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How the prefrontal executive got its stripes

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Summary

Pathways from cortical and subcortical structures give the prefrontal cortex a panoramic view of the sensory environment and the internal milieu of motives and drives. The prefrontal cortex also receives privileged information from the output of the basal ganglia and cerebellum and innervates widely the inhibitory thalamic reticular nucleus that gates thalamo-cortical communication. Connections, in general, are strongly related to the systematic structural variation of the cortex that can be traced to development. Insights from development have profound implications for the special connections of the prefrontal cortex for executive control, learning and memory, and vulnerability in psychiatric and neurologic diseases.

Introduction

One of the most striking features of the prefrontal cortex (PFC) in primates is the wealth of its connections, known even before the introduction of neural tracers that facilitated their study [1, 2]. The rich information is needed for the prefrontal executive to assess what is relevant for the task at hand, disregard signals that are not momentarily essential and abstract rules for goal-directed behavior [3–6]. But other brain structures have diverse connections as well, such as high-order association areas and the basal ganglia. What makes the prefrontal cortex special, if it is special? We provide an overview of principal connections of key prefrontal areas that illustrate their specialization and complementary contributions to executive function. These connections are most parsimoniously understood within the framework of systematic structural variation of the cortical mantle which can be traced to development. The consistent relationship of connections to systematic cortical variation raises the question of whether the timing of development of brain structures favors connections that give prefrontal areas an edge in executive functions.

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Systematic structural variation of the cortex and relationship to connections

Systematic structural variation refers to the gradual changes seen in laminar structure in all cortical systems, whether they are sensory, motor/premotor or prefrontal. Each cortical system, regardless of its placement on the cortical mantle, is composed of areas that at one extreme have fewer than six layers (limbic areas), leading to adjacent areas that have six layers (eulaminate) and finally to eulaminate areas with the best delineated layers. Changes in laminar structure are accompanied by differences in cellular features across areas. These changes are exemplified by a higher density of spines and dendritic branching in pyramidal neurons in limbic than in eulaminate areas [7*,8*,9], a lower myelin density in limbic than in eulaminate areas, and other structural features [10–12]. For most areas of the cortical mantle the structural status of an area can be quantitatively approximated by neuron density (e.g., [10, 13, 14]), especially in the upper layers, which is lower in limbic than in eulaminate areas [15].

The large extent of the prefrontal cortex includes lateral, orbitofrontal, and medial sectors. The PFC shows systematic variation as other cortical systems [15]. Thus, while the dorsolateral PFC (DLPFC) has six well-delineated layers, epitomized by the term ‘frontal granular cortex’ [16], the posterior medial sector of the anterior cingulate cortex (ACC) and the posterior orbitofrontal cortex (pOFC) either lack layer 4 (L4) (agranular) or have a poorly formed L4 (dysgranular) and poor distinction of layers (Fig. 1). Collectively, we call areas of the ACC and pOFC limbic areas, a term also used for areas in other cortical regions that fit this description [17*]. Anterior areas of the medial and orbitofrontal regions are composed of eulaminate areas whose laminar organization is in between the ACC and pOFC and areas of the lateral surface.

The DLPFC is associated with cognitive operations [4]. On the other hand, the ACC and pOFC are associated with motives, drives and emotions. The position of prefrontal areas within the systematic variation of the prefrontal region best describes their connections and ultimately functions [17*]. This principle can be illustrated by the visual cortical connections of DLPFC and pOFC, which differ systematically by their laminar status. Thus, caudal DLPFC receives projections from earlier-processing occipital and temporal visual cortices than the pOFC, whose projections arise from later-processing inferior temporal cortices [17*]. The earlier processing visual association cortices that project to caudal DLPFC have well-delineated laminar structure, which is more elaborate than the later-processing inferior temporal cortices that project to pOFC. These connections thus occur mostly between areas that have comparable laminar status within the respective prefrontal and visual cortical systems. The visual areas that give rise to the prefrontal projections are also functionally distinct: Earlier-processing visual cortices have small receptive fields and process the fine features of sensory stimuli. In contrast, later-processing inferior temporal areas process more holistic aspects of the visual environment. Similar relationships are seen for the connections of DLPFC and pOFC with auditory and somatosensory association cortices [17*, 18, 19].

