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Update article

Neocortical areas, layers, connections, and gene expression☆

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Abstract

Cortical patterns of gene expression provide a new approach to long standing issues of lamination, and area identity and formation. In this review, we summarize recent findings where molecular biological techniques have revealed a small number of area-specific genes in the nonhuman primate cortex. One of these (*occ1*) is strongly expressed in primary visual cortex and is associated with thalamocortical connections. Another gene, *RBP*, is more strongly expressed in association areas. It is not clear whether *RBP* might be linked with any particular connectional system, but several possibilities are raised. We also discuss possible roles of area-specific genes in postnatal development, and conclude with a brief sketch of future directions.
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1. Introduction

The neocortex comprises a number of distinct areas, as mapped by Korbinian Brodmann, among others, in the early 20th century (Garey, 1994). Although it is now widely accepted that the neocortex can be divided into functionally and anatomically distinct areas, the detailed organization is far from clear, and many questions remain concerning area identity, function, and formation.

A comparatively recent approach has been to identify the genes that are specifically expressed in the cortex, with the idea that these might cast light on the molecular and cellular mechanisms underlying cortical area formation and function. Along these lines, we can recall earlier pioneering studies on LAMP (limbic system-associated membrane protein), Cat-301 and latexin (Hendry et al., 1984; Levitt, 1984; Arimatsu et al., 1992). In fact, the combination of information concerning molecular markers such as Cadherins (Suzuki et al., 1997), transcriptional factors (Emx1, SCIP, lhx2, Pax6, etc.), and boundary molecules (Id-2, Ephs, Ephrins, RZR-beta, etc.) with knockout (loss-of-function) and transgenic (mainly gain-of-function) mice technology has significantly advanced basic questions of early cortical determination (Rubenstein et al., 1999; O'Leary and Nakagawa, 2002).

In the first section of this review, we give a brief overview of genetic and epigenetic influences in the formation of cortical areas, as a background to gene expression in the adult. Then, we describe recent findings using molecular biological technologies that identify genes specifically expressed in brain regions or in neocortical areas in the nonhuman primate and discuss their significance. Following this, we attempt to discuss these molecular biological results in relation to what has been learned about neocortical connections on the basis of anatomy and physiology, and conclude with a brief section on area-specific genes in postnatal development.

2. Genetic and epigenetic control of cortical regionalization

The mechanisms of area formation have long been debated. One hypothesis is the 'protomap' model (Rakic, 1988). The protomap model proposes that cells that comprise each area are already predetermined when the precursors are in the ventricular zone. The other model is the 'protocortex' model (O'Leary, 1989). The protocortex model proposes that the fate

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of neocortical cells is not determined until they receive projections from the thalamus. Both hypotheses are based on experimental evidence. Although it has been difficult to determine which hypothesis is correct or to what extent both mechanisms might contribute to neocortical formation, a general consensus seems to have been obtained on this subject. This consensus, based mainly on studies of neocortical formation in genetically manipulated mice, proposes that the early neocortical regionalization is independently determined before the ingrowth of thalamo-cortical projections (Rubenstein et al., 1999; O'Leary and Nakagawa, 2002), and thus is genetically programmed.

Since early neocortical areas and thalamic structures develop independently, a major question is how connections are established between cortical and thalamic regions. A critical role in cortical formation has been attributed to pioneer neurons located in the subplate which send local and long projections between cortical and other structures (McConnell et al., 1989). According to the "handshake hypothesis," axons from the thalamus and from early cortical preplate cells meet in the basal telencephalon and, from this association, further develop to the appropriate target areas (Molnar and Blakemore, 1995). Although this hypothesis is still under debate, accumulating evidence is supportive (see Dwyer and O'Leary, 2001; Lopez-Bendito and Molnar, 2003).

In mice, knockout of transcriptional factor(s) Dlx1/Dlx2 and Ebf1 demonstrates that the early projection patterns of thalamocortical axons are not controlled by factors within the neocortex and dorsal thalamus, but rather by the relative position of thalamic axons that pass through the subcortical telencephalon or basal ganglia primodium (Garel et al., 2003; Garel and Rubenstein, 2004). Eph-related receptors and ligands known to control the retinotectal projection (Drescher, 1997) also have critical roles in regional specificity of thalamocortical projections (Dufour et al., 2003; Bolz et al., 2004). A further example is neurogenin2 (ngn2), a basic HLH (helix loop helix) transcriptional factor which is expressed in the rostral dorsal thalamus and cortex, and which plays a critical role in the establishment of projections from the ventrolateral thalamic nucleus to the motor cortex in mice (Seibt et al., 2003).

Even though early neocortical regionalization is determined without direct connections between the cortex and the thalamus as we see above, once the thalamocortical projections are formed, these are likely to play an important role in further processes of neocortical regionalization and area formation. There are many examples to indicate that thalamocortical projections profoundly influence cortical organization (Rakic, 1988; Windrem and Finlay, 1991; Wiesel and Hubel, 1963; Schlaggar and O'Leary, 1991; Sur et al., 1988; Sharma et al., 2000; Catania and Kaas, 2001).

