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General Cortical and Special Prefrontal Connections: Principles from Structure to Function

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Abstract

How is the vast brain communication system organized? A structural model relates connections to laminar differences between linked areas. The model is based on the principle of systematic structural variation in the cortex, extending from the simplest limbic cortices to eulaminate areas with elaborate lamination. The model accounts for laminar patterns and for the strength and topography of connections between nearby or distant cortices and subcortical structures, exemplified quantitatively for the principal and special prefrontal connections. Widespread connections of limbic areas and focal connections of eulaminate areas yield a broad range of circuit patterns for diverse functions. These diverse pathways innervate excitatory and functionally distinct inhibitory neurons, providing the basis for differential recruitment of areas for flexible behavior. Systematic structural variation likely emerges by timing differences in the development of distinct areas and has important implications for altered connections in diseases of developmental origin.

Contents

INTRODUCTION

The prefrontal cortex has one of the most extensive communication systems in the brain. Complex networks link the prefrontal cortex with the external world through connections with sensory association cortices. The prefrontal cortex is also connected with structures associated with the internal environment because many of its functions are independent of external stimuli—motives, drives, thoughts, and reflections as one ponders the past or plans for the future. How are the numerous connections organized for effortless flow of thoughts and actions? This review focuses on structural principles that help organize and predict connections in mammals. The focus is on nonhuman primates with some references to rats and mice and application to humans.

That the cortex is organized into functional units was a seminal idea (Lorente de Nó 1938) formalized with discoveries of functional repeated columns in the primary somatosensory and visual cortices (Hubel & Wiesel 1968, Mountcastle 1957; reviewed in Callaway 1998, DeFelipe 2002, Mountcastle 1997). In primary sensory cortices, pathways from the thalamus activate neurons in layer 4 of each column, and signals are then transmitted to excitatory and inhibitory neurons in the layers above and below (Douglas & Martin 2004). The concept of columns provided the basis to construct models of visual function (Raizada & Grossberg 2003) and to hypothesize how the cortex could have expanded in evolution by adding functional units (Rakic 2009).

The columnar organization of primary sensory areas was later extrapolated into a general scheme of canonical cortical microcircuits (Douglas & Martin 2004). This scheme was based on the assumption that all cortical areas have six layers (Brodmann 1909) and on the related notion that columns across areas have the same number of neurons (Rockel et al. 1980). Mounting empirical evidence, however, suggests that the idea of a uniform six-layer cortex is an oversimplification. Here I discuss that systematic structural variation across areas is a core organizing principle, and brain connections can be understood and predicted parsimoniously in light of this principle. I refer to the relationship of connections to cortical structure as the structural model for connections. The predictive power of this model is exemplified for the principal connections of prefrontal areas but

applies to the entire cortex. Differences in the timing of development of areas provide a plausible mechanism for the emergence of systematic cortical variation. In turn, structural variation along the cortical mantle yields a broad diversity of connections and neural computations, differential recruitment of areas for flexible behavior, and variable disruption in psychiatric diseases.

GENERAL PRINCIPLES OF CORTICAL STRUCTURE

The principle of systematic variation across the cortical landscape emerged from classic studies [Abbie 1940, Dart 1934, Sanides 1970, von Economo 2009 (1927); reviewed in Pandya et al. 1988]. To understand this principle we must begin with the cortical limbic areas, operationally defined as areas that either lack layer 4 or have a rudimentary layer 4 and are poorly myelinated (hereafter referred to as limbic). Limbic areas thus have fewer than six layers (**Figure 1*c*, *i*, *c*, *ii***). The cortical limbic system occupies the edges of the cortex as a ring above the corpus callosum and the base of the brain, abutting all cortical sensory, high-order association and motor systems (**Figure 1*a***). Areas found adjacent to the limbic areas have a better developed layer 4 and more distinct layers overall, characteristic of cortices with six layers (hereafter referred to as eulaminate; see **Figure 1*c*, *iii–iv***). Within each cortical system, laminar patterning beyond the limbic core appears progressively differentiated in successive eulaminate areas (**Figure 1*a***).

Systematic differences in neuronal density across brain areas have been noted using quantitative methods (Charvet et al. 2013, Collins et al. 2010, Dombrowski et al. 2001, O'Kusky & Colonnier 1982). Cortical areas also vary by spine density and dendritic complexity (Allman & McGuinness 1988, Elston et al. 2001, Kaas 2008). The cortex thus is not uniform by number of layers, by neuronal density, or by other architectonic features. The central principle is that the changes in laminar structure are not random but systematic. Thus, each cortical system, such as the visual, auditory, somatosensory, and prefrontal cortices, is a microcosm of areas whose laminar structure varies systematically. This principle forms the basis for a structural model that helps explain the laminar pattern, the topography, the strength, and the existence or absence of connections within a cortical system (e.g., the visual cortices) or between systems (e.g., visual and prefrontal cortices).

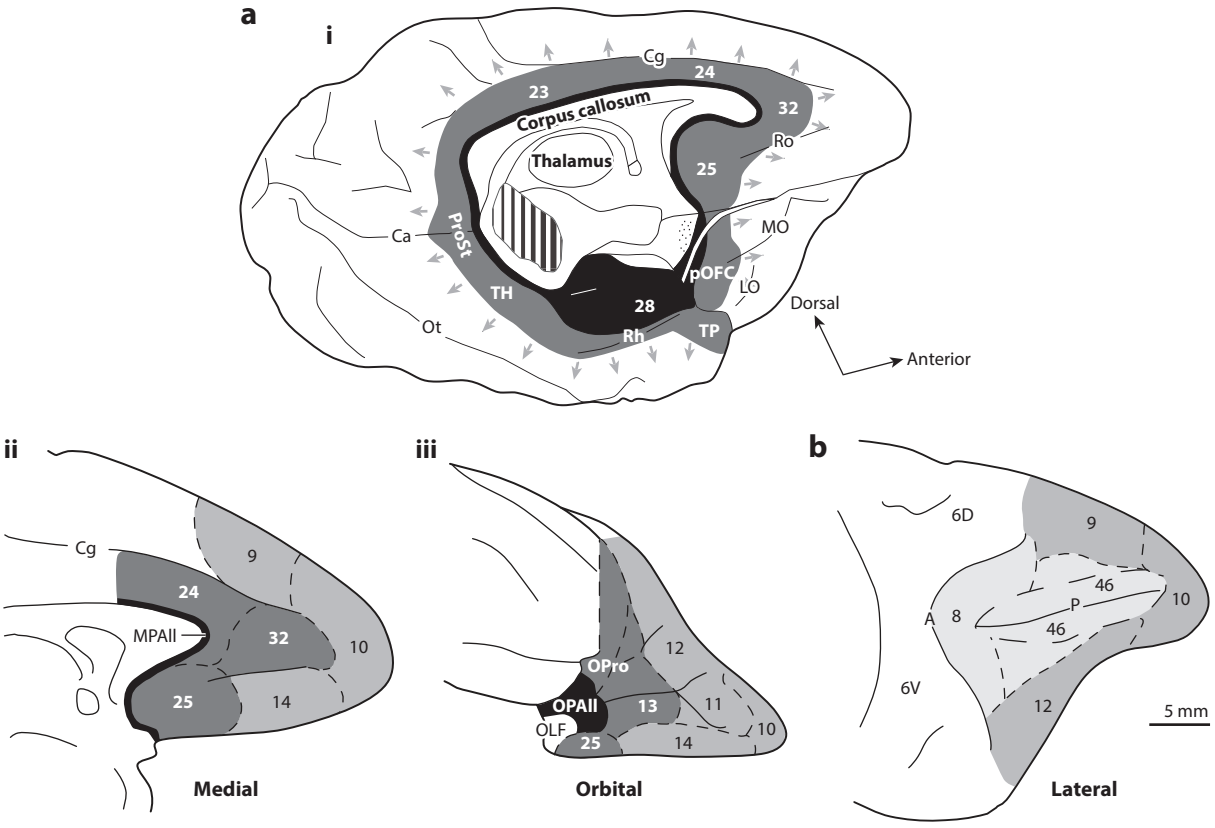
SYSTEMATIC VARIATION AND LAMINAR PATTERNS OF CORTICAL CONNECTIONS

When neural tracers were introduced to map pathways, it became clear that connections between areas are bidirectional but unequal in density and laminar distribution across directions. This rule was illustrated by the connections of the primary visual cortex (V1). Neurons in layer 3 of V1 project to neighboring area V2, where their axons terminate focally in layer 4. Reciprocal and denser pathways emanate from neurons in the deep layers (5 and 6) of V2, and their axons terminate mostly in layer 1 of V1 (Rockland & Pandya 1979). These connections have been called feedforward and feedback, respectively, on the basis of direction in relation to the sensory periphery. Connections fit these patterns for only a subset of linked pairs of cortices. Connections that involve more layers were called "lateral" (Felleman & Van Essen 1991).

At the opposite end of the brain, the laminar distribution of connections of the prefrontal areas also varies, and the pattern of these connections provided an important clue about their organization: Areas along any part of the limbic ring send feedback projections to prefrontal eulaminate cortices. In turn, limbic areas receive feedforward projections from eulaminate areas, regardless of their placement in the cortex (Barbas 1986). The most striking anatomic difference between limbic and eulaminate areas is laminar structure. This observation led to the hypothesis that the structural relationship between linked areas underlies the laminar pattern of their

interconnections. According to the structural model, feedforward connections originate from an area with more elaborate laminar structure than the destination. Feedback refers to connections having the opposite relationship (**Figure 2*a***). Lateral connections link areas with small differences in structure and are distributed in more layers, as predicted by the model in **Figure 2*b***.

Tested quantitatively in the connections within the prefrontal cortical system, the structural model predicted successfully the relative laminar distribution of connections in different layers



for the large majority of connections (Barbas & Rempel-Clower 1997). Quantitative data for prefrontal connections across the hemispheres and ipsilateral connections with distant cortices are also consistent with the structural model (e.g., Barbas et al. 2005, Medalla et al. 2007, Medalla & Barbas 2006, Rempel-Clower & Barbas 2000). The structural model is also supported by analysis of the topography and laminar connection patterns in other cortices (Hilgetag et al. 2008) and by computational analysis of connections using an extensive database (Goulas et al. 2014).