The structurally distinct prefrontal areas differ in another important way: in the laminar origin and termination of their cortical connections. Studies in sensory areas first showed that pathways from primary areas originate in L3 and innervate the middle layers (mostly L4) of later-processing sensory areas. Pathways follow this ‘feedforward’ pattern through higher and higher-order sensory association cortices. But for each connection, reciprocal ‘feedback’ pathways originate from the deep layers (L5 and L6) of later-processing areas and innervate the upper layers (mostly L1) of earlier-processing areas [20]. Implicit in the ‘feedforward’ and ‘feedback’ names is the idea that they reflect the flow of information in sensory systems [20]. As classically described, thalamic sensory relay nuclei innervate L4 of the primary sensory cortices, while the deep cortical layers (mostly L6 but also L5) project back to the thalamus [21]. Feedforward thus refers to pathways that follow signals from the sensory periphery to primary areas and beyond, and feedback refers to pathways that follow a countercurrent route.

The structural model for connections

Similar connection patterns are seen throughout the cortex, including areas that are not primarily sensory (e.g., [22, 23**]). Moreover, most connections considered to fit a ‘feedforward’ or ‘feedback’ pattern are variably distributed within layers, suggesting a graded pattern. What underlies the intriguing regularity of cortical connections? We have shown that the graded laminar pattern of connections is closely associated with the systematic structural variation of the cortex, as depicted for the prefrontal system in Figures 1 and 2. We have called the relationship of connections to the systematic variation of the cortex ‘the structural model for connections’ [22]. Thus, for any pair of linked cortices — whether they are neighbors or not — their interconnections reflect their structural relationship. Accordingly, feedforward describes connections from an area with more elaborate laminar structure, which terminate in an area with less elaborate structure (Fig. 1A–C: from a lighter to a darker grey/black shade; Fig. 2A, blue neurons). Feedback describes connections that have the opposite relationship (Fig. 2A, brown neurons). The laminar distribution of connections reflects the magnitude of their structural differences. Extreme ‘feedforward’ and ‘feedback’ patterns are seen between areas that vary substantially in laminar structure (neuron density) (Fig. 2A), but are not common [24**]. Most connections occur between areas that show small differences in overall structure and thus involve more layers [22] (Fig. 2B).

Prefrontal connections with the thalamus—Connections with the thalamus can be similarly understood. Prefrontal connections with the thalamus always include the mediodorsal (MD) nucleus. But prefrontal areas receive thalamic input from other nuclei as well, including the medial pulvinar, midline, anterior ventral and intralaminar nuclei. The most distributed thalamic connections involve the pOFC and ACC. By contrast, the eulaminar DLPFC has comparatively more restricted thalamic connections which emanate mostly from MD and fewer arise from other nuclei [25]. The terminations of thalamic connections in prefrontal cortices parallel the cortico-cortical. Thus, while MD innervates mostly the middle layers of PFC and sparsely L1 [26], other thalamic nuclei innervate strongly other layers as well, including expansive stretches of L1, L2 and upper L3 [21, 27].

Neurons from thalamic nuclei that innervate L4 are distinct neurochemically and functionally from those that innervate the upper layers [28–30].

PFC connections associated with the internal milieu—Information from the external (sensory) environment is only part of the input to PFC. Decisions and actions are intricately linked to the wishes and motives of individuals. And when it comes to detail and specificity of information from the internal environment, it is the pOFC and ACC areas that are specialized. This specialization is exemplified in the strong and uniquely bidirectional connections of both ACC and pOFC with the amygdala and the hypothalamus, which are associated with the internal milieu [31–34].

The DLPFC uses information to abstract rules for goal-directed behavior [5, 35]. In this context, information from the internal environment must also reach the DLPFC. The systematic cortical variation within the PFC provides a circuit mechanism for this process. Thus, signals from the internal environment reach preferentially the pOFC and ACC, which project to eulaminar areas in a feedback pattern by virtue of their simpler laminar structure (Fig. 2C). The densest pathways from pOFC and ACC are with the neighboring anterior orbital and medial areas [15] (eulaminar I in Fig. 2C). Through sequential pathways from pOFC and ACC, signals ultimately reach the best laminated posterior DLPFC areas, reflecting the sequential changes in laminar structure and connections in the prefrontal system [12, 15] (Fig. 2C). This predominant feedback pattern of transmission is the opposite of the sequential ‘feedforward’ pathways from early- to later-processing sensory areas, and resembles the sequence of information processing in the premotor/motor systems reported in classical and modern studies [36, 37]. Comparable transmission in the motor and emotional systems may not be surprising since both imply internally initiated action.

Evidence of the functional significance of the laminar pattern of connections emerged from recording of activity across layers in the temporal cortex in monkeys engaged in learning and remembering associations between visual stimuli. During retrieval of the mnemonic component of the task, signals flowed in a feedback laminar pattern from a dysgranular limbic area (perirhinal area 36) to eulaminar visual association area TE [38]. In contrast, registration of the sensory cue in the task followed an interlaminar feedforward pattern from eulaminar area TE to dysgranular area 36 [38].