How do thalamocortical projections exert an influence on cortical formation? Two categories of possible mechanisms can be considered. One involves molecules that are associated with or released from thalamic fibers. BDNF is one such factor and has been implicated, for example, in the control of the time course of the critical period for ocular dominance (for example, Huang et al., 1999; Berardi et al., 2000). The neurotransmitter acetylcholine is known to influence various developmental processes. Pulvinocortical connections transiently express acetylcholine; cholinesterase staining shows an early border between striate and extrastriate areas in both monkey and human brains, at a stage earlier than the establishment of cytoarchitectonic borders (Kostovic and Rakic, 1984). Adhesion molecules (Cadherins, etc.) may also play critical roles in sorting specific types of neurons and forming specific types of neural circuitries (Price et al., 2002). Another mechanism is related to neural activity. A classic example is the formation of ocular dominance columns, where the balance of inputs from the left and right eyes has long been considered to be important (Wiesel and Hubel, 1963, 1965a, 1965b).

Nevertheless, continuing work on the ocular dominance system has revealed several new aspects. For example, the segregation of eye-specific projections in monkeys appears to occur earlier than previously reported, and in particular before the reported onset of ganglion cell axonal loss and retinogeniculate synapse elimination. In the lateral geniculate nucleus of fetal monkeys at E69 (about 100 days before birth), inputs from the two eyes are extensively intermingled. By E78, however, intravitreal injections of two distinguishable anterograde tracers (cholera toxin B fragment conjugated to Alexa 488 or Alexa 594) reveal eye-specific segregation in the parvocellular layers and by E84, the adult pattern of segregation is established (Huberman et al., 2005). This is in accord with other work, suggesting that anatomical "proto-columns" are already formed before the start of the critical period in ferrets (Crowley and Katz, 2002; Katz and Crowley, 2002). Possibly, the anatomical columnar structure may be predetermined by genetically programmed mechanisms while visual activity has a critical role in later development.

Intracortical inhibitory circuits shape the geometry of incoming thalamic arbors in kittens, a result that indicates the impact of neuronal activity on cortical columnar architecture (Hensch and Stryker, 2004). This general scheme may be true in other well-studied model sensory systems, such as the rodent barrel cortex (Katz and Crowley, 2002; Lopez-Bendito and Molnar, 2003). Recent studies combining molecular biological techniques and physiology have elegantly revealed mechanisms underlying critical period plasticity in local cortical circuits of ocular dominance columns in mice (Hensch, 2005). Still to be elucidated, however, is how postnatal plasticity is related to the columnar architecture that may be formed before the critical period begins, as described above in cats, ferrets and monkeys.

Cytochrome oxidase (CO) patches in area V1 of monkeys have been another useful model for evaluating genetic and activity-dependent influences. CO patches can be visualized at about E139, almost four weeks before birth (Wong-Riley and Jacobs, 2002). Moreover, early bilateral retinal ablations, carried out before the generation of photoreceptors and bipolar cells (at E81) and before the generation of neurons destined for layer III of area V1, do not prevent the formation of CO patches (Kuljis and Rakic, 1990). The persistence of CO patches in dark-reared newborn monkeys (Horton and Hocking, 1996) is another indication that visual experience is not necessary for their formation.

3. Genes that are specifically expressed in the primate neocortex

In this section, we review differences in gene expression first, across brain regions, and then across cortical areas. In contrast with cross-regional comparisons, only a very small number of genes have been identified with significant area-specific expression. Possible reasons are discussed in Section 3.1.

3.1. Genes that are specifically expressed in different brain regions

DNA microarray analyses from three independent laboratories have examined gene expression patterns in the cerebellum and cortical areas in the anterior cingulate (AnCG) and dorsolateral prefrontal cortex (DLPFC) in humans (Evans et al., 2003). Large numbers of genes (2625, 2405, 3493 genes in the three different laboratories) show a significant difference in expression between the cerebellum and cerebral cortex and 969 of these genes are consistently reported by all three laboratories. These microarray analyses on human postmortem brains suggest that the regional profile of gene expressions is accounted for by particular sets of genes.

Functional classification using gene Ontology tools (Su et al., 2002) identifies functional families enriched in the cerebellum and cerebral cortex. Seventy-four genes were specifically detected in cerebral cortex and 15 genes more specifically detected in cerebellum but not in cerebral cortex. Cortex-specific transcript Ontology shows that genes with a high ratio of enrichment in cortex occur in such categories of gene families as Calmodulin binding, Brain development, Receptor protein kinase and Peptide hormone. These function in similar metabolic pathways. Interestingly, several genes identified by these analyses have been previously implicated in psychiatric disorders. These genes are RGS4 (schizophrenia), NPY (bipolar disorder), cholecystokinin (depression), somatostatin (mania, schizophrenia, Alzheimer's disease), and 5HT2A (major depression and suicide) (Evans et al., 2003).

Microarray assays of expression profiles from different adult mouse brain regions such as neocortex, hippocampus, cerebellum, and midbrain, also indicate that unique gene expression is most significant in the cerebellum, because 23 out of 7089 genes show little expression in other brain regions. More extensive analysis using microarray and bioinformatic methods for 24 brain regions further revealed region-restricted or region-enriched gene expression patterns in adult mice. Zapala et al. (2005) identify 93 genes with expression restricted to a region or specific subregion and, in another set of experiments, they further identified 129 genes that showed clear regional enrichment, yielding 192 unique genes in total.

