support of any newly emerging cognitive capacities. That is, rather than following an evolutionary/developmental pathway wherein organisms develop specialized, dedicated neural hardware to meet each new adaptive challenge, reuse suggests that much local neural structure is conserved but is often combined and recombined by different organisms in different ways to achieve diverse purposes. The fact of functional *differentiation* between parts of the brain need not imply the existence of functional *specialization* in all such cases.

We have, of course, already seen many examples, and such reuse of neural elements to regulate multiple behaviors seems to be the rule rather than the exception in the nervous systems of many animals. Examples of neural reuse can be found across the animal kingdom, suggesting it is a vitally important evolutionary strategy for deploying scarce neural resources to the greatest behavioral and adaptive effect.

> Reuse may also be found in neurons involved in learning and memory. In the pond snail (*Lymnea stagnalis*), the breathing rhythm is generated by three synaptically connected neurons that form a central pattern generator. One of these neurons, RPeD1, is also necessary for many aspects of learning and memory; and removing the RPeD1 cell body can prevent the formation or reconsolidation of long-term memories (Sangha et al., 2003). In honeybees (*Apis mellifera*), a single identified neuron (VUMmx1) in the suboesophageal ganglion mediates the reward pathway in associative olfactory learning, but this neuron has also been implicated in learning phenomena as diverse as second-order conditioning and blocking (Menzel, 2009). (Niven and Chittka, 2010; p. 285)

Similar neuromodulation comes in many guises in vertebrates. A textbook example of neural re-use employing gain and gating

changes is the "duplex" retina: beginning from the receptors, the neurons of the retina can be engaged, de-coupled, or have their processing features entirely reorganized depending on whether they are participating in scotopic, (low light or nocturnal) vision, or photopic, (high light level or diurnal) vision (Palmer, 1998). Vertebrate vision appears to have originally arisen for conditions of high light levels, and adaptations for higher sensitivity in dim light appeared secondarily, employing the same retinal neurons (for a general review, Bowmaker, 2012). Transitions in visual niche have occurred repeatedly, within large taxonomic groups, such as those including sharks and rays (Yopak et al., 2010), at the emergence of the first mammals occupying nocturnal niches, and notably in primates, where diurnal primates emerged from primarily nocturnal stem species (Ross, 2000; Gerkema et al., 2013). At the cellular level, the catalogue of adjustments is long, but one example is illustrative: for low-light vision, the lateral inhibition opposing the responses of the center and periphery of visual receptive field normally seen in diurnal vision is removed, increasing sensitivity and reducing spatial acuity. This alteration can be produced directly, by a change in ambient light level, or predictively, in accord with circadian rhythmicity (Palmer, 1998). Although the nearest-neighbor relationship of retinal cells is preserved in low-light vision, the central specialization of the fovea is essentially removed as well. The basis of receptive field structure in diurnal vision, lateral inhibition, is removed from retina, lateral geniculate and visual cortex in nocturnal vision, yet the same structures are used to see.

The transition from night to day vision in individuals in species that can function in both milieus, notably ourselves, is easy. Interestingly, the wholesale evolutionary transition from a retina adapted to diurnal vision to nocturnal vision (in New World monkeys, Dyer et al., 2009) is similarly easy, harnessing the temporal relationships of neurogenesis seen in the diurnal peripheral retina to change the complement of all types of retinal neurons in one step. The availability of re-use in central nervous system targets of the retina allows this complex transition to be produced by changing timing relations in a few control steps in the retina alone, rather than by respecifying the physiology of each and every participating neuron directly, or worse yet, having to generate a second nocturnal eye.

Finally, there is a good deal of emerging work that points to the importance of the large-scale modulation of neural partnerships in support of cognitive function. For instance, changes in the oscillatory coherence between brain regions (local and long-distance) appear to be important to sensory binding, the modulation of attention, and other cognitive functions (Steinmetz et al., 2000; Uhlhaas et al., 2009; Varela et al., 2001; Fries, 2009; Nacher et al., 2013). The basic finding that cognitive function involves the reuse of the same elements in different configurations is illustrated by two early studies: Friston (1997) demonstrated that whether a given region of inferotemporal cortex was face selective depended on the level of activity in posterior parietal cortex; and McIntosh et al. (1994) report on a region of inferotemporal cortex and a region of prefrontal cortex that both support face identification and spatial attention. In the latter study, McIntosh and colleagues showed that during the face processing task the inferotemporal region cooperated strongly with a region of superior parietal cortex; while during the *attention* task, that same region of parietal cortex cooperated more strongly with the prefrontal area. Similar patterns of changing functional connectivity are observed over developmental time, which suggests that acquiring new skills involves changes to both local and long-distance functional partnerships (Fair et al., 2007, 2009; Supekar et al., 2009).