The structural model thus predicts laminar patterns of connections, constrained by a rule based on the magnitude of the structural similarity/dissimilarity between linked areas (**Figure 2**). In contrast, hierarchical models rely on post hoc data of laminar connection patterns to place areas in a sequential order (Felleman & Van Essen 1991) and are poorly constrained (Hegde & Felleman 2007, Hilgetag et al. 1996). The structural model also challenges the notion that the prefrontal cortex provides only feedback projections to the sensory and other association cortices. Whereas several prefrontal areas have feedback-like connections with areas in other lobes, some are feedforward-like (Barone et al. 2000, Medalla & Barbas 2006, Rempel-Clower & Barbas 2000). As shown in **Figure 2*c–d***, feedforward and feedback connections do not depend on direction but depend on laminar structure.

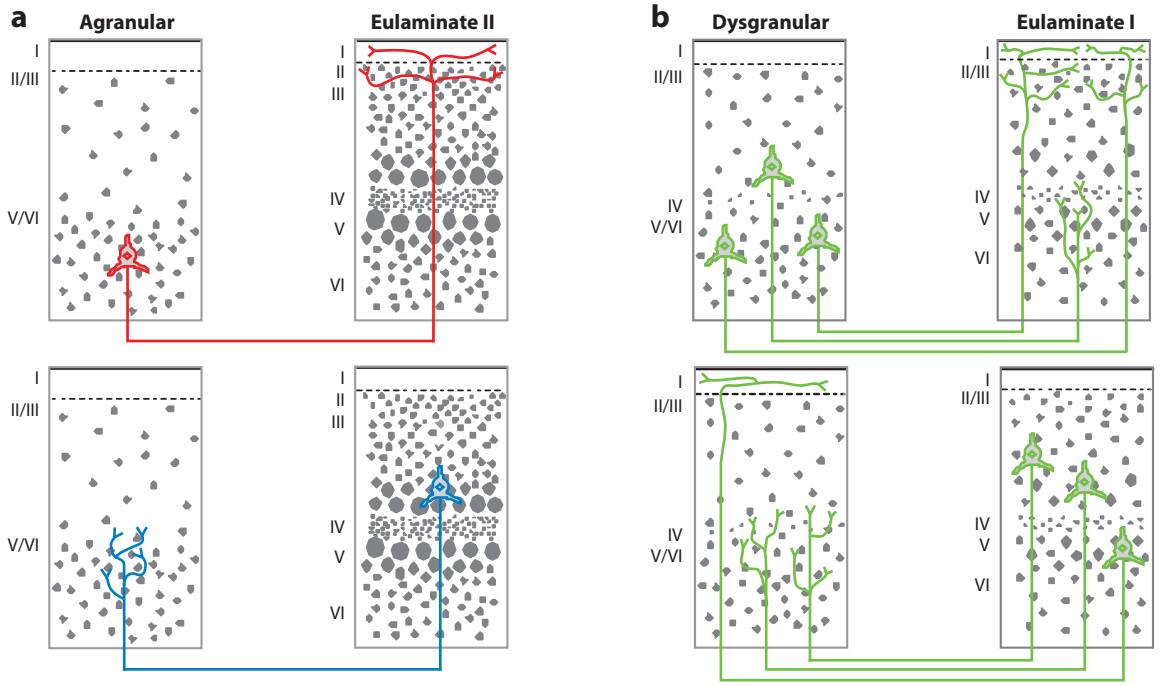
SYSTEMATIC VARIATION AND TOPOGRAPHY OF CORTICAL CONNECTIONS

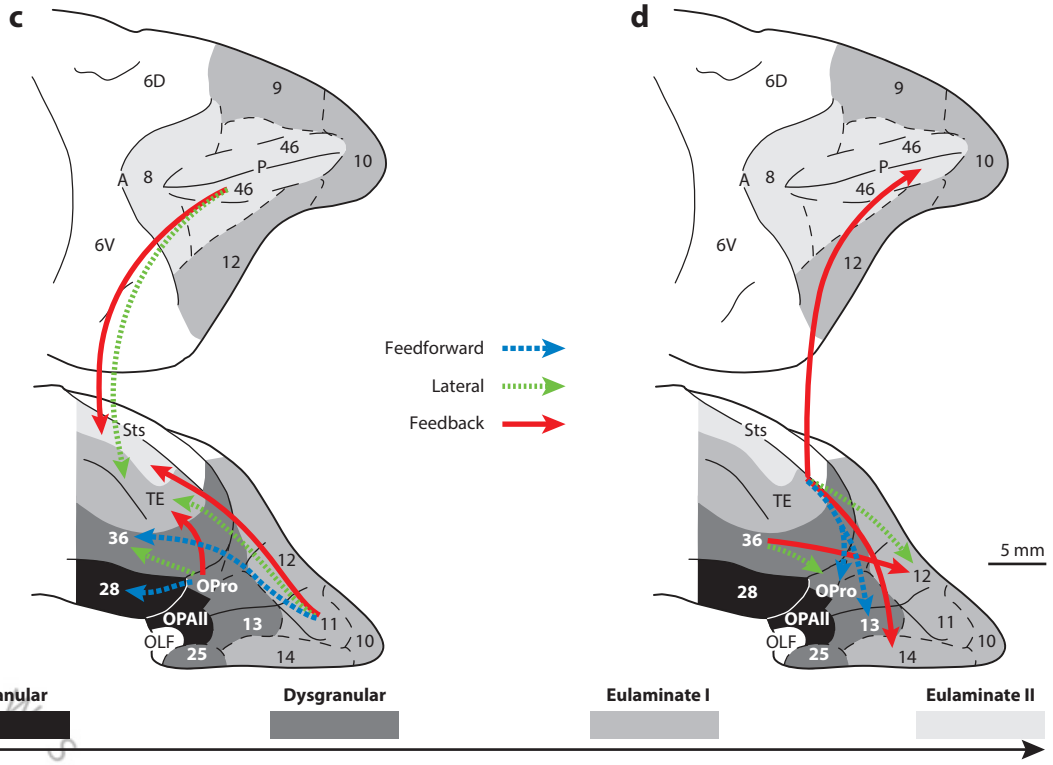
Studies show that neighboring areas are often connected (see Bullmore & Sporns 2012). Distance has been invoked as one factor to explain the decreasing incidence of connections between successively distant areas, as exemplified for visual areas (Markov et al. 2014). But within a cortical system, structure often changes with distance as well (**Figure 3*a***). In addition, a distance model does not explain why connections between some distant areas are strong, such as prefrontal connections with occipital, temporal, and parietal areas.

From the perspective of the structural model, neighboring areas and distant areas that are similar in type are likely connected. Similarity in cortical type is assessed by common features among areas, such as the number and distinction of layers. Classifying areas by type is analogous to grouping people by similarity in height and weight. Cortical type does not depend on the unique features that give an area its architectonic signature (by analogy, facial features) or its topography (by analogy, residence). As seen in **Figure 1*a***, limbic areas in the frontal and occipital lobes are

Figure 1

Systematic variation in cortical structure. (*a*, *i*) Tilted brain shows the medial and partial basal views of the rhesus monkey brain. The cortical limbic system forms a ring at the edge of the cortex and is composed of the simplest types of cortices (*black and dark gray*), and abuts every cortical system. Small arrows (*gray*) depict the onset of gradual laminar differentiation from the limbic cortices to eulaminate areas that have six layers. (*ii*) Medial surface: shows the medial ACC limbic areas (area MPAll, 24, 32, 25); (*iii*) Basal surface: shows the posterior orbitofrontal (pOFC) limbic areas (areas OPAll, OPro, 13). Lighter shade of gray in *ii*, *iii* shows eulaminate-type cortex with six layers; (*b*) the lateral prefrontal cortex is composed of eulaminate cortices. (*c*, *i–iv*) Cartoon depicts systematic laminar changes in cortical types depicted by shades of gray, from the simplest (*i*, *ii*, *black and dark gray*, collectively called limbic cortices), to eulaminate cortices with six layers (*iii*) that show further elaboration (*iv*, *lightest gray*). Eulaminate areas are depicted as two types based on laminar distinction and neuronal density, but finer parcellation into more types is possible and needed for large regions, such as the visual cortical system. Abbreviations: A, arcuate sulcus; Ca, calcarine fissure; Cg, cingulate sulcus; LO, lateral orbital sulcus; MO, medial orbital sulcus; MPAll, medial periallocortex (agranular cortex); OLF, olfactory cortex; OPAll, orbital periallocortex (agranular cortex); OPro, orbital proisocortex (dysgranular cortex); Ot, occipitotemporal sulcus; P, principal sulcus; pOFC, posterior orbitofrontal cortex (areas OPAll, OPro, 13); ProSt, area prostriata; Rh, rhinal sulcus; TH, medial temporal area TH; TP, temporal pole. Notes: Agranular, three-layer cortex with no evidence of layer 4; dysgranular, four-layer cortex with an incipient layer 4; eulaminate, six-layer cortex. All numbers on brains refer to architectonic areas; 6D, dorsal area 6; 6V, ventral area 6 (premotor cortices).





far from each other and are architectonically distinct, but they have in common the simplest types of laminar structure (**Figure 1*a***). Neuronal density per unit volume is often a reliable indicator of type for sensory and association cortices. Other architectonic parameters also help describe cortical types quantitatively (Dombrowski et al. 2001). As novel markers are introduced, investigators will be able to use several discriminant features of cortical type to assess with greater accuracy the degree of structural similarity/dissimilarity among areas.

Distant cortices can be similar in type based on the systematic structural variation within each cortical system. Thus, areas that are similar in type across systems can be connected. This principle is illustrated for projections from visual and auditory association areas to prefrontal areas. The frontal eye field (FEF) within area 8 receives strong projections from occipital visual association and parietal visuomotor areas (**Figure 3*a*,*b***). Projections from visual-related areas to prefrontal area 46 originate in more anterior parietal, and temporal cortices (**Figure 3*a***). Areas 46 and 8 are both eulaminate, but quantitative analysis has shown that the FEF site (**Figure 3*a***) has higher neuronal density than does area 46 (**Figure 3*a***). Similarly, while the visual and visuomotor areas that project to prefrontal areas are all eulaminate, those that project to FEF have a higher neuronal density than do those that project to area 46 (quantitative examples in Medalla & Barbas 2006). Laminar structure in the auditory cortical system is less differentiated overall than that in the visual system. Auditory association areas have connections with more anterior lateral prefrontal areas and with medial prefrontal and orbitofrontal areas (reviewed in Barbas 2000, Medalla & Barbas 2014, Romanski & Averbeck 2009, Yeterian et al. 2012) (**Figure 2*c*-*e***), consistent with the systematic structural variation within the respective auditory and prefrontal systems.