Zapala et al. listed 14 cortex-enriched or cortex-restricted genes. These genes seem to consist of two major categories of transcription related factors (Lasp1: LIM and SH3 protein 1, Tbr1: T-box brain gene 1, Wnt10a: wingless related MMTV integration site 10a) and immune system related proteins (Terb-V13: T-cell receptor beta, variable 13, Ccl27: chemokine ligand 27, Cd6: CD6 antigen, Cd34: CD34 antigen). Transcriptional factors in the brain should play important roles in directing cortical formation. The expression of immune system related proteins is consistent with recently described influences of immune signals in the brain (Boulanger and Shatz, 2004). T-box brain gene 1 appeared with the human microarray analysis reported above. LIM and myosin light chain and their related proteins also show specific expression in both mouse and human cortex. From the gene expression-based brain map, Zapala et al. (2005) propose that adult brain gene expression patterns bear an embryonic imprint that is primarily determined by cascades of signal molecules, as transcriptional factors for regional formation of the brain.

In summary, there are significant differences of gene expression between cerebral cortex and other brain regions. By contrast, among the neocortical areas, there are a very small number of genes that show significant area-specific expression patterns (Evans et al., 2003). Although three laboratories independently showed that 559, 716, or 2697 genes were significantly different between AnCG and DLPFC in human, only four genes have been reproducibly identified by all three laboratories. These four genes are: heat shock binding protein 1 (HSBP1) and the purinergic receptor, P2y1, which were enriched in AnCg relative to DLPFC and cocaine- and amphetamine-regulated transcript (CART) and an unidentified transcript, KIAA0084, which were enriched in DLPFC relative to AnCg. The roles of these genes remain to be elucidated.

Variations across laboratories, such as noted above, are largely due to technical variations such as scanner settings and calibration, and also to individual variations across human subjects. Despite these variations, data are consistent among three laboratories (1) that there are significant differences in the expression level of 969 genes between cerebellum and cortex and (2) that only 4 genes show consistent differences in expression levels between AncG and DLPFC. Thus, the evidence is strong that only a very small number of genes exhibit conspicuous area-specific specializations. This is consistent with the macroarray analysis of 1088 genes in human tissue previously reported by Watakabe et al. (2001), in which only a few genes were found in human with significant differences among three areas (frontal, motor and visual). (Only two out of 1088 genes showed more than a two-fold difference, and no gene showed more than a four-fold difference.)

Two genes that differ by more than two-fold among the three areas are Annexin II (3.6-fold motor/visual areas) and Early Growth Response protein I (EGRI: 2.6-fold). Annexin II, also known as annexin A2, is a member of the Annexin family, which is characterized by Ca^{++}/lipid binding proteins that differ from most other CA^{++}-binding proteins in their Ca^{++} binding sites (Rescher and Gerke, 2004), and are associated with diverse functions. For example, annexin A2 is a high-affinity receptor for β2-glycoprotein I (β2GPI). β2GPI plays a critical role in crosslinking annexin A2 and in transducing an activation signal to endothelial cells (Wolberg and Roubey, 2005; Zhang and McCrae, 2005), thereby causing the antiphosolipid syndrome (APS: Meroni et al., 2004). Annexin II also may play critical roles in other physiological and pathological cell responses but its role in the nervous system is still largely

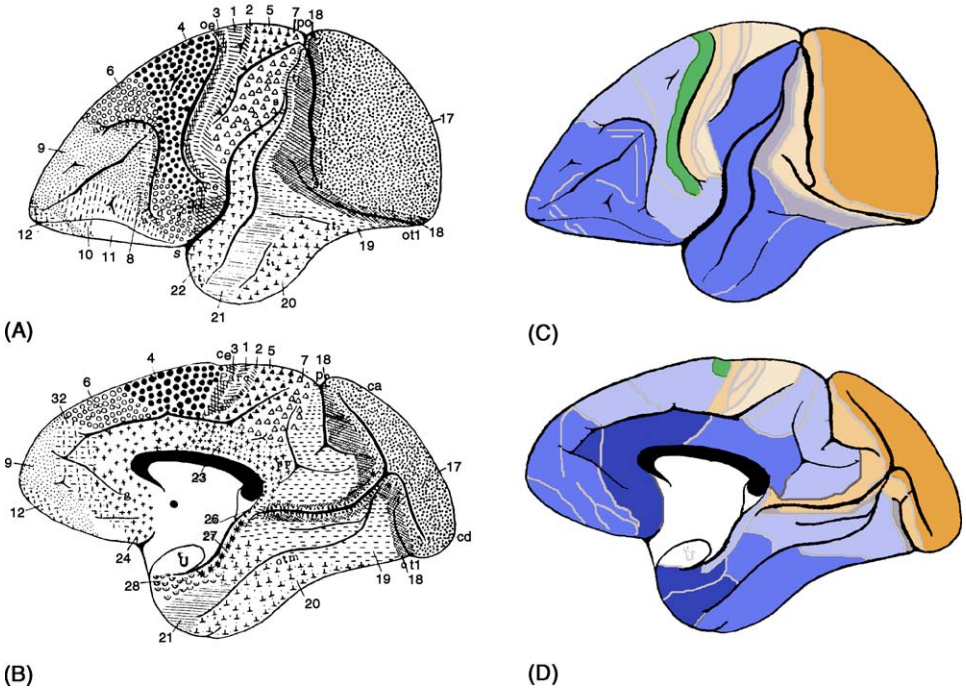


Fig. 1. Expression patterns of primate neocortical area-specific genes. (A and B) Cytoarchitectonic cortical areas in the guenon monkey, as distinguished by Brodmann, from the lateral (A) and medial (B) views. (C and D) Illustration of area-specific gene expression. Expression of three area-specific genes is illustrated based on the following data in macaques. *occ1* (brown) is expressed in primary sensory areas, particularly in visual cortex (Tochitani et al., 2001). *RBP* (blue) is expressed in association areas (Komatsu et al., 2005). *gdf7* (green) is expressed in the motor area (Watakabe et al., 2001). Shaded dark, light, and pale colors indicate strong, moderate and weak expression of each gene. Mixed color areas of pale blue and brown indicate where both *RBP* and *occ1* are expressed in different layers (see Figs. 2 and 3). Note that the green colored area indicates the area from which the samples for RT-PCR and northern analysis were taken (Watakabe et al., 2001) (Drawing of C and D is courtesy of Dr. Yusuke Komatsu).