Our examples, due to the specializations of the authors, are principally drawn from vision and human cognition, but it is worth noting that it presents little challenge to find comparable examples in motivational and emotional domains. In voles, the transition from principally promiscuous to principally monogamous mating systems, both between species, between individuals, and perhaps over development, is thought to involve the interposition of a vasotocin or oxytocin receptor gate involving individual recognition in basic reinforcement circuitry (Insel and Young, 2001). Adjustment of sensory gain can be seen in the stress-induced analgesia observed in both rodents and humans (Akil et al., 1984; Bargmann, 2012). Stress can also change the configuration of large scale brain networks across a number of species including humans (Hermans et al., 2011), including early-stage sensory processing depending on emotional arousal, as demonstrated in V1 by Mourao-Miranda et al. (2003).

Some intriguing further evidence for the reuse of larger neural elements comes from data-mining large collections of human neuroimaging studies. For example, Poldrack (2006) estimated the selectivity of Broca's area by performing a Bayesian analysis of 3222 imaging studies from the BrainMap database (Laird et al., 2005). He concludes that current evidence for the notion that Broca's area is a "language" region is fairly weak, in part because it was more frequently activated by non-language tasks than by language-related ones. Similarly, several whole-brain statistical analyses of large collections experiments from BrainMap (Laird et al., 2005), Neurosynth (Yarkoni et al., 2011) and other sources demonstrate that most regions of the brain—even fairly small regions—appear to be activated by multiple tasks across diverse task categories (Anderson, 2010; Anderson and Penner-Wilger, 2013; Anderson et al., 2013).

The observable large-scale patterns of use and reuse of individual regions of the brain across multiple circumstances suggests that this functional diversity is a reflection of the evolutionary and developmental history of the human brain. For instance, it appears that, *ceteris paribus*, the "older" regions of the human cortex, the primary sensory areas possessed by every mammal (Krubitzer, 2009) as distinguished from the various association regions which appear selectively in larger brains, tend to be used in more tasks—presumably because they've been around for longer, and have thus had more opportunity to be incorporated into multiple functional coalitions (Anderson, 2007). In addition, more recently emerging cognitive functions, such as language, appear to be supported by more and more widely scattered brain regions than are evolutionarily older functions such as vision and attention (Anderson, 2010; Anderson and Penner-Wilger, 2013). Again, this makes sense in light of both progressive functional differentiation and evolutionary continuity, for the later a given cognitive process or behavioral competence emerges, the greater the number and diversity of neural structures that will be available

to support the new competence, and there is little reason to believe the useful structures will be near one another in the brain.

Thus, while massive modularity and neural reuse both agree that functional brain architecture needs to be understood in an evolutionary framework, these positions differ on the question of where and how evolutionary pressures are likely to be felt. In particular, it is important to notice the following crucial implication of widespread neural reuse for massive modularity: insofar as these different cognitive and behavioral capacities are supported by reusing many of the same neural elements in different functional coalitions, it is hard to see how it would be possible to separately target and modify these coalitions via natural selection [or by any other means; for further discussion see (Anderson, 2010, 2014)]. Functional "modules" that are built out of shared parts will rarely be separately modifiable; these findings thus encourage a shift in thinking away from massive modularity and individually tailored and inherited solutions to adaptive problems, and toward models that favor more concerted evolution.

FUNCTIONAL DIFFERENTIATION WITHIN A GENERIC NERVOUS SYSTEM: THREE EVO-DEVO SOLUTIONS

All of the foregoing does raise a crucial question: how can one get specialized, differential, heritable function in nervous systems where concerted evolution appears necessary for both functional and architectural reasons? The key is seeing how evolutionary and developmental mechanisms can work together. We will describe three evo-devo interactions for which evidence exists. The first is a canonical example of "evolvability" in which existing information processing mechanisms accept and immediately employ a new dimension of sensory information when it is made available by a genetic change in the sensory periphery. The second example explores the interaction between motivational "presets" and the population of the central nervous system with the information the organism then preferentially acquires. Finally, we will discuss mechanisms of active search for available neural resources.