The primary olfactory areas have, at most, three layers (Shepherd 2011) and no connections with the lateral eulaminate prefrontal sector. In contrast, the posterior part of the orbitofrontal cortex (pOFC) and the posterior medial region in the anterior cingulate cortex (ACC) are made up of limbic-type areas, and they are connected with the olfactory areas (Barbas & Pandya 1989, García-Cabezas & Barbas 2014, Morecraft et al. 1992, Nauta 1979, Yakovlev 1948).

The ACC and pOFC regions have robust connections with other limbic cortices associated with the internal environment: core functions of motives and drives (Barbas 1993, Carmichael et al. 1994, Morecraft et al. 1992, Vogt & Pandya 1987). These limbic prefrontal cortices have kept pace with lateral prefrontal areas in evolution and are connected with them (e.g., Nauta 1971, 1972). This linkage provides the anatomic basis for mutual influence of the processes of emotion and cognition and for their disruption in psychiatric diseases (Barbas 1995, Damasio 1994, Lindquist et al. 2012, Pessoa 2013, Ray & Zald 2012, Salzman & Fusi 2010). The two limbic prefrontal regions are also distinguished by other cortical connections. The pOFC receives

Figure 2

Predictions of the structural model for connections. (*a*) Laminar patterns predicted in the connections between areas that differ markedly in cortical type: (*Top*) Pathways from a cortex with less elaborate structure originate in the deep layers and terminate in the upper layers of a cortex with more elaborate structure (*red*, feedback). (*Bottom*) A pathway in the reverse direction (*blue*) originates in the upper layers and terminates in the middle layers (feedforward). (*b*) Predictions of the structural model linking areas with small differences in structure: (*Top*) A pathway from an area with less elaborate structure to an area with more elaborate structure; (*Bottom*) A pathway in the reverse direction. (*c*,*d*) Pathways from prefrontal to temporal cortices and temporal to prefrontal. Pathways are color-coded as feedforward (*blue*, terminating mostly in middle layers 3b–5a), feedback (*red*, terminating mostly in superficial layers 1–3a), and lateral (*green*, terminating in all layers). (*c*,*d*) Demonstrate two connection rules: First, strong connections can link nearby or distant cortices that are of the same or comparable type (*depicted by shades of gray*); second, the predominant laminar pattern of connections depends on the type difference between linked cortices (*shown by shades of gray*) but not necessarily on the direction from frontal to temporal or vice versa. Abbreviations of sulci and architectonic areas are provided in the caption for **Figure 1**. Additional abbreviations: TE, inferior temporal visual area; Sts, superior temporal sulcus. Panels *c*, *d* based on Rempel-Clower & Barbas (2000).

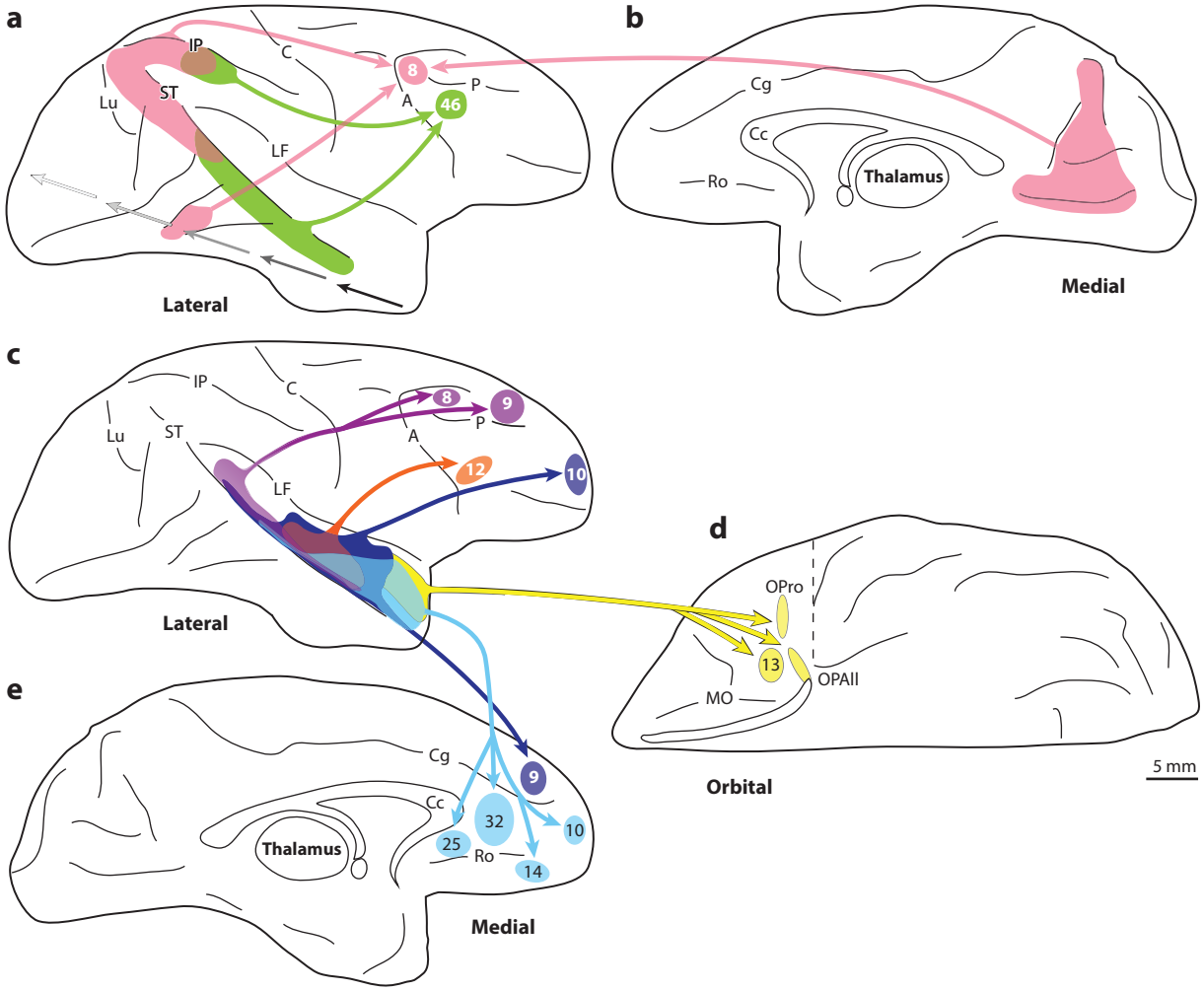


Figure 3

The rule that distant areas of comparable cortical type are interconnected is exemplified in the projections from visual and auditory association cortices to prefrontal cortices. (*a*,*b*) Pathways from visual cortices to area 8 (*pink*) originate in posterior visual cortices; pathways from more anterior visual cortices innervate area 46 (*green*). These connections are consistent with the principle of type similarity between linked areas, as summarized by the progression of changes in cortical type along the ventral visual pathway (*a*, *black to light gray arrows*). (*c–e*) Extensive projections from auditory association cortices to (*c*) lateral, (*d*) orbital, and (*e*) medial prefrontal cortices originate from caudal auditory to progressively more rostral auditory association cortices. Abbreviations: A, arcuate sulcus; C, central sulcus; Cc, corpus callosum; Cg, cingulate sulcus; IP, intraparietal sulcus; LF, lateral fissure; Lu, lunate sulcus; MO, medial orbital sulcus. Ro, rostral sulcus; ST, superior temporal sulcus. OPAll, OPro, and 13 are orbital limbic areas, collectively called pOFC in the text. Panels *c–e* adapted from Medalla & Barbas (2014).

an overview of the entire external environment from higher-order sensory cortices. In contrast, the sensory-related ACC connections are mostly with auditory association cortices (Barbas et al. 1999).

Connections thus can be summarized by a type-similarity rule as follows: Most of the connections, and particularly those that are the strongest, occur between areas that are comparable in

cortical type or differ by 1–2 sequential types (Barbas & Pandya 1989). Similarity in cortical type thus helps explain connections between neighboring as well as between distant areas.

RELATIONSHIP OF CONNECTIONS TO CORTICAL INHIBITORY SYSTEMS

Why do connection patterns matter? Cortical pathways that terminate in different layers engage excitatory as well as inhibitory neurons that vary greatly in prevalence, functional type, and efficacy of inhibition. Cortical pathways thus influence the balance of excitation and inhibition and the disruption of this balance in brain diseases. In the prefrontal cortex, inhibitory control is essential for selective attention and flexible behavior. Even mild cognitive decline of prefrontal origin in humans weakens the suppression of distracting stimuli in the auditory cortex and impairs performance on discrimination tasks (Chao & Knight 1997).

There are various mechanisms of inhibition in the cortex (reviewed in Greengard 2001). A brief discussion here focuses on cortical γ-aminobutyric acid (GABA)-ergic neurons, which constitute 25–30% of all cortical neurons in primates (Jones 2009). Cortical pathways in primates are excitatory and largely innervate other excitatory neurons, but ~10% to more than 20% of the synapses are on inhibitory neurons. These percentages apply to pathways that enter or leave the white matter but do not apply to connections within cortical columns.