The PFC has special connections

The rules of the structural model thus provide the circuit mechanism for relaying signals to DLPFC from the external environment through feedforward pathways from sensory association cortices, and from the internal environment through sequential feedback pathways from pOFC and ACC. Importantly, the PFC differs from other areas by receiving privileged information from the entire cortex through the output of two major structures: the basal ganglia and the cerebellum (Fig. 2D, E). These large structures receive massive projections from the entire cortex but their specialized output for sequencing information [39–43] is directed to only a few thalamic nuclei, including the ventral anterior and MD, which project strongly to PFC [40, 41, 44].

Specific areas of the caudal DLPFC, the pOFC, and the amygdala, also project widely to the entirely inhibitory thalamic reticular nucleus (TRN), which gates thalamo-cortical communication. These pathways — which innervate mostly the frontal sector of TRN — remarkably also extend to the sensory sectors of TRN [45, 46]. These widespread pathways to TRN provide a circuit mechanism for the prefrontal executive to focus on relevant stimuli and eliminate distracters early in neural processing [45, 47], and within the context of motives and emotions that drive actions [46].

Systematic structural variation of the cortex has its roots in development

In view of its significance for connections, how does cortical systematic variation arise? We previously suggested that differences in cortical laminar architecture may be explained by differences in the timing of development of different prefrontal areas [10]. Moreover, the timing must vary in a specific way. Because limbic areas have a lower density of neurons than eulaminate areas, especially in the upper layers (Fig. 1D–G) [15], we hypothesized that they must have a shorter developmental period than eulaminate areas [10]. And because the cortex develops from inside-out (deep layers develop first [48]), a shorter developmental period would render the late-developing upper layers less populated in limbic areas, as seen in pOFC and ACC areas [10]. This hypothesis is consistent with available developmental data in primates: limbic areas complete their development first, whereas the best laminated area 17 (which also has the highest density of neurons in the primate cortex [24**, 49]), has the longest period of development [50–53].

In this context, the primate subventricular zone (SVZ) of the developing cortex is more complex than in the rodent, and can be subdivided into an inner (ISVZ) and outer (OSVZ) zone [54–57]. These specializations of the primate cortex vary significantly across prospective cortical areas (Fig. 3). In the developing human embryo, prospective limbic paracingular and parainsular regions undergo fewer mitoses than prospective eulaminate areas, due mostly to higher proliferative activity in the OSVZ in prospective eulaminate areas [57]. As shown in Figure 3, the OSVZ is very small below prospective limbic areas, whereas it dominates below prospective eulaminate areas. The thickness and cell density of the OSVZ — which gives rise to neurons mostly in the upper layers — increases progressively from prospective limbic to prospective eulaminate cortices. As development progresses, in the cortical plate of prospective limbic areas neuron density is lower and maturation is more advanced than in eulaminate areas (Fig. 4). These novel observations provide evidence that the systematic variation in the cortex can be traced to development.

The systematic structural variation of the cerebral cortex in primates has significant implications for function because it is linked to the topography, pattern, strength and even absence of connections, as shown by analyses of extensive databases of the cortical visual connectome [24**]. Distinct genes may initiate development across cortices, but as areas develop sequentially self-organization may lead to the remarkably predictable patterns of connections. The distribution of functionally distinct types of inhibitory neurons also differs across cortices, as seen in the primate PFC and other regions [10]. Superimposing connections onto gradients of functionally distinct inhibitory neurons can provide a powerful model to investigate dynamic transitions in brain states. Cortical structural transitions may

thus underlie functional transitions and the dynamic recruitment of areas in behavior, as described in the literature [58, 59, 60*, 61, 62*, 63–66].

Conclusions

Viewing connections within the structural model that is based on the systematic variation of the cortex helps explain their exquisite regularity in topography, strength, and laminar distribution. The challenge in future work is to fill the gap of developmental data for most areas in primates. This information is needed to investigate whether the timing or proximity during development may have provided the PFC with connections that other areas lack. Our prediction that limbic areas have a shorter and earlier period of development than eulaminate prefrontal areas [10] is supported by empirical data [53]. Consequently, limbic areas may have a competitive advantage to connect widely with a variety of subcortical structures (Fig. 2C) which develop before the cortex [67]. The feedback mode of connection of limbic cortices is also consistent with their early development, as is their termination in L1, a layer that is present in all areas at the onset of neurogenesis [68, 69**]. The pOFC and ACC may convey signals on the status of the internal environment to DLPFC through feedback pathways, as depicted in Figure 2C, in a pattern predicted by the structural model for connections. Privileged information about the status of the entire external and internal environments also reaches the PFC from the output of the basal ganglia and the cerebellum. Widespread projections from some PFC areas, the thalamic MD, and the amygdala innervate the thalamic TRN and may allow early selection of relevant signals for goal-directed decision and action. Tracing the systematic structural variation of the cortex to the timing of development has significant implications for brain organization and connections and opens the door to probe why some areas are mutable and suitable for learning and memory but also vulnerable to neurologic and psychiatric diseases.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

