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How the prefrontal executive got its stripes

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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.

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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.

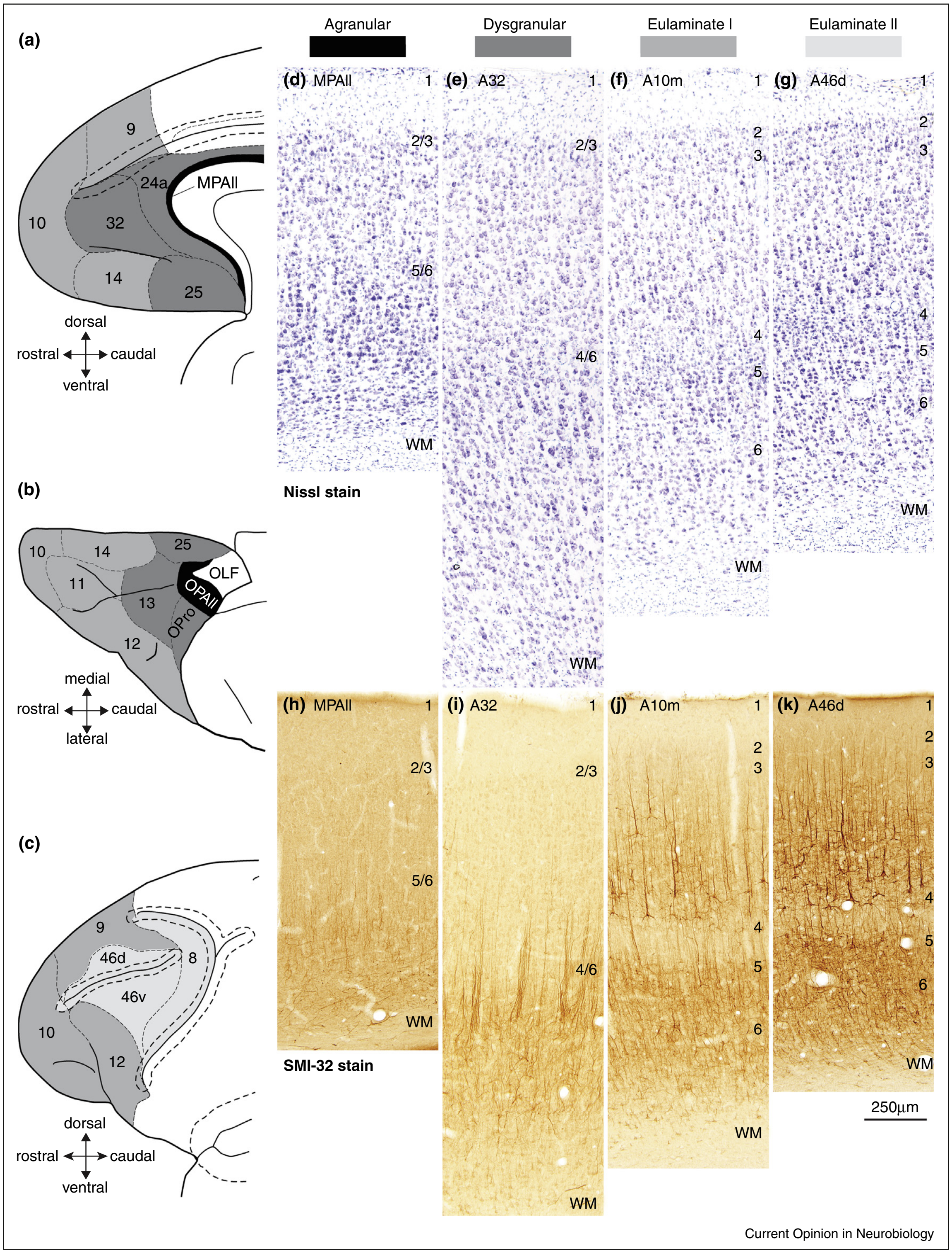
Systematic structural variation of the cortex and relationship to connections

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 (Figure 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

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