unknown. EGR1, also known as NGFI-A/Krox-24/*zif-268*, is an immediate early gene and may play important roles in memory reconsolidation (Lee et al., 2004) and cognitive memory (Miyashita, 2004). It is up-regulated in hippocampus and cortex during REM sleep (Maquet, 2001). As levels of EGR1 are highest in frontal, moderate in visual, and lowest in motor areas, there may be some preferential area-specific roles in the cortex.

Extensive differential display analysis across five monkey neocortical areas (FDΔ, FA, TE, OA, OC) also showed that only three genes have a significantly different expression level (defined as more than maximal 10-fold difference among the areas examined; Watakabe et al., 2001; Tochitani et al., 2001; Komatsu et al., 2005: see Fig. 1). The detailed expression profiles are described in the following section.

From these data, one might conclude that the difference in gene expression between neocortical areas is much smaller than that observed between neocortex and other brain regions (see Table 1). It is important to note that this does not mean that there is no difference in gene expression among areas. Rather, it suggests that area distinctness is mainly determined by the *concerted* interaction of many genes which individually exhibit rather small differences of expression within the neocortical areas (see also Sugino et al., 2006).

3.2. Genes that are specifically expressed in primate neocortical areas

As mentioned above, using the PCR based differential display method, three genes have been reported that are specifically expressed in primate neocortical areas (Fig. 1). One is the *occ1* gene, isolated from and highly expressed in the primate visual cortex, which has turned out to be the macaque homologue of mouse TSC-36 and human FRP (follistatin-related protein) (Tochitani et al., 2001). Although the function

Table 1
Genes specifically expressed in the brain and neocortical areas

References	Number of genes examined	Specific expression in the brain	Neocortical area specific genes[a]
Evans et al. (2003)	12652	74 (0.58%) only in cerbral cortex	4 (0.036%)
Zapala et al. (2005)	7852	14 (0.18%) cortex specific or enriched genes	NT
Watakabe et al. (2001)	1088	NT	0 (<0.09%)[b]

[a] See text for the definition for each data source. Note that criteria for area-specific genes are different among the sources listed.
[b] More than four-fold difference among three areas (prefrontal, motor and occipital).

of *occ1* is still unknown, its expression showed several characteristic features. (1) In the adult primate neocortex, *occ1* is expressed in the primary visual cortex and its expression clearly defines the V1 and V2 border (Fig. 2). (2) In V2, a relatively strong expression is specifically observed in the deeper layer III, a zone which is likely to receive the projections from the pulvinar thalamic nucleus (Levitt et al., 1995; Rockland et al., 1999). (3) Of the other neocortical areas, the primary auditory and somatosensory cortices show some significant expression although the level is much lower than that in the primary visual cortex. (4) In monkeys where retinal activity was arrested by TTX injection into one eye, the expression was specifically reduced in the monocularly deprived columns in V1. Thus, the expression is activity-dependent in the primary visual cortex. (5) The expression is markedly enhanced during postnatal development (Tochitani et al., 2003). Together, these features suggest that *occ1* expression is associated with mechanisms that control primary sensory areas, particularly the primary visual cortex.

There are two modes of *occ1* expression in monkey neocortex (Takahata et al., 2005). In one mode, *occ1* is expressed in excitatory cells in primary sensory areas, particularly in visual cortex, and this is specific to primates. In the other mode, *occ1* is expressed in parvalbumin positive GABAergic interneurons