* Of special interest

** Of outstanding interest

1. Pandya DN, Kuypers HGJM. Cortico-cortical connections in the rhesus monkey. *Brain Res.* 1969; 13:13–36. [PubMed: 4185124]
2. Jones EG, Powell TPS. An anatomical study of converging sensory pathways within the cerebral cortex of the monkey. *Brain.* 1970; 93:793–820. [PubMed: 4992433]
3. Goldman-Rakic PS. Topography of cognition: Parallel distributed networks in primate association cortex. *Annu Rev Neurosci.* 1988; 11:137–156. [PubMed: 3284439]
4. Fuster, JM. *The prefrontal cortex.* 4th. London (UK): Elsevier/Academic Press; 2008.
5. Miller EK, Freedman DJ, Wallis JD. The prefrontal cortex: categories, concepts and cognition. *Philos Trans R Soc Lond B Biol Sci.* 2002; 357:1123–1136. [PubMed: 12217179]

6. Funahashi S, Kubota K. Working memory and prefrontal cortex. *Neurosci Res.* 1994; 21:1–11. [PubMed: 7708289]
7. Sasaki T, Aoi H, Oga T, Fujita I, Ichinohe N. Postnatal development of dendritic structure of layer III pyramidal neurons in the medial prefrontal cortex of marmoset. *Brain Struct Funct.* 2015; 220:3245–3258. [PubMed: 25064470] ** The authors describe systematic variation in dendritic structure of pyramidal neurons across cortices that includes limbic and eulaminate medial prefrontal areas in a primate brain. The relationship of these features to the placement of the cortical areas within the systematic variation of the cortex is evident.
8. Elston GN, Fujita I. Pyramidal cell development: postnatal spinogenesis, dendritic growth, axon growth, and electrophysiology. *Front Neuroanat.* 2014; 8:78. [PubMed: 25161611] * This review summarizes the major advances in the last fifteen years in dendritic structure, dendritic development, spine density and spinogenesis across cortices of the primate brain.
9. Amatruddo JM, Weaver CM, Crimins JL, Hof PR, Rosene DL, Luebke JI. Influence of highly distinctive structural properties on the excitability of pyramidal neurons in monkey visual and prefrontal cortices. *J Neurosci.* 2012; 32:13644–13660. [PubMed: 23035077]
10. Dombrowski SM, Hilgetag CC, Barbas H. Quantitative architecture distinguishes prefrontal cortical systems in the rhesus monkey. *Cereb Cortex.* 2001; 11:975–988. [PubMed: 11549620]
11. García-Cabezas MA, Barbas H. Area 4 has layer IV in adult primates. *Eur J Neurosci.* 2014; 39:1824–1834. [PubMed: 24735460]
12. Mackey S, Petrides M. Architecture and morphology of the human ventromedial prefrontal cortex. *Eur J Neurosci.* 2014; 40:2777–2796. [PubMed: 25123211]
13. Collins CE, Airey DC, Young NA, Leitch DB, Kaas JH. Neuron densities vary across and within cortical areas in primates. *Proc Natl Acad Sci U S A.* 2010; 107:15927–15932. [PubMed: 20798050]
14. Charvet CJ, Cahalane DJ, Finlay BL. Systematic, cross-cortex variation in neuron numbers in rodents and primates. *Cereb Cortex.* 2015; 25:147–160. [PubMed: 23960207]
15. Barbas H, Pandya DN. Architecture and intrinsic connections of the prefrontal cortex in the rhesus monkey. *J Comp Neurol.* 1989; 286:353–375. [PubMed: 2768563]
16. Warren, JM.; Akert, K. *The Frontal Granular Cortex and Behavior.* New York: McGraw-Hill; 1964.
17. Barbas H. General Cortical and special Prefrontal Connections: Principles from Structure to Function. *Annu Rev Neurosci.* 2015; 38:269–289. [PubMed: 25897871] * Review of the rules of the structural model and more detailed connections of the prefrontal cortex, including the interface of pathways with distinct classes of inhibitory neurons in primates and some comparison with rodents.
18. Plakke B, Romanski LM. Auditory connections and functions of prefrontal cortex. *Front Neurosci.* 2014; 8:199. [PubMed: 25100931]
19. Medalla M, Barbas H. Specialized prefrontal "auditory fields": organization of primate prefrontal-temporal pathways. *Front Neurosci.* 2014; 8:77. [PubMed: 24795553]
20. Felleman DJ, Van Essen DC. Distributed hierarchical processing in the primate cerebral cortex. *Cereb Cortex.* 1991; 1:1–47. [PubMed: 1822724]
21. Jones, EG. *The Thalamus.* New York: Cambridge University Press; 2007.
22. Barbas H, Rempel-Clower N. Cortical structure predicts the pattern of corticocortical connections. *Cereb Cortex.* 1997; 7:635–646. [PubMed: 9373019]
23. Goulas A, Uylings HB, Stiers P. Mapping the hierarchical layout of the structural network of the macaque prefrontal cortex. *Cereb Cortex.* 2014; 24:1178–1194. [PubMed: 23258344] ** Comparison of hierarchical models within the prefrontal cortex in primates. The authors test a hierarchical model reported in the literature, which was based on functional and structural imaging in humans, and the structural model based on tract tracing data in the macaque cortex obtained from a large public database.
24. Hilgetag CC, Medalla M, Beul S, Barbas H. The primate connectome in context: principles of connections of the cortical visual system. *NeuroImage.* 2016; 134:685–702. [PubMed: 27083526] ** This paper is based on analyses of four extensive databases on visual cortical connections in macaques to test the predictive power of models of the organization of connections. The findings