Cortical GABAergic neurons are diverse in morphology, distinguished by a rich and varied axonal ramification confined within the cortex (Ascoli et al. 2008, DeFelipe 2002, Markram et al. 2004). There is no general agreement on or consistency in the morphologic classification of inhibitory neurons (Defelipe et al. 2013). GABAergic neurons in primates, however, can be classified by expression of the calcium-binding proteins calbindin (CB), parvalbumin (PV), or calretinin (CR). This classification has several advantages, even though each neurochemical class includes more than one morphologic type. In primates, these neurochemical classes are largely nonoverlapping. Moreover, each class of inhibitory neurons has preferential laminar distributions and innervates specific parts of nearby neurons. CR is expressed in inhibitory neurons found mostly in layers 1-2a. CB neurons are concentrated mostly in layers 2-3a. Generally, CB and CR neurons include morphologic types with vertically oriented axons and innervate segments of the dendritic tree of nearby neurons. PV labels the morphologic types of basket and chandelier neurons, which are found predominantly in the middle-deep layers (DeFelipe 1997) and innervate perisomatic elements of nearby neurons. The density of each neurochemical class varies across areas. For example, in ACC and pOFC areas, CB neurons are more densely distributed than are PV neurons, whereas in lateral eulaminate areas, they are more balanced (Dombrowski et al. 2001).

The systematic variation of the cortex is thus accompanied by variation in the cortical inhibitory system. Consequently, laminar-specific connections originate and terminate in areas and layers in which inhibitory neurons vary in overall density, prevalence of neurochemical class, and synaptic efficacy. The interface of laminar-specific pathways with functionally distinct classes of inhibitory neurons across areas provides a powerful model to investigate differential effects of pathways across areas.

SYSTEMATIC VARIATION AND CONNECTIONS IN OTHER MAMMALIAN SPECIES

Compared with gyrencephalic primates, rats and mice have only a few cortical areas (see Krubitzer 2009), including some frontal areas (Uylings et al. 2003). Connectional, physiologic, and behavioral attributes suggest that the prelimbic cortex in rats is comparable to ACC area 32 and the infralimbic cortex in primates to area 25 (Gabbott et al. 2005, Vertes 2004, Vogt et al. 2013). The prelimbic

cortex is implicated in motivational and cognitive aspects of behavior (Groenewegen & Uylings 2000; Uylings et al. 2003; Vertes 2004, 2006), combining functions attributed to parts of the ACC and dorsolateral prefrontal areas in primates. The orbital region in rats also shares some functions with the infralimbic cortex (Chudasama & Robbins 2003).

The rodent cortex is less differentiated than the primate cortex, and yet, in spite of its overall simplicity, the rat cortex also shows structural differences. As in primates, the primary areas are the best laminated in rodents, exemplified by the structural elegance and exquisite functional specificity of the somatosensory barrel cortex (Petersen 2007). The predictions of the structural model are consistent with cortical connection data in rats and other species (Coogan & Burkhalter 1990, Hilgetag & Grant 2010; see Barbas 1986 for discussion of other species).

Rats and mice also differ from primates because they have fewer inhibitory neurons, amounting to ~15% of all cortical neurons (Woodruff & Yuste 2008). Inhibitory neurons in rodents show less specificity in their neurochemistry than do inhibitory neurons in primates. Aside from the class of PV neurons and perhaps those that express somatostatin, other groups show overlapping expression of CR and a variety of peptides (Kawaguchi & Kubota 1997, Wonders & Anderson 2006, Xu et al. 2010). PV neurons are the most prevalent class in the cortex in rats and mice but not in primates, at least not in the prefrontal cortices of primates that have been studied (Dombrowski et al. 2001, Gabbott & Bacon 1996, Wonders & Anderson 2006, Xu et al. 2010).

SYSTEMATIC CORTICAL VARIATION AND SUBCORTICAL CONNECTIONS

The principle of systematic cortical variation also helps summarize subcortical connections with the cortex. Eulaminate prefrontal cortices overall have fewer and more focal connections with subcortical structures than do the limbic cortices. For example, most thalamic neurons that project to lateral eulaminate areas are found in the mediodorsal (MD) nucleus—the principal thalamic nucleus for the prefrontal cortex—whereas only a few originate in other thalamic nuclei. Limbic prefrontal cortices are innervated by MD, as well, but are also innervated, to a significant extent, by other thalamic nuclei: anterior, intralaminar, midline, ventral, and the medial pulvinar (Dermon & Barbas 1994).

The thalamus is connected with the cortex via two parallel and bidirectional pathways in all systems (reviewed in Jones 2007). Pathways from the various relay thalamic nuclei terminate focally in the middle cortical layers, like feedforward corticocortical pathways. Parallel thalamic pathways innervate the superficial layers of each area, akin to feedback corticocortical pathways. The latter emanate from different neurons within a thalamic nucleus than in the relay pathways (Jones 2007), or they emanate from different nuclei. MD innervates the middle layers of prefrontal areas abundantly and layer 1 sparsely (Giguere & Goldman-Rakic 1988). But pathways from other thalamic nuclei innervate robustly the upper layers as well as the middle layers of prefrontal cortices (Haber 2003, Zikopoulos & Barbas 2007b).

Hypothalamic pathways also reach all prefrontal areas in rats and primates (Nauta & Haymaker 1969, Rempel-Clower & Barbas 1998). The hypothalamic system, which is often regarded as diffuse, also conforms to the general structural scheme by innervating limbic areas robustly and eulaminate cortices sparsely. Limbic prefrontal areas uniquely reciprocate with projections to the hypothalamus, which innervates brain stem and spinal autonomic structures (Rempel-Clower & Barbas 1998). Limbic prefrontal areas thus have rapid access to vital autonomic organs, such as the heart, lungs, and gut, during emotional arousal.

Limbic prefrontal areas are also the major targets of pathways from the hippocampus (CA1 and subiculum), which reach the ACC and, to some extent, the orbitofrontal cortex (Barbas &

Blatt 1995, Insausti & Munoz 2001, Rosene & Van Hoesen 1977). The hippocampal pathways are reciprocated only indirectly through strong projections from the ACC to the entorhinal cortex and from the pOFC mostly to the perirhinal cortex (Bunce et al. 2013, Insausti & Munoz 2001, Rempel-Clower & Barbas 2000).

The amygdala has a wider reach on the prefrontal cortex than does the hippocampus. Nevertheless, the amygdala innervates most densely the limbic prefrontal areas, and especially the pOFC, and to a lesser extent the eulaminate areas (Ghashghaei et al. 2007, Porrino et al. 1981, Timbie & Barbas 2014). Like the pOFC, the amygdala receives a broad overview of the entire external environment through late-processing sensory cortices in rats and primates (McDonald 1998, Price 2003, Turner et al. 1980).

Sensory pathways that reach the pOFC indirectly via the amygdala may convey signals about the significance of stimuli (Barbas 1995). Can the laminar patterns of these pathways reveal the flow of information in this complex system? The amygdala receives projections from eulaminate temporal sensory association areas, which originate from layer 3, as in feedforward pathways (Hoistad & Barbas 2008). These projection neurons were labeled retrogradely after bidirectional tracers were injected into the amygdala (**Figure 4*a***). The same experiments show that axons from the amygdala innervate all layers of the pOFC (**Figure 4*c***) to a different extent. One prominent innervation pattern shows dense patches of amygdalar terminations in the middle layers of the pOFC (Ghashghaei et al. 2007), akin to feedforward projections (**Figure 4*b*,*c***). These serial projections resemble the sequential pathways from earlier to later processing in sensory areas. By analogy, serial pathways from temporal sensory cortices to the amygdala and then to the pOFC may convey signals about the significance of stimuli. **Figure 4*a*** also shows that projection neurons shift to the deep layers (feedback) in nearby limbic area 28, which also projects to the amygdala (**Figure 4*a***). These patterns are consistent with predictions from the structural model, even when one structure is not cortical, such as the amygdala (see also Ghashghaei et al. 2007).

The limbic prefrontal cortices have strong reciprocal projections to the amygdala. In contrast, eulaminate areas have few, if any, projections to the amygdala. The ACC innervates the central and other efferent nuclei of the amygdala, which innervate downstream autonomic structures. A prominent pathway from the pOFC robustly innervates the inhibitory intercalated amygdalar neurons (Ghashghaei & Barbas 2002), which have a key role in the internal processing of the amygdala (Jongen-Relo & Amaral 1998, Saha et al. 2000). In rats and mice, pathways from prelimbic and infralimbic cortices project to the intercalated neurons as well (Cassell & Wright 1986, Pinto & Sesack 2008, Sesack et al. 1989).

SPECIAL CIRCUITS OF THE PREFRONTAL CORTEX

The prefrontal cortex differs from other association areas by receiving privileged information through the thalamus from two major structures: the basal ganglia and the cerebellum. The cortex, in general, projects to the basal ganglia and to the pontine nuclei of the cerebellum (Haber 2003, Schmahmann & Pandya 2008). But output pathways from the basal ganglia and the cerebellum preferentially innervate motor-related thalamic nuclei and MD, which are connected mostly with motor, premotor, and prefrontal cortices (see Barbas et al. 2013). The basal ganglia and the cerebellum specialize in sequencing information seamlessly for habits, language, and actions (reviewed in Barbas et al. 2013, Graybiel 2008). Frontal thalamic nuclei thus receive distilled information from the neuraxis through the basal ganglia and the cerebellum and broadcast it to the prefrontal cortex. These pathways facilitate fluid streaming of thoughts and actions in a broad range of operations from simple routines to complex cognition attributed to the prefrontal cortex (**Figure 5**).

