Recent advances in cell labeling and imaging techniques have dramatically expanded our knowledge of the neural precursor cells responsible for corticogenesis. In particular, radial glial cells are now known to generate several classes of restricted progenitors and neurons. While radial glial cells in the ventricular zone have received the most attention, it has become increasingly clear that a distinct subclass of radial glial cells situated in the subventricular zone (SVZ) and intermediate zone also play an important role in corticogenesis. These delaminated radial glial cells, which lack an apical process attached to the ventricular surface but maintain a basal process, were discovered over 3 decades ago. Recently, they have been further characterized as cortical progenitors and renamed outer, intermediate, or basal radial glia (bRG). Some of these studies indicated that bRG abundance in the outer SVZ (oSVZ) is correlated with enhanced gyrencephaly, particularly in primates and especially human, and therefore suggested that bRG may be responsible for the emergence and evolution of cerebral convolutions. In this issue of Cerebral Cortex, 2 papers provide new information about bRG in common marmosets, a near-lissencephalic primate, and in agouti, a near-gyrencephalic rodent (Garcia-Moreno et al. 2011; Kelava et al. 2011). They demonstrate that bRG are abundant and proliferate in inner as well as oSVZ, in both species. Together, these findings indicate that bRG and the oSVZ might not be correlated with gyriﬁcation or phylogeny. Rather, differential regulation of bRG and other progenitor types may enhance the adaptability and diversity of cortical morphogenesis.

Keywords: cerebral cortex evolution, intermediate progenitors, Sox2, Tbr2

Introduction
The intricate pattern and degree of cortical gyriﬁcation, which culminates in the complexity of primate brain—most notably human, has long fascinated neurobiologists and has prompted a search for the mechanisms and signiﬁcance of this remarkable biological event. For more than 3 decades, the radial unit hypothesis (RUH; Rakic 1988) has served as the model for understanding developmental expansion of the cortex. With recent modiﬁcations incorporating new ﬁndings on cellular diversity and interrelationships between neural precursor cells (reviewed in Rakic 2009), the RUH explains how expansion in the number of apical radial glial (aRG) in the early embryonic ventricular zone leads to increased telencephalic surface area during development and evolution. In addition, the RUH also posits that molecular and cellular dynamics within the aRG specify basic parameters of cortical layer production, forming a foundation for the related protomap hypothesis, which proposes how individual cortical areas differentially enlarge and how new areas become introduced (Rakic 2009). These basic tenets of the RUH have been well supported by examples in the scientiﬁc literature.

Recent progress in characterizing several types of cortical progenitor cells, and distinct progenitor zones or compartments, has fostered elaboration of this model and prompted speculation on the role of speciﬁc progenitor types in producing gyriﬁcation. In particular, intermediate progenitors (IPs) derived from aRG and, more recently basal radial glia (bRG), have been proposed to provide the substrate for gyriﬁcation (Martínez-Cerdeño et al. 2007; Reillo et al. 2011).

Introduction

The bRG in the SVZ and to a lesser extent, in the intermediate zone, ﬁrst recognized using the Golgi method (Schmechel and Rakic 1979), have recently become further characterized by immunohistochemistry and time-lapse imaging (Fietz et al. 2010; Hansen et al. 2010; Garcia-Moreno et al. 2011; Kelava et al. 2011; Reillo et al. 2011) and subdivided into distinct cortical progenitor cell types, that have been progressively deﬁned through rapid advances in cellular imaging, lineage tracing, and molecular proﬁling (Fig. 1A). Until as recently as about 15 years ago, it was widely believed that all cortical neurons are produced from germinal cells around the ventricular surface of the dorsal telencephalon. This view was overturned ﬁrst by reports in the late 1990s that most (if not all) γ-aminobutyric acidergic (GABAergic) interneurons in
The newfound molecular and morphological understanding of the multiple neural precursor cell types in the developing neocortex has renewed efforts to assign individual roles to each type of proliferative cell. It is now clear that a substantial degree of amplification by bIPs and bRG during embryonic development increases the size of the cortical neuron population and that this secondary proliferation may be utilized to a greater extent in species with larger brains. In particular, studies have suggested that specialized proliferation in the IP and bRG populations can increase both cortical surface area and thickness and thereby underlie the high degree of gyriﬁcation in primates and carnivores (Martínez-Cerdeño et al. 2007; Reillo et al. 2011). However, it is also clear that regulation of antecedent precursors in the VZ, chieﬂy aRG, also play a large role in gyriﬁcation. For example, studies in mouse mutants indicate that overproliferation of VZ neural precursors, caused either by constitutive expression of β-catenin (Chenn and Walsh 2002) or by deletion of Caspase-9 (Kim et al. 1998), leads to an expanded neocortical wall with greater surface area displaying aberrant gyri and sulci in the normally lissencephalic mouse brain. In humans, activating mutations of the fibroblast growth factor receptor 3 (FGFR3) gene result in macrocephaly, with premature and exaggerated cortical gyriﬁcation, apparently due to expansion of the aRG population (Hevner 2005).