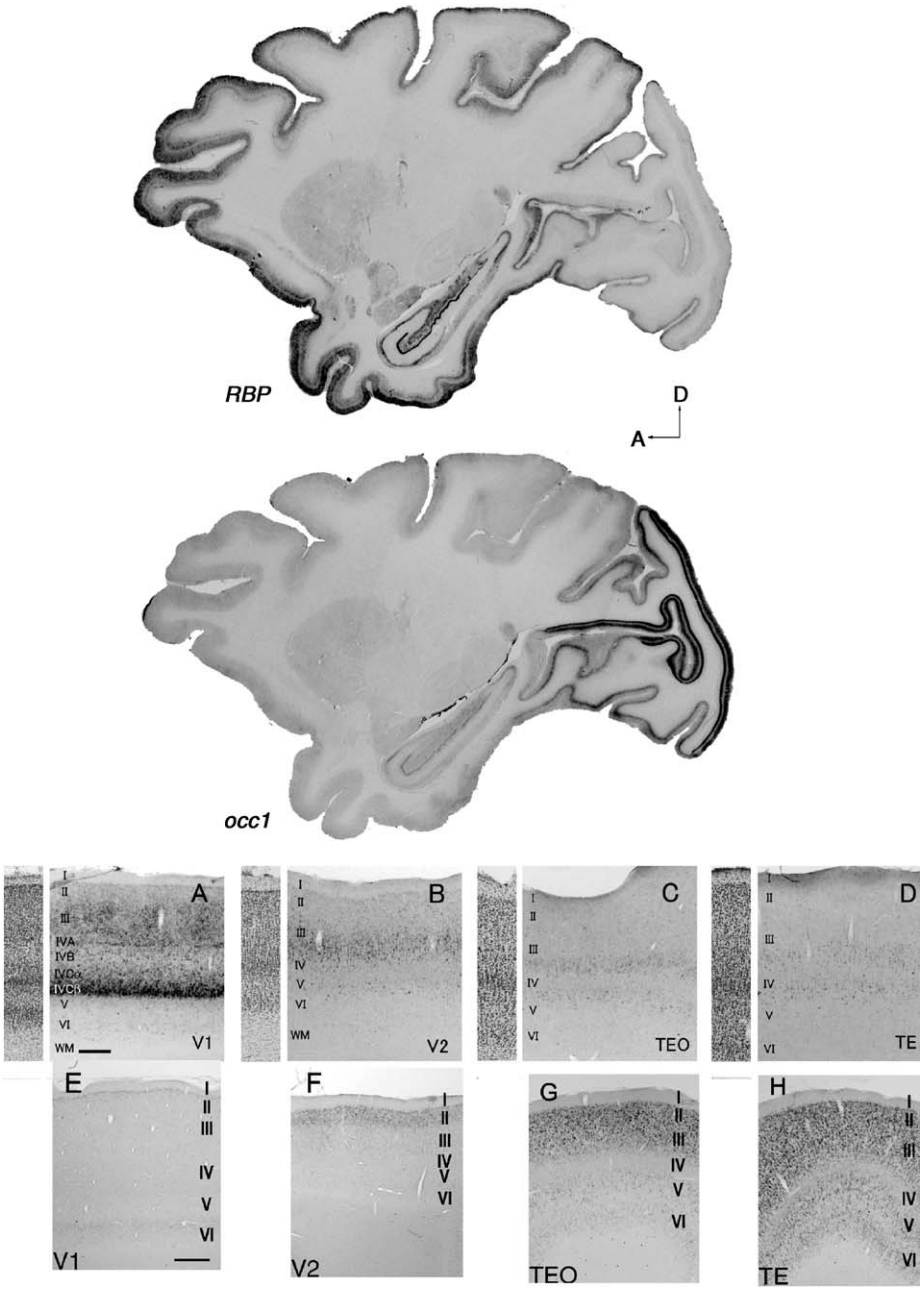


Fig. 2. Top: expression of *occ1* and *RBP* in the primate neocortex. The same figure is used in Fig. 5A in Komatsu et al., 2005. Bottom: expression of *occ1* (A–D) and *RBP* (E–H) in the ventral visual pathway (the same figure is used in Fig. 1 of Takahata et al., 2005 and Fig. 3 of Komatsu et al., 2005). The small panels at the side of each photograph (A–D) indicate Nissl stained preparations of the same area.

throughout neocortex. The *occ1* expression in excitatory neurons is activity dependent and strictly regulated by thalamocortical projections.

The role of afferent activity in the gene expression of primate neocortex has been extensively studied (see Jones, 1990 for review). In the visual cortex of adult monkeys, levels of immunoreactivity (IR) of GABA, GAD and tachykinins are reduced in deprived ocular dominance columns within 24 h of intraocular injection of TTX, while levels of IR of CAMK II kinase are increased (Jones, 1990). Activity-dependent synaptic plasticity and regulation of glutamate receptors in the mammalian visual cortex are also reported (Fox and Daw, 1993; Bear, 1996; Catalano et al., 1997). The change in *occ1* expression by monocular deprivation is similar to that of tachykinins and CAMK II-β mRNAs, in that mRNA levels are decreased within five days in the deprived columns (Benson et al., 1994; Tighilet et al., 1998). However, *occ1* expression is unique in its highly specific and activity-dependent expression, presumably by excitatory spiny stellate neurons of the primate visual cortex as described above.

A second gene is *RBP* (retinol-binding protein), which is only barely expressed in the primate visual cortex, and turns out to be specific for association areas. *RBP* expression also shows characteristic features. (1) Its expression is high in sensory association areas, higher association areas and limbic areas, but low in the primary sensory areas. Expression is complementary to that of *occ1* and to thalamo-cortical parvalbumin immunoreactivity (PV-IR) in primary sensory areas. (2) In early sensory pathways, the expression is limited to superficial layers only (in particular, layer II). In higher sensory areas, the expression is expanded into layers III and then V. (3) In higher-order association areas, *RBP* is expressed throughout all layers except layer IV. (4) This characteristic distribution of *RBP* is mainly formed during postnatal development. RBP probably regulates the concentration of retinoic acid (RA) by the delivery of retinol, which is converted into RA in cells as described in the next paragraph. Although the role of RA in the mature brain is not yet known, the characteristic expression of *RBP* within association areas may provide a clue to the molecular basis of the formation and function of these areas.

Retinol (Vitamin A) is bound to RBP, effectively transported into plasma, and used for the substrate of retinal aldehyde dehydrogenase (RALDH) which irreversibly converts retinol into retinoic acid (RA). RA is a potent morphogen in a variety of developmental processes (e.g., Gilbert, 2003). A recent study in the mouse suggests that RALDH is transiently expressed in the postnatal brain (Wagner et al., 2002). Since RA is a potent regulator, RBP may be a critical modulator of RA, and may thereby influence the formation, maintenance, and/or function of association areas.