indicate that the structural model consistently and most parsimoniously helps explain the existence as well as absence, strength and laminar distribution of visual cortical connections.

25. Dermon CR, Barbas H. Contralateral thalamic projections predominantly reach transitional cortices in the rhesus monkey. *J Comp Neurol.* 1994; 344:508–531. [PubMed: 7523458]
26. Giguere M, Goldman-Rakic PS. Mediodorsal nucleus: Areal, laminar, and tangential distribution of afferents and efferents in the frontal lobe of rhesus monkeys. *J Comp Neurol.* 1988; 277:195–213. [PubMed: 2466057]
27. McFarland NR, Haber SN. Thalamic relay nuclei of the basal ganglia form both reciprocal and nonreciprocal cortical connections, linking multiple frontal cortical areas. *J Neurosci.* 2002; 22:8117–8132. [PubMed: 12223566]
28. Jones EG. Viewpoint: the core and matrix of thalamic organization. *Neuroscience.* 1998; 85:331–345. [PubMed: 9622234]
29. Timbie C, Barbas H. Pathways for emotions: Specializations in the amygdalar, mediodorsal thalamic, and posterior orbitofrontal network. *J Neurosci.* 2015; 35:11976–11987. [PubMed: 26311778]
30. Mitchell AS, Sherman SM, Sommer MA, Mair RG, Vertes RP, Chudasama Y. Advances in understanding mechanisms of thalamic relays in cognition and behavior. *J Neurosci.* 2014; 34:15340–15346. [PubMed: 25392501]
31. Rempel-Clower NL, Barbas H. Topographic organization of connections between the hypothalamus and prefrontal cortex in the rhesus monkey. *J Comp Neurol.* 1998; 398:393–419. [PubMed: 9714151]
32. Ghashghaie HT, Hilgetag CC, Barbas H. Sequence of information processing for emotions based on the anatomic dialogue between prefrontal cortex and amygdala. *NeuroImage.* 2007; 34:905–923. [PubMed: 17126037]
33. Kim MJ, Loucks RA, Palmer AL, Brown AC, Solomon KM, Marchante AN, Whalen PJ. The structural and functional connectivity of the amygdala: from normal emotion to pathological anxiety. *Behav Brain Res.* 2011; 223:403–410. [PubMed: 21536077]
34. Ongur D, An X, Price JL. Prefrontal cortical projections to the hypothalamus in macaque monkeys. *J Comp Neurol.* 1998; 401:480–505. [PubMed: 9826274]
35. Fuster JM. Executive frontal functions. *Exp Brain Res.* 2000; 133:66–70. [PubMed: 10933211]
36. Penfield, W. Clinical observations on epileptic mechanisms. In: Penfield, W.; Jasper, H., editors. *Epilepsy and the functional anatomy of the human brain.* Little, Brown and Company; 1954.
37. Tucker DM, Brown M, Luu P, Holmes MD. Discharges in ventromedial frontal cortex during absence spells. *Epilepsy Behav.* 2007; 11:546–557. [PubMed: 17728188]
38. Takeuchi D, Hirabayashi T, Tamura K, Miyashita Y. Reversal of interlaminar signal between sensory and memory processing in monkey temporal cortex. *Science.* 2011; 331:1443–1447. [PubMed: 21415353]
39. Leiner HC. Solving the mystery of the human cerebellum. *Neuropsychol Rev.* 2010; 20:229–235. [PubMed: 20809199]
40. Stoodley CJ, Schmahmann JD. Evidence for topographic organization in the cerebellum of motor control versus cognitive and affective processing. *Cortex.* 2010; 46:831–844. [PubMed: 20152963]
41. Haber S, McFarland NR. The place of the thalamus in frontal cortical-basal ganglia circuits. *Neuroscientist.* 2001; 7:315–324. [PubMed: 11488397]
42. Groenewegen HJ. The basal ganglia and motor control. *Neural Plast.* 2003; 10:107–120. [PubMed: 14640312]
43. Strick PL, Dum RP, Fiez JA. Cerebellum and nonmotor function. *Annu Rev Neurosci.* 2009; 32:413–434. [PubMed: 19555291]
44. Barbas H, García-Cabezas MA, Zikopoulos B. Frontal-thalamic circuits associated with language. *Brain Lang.* 2013; 126:49–61. [PubMed: 23211411]
45. Zikopoulos B, Barbas H. Pathways for emotions and attention converge on the thalamic reticular nucleus in primates. *J Neurosci.* 2012; 32:5338–5350. [PubMed: 22496579]

