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Determinants of primate neurogenesis and the deployment of top-down generative networks in the cortical hierarchy

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What I cannot create I do not understand — Richard Feynman 1978

Because primate cortical development exhibits numerous specific features, the mouse is an imperfect model for human cortical development. Expansion of supragranular neurons is an evolutionary feature characterizing the primate cortex. Increased production of supragranular neurons is supported by a germinal zone innovation of the primate cortex: the Outer SubVentricular Zone, which along with supragranular neurons constitute privileged targets of primate brain-specific gene evolution. The resulting cell-type diversity of human supragranular neurons link cell and molecular evolutionary changes in progenitors with the emergence of distinctive architectural features in the primate cortex. We propose that these changes are required for the expansion of the primate cortical hierarchy deploying top-down generative networks with potentially important consequences for the neurobiology of human psychiatric disorders.

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Introduction

One might expect the question 'how do you build the structure that allows me to think', pertinent to understanding who we are and where we are going. Until recently the question was difficult to address because of the dominance of the mouse model for cortical development. Moreover, given the numerous observations that point to the specificity of human and non-human primate cortical neurogenesis it was uncertain how relevant the mouse development work would be to understanding the thinking human brain. However, the development of the primate cortex has made recently sufficient progress to pave the way for direct insight into the developmental underpinning of the cognitive architecture supporting higher cognitive functions.

The enlarged human and non-human primate neocortex contains a significantly greater number of neurons than that found in brains of equivalent size in other orders (rodents, cetaceans, ungulates) as well as a higher neuronal density [1].The six-layered primate cortex is characterized by a selective enlargement and complexification of the supragranular layer (SG) compartments, which culminate in human [2]. This specific expansion of SG neurons results in a massive increase in cortico-cortical connections that has no equivalent in other mammals. This expanded SG network is considered to underlie specific information processing features as well as highly developed computational abilities of the primate cortex.

Research into the neurogenesis of non-human primate cortex was pioneered by Pasko Rakic whose early work in the macaque visual system uncovered distinctive features in primate corticogenesis [3]. Pulse injections of tritiated thymidine allowed radioactive labeling of cortical progenitors in S-phase and identified neurons undergoing their final round of mitosis. This made it possible to examine the spatio-temporal dynamics of cortical layer and area formation [4]. This showed that compared to mouse, in addition to being prolonged, laminar neurogenesis in macaque is sharply demarcated, particularly in superficial layers 4, 3 and 2 [3]. Additional experiments using this technique showed that the cell-cycle in primate is considerably slower than in mouse, but that in both species, spatio-temporal regulation of the cell-cycle contributes to defining cortical cytoarchitecture [4].

The detailed description of the developing macaque neuroepithelium by Smart *et al.* revealed key features of primate cortical development [5]. One major salient feature is the development of the expanded subplate, a mainly transient structure located below the cortical plate. The magnitude of subplate expansion in macaque and even more so in human led to speculation that this transient structure participates in the formation of connectivity [6]. Given that the subplate plays a major role in