For the first example, cooperation between evolutionary and developmental mechanisms can be seen in the case of color vision plasticity (Neitz et al., 2002). A remarkable fact about color vision is that there is very little inter-individual variation in performance, despite immense differences in the (largely) genetically specified ratio of L to M cones in the retina. There is, for instance, almost zero variation in the wavelength of light judged to be "uniquely yellow" (without red or green tint), despite a 25 fold variation in LM cone ratio (Williams et al., 1993).

In a series of experiments, (Neitz et al., 2002) systematically altered the color environments of several adult subjects through the use of colored contacts, special lighting schemes and similar measures. They showed that there exists a cortical mechanism for adjusting the sensory gain, such that the signal received from the L and M cones remains in equilibrium under prevailing environmental conditions—that is, given the mean chromaticity of the experienced environment. They hypothesize that this developmental mechanism allows for standardized color vision despite genetic and environmental variation. The selective advantage of such standardized color vision would tend to stabilize the evolutionary and developmental mechanisms that produce it. They hypothesize that this is the identical mechanism that permits the trichromacy that normally arises by the mutation of one opsin in about two thirds of female New World monkeys in the absence of any known brain changes (Jacobs, 2012), and the rapid emergence of behavioral trichromacy after "knock-in" of a third opsin into normally dichromatic monkeys (Mancuso et al., 2009).

For our second evo-devo example, the motivational "presets" which certainly vary between species and may vary between individuals, will certainly alter which environments individuals select, what sensory stimulation they seek, and thus how their brain, and particularly the cortex, becomes populated with information. For example, some species of birds are solitary, and are made anxious or aggressive by the presence of conspecifics, while others have the opposite response, related to non-apeptide distribution in the basal forebrain (Goodson et al., 2012). The progeny of these birds, whether or not the individual offspring itself has the corresponding motivational bias, will grow up in an environment absent of most other birds in the first case, and full of birds in the second. The most well-known example in the human literature of such a "preset" is the preference of infants to look at the human face. Human infants prefer to look at face-like configurations (Johnson, 2011), and will work hard and learn quickly for social reinforcement (Goldstein and Schwade, 2008). Even with the initial preference for faces, being likely subcortical (Johnson, 2001), the advantages of the eye coloration and our contrasting sclera enabling gaze-tracking, and enthusiasm for social learning, it still takes 7–10 years for the representation of faces in the cortex of human children to begin to approximate adult organization (Cohen Kadosh et al., 2011). In autism, abnormal social interaction, abnormalities in both early and late patterns of eye movements, and alteration of face-processing regions in the cortex all co-occur (Kennedy and Adolphs, 2012). The predisposing condition to produce a cortex with a substantial percentage of its volume involved in processing faces and the nuances of emotional expression might only need motivated coupling of early eye and head movements toward expressive faces over long developmental time. The question of how this information is allocated to regions is a question that can be studied phylogenetically, developmentally, and in the service of individual differences.

Finally we consider active search for coordinated input. In addition to instances of sensory gain modulation involving the tuning of local neural responses, there is some suggestive evidence for a neural "search" mechanism that works to establish functional partnerships between cells and between cortical regions. For instance, learning to control an artificial limb via a direct cortical interface (a so-called brain-machine interface, or BMI) appears to involve both an alteration of the tuning curves for individual cells, and also a change in the patterns of functional correlation between cells in the local network. Lebedev and Nicoleilis (2006) describe the neural effects of the learning process this way:

> [C]ontinuous BMI operations in primates lead to physiological changes in neuronal tuning, which include changes in preferred direction and direction tuning strength of neurons (Taylor et al., 2002; Carmena et al., 2003; Lebedev et al., 2005). In addition, broad changes in pair-wise neuronal correlation can be detected after BMIs are switched to operate fully under brain-control mode (Carmena et al., 2003; Lebedev et al., 2005).

> Along with these physiological adaptations of neuronal firing patterns, behavioral performance improves as animals learn to operate BMIs effectively (Taylor et al., 2002; Carmena et al., 2003; Lebedev et al., 2005). Initial training to operate a BMI is characterized by an increase in neuronal firing rate variance, which cannot be simply explained by changes in limb or actuator movements (Zacksenhouse et al., 2005). As the quality of BMI control improves, initial elevation of neuronal firing variability subsides. (Lebedev and Nicoleilis, 2006: 542)

In so far as oscillatory coherence between cells is a sign of functional cooperation, then it is intriguing to note that one effect of the observed increase in neuronal firing rate variance is to implement a walk through cellular coherence space. That is, as the firing rates of the cells change, they will come into synchrony with a series of different partners over time. The suggestion is that the partnerships that produce the desired effects will be strengthened, with the end result being the establishment of a set of neural partnerships (via "broad changes in pair-wise neuronal correlation") able to control the limb.