One surprising feature is that the expression of *occ1* is quite complementary to that of *RBP* as seen in Fig. 2. In V2, *occ1* signals are specifically high in lower layer III. These signals seem to be well matched with the laminar distribution of pulvinocortical projections, as visualized by WGA-HRP and CO staining (Levitt et al., 1995 and see Section 5). As we already described, in V1 *occ1* signals are highly expressed in cells postsynaptic to LGN projections. Therefore, cells that show high *occ1* expression in other areas of monkey neocortex may be inferred to receive thalamocortical projections. This suggests that some degree of arealization is controlled by thalamocortical projections even beyond the primary sensory areas; but other mechanisms also need to be considered in view of the sharp contrast between expression patterns of *occ1* and *RBP*, as will be discussed in Section 6.

A third area-specific gene is *gdf-7* (Fig. 1). This gene is specifically expressed in the primate motor cortex (Watakabe et al., 2001). *gdf-7* plays important roles in the determination of dorsal spinal interneurons and cerebellar neurons (Lee et al., 1998; Alder et al., 1999); but its role in the neocortex remains to be established.

Thus, by the differential display method, we know that some genes are specifically expressed in certain primate neocortical areas, but these genes are very limited in number (Table 1). To further determine the significance of this rare class of genes in neocortical formation, the differentially expressed genes are being further systematically isolated using the RLCS (restriction landmark c-DNA scanning) method. The RLGS (restriction landmark genomic scanning) method was originally developed for genomic DNA (Hayashizaki et al., 1993) and modified as RLCS for cDNA (Suzuki et al., 1996). With the combination of two restriction enzymes and two-dimensional gel electrophoresis, nearly one thousand species of cDNA can be classified in a polyacrylamide gel. Using about a dozen pairs of combination of restriction enzymes, five genes were found that exhibited more than a five-fold difference among neocortical areas (frontal, motor, temporal, and primary visual cortices), a fraction which corresponds to roughly about 0.05% of the RNA species examined (Komatsu and Yamamori, unpublished observation). This value is very close to the value estimated in Table 1. Given the number of 23,000 total genes in the human genome, the fraction of 0.05% corresponds to 11 to 12 genes. These values may be affected by several factors such as the percentage of total RNA species expressed in the brain (approximately 50%; Chikaraishi et al., 1978), overlapping RNA species within different combinations of restriction enzymes, overlooking of less abundant RNA species. In any event, however, it can be concluded with confidence that genes that show marked cross-area differences do exist, but that their number is very limited.

3.3. What does area-specific gene expression mean?

Since tissue used for extracting RNA from a particular area contains many types of cells, the ratios of gene expression among different areas only reflect the average of all cells in each area. In the extreme case, if area specialization occurs only in a particular type of neuron, its expression ratio is very much diluted by other mRNAs. Accordingly, any specific expression is masked when the ratios of expression of a single gene are compared between areas by extracting RNA from tissue samples that contain a very large number of cells. To overcome

this, neuronal subtype-specific genes can be isolated. For example, genes that control corticospinal motor neuron development in vivo in mouse have been isolated using microarray techniques, but only after retrograde fluorescent labeling and cell sorting (Arlotta et al., 2005). Therefore, even if such genes exist in adult monkey motor cortex, they cannot be detected by simply comparing extracted RNA from motor cortex to that from other areas. In this regard, it is even more surprising that we were able to detect such area-specific genes as *occ1* and *RBP* by simply comparing extracted RNA species among different areas. The existence of this type of gene implies a common feature among many types of neurons, if not all neurons, within a certain area. The meaning of this type of gene may require the elucidation of this shared quality.

4. Gene expression and cortical areas

Areas are a basic feature of cortical organization, and the definition of a cortical area has been discussed many times (for recent reviews, see Kaas, 2005; Rosa and Tweedale, 2005, and other articles in Philosophical Transactions, volume 360). Strikingly, the rare area-specific genes show a close correspondence with the major classical subdivisions of primary sensory, primary motor, limbic, and associational areas (Fig. 1). Our understanding of these specializations is still elementary, and gene expression profiles provide a new tool for probing the issues of area identity and differentiation.

Primary sensory areas in particular are easily distinguishable by multiple criteria, and share certain common features. They have a cell dense layer IV which contains a specialized cell type (spiny stellate cells), they receive connections from specific sensory thalamic nuclei, they are organized according to robust topographic and feature maps, and they have sharp borders with adjoining areas. Calcium binding proteins (e.g., Jones et al., 1995 for auditory cortex) and transmitter receptors (Zilles et al., 2004), among other substances, commonly give an accurate identification of primary areas. Inactivation experiments have shown that receptive field properties in the primary areas are dependent on thalamocortical connections (Bullier et al., 1994).

Are area-specific genes related to one or more of the features? For *occ1*, expression is dependent on retinal input through the LGN, as shown by the monocular injections of TTX. Furthermore, in the primary areas, *occ1* is expressed by the excitatory neurons in the major thalamorecipient layers (Takahata et al., 2005). Thus, for this gene, as already stated, there is a strong association with thalamocortical inputs.