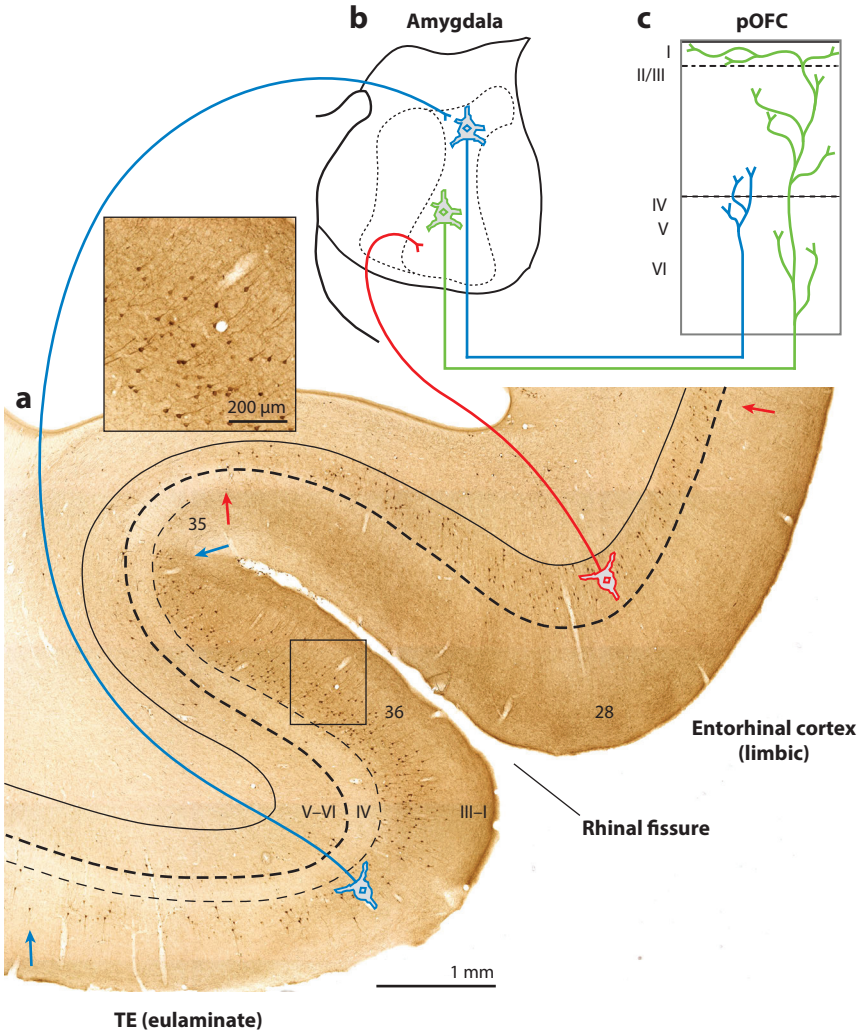


Figure 4

Sequential laminar-specific pathways and hypothesis for the flow of information for emotions. Projection neurons in temporal areas were labeled retrogradely (*brown*) after injecting a bidirectional neural tracer in the amygdala. Thick dotted line shows the upper border of layer 5; thin dotted line shows the upper border of layer 4. Blue arrows depict feedforward pathways from temporal sensory areas (*a*) to the amygdala (*b*) and from the amygdala to the pOFC (*c*). (*a*) Cross section through temporal cortex shows that eulaminate visual area TE and the adjacent polymodal region (*blue arrows*) project to the amygdala from neurons in layer 3 (*labeled neurons*, *brown*, *shown in inset at higher magnification*). (*b*,*c*) Amygdalar pathways terminate in all layers of the pOFC, but a prominent pattern includes dense axon patches in the middle layers (*c*, *blue*). The laminar patterns of these serial pathways are akin to feedforward pathways in sensory cortices; in this system, they may provide information about the significance of stimuli. Note the shift in the origin of labeled neurons to the deep layers in the limbic entorhinal area 28 (*a*, *red arrows*, *feedback*). Structural transitions in this region proceed from the limbic entorhinal area 28 (agranular) to eulaminate area TE1 (visual association area). These patterns are consistent with the predictions of the structural model.

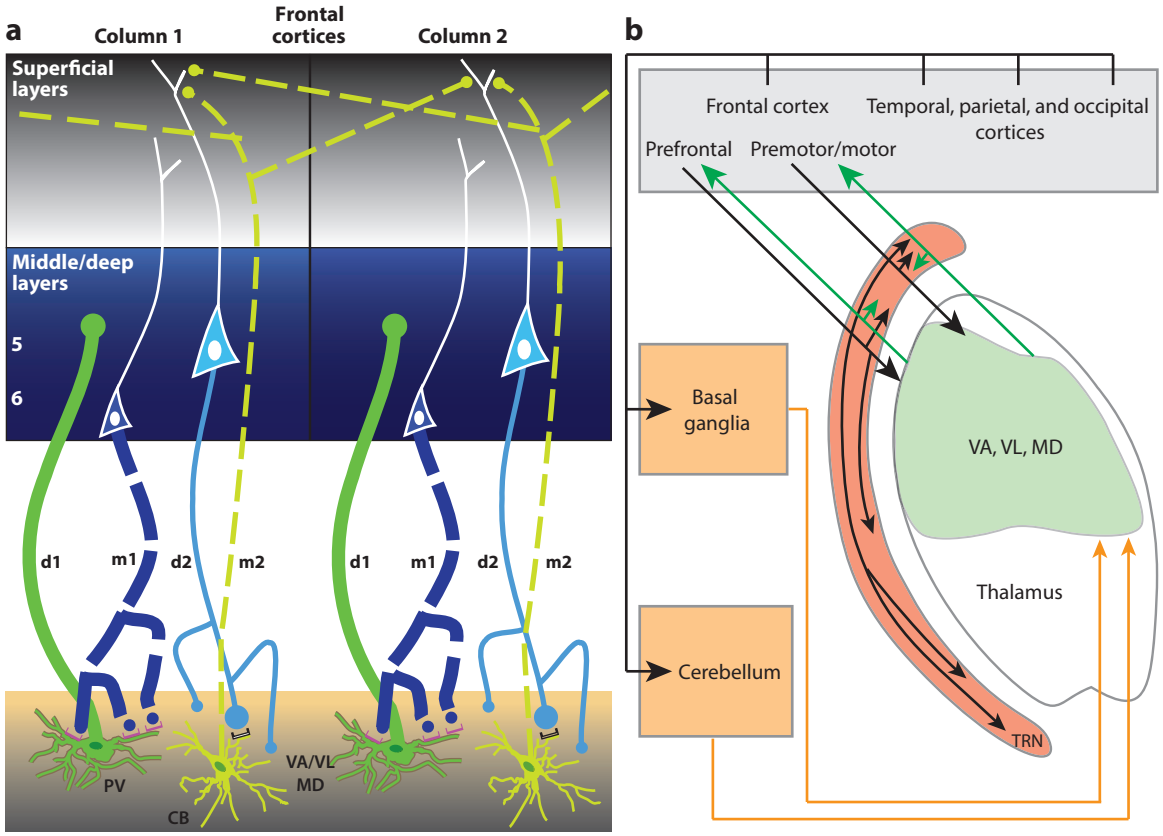


Figure 5

Dual pathways link the thalamus with the cortex. (*a*) A focal driver (d1) pathway from the thalamus innervates the middle layers of the cortex (3b–5a), reciprocated by a modulatory (m1) cortical pathway from layer 6 to the thalamus. A parallel 'modulatory' (m2) pathway from the thalamus terminates widely in the upper layers (1–3a), impinging on the apical dendrites of layer 5 neurons (*light blue*) that project back to the thalamus (d2). The parallel pathways may allow differential recruitment of areas in behavior: activity in column 1 (*a*) may eventually spread to column 2 and beyond through activation of pathways between the thalamus and cortex, amygdala and cortex, or corticocortical pathways. Special pathways link the prefrontal cortex with subcortical structures. (*b*) Thalamic nuclei that are a hub for the output of the basal ganglia and the cerebellum are connected preferentially with the frontal cortex (prefrontal and premotor/motor cortices, *black and green arrows*). The inhibitory thalamic reticular nucleus (TRN) similarly receives topographic projections from the entire cortex (not shown), but some prefrontal areas project widely to TRN, including its sensory and motor sectors (*black arrows on TRN*). These special projections may facilitate selective attention and executive function in prefrontal cortex. Panel *a* adapted from Zikopoulos & Barbas (2007b).

Special projections from select prefrontal areas also innervate the inhibitory thalamic reticular nucleus (TRN), which is thought to filter signals through the thalamus and the cortex (Crick 1984). Whereas all other cortices project topographically to the TRN, lateral prefrontal areas 46/9, the pOFC, and the amygdala innervate the frontal sector of the TRN as well as the sensory and motor sectors of the TRN (Zikopoulos & Barbas 2007a, 2012) (**Figure 5*b***). These widespread projections from select prefrontal areas and from the amygdala may control an attentional system through the TRN that filters signals at an early stage of processing. Preferential connections with hub thalamic nuclei and the TRN likely contribute to the specialization of the prefrontal cortex in executive control.

SYSTEMATIC CORTICAL VARIATION AND FLEXIBLE FUNCTION

What is the functional significance of systematic cortical variation and connections? A consequence of this scheme is that functional columns are not uniform and canonical as originally thought but instead must vary across cortices, as physiologic studies now show (Godlove et al. 2014). Variable connections engage different neurocognitive maps (Mesulam 2008). Diversity in connection patterns allows specific or broad recruitment of areas depending on behavioral demands. Lateral prefrontal areas receive mostly focal feedforward thalamic projections and input from early sensory association cortices for cognitive operations (Funahashi & Kubota 1994, Fuster 1989, Goldman-Rakic 1988, Miller & Cohen 2001, Petrides 2000). But the activity of these eulaminate areas can be modified by widespread feedback projections from areas with a simpler structure, which are richly innervated by the amygdala and many thalamic nuclei. Axons from these subcortical structures terminate not only in the middle layers, but also expansively in the upper layers where they come in contact with the apical dendrites of neurons from layer 5. If sufficiently strong, activity in the upper layers can spread to adjacent sites, influencing nearby areas and beyond, as depicted in **Figure 5*a*** (Zikopoulos & Barbas 2007b). Neurons in layer 5 project to the basal ganglia and the amygdala; some also project to the thalamus and other cortices, which provides a mechanism for the spread of activation through the thalamus and the cortex (Sherman & Guillery 1996).

Laminar-specific connections also suggest differential recruitment of functionally distinct classes of inhibitory neurons that have preferential laminar distributions. For example, the ACC projects to the entorhinal cortex, where it innervates all layers, as predicted by the structural model. In the upper layers of the entorhinal cortex, ACC axons innervate CR neurons preferentially, whereas in the deep layers they innervate PV neurons (Bunce et al. 2013). These patterns have functional implications. CR neurons in the upper layers inhibit other inhibitory neurons (Meskenaite 1997) and, thus, disinhibit pyramidal neurons, suggesting that signals from the ACC may gain facilitated access to the hippocampus. By comparison, because PV neurons exercise strong perisomatic inhibition of nearby excitatory neurons, the ACC pathway may gate the hippocampal output to other areas through the deep entorhinal layers. The interface of pathways with functionally distinct classes of inhibitory neurons sets the stage for shifts in cortical rhythms, influenced by attention, context, and memory for complex behavior (see Bartos et al. 2007, Buzsáki & Wang 2012, Cannon et al. 2014, Canolty & Knight 2010, Fell & Axmacher 2011, Isaacson & Scanziani 2011, Massi et al. 2012, Schroeder & Lakatos 2009, Sohal et al. 2009, Tognoli & Kelso 2014).