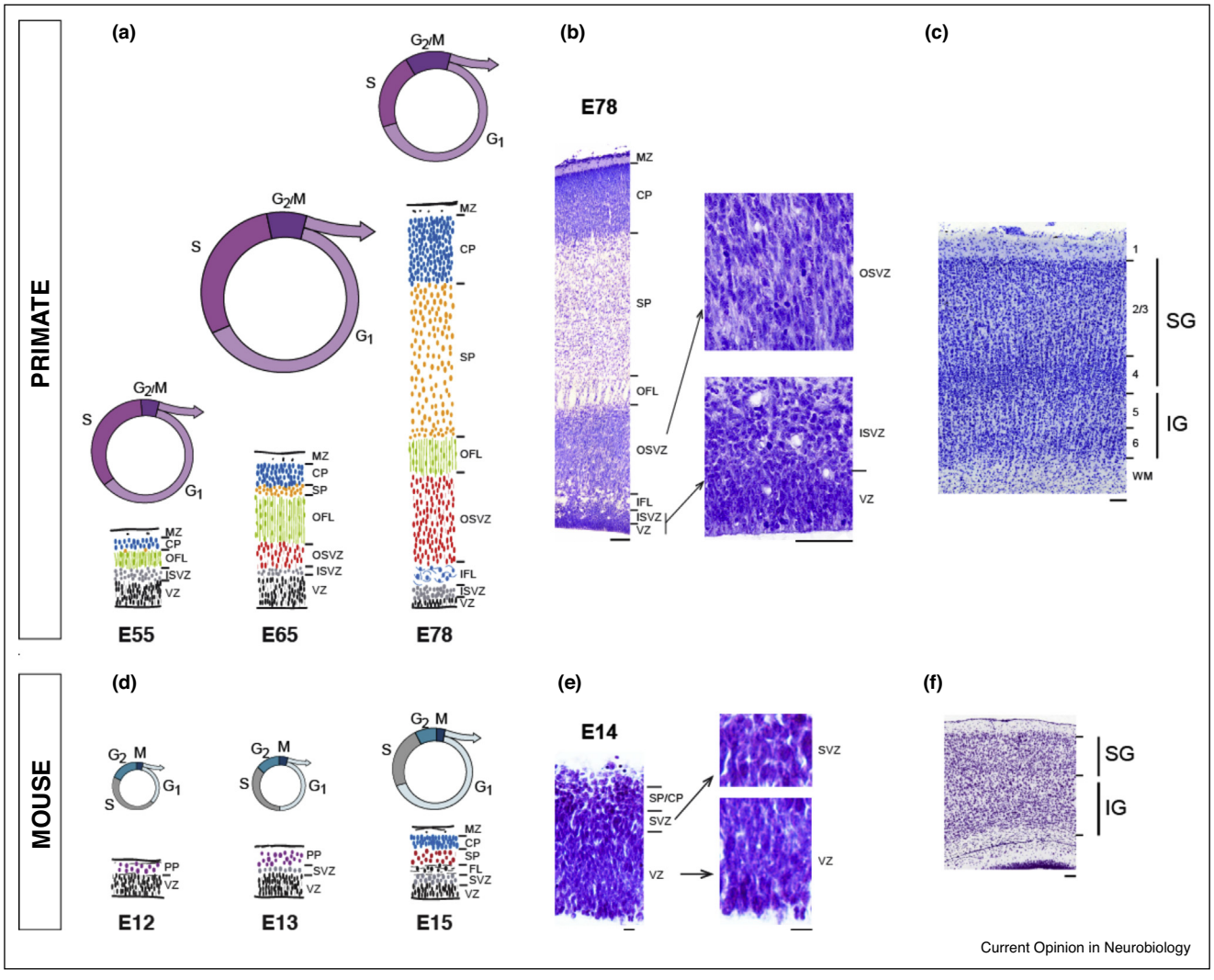
shaping the formation and plasticity of the thalamocortical pathway [7], its expansion likely reflects the increased importance of the thalamus in distributed control in primate cognition [8].

The second major salient primate-specific feature in the neuroepithelium highlighted by Smart *et al.* corresponded to a primate germinal zone (GZ) innovation: the outer subventricular zone (OSVZ) [5], which we argue below has had a major impact on human cortex structure and cognitive function.

The OSVZ: a uniquely structured and expanded germinal zone to build the primate cortex

The OSVZ of the primate is a complex structure defined by several morphological features (Figure 1a,b). The OSVZ originates from an expansion of the subventricular

Figure 1



Conspicuous anatomical features of the developing primate cortex, compared with the mouse.
(a),**(d)** Drawings of transects through presumptive Area 17 in the macaque (a) and dorsal cortex in the mouse (d) at key developmental stages. The thickness of each compartment is drawn to a common scale. In the monkey, E65 corresponds to the production of infragranular (IG) and E78 to that of supragranular (SG) layers. Cell-cycle duration (in purple) is shorter at E78 than at E65. This contrasts with the progressive lengthening of the cell-cycle in the mouse (in blue). Note, VZ decline and OSVZ expansion at the time of SG neuron production in the primate. The OSVZ is bordered apically by IFL, basally by OFL. **(b)**,**(e)** Higher-power views of the GZ in non-human primate (b) and mouse (e). (b) Note the radial organization of tissue and the presence of mitotic figures (upper panel). View of the ISVZ and VZ (lower panel). Note, presence of mitotic figures among the irregularly orientated nuclei of the ISVZ. In the VZ, nuclei are radially arranged and mitotic figures lie towards the ventricular surface, indicating ongoing interkinetic nuclear migration typical of the VZ. **(c)**,**(f)** Nissl stained sections of Area17 in the adult macaque and mouse cortices, respectively; note, the expanded SG layer in the primate. Scale bars: 100 μm ((b),(c),(f)); 10 μm (e). Abbreviations: Ventricular Zone (VZ); Subventricular Zone (SVZ); Inner SVZ (ISVZ); Outer SVZ (OSVZ); Inner Fibre Layer (IFL); Outer Fibre Layer (OFL); Subplate (SP); Cortical Plate (CP); Marginal Zone (MZ).