Similar search mechanisms may be behind cases of sensory substitution, in which input from one sensory modality (e.g., touch) is used to provide information normally provided by another (e.g., vision), as with the use of a prosthetic camera that transmits information via mechanical or electrical stimulation to the skin (Bach-y-Rita et al., 1969), an effect generated more prosaically when using Braille dots for reading. As is by now quite well known, in such cases parts of the brain that would normally support processing of information in the original sensory modality can come to support the processing of input in the new modality (Pascual-Leone and Hamilton, 2001; Merabet et al., 2004). Thus can occipital cortex, normally associated with visual processing come to support tactile processing in these and other cases (Zangaladze et al., 1999; Amedi et al., 2002; Merabet et al., 2004; Pietrini et al., 2004). In one particularly interesting case, Merabet et al. (2008) taught sighted individuals to read Braille while blindfolded, and verified using both fMRI and rTMS that occipital cortex was part of the supporting network for the skill. However, after removing the blindfolds, participants remained able to read Braille but no longer showed activation in occipital cortex. The skill was now "presumably supported by activity at brain regions other than the occipital cortex." (Merabet et al., 2008; p. 8)

Together, these and other pieces of evidence suggest that the mechanisms underlying neurofunctional development (early as well as late skill acquisition) include a process of active search: the rapid testing of multiple neural partnerships to identify functionally adequate options, in some cases multiple alternative possibilities, leading to a degenerate functional network that can be modulated depending on circumstances and task demands (Sporns, 2011; Bargmann, 2012; see Anderson, 2014 for extensive discussion).

Although the foregoing can hardly be said to establish this fact, if granted the assumption that the brain possesses mechanisms for functional development that include both the ability to tune local neural structure in response to task-relevant statistical properties in inputs, and the ability to perform a "search" for functional partnerships between structural elements at various spatial scales, then it becomes possible to see how systematic, heritable, and relatively consistent functional differentiation in the brain could occur in the absence of targeted modular or mosaic selection. Given a set of early developing and stereotyped neural projections from sensory afferents, and assuming an environment that is largely conserved over generations, local tuning mechanisms would be sufficient to produce local networks with specific and predictable functional structures and response tendencies. A set of such neural structures with different functional biases (different input-output mappings) would be enough to allow an ongoing process of neural search to identify and consolidate the sets of partnerships that reliably supported skills being acquired during development. Consistency in the early development of functional biases and in the nature of the tasks being learned by the organism would be sufficient on this model to produce relatively consistent large-scale functional networks, without the need for direct evolutionary targeting. Indeed, in a functionally differentiated but non-modular brain, selection pressures might work not to produce particular specializations, but rather to stabilize the availability of a diverse mixture of computational properties in the entire brain (Atallah et al., 2004) coupled with a range of cortical biases that, given sensory inputs and the interactions between regions (Johnson, 2001, 2011) reliably produces the functional architecture we observe.

SUMMARY AND CONCLUSIONS

So, then, how do we resolve the apparent paradox that existing developmental processes must have been selected both to be robust to perturbations and accidents, but not so robust as to be unevolvable? The key lies in seeing how the nature of evolutionary adaptations of the brain and developmental mechanisms are intertwined and mutually supporting. For instance, insofar as the properties of environments are generally conserved between generations, then developmental mechanisms that are sensitive to those properties will reliably produce "heritable" specializations, while still being able to compensate when environments change. Here it is worth emphasizing as well the various ways in which the behavior of organisms themselves serves to change and stabilize the environment through various kinds and degrees of niche construction (Odling-Smee et al., 2003; Richerson and Boyd, 2005). When this is combined with the insight that the brain has a meta-modal, domain general organization (Pascual-Leone and Hamilton, 2001; Anderson, 2010), it becomes possible to see how brain architecture can be robust to perturbations and reliably produce a diverse range of different specialized processing operators whose cooperation can support species-typical behaviors. When either opportunity or disaster strikes, the absence of genetically-specified, domain-specific, stereotyped, modular structures and the multiple mechanisms of neuroplasticity permit evolvability.

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