Cortical circuits are also modulated by neurotransmitter-specific pathways from the basal forebrain and brain stem, such as the cholinergic and dopaminergic pathways (Hasselmo & Sarter 2011, Robbins & Arnsten 2009, Zaborszky et al. 2013). These subcortical pathways show preferential laminar distributions and specialization in primates (García-Cabezas et al. 2009). Cholinergic and dopaminergic systems innervate eulaminate cortices sparsely and the ACC and the pOFC robustly. The ACC and pOFC uniquely project back to the basal forebrain (e.g., Ghashghaei & Barbas 2001).

SYSTEMATIC CORTICAL VARIATION IN DEVELOPMENT IN HEALTH AND DISEASE

How do graded patterns in laminar structure arise across the cortical mantle? We have advanced the hypothesis that differences in the timing of development among areas explain their systematic structural variation (Dombrowski et al. 2001). According to this hypothesis, the developmental period is shortest in areas with the simplest structure and longest in areas with the most elaborate

structure. There are only sparse data on primate cortical development, but one study showed the course of development of four areas in rhesus monkeys: an ACC limbic area; anterior orbital area 11 with intermediate structure; prefrontal area 46 with more elaborate structure (**Figure 1**); and V1 (Rakic 2002), which has more distinct layers and higher neuronal density than does any other area in the primate cortex (O'Kusky & Colonnier 1982). These areas completed their development from earliest to latest (in that order). Further developmental studies are needed to determine if areas of comparable type across cortical systems develop at the same time.

The early development of limbic cortices may also explain why they project from neurons in their deep layers (which develop first) and terminate in layer 1 of other areas. Layer 1 is also present at the onset of neurogenesis in all areas (Marin-Padilla 1970). The early development of limbic cortices may also help explain their widespread connections and likely tonic influence on the neocortex (Barbas 1995). Limbic cortices appear to retain some developmental features into adulthood. One of these features is the persistent expression in the ACC of the growth associated protein (GAP-43), which has a role in axon growth and guidance in all areas in ontogeny (Benowitz & Routtenberg 1997). GAP-43 and myelin proteins are mutually antagonistic (Kapfhammer & Schwab 1994). The persistent expression of GAP-43 thus helps explain the low myelin content in the ACC in adulthood, a feature that may allow the axon remodeling and plasticity needed for learning and memory associated with this region. The ACC is also implicated in monitoring functions (Carter et al. 1998), which may be mediated by the ACC's unusually extensive connections with other prefrontal cortices (Barbas et al. 1999). These widespread connections may be promoted by GAP-43, providing a plausible developmental mechanism that optimizes the ACC's monitoring function.

The developmental hypothesis for the emergence of systematic cortical variation has profound implications for diseases with roots in development. Accordingly, the timing of a given insult in gestation—whether of genetic origin or due to disturbances in utero—can affect specific areas, layers, neurons, and their connections. In schizophrenia, for example, there is a loss of pyramidal neurons in the deep layers of the ACC (Benes et al. 2001). According to the rules of the structural model, the deep layers of the limbic ACC region innervate the upper layers of eulaminate prefrontal areas associated with cognition. When axons from the ACC form synapses with inhibitory neurons in lateral prefrontal areas, the preferential postsynaptic targets are CB neurons (Medalla & Barbas 2009, Medalla & Barbas 2010). Physiologic and computational studies in the lateral prefrontal cortex reveal that CB inhibitory neurons are synaptically suited to reduce noise and enhance signals in cognitive tasks (Wang et al. 2004). The pathway from the ACC to the lateral prefrontal cortices thus may be weakened in schizophrenia. By contrast, the same pathway may be enhanced in autism owing to higher-than-normal expression of GAP-43 and exuberant axon branching below the ACC, suggesting increased connectivity with the prefrontal cortices (Zikopoulos & Barbas 2010). Schizophrenia and autism thus may affect the same pathway and the process of attention in opposite ways, resulting in distractibility in schizophrenia and an inability to shift attention flexibly in autism. Differences in the timing of insult may help explain differences in the symptomatology in these diseases, as well as individual variability within a broad spectrum of a disease.

The complex circuits of the prefrontal cortex thus may be simplified in light of the principle of systematic cortical variation and explained by genetic control of the developmental clock. Interplay of genetic, ontogenetic, and epigenetic factors may lead to self-organization that helps explain the varied structural and connectional patterns in adults. As more developmental data emerge, it will be intriguing to investigate whether the timing and spatial layout of subcortical structures in development help endow the prefrontal cortex with special connections for executive function by being at the right place at the right time.

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LITERATURE CITED

Abbie AA. 1940. Cortical lamination in the Monotremata. *J. Comp. Neurol.* 72:429–67

Allman J, McGuinness E. 1988. Visual cortex in primates. See Steklis & Erwin 1988, pp. 279–326

Ascoli GA, Alonso-Nanclares L, Anderson SA, Barrionuevo G, Benavides-Piccione R, et al. 2008. Petilla terminology: nomenclature of features of GABAergic interneurons of the cerebral cortex. *Nat. Rev. Neurosci.* 9:557–68

Barbas H. 1986. Pattern in the laminar origin of corticocortical connections. *J. Comp. Neurol.* 252:415–22

Barbas H. 1993. Organization of cortical afferent input to orbitofrontal areas in the rhesus monkey. *Neuroscience* 56:841–64

Barbas H. 1995. Anatomic basis of cognitive-emotional interactions in the primate prefrontal cortex. *Neurosci. Biobehav. Rev.* 19:499–510

Barbas H. 2000. Complementary role of prefrontal cortical regions in cognition, memory and emotion in primates. *Adv. Neurol.* 84:87–110

Barbas H, Blatt GJ. 1995. Topographically specific hippocampal projections target functionally distinct prefrontal areas in the rhesus monkey. *Hippocampus* 5:511–33

Barbas H, García-Cabezas MA, Zikopoulos B. 2013. Frontal-thalamic circuits associated with language. *Brain Lang.* 126:49–61

Barbas H, Ghashghaei H, Dombrowski SM, Rempel-Clower NL. 1999. Medial prefrontal cortices are unified by common connections with superior temporal cortices and distinguished by input from memory-related areas in the rhesus monkey. *J. Comp. Neurol.* 410:343–67

Barbas H, Hilgetag CC, Saha S, Dermon CR, Suski JL. 2005. Parallel organization of contralateral and ipsilateral prefrontal cortical projections in the rhesus monkey. *BMC Neurosci.* 6:32

Barbas H, Pandya DN. 1989. Architecture and intrinsic connections of the prefrontal cortex in the rhesus monkey. *J. Comp. Neurol.* 286:353–75

Barbas H, Rempel-Clower N. 1997. Cortical structure predicts the pattern of corticocortical connections. *Cereb. Cortex* 7:635–46

Barone P, Batardiere A, Knoblauch K, Kennedy H. 2000. Laminar distribution of neurons in extrastriate areas projecting to visual areas V1 and V4 correlates with the hierarchical rank and indicates the operation of a distance rule. *J. Neurosci.* 20:3263–81

Bartos M, Vida I, Jonas P. 2007. Synaptic mechanisms of synchronized gamma oscillations in inhibitory interneuron networks. *Nat. Rev. Neurosci.* 8:45–56

Benes FM, Vincent SL, Todtenkopf M. 2001. The density of pyramidal and nonpyramidal neurons in anterior cingulate cortex of schizophrenic and bipolar subjects. *Biol. Psychiatry* 50:395–406

Benowitz LI, Routtenberg A. 1997. GAP-43: an intrinsic determinant of neuronal development and plasticity. *Trends Neurosci.* 20:84–91

Brodmann K. 1909. *Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues*. Leipzig, Ger.: Verlag von Johann Ambrosius Barth

Bullmore E, Sporns O. 2012. The economy of brain network organization. *Nat. Rev. Neurosci.* 13:336–49

Bunce JG, Zikopoulos B, Feinberg M, Barbas H. 2013. Parallel prefrontal pathways reach distinct excitatory and inhibitory systems in memory-related rhinal cortices. *J. Comp. Neurol.* 512:4260–83

Buzsáki G, Wang XJ. 2012. Mechanisms of gamma oscillations. *Annu. Rev. Neurosci.* 35:203–25

Callaway EM. 1998. Local circuits in primary visual cortex of the macaque monkey. *Annu. Rev. Neurosci.* 21:47–74

Cannon J, McCarthy MM, Lee S, Lee J, Borgers C, et al. 2014. Neurosystems: brain rhythms and cognitive processing. *Eur. J. Neurosci.* 39:705–19

Canolty RT, Knight RT. 2010. The functional role of cross-frequency coupling. *Trends Cogn. Sci.* 14:506–15

Carmichael ST, Clugnet MC, Price JL. 1994. Central olfactory connections in the macaque monkey. *J. Comp. Neurol.* 346:403–34

Carter CS, Braver TS, Barch DM, Botvinick MM, Noll D, Cohen JD. 1998. Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science* 280:747–49

Cassell MD, Wright DJ. 1986. Topography of projections from the medial prefrontal cortex to the amygdala in the rat. *Brain Res. Bull.* 17:321–33

Chao LL, Knight RT. 1997. Prefrontal deficits in attention and inhibitory control with aging. *Cereb. Cortex* 7:63–69

Charvet CJ, Cahalane DJ, Finlay BL. 2013. Systematic, cross-cortex variation in neuron numbers in rodents and primates. *Cereb. Cortex* 25:147–60

Chudasama Y, Robbins TW. 2003. Dissociable contributions of the orbitofrontal and infralimbic cortex to Pavlovian autoshaping and discrimination reversal learning: further evidence for the functional heterogeneity of the rodent frontal cortex. *J. Neurosci.* 23:8771–80