zone (SVZ) and is characterized by a highly compact and radial organization (Figure 1b). The cytoarchitecture of the OSVZ distinguishes it from a classically randomly organized SVZ that these authors referred to as an inner SVZ (ISVZ) [5]. The OSVZ in the occipital lobe is bounded by two conspicuous fiber layers that provide a complex microenvironment: the inner fiber layer (IFL) and the outer fiber layer (OFL). The OSVZ and ISVZ are separated by the IFL, which corresponds to corticofugal axons [9], while the OFL houses in-growing thalamocortical axons [5,10]. The existence of the OSVZ and ISVZ as distinct pools of basal progenitors has been subsequently confirmed in the human developing cortex [11–13]. While the presence of a dense, radially structured OSVZ is a hallmark of developing primate cortices [12–14], suggestions of a sparser basal progenitor layer GZ have been described in non-primates with large and/or convoluted cortices including large brained rodents [13,15,16].

In monkey and human, before the major phase of upper neuron production there is a rapid decline of the VZ accompanied by an expansion of the OSVZ [5,12] suggesting that the OSVZ is the principal source of SG neurons, subsequently confirmed by birthdating experiments [17]. The enlarged OSVZ therefore provides the infrastructure needed to build large primate cortices principally via contributions to the SG layers (Figure 1c). The mechanisms responsible for OSVZ expansion are linked to the high proliferative capacity of its progenitors via modulation of cell-cycle dynamics [17,18]. The mid-corticogenesis upsurge in symmetric proliferative divisions paralleled by a shortening of cell-cycle duration in OSVZ progenitors ensures the timely amplification of the SG neurons progenitor pool [18], responsible for augmented SG layers in primates [19]. The impact of cell-cycle regulation of OSVZ progenitors on SG neuron production has been experimentally demonstrated in the monkey occipital cortex [17].

Note that due to its structural features, the role of the OSVZ goes beyond that of generating increased SG neuron numbers. The radial morphology and organization of OSVZ progenitors ensures a scaffolding function previously attributed to radial glia [20]. This feature allows accommodating waves of postmitotic neurons that embark on radial migration, thereby ensuring the maintenance of topographic relationships between the GZ and the cortical plate as postulated by the radial unit hypothesis [21].

The OSVZ: a complex niche for proliferation of heterogeneous interconnected progenitors

The primate OSVZ is specifically enriched in locally produced ECM molecules self-providing the appropriate niche for sustained proliferation of its progenitors [13,22,23]. The large progenitor pool of the primate OSVZ, referred to collectively as basal Radial Glial cells (bRGs), is characterized by radial glial morphological features in a large fraction of progenitors (>75%) as well as by a striking heterogeneity [18,24]. Live imaging in macaque and human showed that morphological properties of the progenitors condition their proliferative behavior [18,24]; bRG morphotypes with higher number of processes exhibit increased rates of proliferation [18,24,25]. All OSVZ progenitor types are able to undergo proliferative symmetric divisions, as well as to self-renew and give rise directly to a neuron, albeit with distinctive behavioral signatures [18,26] (Figure 2a) (see Ref. [18] for a detailed description of the specific cellular features of OSVZ progenitors).