The distinguishing features of association cortices are less clear. In contrast with primary areas: (1) there is less or no input from specific sensory thalamic nuclei and (2) functional maps show less orderly or, for higher association areas, no topography (Tanaka, 1996, 2003). (3) Association areas are connected with more areas and nuclei (Felleman and Van Essen, 1991) and (4) there is some likelihood that areas have different levels or even kinds of plasticity potential. As one indication of this, high frequency electrical stimulation of horizontal intrinsic connections in layers II and III evokes LTP of synaptic transmission efficacy in this system in area TE, but LTD in V1 (Murayama et al., 1997; Fujita, 2002). (5) A particularly important difference may be the distribution of specialized cell types. So far, association areas have been thought not to have specialized cell types, but rather to show quantitative differences in the relative proportions of different cell types. These trends are rather clear for interneurons, which over the last few years have been better characterized than pyramidal cells. For example, calretinin-positive bipolar interneurons and parvalbumin-positive chandelier interneurons are more abundant in area TE than in area V2 in monkeys (DeFelipe et al., 1999). Thus, in contrast with primary areas, where spiny stellate cells form a distinct population, cell types may be more uniform in association areas. Further investigations using cell-type specific markers and histochemical confirmation of genetic profiling (e.g. Arlotta et al., 2005) may be able to resolve this issue. (6) Another characterization of association cortices is that borders with adjoining areas are often difficult to determine (Roland and Zilles, 1998). An interesting possibility is that sharp borders might specifically characterize ‘‘core’’ areas, such as visual area MT, or the sensory areas, while the greater proportion of association cortex may have only gradual transitions (Rosa and Tweedale, 2005 and their Fig. 12). Sharp borders may be associated with thalamocortical projections from specific thalamic nuclei, since these tend to coincide closely, at least in the primate, with primary areas. For the early visual areas, callosal connections sharply demarcate the border, corresponding to the vertical meridian representation, between areas V1 and V2; but even this constitutes a broad zone of about 6.0 mm (Newsome and Allman, 1980), and for V4 and higher order areas, callosal connectivity is at best only an approximate indicator of borders (Van Essen et al., 1984). Although it has become standard to divide the cortex into area units, there is some evidence in favor of regional or gradient-like organization even in the adult brain. In rodents, one immediately thinks of the discovery of LAMP and its localization to multiple areas within the classical limbic region (Levitt, 1984). Similarly, latexin, a carboxypeptidase A inhibitor, is expressed in intrahemispheric corticocortical neurons in the deeper layers, throughout the lateral sector of neocortex (Arimatsu et al., 1999, 2003; Bai et al., 2006).

As additional evidence in favor of gradient-like organization, during early corticogenesis, at least two modes of grouping cells have been distinguished on the basis of gene expression patterns: (1) a parcellation of cells into defined domains and (2) graded patterning across the full anteroposterior extent (Donoghue and Rakic, 1999). Further, in earlier work on connectivity in adult cats, the suggestion was made of family clusters of cortical areas, linked by common thalamocortical inputs (Graybiel and Berson, 1981). The distribution patterns of transmitter receptors are suggested to reveal neurochemical families of areas (Zilles et al., 2004). Finally, for the well investigated primate ventral visual pathway, consistent evidence from multiple sources has suggested a gradient-like organization (Condé et al., 1996 and reviews in Rockland, 1997, and Fujita, 2002). That is, immunoreactivity for AMPA-type glutamate receptor subunits gradually increases from primary visual cortex to inferotemporal areas

(Xu et al., 2003); parvalbumin immunoreactivity decreases (Kondo et al., 1994; Ichinohe and Rockland, 2005). The density of terminations positive for zinc, an activity-related substance used by some glutamatergic synapses, increases from area V4 through perirhinal cortex (Fig. 3, and Ichinohe and Rockland, 2005). The basal dendritic morphology of pyramidal neurons is reported to show increased "complexity," as judged by increased branching and greater number of spines (Elston, 2002).

It is possible to see a striking parallel between cortical regional gradients and the increasing density and laminar recruitment of *RBP* signals, with progression from area V1 (Fig. 3). As already described, *RBP* expression is restricted to a thin, uppermost portion of layer II in area V1, expands progressively deeper into supragranular layers II and III in areas V2, V4, and TEO, and, in area TE, includes infragranular labeling (Komatsu et al., 2005).

There may still be many surprises concerning cortical area identity and organization. A recent microelectrode mapping study in rats reports finding a concentration of multisensory neurons preferentially at the borders of unimodal visual, somatosensory, and auditory cortices (Wallace et al., 2004). The authors interpret these as transitional multisensory zones that are interposed between modality-specific cortical domains. There are also issues of individual variability. Primary area V1 is a good example where area size and placement of borders is well-known to vary across individuals (in monkey: Van Essen et al., 1984, 2001). Similarly, a detailed re-examination of the rat vibrissa motor cortex reports that the transition between