Collins CE, Airey DC, Young NA, Leitch DB, Kaas JH. 2010. Neuron densities vary across and within cortical areas in primates. *PNAS* 107:15927–32

Coogan TA, Burkhalter A. 1990. Conserved patterns of cortico-cortical connections define areal hierarchy in rat visual cortex. *Exp. Brain Res.* 80:49–53

Crick F. 1984. Function of the thalamic reticular complex: the searchlight hypothesis. *PNAS* 81:4586–90

Damasio AR. 1994. *Descartes' Error: Emotion, Reason, and the Human Brain*. New York: Putnam

Dart RA. 1934. The dual structure of the neopallium: its history and significance. *J. Anat.* 69:3–19

DeFelipe J. 1997. Types of neurons, synaptic connections and chemical characteristics of cells immunoreactive for calbindin-D28K, parvalbumin and calretinin in the neocortex. *J. Chem. Neuroanat.* 14:1–19

DeFelipe J. 2002. Cortical interneurons: from Cajal to 2001. *Prog. Brain Res.* 136:215–38

Defelipe J, López-Cruz PL, Benavides-Piccione R, Bielza C, Larrañaga P, et al. 2013. New insights into the classification and nomenclature of cortical GABAergic interneurons. *Nat. Rev. Neurosci.* 14:202–16

Dermon CR, Barbas H. 1994. Contralateral thalamic projections predominantly reach transitional cortices in the rhesus monkey. *J. Comp. Neurol.* 344:508–31

Dombrowski SM, Hilgetag CC, Barbas H. 2001. Quantitative architecture distinguishes prefrontal cortical systems in the rhesus monkey. *Cereb. Cortex* 11:975–88

Douglas RJ, Martin KA. 2004. Neuronal circuits of the neocortex. *Annu. Rev. Neurosci.* 27:419–51

Elston GN, Benavides-Piccione R, DeFelipe J. 2001. The pyramidal cell in cognition: a comparative study in human and monkey. *J. Neurosci.* 21:RC163

Fell J, Axmacher N. 2011. The role of phase synchronization in memory processes. *Nat. Rev. Neurosci.* 12:105–18

Felleman DJ, Van Essen DC. 1991. Distributed hierarchical processing in the primate cerebral cortex. *Cereb. Cortex* 1:1–47

Funahashi S, Kubota K. 1994. Working memory and prefrontal cortex. *Neurosci. Res.* 21:1–11

Fuster JM. 1989. *The Prefrontal Cortex*. New York: Raven Press

Gabbott PLA, Bacon SJ. 1996. Local circuit neurons in the medial prefrontal cortex (areas 24a,b,c, 25 and 32) in the monkey: II. Quantitative areal and laminar distributions. *J. Comp. Neurol.* 364:609–36

Gabbott PLA, Warner TA, Jays PR, Salway P, Busby SJ. 2005. Prefrontal cortex in the rat: projections to subcortical autonomic, motor, and limbic centers. *J. Comp. Neurol.* 492:145–77

García-Cabezas MA, Barbas H. 2014. A direct anterior cingulate pathway to the primate primary olfactory cortex may control attention to olfaction. *Brain Struct. Funct.* 219:1735–54

García-Cabezas MA, Martínez-Sánchez P, Sánchez-González MA, Garzón M, Cavada C. 2009. Dopamine innervation in the thalamus: monkey versus rat. *Cereb. Cortex* 19:424–34

Ghashghaei HT, Barbas H. 2001. Neural interaction between the basal forebrain and functionally distinct prefrontal cortices in the rhesus monkey. *Neuroscience* 103:593–614

Ghashghaei HT, Barbas H. 2002. Pathways for emotions: interactions of prefrontal and anterior temporal pathways in the amygdala of the rhesus monkey. *Neuroscience* 115:1261–79

Ghashghaei HT, Hilgetag CC, Barbas H. 2007. Sequence of information processing for emotions based on the anatomic dialogue between prefrontal cortex and amygdala. *NeuroImage* 34:905–23

Giguere M, Goldman-Rakic PS. 1988. Mediodorsal nucleus: areal, laminar, and tangential distribution of afferents and efferents in the frontal lobe of rhesus monkeys. *J. Comp. Neurol.* 277:195–213

Godlove DC, Maier A, Woodman GF, Schall JD. 2014. Microcircuitry of agranular frontal cortex: testing the generality of the canonical cortical microcircuit. *J. Neurosci.* 34:5355–69

Goldman-Rakic PS. 1988. Topography of cognition: parallel distributed networks in primate association cortex. *Annu. Rev. Neurosci.* 11:137–56

Goulas A, Uylings HB, Stiers P. 2014. Mapping the hierarchical layout of the structural network of the macaque prefrontal cortex. *Cereb. Cortex* 24:1178–94

Graybiel AM. 2008. Habits, rituals, and the evaluative brain. *Annu. Rev. Neurosci.* 31:359–87

Greengard P. 2001. The neurobiology of slow synaptic transmission. *Science* 294:1024–30

Groenewegen HJ, Uylings HB. 2000. The prefrontal cortex and the integration of sensory, limbic and autonomic information. *Prog. Brain Res.* 126:3–28

Haber SN. 2003. The primate basal ganglia: parallel and integrative networks. *J. Chem. Neuroanat.* 26:317–30

Hasselmo ME, Sarter M. 2011. Modes and models of forebrain cholinergic neuromodulation of cognition. *Neuropsychopharmacology* 36:52–73

Hegde J, Felleman DJ. 2007. Reappraising the functional implications of the primate visual anatomical hierarchy. *Neuroscientist* 13:416–21

Hilgetag CC, Grant S. 2010. Cytoarchitectural differences are a key determinant of laminar projection origins in the visual cortex. *NeuroImage* 51:1006–17

Hilgetag CC, Medalla M, Barbas H. 2008. Relationship of connection patterns to the architecture of the primate visual cortex. *Soc. Neurosci. Meet. Plann.* Abstr. 38

Hilgetag CC, O'Neill MA, Young MP. 1996. Indeterminate organization of the visual system. *Science* 271:776–77

Höistad M, Barbas H. 2008. Sequence of information processing for emotions through pathways linking temporal and insular cortices with the amygdala. *NeuroImage* 40:1016–33

Hubel DH, Wiesel TN. 1968. Receptive fields and functional architecture of monkey striate cortex. *J. Physiol.* 195:215–43

Insausti R, Munoz M. 2001. Cortical projections of the non-entorhinal hippocampal formation in the cynomolgus monkey (*Macaca fascicularis*). *Eur. J. Neurosci.* 14:435–51

Isaacson JS, Scanziani M. 2011. How inhibition shapes cortical activity. *Neuron* 72:231–43

Jones EG. 2007. *The Thalamus*. New York: Cambridge Univ. Press

Jones EG. 2009. The origins of cortical interneurons: mouse versus monkey and human. *Cereb. Cortex* 19:1953–56

Jongen-Relo AL, Amaral DG. 1998. Evidence for a GABAergic projection from the central nucleus of the amygdala to the brainstem of the macaque monkey: a combined retrograde tracing and in situ hybridization study. *Eur. J. Neurosci.* 10:2924–33

Kaas JH. 2008. The evolution of the complex sensory and motor systems of the human brain. *Brain Res. Bull.* 75:384–90

Kapfhammer JP, Schwab ME. 1994. Inverse patterns of myelination and GAP-43 expression in the adult CNS: neurite growth inhibitors as regulators of neuronal plasticity? *J. Comp. Neurol.* 340:194–206

Kawaguchi Y, Kubota Y. 1997. GABAergic cell subtypes and their synaptic connections in rat frontal cortex. *Cereb. Cortex* 7:476–86

Krubitzer L. 2009. In search of a unifying theory of complex brain evolution. *Ann. N. Y. Acad. Sci.* 1156:44–67

Lindquist KA, Wager TD, Kober H, Bliss-Moreau E, Barrett LF. 2012. The brain basis of emotion: a meta-analytic review. *Behav. Brain Sci.* 35:121–43

Lorente de Nó R. 1938. The cerebral cortex: architecture, intracortical connections and motor projections. In *Physiology of the Nervous System*, ed. JF Fulton, pp. 291–325. London: Oxford Univ. Press

Marin-Padilla M. 1970. Prenatal and early postnatal ontogenesis of the human motor cortex: a Golgi study. I. The sequential development of the cortical layers. *Brain Res.* 23:167–83

Markov NT, Vezoli J, Chameau P, Falchier A, Quilodran R, et al. 2014. Anatomy of hierarchy: feedforward and feedback pathways in macaque visual cortex. *J. Comp. Neurol.* 522:225–59

Markram H, Toledo-Rodriguez M, Wang Y, Gupta A, Silberberg G, Wu C. 2004. Interneurons of the neocortical inhibitory system. *Nat. Rev. Neurosci.* 5:793–807

Massi L, Lagler M, Hartwich K, Borhegyi Z, Somogyi P, Klausberger T. 2012. Temporal dynamics of parvalbumin-expressing axo-axonic and basket cells in the rat medial prefrontal cortex in vivo. *J. Neurosci.* 32:16496–502

McDonald AJ. 1998. Cortical pathways to the mammalian amygdala. *Prog. Neurobiol.* 55:257–332

Medalla M, Barbas H. 2006. Diversity of laminar connections linking periarcuate and lateral intraparietal areas depends on cortical structure. *Eur. J. Neurosci.* 23:161–79

Medalla M, Barbas H. 2009. Synapses with inhibitory neurons differentiate anterior cingulate from dorsolateral prefrontal pathways associated with cognitive control. *Neuron* 61:609–20

Medalla M, Barbas H. 2010. Anterior cingulate synapses in prefrontal areas 10 and 46 suggest differential influence in cognitive control. *J. Neurosci.* 30:16068–81

Medalla M, Barbas H. 2014. Specialized prefrontal "auditory fields": organization of primate prefrontal-temporal pathways. *Front. Neurosci.* 8:77

Medalla M, Lera P, Feinberg M, Barbas H. 2007. Specificity in inhibitory systems associated with prefrontal pathways to temporal cortex in primates. *Cereb. Cortex* 17(Suppl. 1):i136–50