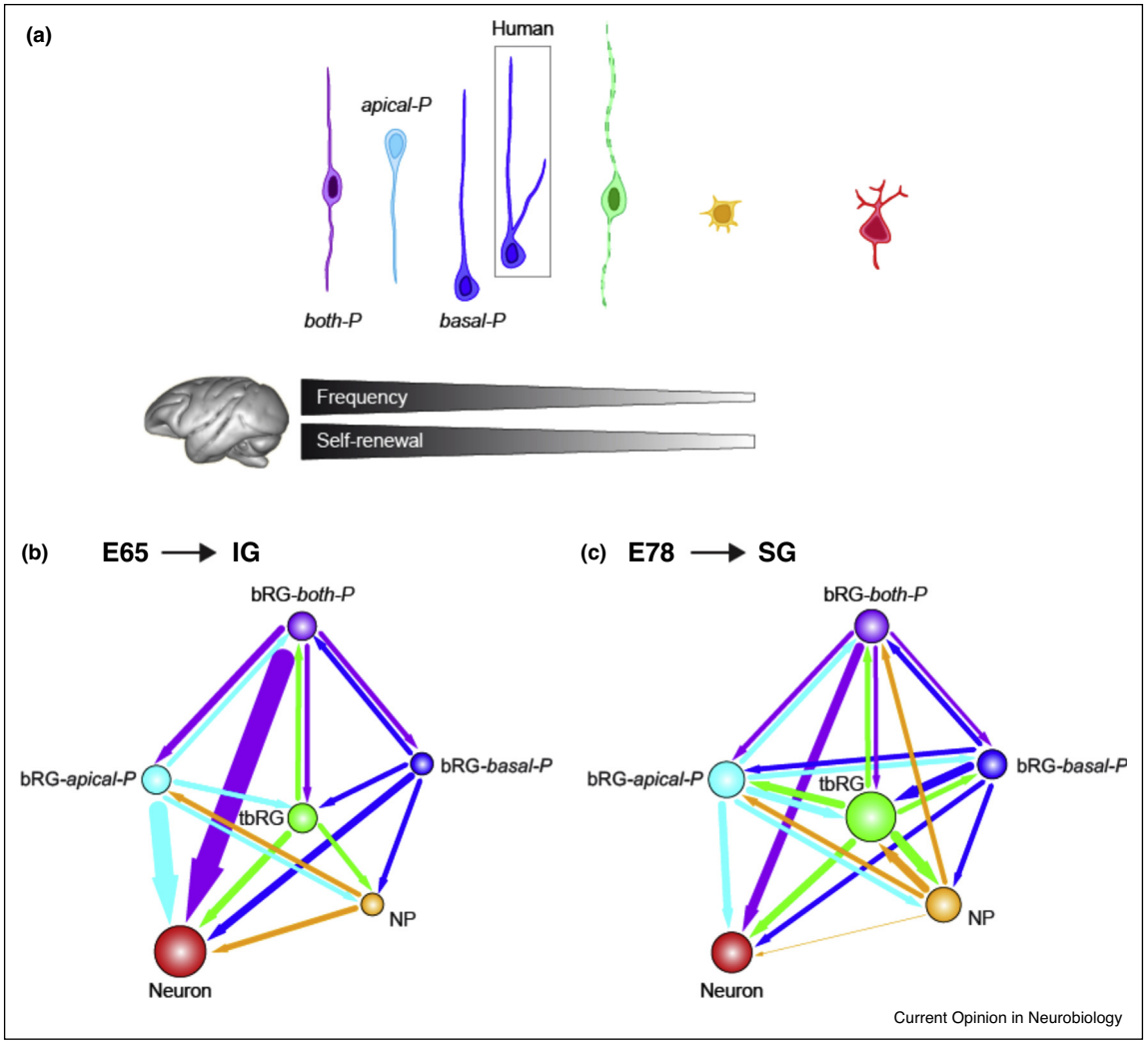
Real time imaging of embryonic macaque cortex reveals the highly dynamic behavior of the OSVZ progenitor radial processes, which it is hypothesized, provides the platform to integrate signals from VZ and ISVZ (via apical processes) as well as from postmitotic neurons in the subplate and cortical plate (via basal processes) [4,27,28]. In addition, the OSVZ progenitor proliferation dynamics are likely influenced by extrinsic signals relayed by thalamic fibers (OFL) which come into close proximity of the OSVZ in primates [5,10] (Figure 1a) or by axons from immature cortical neurons navigating in the IFL [9]. The integration of these local and extrinsic signals from the germinal and postmitotic microenvironments likely impact on cell-cycle and/or neurogenic rates [15,29].