46. John YJ, Zikopoulos B, Bullock D, Barbas H. The emotional gatekeeper: A computational model of attentional selection and suppression through the pathway from the amygdala to the thalamic reticular nucleus. *PLoS Comput Biol.* 2016; 12:e1004722. [PubMed: 26828203]
47. Zikopoulos B, Barbas H. Circuits for multisensory integration and attentional modulation through the prefrontal cortex and the thalamic reticular nucleus in primates. *Rev Neurosci.* 2007; 18:417–438. [PubMed: 18330211]
48. Sidman RL, Rakic P. Neuronal migration, with special reference to developing human brain: a review. *Brain Res.* 1973; 62:1–35. [PubMed: 4203033]
49. O'Kusky J, Colonnier M. A laminar analysis of the number of neurons, glia, and synapses in the visual cortex (area 17) of adult macaque monkeys. *J Comp Neurol.* 1982; 210:278–290. [PubMed: 7142443]
50. Granger B, Teklaia F, Le Sourd AM, Rakic P, Bourgeois JP. Tempo of neurogenesis and synaptogenesis in the primate cingulate mesocortex: comparison with the neocortex. *J Comp Neurol.* 1995; 360:363–376. [PubMed: 8522653]
51. Rakic P, Nowakowski RS. The time of origin of neurons in the hippocampal region of the rhesus monkey. *J Comp Neurol.* 1981; 196:99–128. [PubMed: 7204668]
52. Rakic P. Differences in the time of origin and in eventual distribution of neurons in areas 17 and 18 of visual cortex in rhesus monkey. *Exp Brain Res Suppl.* 1976; 1:244–248.
53. Rakic P. Neurogenesis in adult primate neocortex: an evaluation of the evidence. *Nat Rev Neurosci.* 2002; 3:65–71. [PubMed: 11823806]
54. Smart IH, Dehay C, Giroud P, Berland M, Kennedy H. Unique morphological features of the proliferative zones and postmitotic compartments of the neural epithelium giving rise to striate and extrastriate cortex in the monkey. *Cereb Cortex.* 2002; 12:37–53. [PubMed: 11734531]
55. Fietz SA, Kelava I, Vogt J, Wilsch-Brauninger M, Stenzel D, Fish JL, Corbeil D, Riehn A, Distler W, Nitsch R, et al. OSVZ progenitors of human and ferret neocortex are epithelial-like and expand by integrin signaling. *Nat Neurosci.* 2010; 13:690–699. [PubMed: 20436478]
56. Hansen DV, Lui JH, Parker PR, Kriegstein AR. Neurogenic radial glia in the outer subventricular zone of human neocortex. *Nature.* 2010; 464:554–561. [PubMed: 20154730]
57. Reillo I, Romero CD, García-Cabezas MA, Borrell V. A Role for Intermediate Radial Glia in the Tangential Expansion of the Mammalian Cerebral Cortex. *Cereb Cortex.* 2011; 21:1674–1694. [PubMed: 21127018]
58. Friston K. A theory of cortical responses. *Philos Trans R Soc Lond B Biol Sci.* 2005; 360:815–836. [PubMed: 15937014]
59. Tognoli E, Kelso JA. The metastable brain. *Neuron.* 2014; 81:35–48. [PubMed: 24411730]
60. Chanes L, Barrett LF. Redefining the Role of Limbic Areas in Cortical Processing. *Trends Cogn Sci.* 2016; 20:96–106. [PubMed: 26704857] * This paper integrates principles from predictive coding and the structural model in the study of corticocortical connections. The authors suggest that predictions flow from limbic to eulaminar areas and prediction errors flow in the opposite direction.
61. Vogels TP, Rajan K, Abbott LF. Neural network dynamics. *Annu Rev Neurosci.* 2005; 28:357–376. [PubMed: 16022600]
62. Murray JD, Bernacchia A, Freedman DJ, Romo R, Wallis JD, Cai X, Padoa-Schioppa C, Pasternak T, Seo H, Lee D, et al. A hierarchy of intrinsic timescales across primate cortex. *Nat Neurosci.* 2014; 17:1661–1663. [PubMed: 25383900] * Timescales obtained from physiological databases show intrinsic fluctuations across several cortical areas in the monkey cortex. Earlier-processing sensory areas have shorter timescales compared to later-processing and high-order association areas, in patterns that correlate with hierarchical levels related to cortical structure and laminar patterns of connections.
63. Buffalo EA, Fries P, Landman R, Buschman TJ, Desimone R. Laminar differences in gamma and alpha coherence in the ventral stream. *Proc Natl Acad Sci U S A.* 2011; 108:11262–11267. [PubMed: 21690410]
64. Miller KD. Canonical computations of cerebral cortex. *Curr Opin Neurobiol.* 2016; 37:75–84. [PubMed: 26868041]