Previously, regulation of bIP proliferation has been proposed as a mechanism for cortical expansion due to the evidence showing that species with expanded telencephalon, such as ferret, monkey, and human, all display increases in the number of bIP cells in the SVZ (Martínez-Cerdeño et al. 2007).
However, the particular influence of bIPs on surface area is still a matter of debate since these cells are not connected to the apical or basal surfaces of the neocortical wall, and experimental evidence continues to implicate aRG in the control of cortical surface area and IPs in the control of laminar thickness (Pontious et al. 2008). Thus, neuronal output from the bIP population is likely to impact mainly cortical thickness rather than surface area.

More recently, the characterization of bRG in ferrets and humans (Fietz et al. 2010; Hansen et al. 2010; Reillo et al. 2011) as well as mice (Shitamukai et al. 2011; Wang et al. 2011) indicated a correlation between bRG abundance and gyrification. The proposed mechanism by which bRG modulate cortical surface area is by functioning as new radial units that are displaced from the ventricular surface and only tethered to the pial surface (Reillo et al. 2011). In addition, it was suggested that increased local proliferation of bRG would then add radial units and yield an expanded surface area of the cortex in that region relative to the ventricular area, potentially generating a gyrus or leading to expansion in a cortical area. This proposed link between bRG number and gyrification is now questioned by 2 new articles in this issue of *Cerebral Cortex* (Garcia-Moreno et al. 2011; Kelava et al. 2011). In addition, the uniqueness of the oSVZ to gyrencephalic species is also now countered.

**Basal Radial Glia Are Abundant in Lissencephalic Marmoset and Gyrencephalic Agouti**

Gyrencephaly is highly correlated with overall brain and body size, but not with phylogeny, as examples of lissencephalic and gyrencephalic brains can be found among most mammalian orders (Pillay and Manger 2007; Lui et al. 2011) including marsupials that separated from primate millions years before rodents. This suggests the possibility that rodent predecessors may have convolutions that have been lost in rats and mice, leading to a decrease in overall cortical but an increase olfactory system processing. In our own order, while most primates have large surface, gyrencephalic cortex, very small primates such as the bushbaby and the marmoset are lissencephalic. Conversely, most rodents have lissencephalic cortex, but larger rodents such as agouti and capybara are gyrencephalic.

In this issue of *Cerebral Cortex*, 2 new studies examine marmoset and agouti cortex to test for correlations between bRG abundance, oSVZ expansion, gyrencephaly, and phylogeny. The paper by Kelava et al. (2011) examined marmosets and found that, despite lissencephalic cortical morphology, bRG were observed with similar abundance in marmosets as in the developing human and ferret cortex. Furthermore, bRG were not restricted to the oSVZ but were equally abundant in the iSVZ. These findings indicate first that bRG proliferation is not sufficient to cause gyrencephaly and second that bRG are not restricted to the oSVZ. Accordingly, the authors propose that these progenitors should not be called “oSVZ progenitors” or “outer radial glia” as in some previous studies but instead propose the bRG nomenclature followed here. Also, from comparing the gyrification index of multiple primate species, the authors conclude that marmosets probably evolved from a gyrencephalic ancestral predecessor.

The paper by Garcia-Moreno et al. (2011) likewise studied marmosets, where results were very similar to those observed by Kelava et al. (2011). In addition, Garcia-Moreno et al. (2011) studied agouti, a rodent with a moderate degree of gyrencephal
and bRG clearly indicates that the decision to make a larger cortex, or subregions of cortex, is made early on by the neural stem cells in the VZ. This of course does not negate the evidence that proliferation in the SVZ plays an important role in generating neuronal diversity in the upper cortical layers, which increases during evolution.

Conclusions

Along with previous studies, the new papers in this issue of Cerebral Cortex provide important examples demonstrating that bRG abundance is not directly linked to gyrencephaly (Fig. 2). Therefore, other mechanisms of progenitor regulation must also be taken into account. For example, regional differences in the proliferation of bRG and IPs may contribute to the formation of gyri and sulci. It is now important to identify and characterize potential modulators of IP and bRG genesis, such as specific afferent innervation and to determine whether these factors operate in regions of the neuroepithelium underlying sites of gyri and sulci formation. It is also important to remember that the mechanisms leading to the formation of gyri may not necessarily be the inverse of those producing sulci. In other words, cortical sulcation may occur by mechanisms distinct from gyrification, including neuropil reduction or axonal tension. Thalamic innervation and intrinsic molecular programs in the ventricular neural progenitors are likely to also play coordinate roles in this process.

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References