Live imaging shows that primate SG neurons are generated through indirect neurogenesis, subsequent to numerous rounds of division and via complex, stochastic and non-hierarchical progenitor lineages, including bidirectional transitions [18]. The lineage relationships are temporally modulated, and show increased complexity in SG progenitors compared to infragranular (IG) neuron progenitors [18] (Figure 2b,c). Beyond their impact on the expansion of the progenitor pool, the local and extrinsic signals converging on the OSVZ could be pivotal in modulating the stochastic lineages via their influence on distinct transcriptional sequences in progenitors that will in turn determine postmitotic transcriptional programs generating SG neuronal diversity [30]. The spatiotemporal orchestration of these extracellular signals might therefore convey flexibility in the phenotypic fine-tuning of SG neurons during the protracted primate corticogenesis.

The OSVZ: a pivotal target for cortical evolution in the human/primate lineage

OSVZ progenitors are characterized by unique cellular features (*cf.* above) that converge to greatly increase their potential for amplification [18,31], suggesting they might have been the target of critical evolutionary changes in the primate lineage. MiRNAs as well as their target genes, show the fastest rates of human-specific evolutionary change [32], suggesting a potential key role in brain

Figure 2

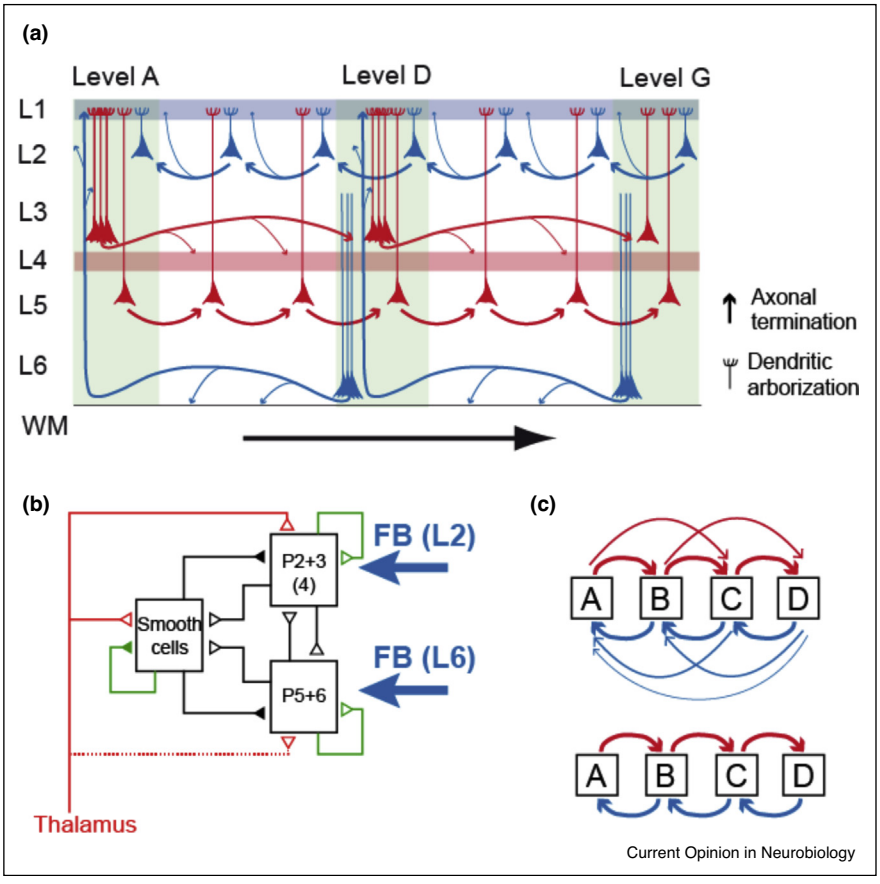


Heterogeneity of OSVZ progenitors morphotypes and lineages.
(a) OSVZ progenitors in the non human primate (macaque) include a prevalence of radially oriented progenitors bearing apical and/or basal processes. Non polarized progenitors (NP) are scarcer. Four bRGs cells identified in the macaque [18]: bipolar bRGs bearing a basal and apical process (both-P); bRGs bearing an apical process (apical-P), bRGs bearing a basal process (basal-P); bRGs exhibiting transient apical and/or basal processes (tbRGs). In human cortex, an additional type has been observed, which bears a bifurcated basal process [24]. Self-renewal abilities are increased in bipolar bRGs. **(b),(c)** State transition diagrams illustrating the lineage relationships in macaque OSVZ at E65 and E78 [18]. Nodes represent progenitor types (states) and directed edges the transitions between progenitors. Size of nodes is proportional to the frequency of each progenitor type with respect to the total numbers of precursors, thickness of the arrows indicates transition frequency with respect to the total number of transitions. The position of the nodes with respect to the vertical axis is determined by the mean rank of occurrence of each precursor type in the lineage trees. All transitions except neurogenic are bidirectional. Note the different topology of state transition diagrams for IG and SG neurons progenitors, indicating a higher complexity for SG progenitor lineages.

evolution. The monkey OSVZ is enriched in primate-specific miRNAs [33]. Some of these primate-specific miRNAs target cell-cycle genes, indicating that evolutionary novel regulatory elements control proliferation in OSVZ progenitors [33,34].