65. Grossberg S. Adaptive Resonance Theory: how a brain learns to consciously attend, learn, and recognize a changing world. *Neural Netw.* 2013; 37:1–47. [PubMed: 23149242]
66. Kopell NJ, Gritton HJ, Whittington MA, Kramer MA. Beyond the connectome: the dynamome. *Neuron.* 2014; 83:1319–1328. [PubMed: 25233314]
67. Finlay BL, Darlington RB. Linked regularities in the development and evolution of mammalian brains. *Science.* 1995; 268:1578–1583. [PubMed: 7777856]
68. Marin-Padilla M. Dual origin of the mammalian neocortex and evolution of the cortical plate. *Anat Embryol (Berl).* 1978; 152:109–126. [PubMed: 637312]
69. Marin-Padilla M. Human cerebral cortex Cajal-Retzius neuron: development, structure and function. A Golgi study. *Front Neuroanat.* 2015; 9:21. [PubMed: 25774125] ** The author describes the development of layer I of the human cortex. This is the first cortical layer to appear in development along with an undifferentiated proliferative ventricular zone.
70. Campbell MJ, Morrison JH. Monoclonal antibody to neurofilament protein (SMI-32) labels a subpopulation of pyramidal neurons in the human and monkey neocortex. *J Comp Neurol.* 1989; 282:191–205. [PubMed: 2496154]

Highlights

- 1.** The cerebral cortex varies systematically in laminar structure and cellular features
- 2.** Connections are best summarized within the framework of cortical systematic variation
- 3.** Prefrontal limbic areas have two-way connections with the amygdala and hypothalamus
- 4.** Prefrontal cortex has privileged access to the basal ganglia and cerebellar output
- 5.** The systematic structural variation of the cortex emerges in development

Figure 1.

Systematic structural variation in laminar architecture of prefrontal areas. **A–C**, Maps of the macaque monkey prefrontal cortex show areal boundaries according to the map in [15]. **A**, Medial view; **B**, Orbital (basal) view; **C**, Lateral view. Areas lacking L4 (agranular) are shown in black; gray scale from darker to lighter depicts areas with gradual increases in laminar distinction, density of neurons in L4 and increase in the density of neurons in the upper layers. **D–G**, Photomicrographs from coronal sections stained with Nissl show areas belonging to different cortical types in PFC. **D**, A medial area without L4 (medial

periallocortex, MPAll). **E**, An area with a rudimentary L4 (dysgranular A32). Agranular and dysgranular (limbic) areas have a lower density of neurons, especially in the upper layers than six-layered (eulaminate areas). **F**, Eulaminate area 10m has six layers. **G**, Area 46d is also eulaminate but L4 is denser than in A10m [10]. **H–K**, Photomicrographs from adjacent sections to those depicted in D–G stained for SMI-32, which labels a subset of large pyramidal projection neurons mostly in L3 and L5, and is used as an architectonic marker [70]. **H**, In agranular area MPAll only a few neurons are labeled and are restricted to L5–6. **I**, In dysgranular A32 there are more labeled neurons, which are found mostly in L5. **J**, In eulaminate area 10 labeled neurons form a band in L3 and another in L5; the unstained tissue between the bands corresponds to L4. **K**, In A46d there are more neurons that are positive for SMI-32. Abbreviations: A10m, area 10 medial; A32, area 32; A46d, area 46 dorsal; MPAll, medial periallocortex (agranular); OLF, primary olfactory cortex; OPAll, orbital periallocortex (agranular); OPro, orbital proisocortex (dysgranular); SMI-32: antibody for neurofilament H non-phosphorylated protein; WM, white matter. Numerals correspond to cortical layers. Calibration bar in K applies to D–K.