Meskenaite V. 1997. Calretinin-immunoreactive local circuit neurons in area 17 of the cynomolgus monkey, *Macaca fascicularis*. *J. Comp. Neurol.* 379:113–32

Mesulam M. 2008. Representation, inference, and transcendent encoding in neurocognitive networks of the human brain. *Ann. Neurol.* 64:367–78

Miller EK, Cohen JD. 2001. An integrative theory of prefrontal cortex function. *Annu. Rev. Neurosci.* 24:167–202

Morecraft RJ, Geula C, Mesulam MM. 1992. Cytoarchitecture and neural afferents of orbitofrontal cortex in the brain of the monkey. *J. Comp. Neurol.* 323:341–58

Mountcastle VB. 1957. Modality and topographic properties of single neurons of cat's somatic sensory cortex. *J. Neurophysiol.* 20:408–34

Mountcastle VB. 1997. The columnar organization of the neocortex. *Brain* 120(Pt. 4):701–22

Nauta WJH. 1971. The problem of the frontal lobe: a reinterpretation. *J. Psychiatr. Res.* 8:167–87

Nauta WJH. 1972. Neural associations of the frontal cortex. *Acta Neurobiol. Exp.* 32:125–40

Nauta WJH. 1979. Expanding borders of the limbic system concept. In *Functional Neurosurgery*, ed. T Rasmussen, R Marino, pp. 7–23. New York: Raven Press

Nauta WJH, Haymaker W. 1969. Hypothalamic nuclei and fiber connections. In *The Hypothalamus*, ed. W Haymaker, E Anderson, WJH Nauta, pp. 136–209. Springfield, IL: Thomas

O'Kusky J, Colonnier M. 1982. A laminar analysis of the number of neurons, glia, and synapses in the visual cortex (area 17) of adult macaque monkeys. *J. Comp. Neurol.* 210:278–90

Pandya DN, Seltzer B, Barbas H. 1988. Input-output organization of the primate cerebral cortex. See Steklis & Erwin 1988, pp. 39–80

Pessoa L. 2013. *The Cognitive-Emotional Brain*. Cambridge, MA: MIT Press

Petersen CC. 2007. The functional organization of the barrel cortex. *Neuron* 56:339–55

Petrides M. 2000. Frontal lobes and memory. In *Handbook of Neuropsychology*, ed. F Boller, J Grafman, pp. 67–84. Amsterdam: Elsevier Sci.

Pinto A, Sesack SR. 2008. Ultrastructural analysis of prefrontal cortical inputs to the rat amygdala: spatial relationships to presumed dopamine axons and D1 and D2 receptors. *Brain Struct. Funct.* 213:159–75

Porrino LJ, Crane AM, Goldman-Rakic PS. 1981. Direct and indirect pathways from the amygdala to the frontal lobe in rhesus monkeys. *J. Comp. Neurol.* 198:121–36

Price JL. 2003. Comparative aspects of amygdala connectivity. *Ann. N. Y. Acad. Sci.* 985:50–58

Raizada RD, Grossberg S. 2003. Towards a theory of the laminar architecture of cerebral cortex: computational clues from the visual system. *Cereb. Cortex* 13:100–13

Rakic P. 2002. Neurogenesis in adult primate neocortex: an evaluation of the evidence. *Nat. Rev. Neurosci.* 3:65–71

Rakic P. 2009. Evolution of the neocortex: a perspective from developmental biology. *Nat. Rev. Neurosci.* 10:724–35

Ray RD, Zald DH. 2012. Anatomical insights into the interaction of emotion and cognition in the prefrontal cortex. *Neurosci. Biobehav. Rev.* 36:479–501

Rempel-Clower NL, Barbas H. 1998. Topographic organization of connections between the hypothalamus and prefrontal cortex in the rhesus monkey. *J. Comp. Neurol.* 398:393–419

Rempel-Clower NL, Barbas H. 2000. The laminar pattern of connections between prefrontal and anterior temporal cortices in the rhesus monkey is related to cortical structure and function. *Cereb. Cortex* 10:851–65

Robbins TW, Arnsten AFT. 2009. The neuropsychopharmacology of fronto-executive function: monoaminergic modulation. *Annu. Rev. Neurosci.* 32:267–87

Rockel AJ, Hiorns RW, Powell TP. 1980. The basic uniformity in structure of the neocortex. *Brain* 103:221–44

Rockland KS, Pandya DN. 1979. Laminar origins and terminations of cortical connections of the occipital lobe in the rhesus monkey. *Brain Res.* 179:3–20

Romanski LM, Averbeck BB. 2009. The primate cortical auditory system and neural representation of conspecific vocalizations. *Annu. Rev. Neurosci.* 32:315–46

Rosene DL, Van Hoesen GW. 1977. Hippocampal efferents reach widespread areas of cerebral cortex and amygdala in the rhesus monkey. *Science* 198:315–17

Saha S, Batten TF, Henderson Z. 2000. A GABAergic projection from the central nucleus of the amygdala to the nucleus of the solitary tract: a combined anterograde tracing and electron microscopic immunohistochemical study. *Neuroscience* 99:613–26

Salzman CD, Fusi S. 2010. Emotion, cognition, and mental state representation in amygdala and prefrontal cortex. *Annu. Rev. Neurosci.* 33:173–202

Sanides F. 1970. Functional architecture of motor and sensory cortices in primates in the light of a new concept of neocortex evolution. In *The Primate Brain: Advances in Primatology*, ed. CR Noback, W Montagna, pp. 137–208. New York: Appleton-Century-Crofts Educational Division/Meredith Corporation

Schmahmann JD, Pandya DN. 2008. Disconnection syndromes of basal ganglia, thalamus, and cerebrocerebellar systems. *Cortex* 44:1037–66

Schroeder CE, Lakatos P. 2009. Low-frequency neuronal oscillations as instruments of sensory selection. *Trends Neurosci.* 32:9–18

Sesack SR, Deutch AY, Roth RH, Bunney BS. 1989. Topographical organization of the efferent projections of the medial prefrontal cortex in the rat: an anterograde tract-tracing study with Phaseolus vulgaris leucoagglutinin. *J. Comp. Neurol.* 290:213–42

Shepherd GM. 2011. The microcircuit concept applied to cortical evolution: from three-layer to six-layer cortex. *Front. Neuroanat.* 5:30

Sherman SM, Guillery RW. 1996. Functional organization of thalamocortical relays. *J. Neurophysiol.* 76:1367–95

Sohal VS, Zhang F, Yizhar O, Deisseroth K. 2009. Parvalbumin neurons and gamma rhythms enhance cortical circuit performance. *Nature* 459:698–702

Steklis HD, Erwin J, eds. 1988. *Comparative Primate Biology*, Volume 4: *Neurosciences*. New York: Alan R. Liss

Timbie C, Barbas H. 2014. Specialized pathways from the primate amygdala to posterior orbitofrontal cortex. *J. Neurosci.* 34:8106–18

Tognoli E, Kelso JA. 2014. The metastable brain. *Neuron* 81:35–48

Turner BH, Mishkin M, Knapp M. 1980. Organization of the amygdalopetal projections from modality-specific cortical association areas in the monkey. *J. Comp. Neurol.* 191:515–43

Uylings HB, Groenewegen HJ, Kolb B. 2003. Do rats have a prefrontal cortex? *Behav. Brain Res.* 146:3–17
Vertes RP. 2004. Differential projections of the infralimbic and prelimbic cortex in the rat. *Synapse* 51:32–58
Vertes RP. 2006. Interactions among the medial prefrontal cortex, hippocampus and midline thalamus in emotional and cognitive processing in the rat. *Neuroscience* 142:1–20
Vogt BA, Hof PR, Zilles K, Vogt LJ, Herold C, Palomero-Gallagher N. 2013. Cingulate area 32 homologies in mouse, rat, macaque and human: cytoarchitecture and receptor architecture. *J. Comp. Neurol.* 521:4189–204
Vogt BA, Pandya DN. 1987. Cingulate cortex of the rhesus monkey: II. Cortical afferents. *J. Comp. Neurol.* 262:271–89
von Economo C. 1927/2009. *Cellular Structure of the Human Cerebral Cortex*, transl./ed. LC Thriarhou. Basel, Switz.: Karger
Wang XJ, Tegner J, Constantinidis C, Goldman-Rakic PS. 2004. Division of labor among distinct subtypes of inhibitory neurons in a cortical microcircuit of working memory. *PNAS* 101:1368–73
Wonders CP, Anderson SA. 2006. The origin and specification of cortical interneurons. *Nat. Rev. Neurosci.* 7:687–96
Woodruff A, Yuste R. 2008. Of mice and men, and chandeliers. *PLOS Biol.* 6:e243
Xu X, Roby KD, Callaway EM. 2010. Immunochemical characterization of inhibitory mouse cortical neurons: three chemically distinct classes of inhibitory cells. *J. Comp. Neurol.* 518:389–404
Yakovlev PI. 1948. Motility, behavior and the brain: stereodynamic organization and neurocoordinates of behavior. *J. Nerv. Ment. Dis.* 107:313–35
Yeterian EH, Pandya DN, Tomaiuolo F, Petrides M. 2012. The cortical connectivity of the prefrontal cortex in the monkey brain. *Cortex* 48:58–81
Zaborszky L, Csordas A, Mosca K, Kim J, Gielow MR, et al. 2013. Neurons in the basal forebrain project to the cortex in a complex topographic organization that reflects corticocortical connectivity patterns: an experimental study based on retrograde tracing and 3D reconstruction. *Cereb. Cortex* 25:118–37
Zikopoulos B, Barbas H. 2007a. Circuits for multisensory integration and attentional modulation through the prefrontal cortex and the thalamic reticular nucleus in primates. *Rev. Neurosci.* 18:417–38
Zikopoulos B, Barbas H. 2007b. Parallel driving and modulatory pathways link the prefrontal cortex and thalamus. *PLOS ONE* 2:e848
Zikopoulos B, Barbas H. 2010. Changes in prefrontal axons may disrupt the network in autism. *J. Neurosci.* 30:14595–609
Zikopoulos B, Barbas H. 2012. Pathways for emotions and attention converge on the thalamic reticular nucleus in primates. *J. Neurosci.* 32:5338–50