Recently, several primate and human-specific genes enriched in OSVZ progenitors have been identified. Their role in progenitor expansion and cortical architecture has been explored via forced expression in the mouse cortex [35–37]. The ectopic expression of these human specific genes increased progenitor proliferation and led to the emergence of OSVZ-like progenitors in the mouse embryonic cortex. This resulted in an increase in cortical thickness and neuron number. Of note, forced expression of the human specific duplicated gene ARHGAP11B led

Figure 3



Dual counterstream architecture of inter-areal pathways.
(a) Parent neurons in layer (L) 3 and L5 have feedforward (FF) projections (red) to higher order areas reciprocated by feedback (FB) projections (blue) in L2 and the L6. Simultaneous tracer injections in high and low areas show that the upper layer counterstream has near 100% segregation, that is, the FF (FB) neurons do not send axon collaterals to lower (higher) order areas. The L2 FB stream has a relatively restricted projection distances is thought to target L2 L1, L6 FB has longer projection distances, over short distances targeting lower layers and over long distances targeting upper layers including L1. Note that all layers except L6 have pyramidal cell with apical tufts in the predominant FB layer, L1. **(b)** The canonical microcircuit showing the two FB pathways targeting L2 and L6. Modified from Ref. [50], green arrows massive local within layer recurrent circuits; **(c)** The incorrectly assumed serial processing (lower) between areas that is not observed in the cortex, where instead each areas project to nearly all upper and lower stream areas (all to all). This configuration leads to a large increase in SG layer neurons with evolutionary increasing numbers of cortical areas. Adapted from Ref. [44••].

to different results in mouse [35] and ferret [38], likely reflecting species-specific differences in the capacity to accommodate experimentally increased numbers of progenitors and neurons. Boosting proliferation and inducing OSVZ-like progenitors in non-primate cortices does not address the physiological role of primate and human-specific genes in human brain expansion. This major caveat has been resolved in a recent study where ARHGAP11B was expressed in the cortex of the marmoset, a new world primate with a near-lissencephalic cortex [39••]. When expressed under the control of its own human promoter in transgenic marmosets, ARHGAP11B induced an expansion of the OSVZ as well as a selective increase in numbers of SG neurons. This was accompanied by an expansion and an increase in thickness of the cortex, as well as nascent gyrification. The ARHGAP11B mediated humanization of the marmoset fetal cortex unequivocally demonstrates the involvement of a human specific duplicated gene in the expansion of both OSVZ and consequently the SG layers.

A comprehensive study of the spatiotemporal dynamics of transcriptomic and epigenetic changes during human brain development has demonstrated the relationship between specific cell-type gene expression and epigenetic modifications, including methylation status and regulatory elements [40]. A recent study has highlighted that human evolved regulatory elements including HARs (human accelerated regions) and HEGs (human gained enhancers) target genes that are highly enriched in the

human OSVZ [41••]. Interestingly, these human specific regulatory elements also target SG genes [41••], adding to the observation that genes with human-specific expression pattern act preferentially in bRGs and SG neurons [42••].