Figure 2.

The relational rules of the structural model, and specialized and complementary pathways to distinct prefrontal sectors. **A**, Feedback pathways originate in an area with less elaborate laminar structure than the destination (brown neurons); feedforward describes pathways that have the opposite relationship (blue neurons). These patterns describe connections between areas that differ considerably in overall laminar structure. **B**, Intermediate patterns of connections as seen between areas with small differences in laminar structure. **C**, The amygdala and hypothalamus have strong and reciprocal connections with the limbic

prefrontal cortices (ACC and pOFC), and weaker and unidirectional pathways to eulamine areas. Proposed circuit mechanism for transmission of signals from the internal (emotional) environment to DLPFC (eulamine II) through sequential predominantly feedback pathways based on the rules of the structural model. **D**, Preferential output from the basal ganglia to the frontal cortex. All cortical areas project to the input nuclei of the basal ganglia (caudate and putamen) but only frontal cortices (motor, premotor and prefrontal) receive the output of the basal ganglia via the thalamus. The simplified diagram shows only the 'direct' pathway through the basal ganglia. **E**, The frontal cortex receives the output of the cerebellum through the thalamus. All cortical areas project to the cerebellar cortex via the pontine nuclei. The output of the cerebellum through the deep cerebellar nuclei projects to thalamic nuclei that are connected with the frontal cortex (motor, premotor and prefrontal). Green arrows represent excitatory pathways; red arrows represent inhibitory pathways. ACC: anterior cingulate cortex; GPi: globus pallidus internus; pOFC: posterior orbitofrontal cortex; SNr: substantia nigra reticulata.

Figure 3.

Systematic variation in development of frontal cortical areas in the human. **A–D**, Photomicrographs from a human fetus of 17 week gestational age stained with Nissl. Germinal zones and prospective cortical layers are named according to [54]. Upper panels (A–D) at high magnification were taken from the coronal section below (center panel left). **A**, The germinal zones of the prospective cingulate cortex above the corpus callosum (cc) are composed of thin ventricular (VZ) and subventricular (SVZ) zones; the SVZ has no sublayers. **B**, The SVZ of the dorsal part of the prospective cingulate cortex is divided into

inner (ISVZ) and outer (OSVZ) zones. **C**, The OSVZ is more prominent in prospective dorsolateral areas. **D**, The OSVZ increases progressively in thickness and cell density in a lateral direction. **E–H**, Photomicrographs from a human fetus of 20 weeks gestational age stained with Nissl. The bottom panel (left) shows a coronal section at low magnification and the levels of photomicrographs E–H (top). **E**, The germinal zones of the prospective cingulate cortex close to the corpus callosum (cc) are thicker compared to A, but the SVZ does not show two subzones. **F**, Dorsal cingulate cortex shows thicker VZ and SVZ divided into ISVZ and OSVZ. **G**, Prospective dorsal eulaminar areas have thicker VZ and ISVZ than prospective cingulate areas, but the OSVZ predominates. **H**, The thickness of the OSVZ increases progressively in a mediolateral direction. Abbreviations: cc, corpus callosum; CP, cortical plate; ISVZ, inner subventricular zone; IZ, intermediate zone; LGE, lateral ganglionic eminence; MZ, marginal zone; OSVZ, outer subventricular zone; SP, subplate; SVZ, subventricular zone; VZ, ventricular zone. Calibration bar in F applies to A–H.

Figure 4.

Systematic structural variation seen by neuron density and maturation in cortical development in human. **A**, Coronal section of the developing frontal cortex of a human fetus (17 weeks gestational age) shows the levels of photomicrographs below (**B–E**). **B–E**, Photomicrographs of the cortical plate of prospective cingulate (**B–C**) and dorsolateral (**D–E**) areas show higher neuron density in prospective dorsolateral eulaminar areas. **F**, Coronal section of the developing frontal cortex of a human fetus (20 weeks gestational age) marks the levels of the photomicrographs **G–J**. **G–H**, Some cells in the cortical plate of prospective

cingulate areas show features of neuronal maturation and pyramidal shape with a large nucleus (inset, black arrows); other cells are still immature and have a small and darkly stained nucleus with scant cytoplasm (inset, black arrowheads). **I–J**, In prospective eulaminate areas most cells are immature (inset, black arrowheads). Rectangles in G–J mark the area in the inset shown at higher magnification. Abbreviations are as in Figure 3. Main calibration bar in J applies to B–E and G–J. Inset calibration bar in J applies to insets in G–J. (Note: Figures 3 and 4 are a reexamination of material from an earlier paper [57]).