Expansion of supragranular layers: the necessary substrate for an increasingly efficient information processing in the primate cortex

Cortical areas are interconnected by a dense network to form a highly distributed hierarchy containing multiple parallel streams spanning a dozen or so levels in primates. The long-distance connections between areas are stereotypically organized with respect to cortical layers; connections targeting layer 4 form feedforward (ascending) pathways, that are reciprocated by connections avoiding layer 4 forming feedback (descending) pathways (Figure 3). The ensemble of feedforward and feedback pathways defines a structural hierarchy, which in turn supports a functional hierarchy [43]. It is hypothesized that structural and functional hierarchies represent formal signatures of the integration of long-distance inputs into the local circuit (see Ref. [44••] for a more detailed description of hierarchical processing in the cortex).

The local circuit is made up of over 80% of the synapses in the cortex, which form recurrent circuits that amplify minute inputs from the 30 to 50 or so long-distance inputs to any given area [44••]. Modern theories of information processing in the cortex are largely centered on the nature of the interaction of feedforward and feedback pathways. Feedforward connections convey signals from the sensory periphery, while feedback connections constitute top-down generative networks that are thought to relay expectations from higher order areas. Recent anatomical studies have shown that feedforward and feedback connections form two separate counterstreams in the supra and infragranular compartments (dual counterstream architecture) [44••] (Figure 3). Predictive processing theory postulates that the interaction of these two pathways computationally defines the mismatch between the expectation and feedforward signal, thereby allowing the elaboration of a residual error signal, which constitutes the ascending message between hierarchical levels [45,46]. The reiteration of these processes across multiple levels is thought to allow the brain to actively infer the causes of sensory stimulus.

The major site of convergence of the feedforward and feedback pathways in both the upper and lower compartments, is in the supragranular layers [44••], which are hypothesized to house a rich repertoire of cells including expectation units, error units encoding the magnitude of the mismatch of interactions as well as modulatory precision units [47]. Feedforward and feedback connections of a given area target a great many of the upstream and downstream targets [44••]. The large increase in the number of cortical areas as one goes up the phylogenetic series, suggests a parallel increase in the numbers and complexity of the circuits implementing the interactions pathways between feedforward and feedback pathways.

Conclusion and perspectives

Our hypothesis is that implementation of predictive processing in the cortex entails that the observed evolutionary increase in the number of cortical areas in the human brain would require the expansion of the numbers of SG neurons. Recent studies comparing glutamatergic cell-types in the SG layers of mouse and human show that these quantitative differences are accompanied by qualitative cellular changes [48••]. Using a patch-seq platform to morphologically and physiologically characterize transcriptionally defined human glutamatergic cell types, these authors showed that SG neuron types in human cortex are much more phenotypically diverse than in rodent. These findings therefore support that the evolutionary expansion of the SG layers of the cortex is accompanied by an increase in the sophistication of its circuits, which as we develop below is in accordance with the interpretation of psychiatric disorders in terms of predictive processing theory.

The top-down generative networks are thought to relay expectations based on prior beliefs concerning the causes of sensory data. Interaction of the top-down network with ascending connections from the sensory periphery allows updating of prior beliefs to become posterior beliefs. Computational theories of brain function that posit inference as the process of forming beliefs are cast in a Bayesian framework and map well to the physiology and anatomy of hierarchy [49•]. The emerging field of computational psychiatry explores the interpretation of neuropsychiatric disorders in terms of false beliefs, where Bayesian computational neuropsychology map particular syndromes to abnormal priors and neurobiological origins [49•]. One likely cause of abnormal interactions of the ascending and descending pathways are the cellular elements implementing processing coding which are expected to be in the SG layers [47]. This suggests that the unique functions of human specific cortical neuron types might have to be sought in developmentally humanized animal models. The fact that SG neuron types show considerably more heterogeneity in primate compared to mouse, might go some way to explain the failure of the mouse model in drug development for neuropsychiatric disorders. As the integration of the different cell types into the local microcircuit becomes elucidated, via the exploration of humanized animal models, so will our knowledge of the implementation of predictive coding and its failure in brain pathologies.

Conflict of interest statement

Nothing declared.

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