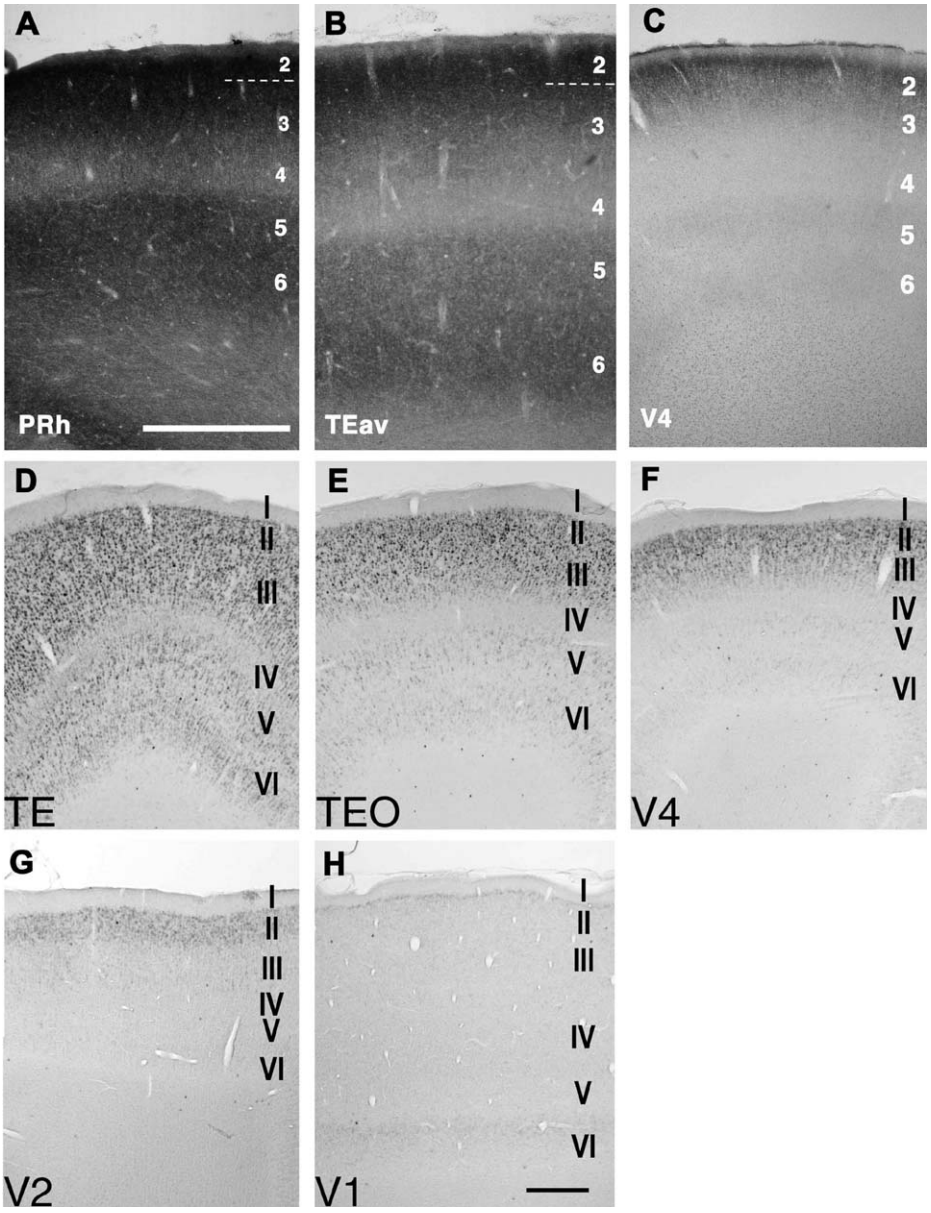


Fig. 3. *RBP* expression shows a gradient-like distribution along the ventral visual pathway. This is paralleled by several other substances (see text). (A–C) Zinc-positive terminations (corresponding to a subset of non-thalamocortical glutamatergic synapses) become less dense and involve fewer layers, from perirhinal cortex to early visual areas (modified from Ichinohe and Rockland, 2005). (D–H) *RBP* expression is denser and involves more layers in temporal cortical areas, in contrast with early visual areas (layer numbers are shown by Roman numerals). Note that the same figures shown in Fig. 3E–H are shown for D, E, G and H. Scale bars = 1.0 mm in A–C, 0.5 mm in D–H.

lateral and medial agranular areas can be abrupt (within <100 μm), semiabrupt, or continuous (smooth changes in laminar patterns over 200–300 μm; Brecht et al., 2004). These intriguing results point out the need for continued work on what happens at inter-areal borders between different types of areas and in different species.

5. Gene expression and connections

Understanding the possible relation of connectional systems to gene expression profiles is difficult because of the severe lack of information on connectional interactions and efficacy, especially in association areas (Vanduffel et al., 1997; Rockland, 1998). For now, laminar coincidence of connectivity patterns and gene expression can sometimes provide some clues. In monkey area V1, *occ1* is highly expressed in thalamo-recipient layers IVC and IVA. It is expressed as well in the CO patches in layer III, which correspond to a subset of thalamocortical connections (Tochitani et al., 2001; Takahata et al., 2005). In addition to the laminar coincidence, the expression of *occ1* in area V1 is activity dependent, consistent with the important role of thalamocortical connections in area V1. In area V2, the laminar distribution of *occ1* signals in area V2, in deeper layer III, is suggestive of an association with thalamocortical terminations from the pulvinar (Tochitani et al., 2001). In areas V4, TEO, and TE, *occ1* signals are similarly expressed in deep layer III, and in addition in layer V (Takahata et al., 2005). This laminar distribution closely matches with the laminar distribution of pulvinocortical terminations in these areas (Levitt et al., 1995; Rockland et al., 1999). Other connections, however, also preferentially terminate in layers III and V, and on the basis of laminar coincidence alone these would need to be considered as possibly related to *occ1* expression. Intrinsic horizontal connections, for example, are concentrated in layers III and V and callosal and some ipsilateral cortical connections partially or wholly target these layers.

For *RBP*, there is no evidence that its expression is activity dependent, even in primary visual cortex (Komatsu et al., 2005). Can we deduce anything from laminar coincidence of connectivity patterns and *RBP* expression? There are several potentially significant observations. First, *RBP* expression consistently avoids layer IV. Thus, its expression may be complementary to systems that terminate in the middle layers. These would include feedforward cortical connections. Thalamocortical connections from the pulvinar and mediodorsal thalamus terminate in lower layer III and upper layer IV (Fig. 4). Alternately, there might be a direct association with inputs that avoid layer IV; for example, feedback cortical connections, and/or amygdalocortical connections (Fig. 5), and/or a component of thalamocortical connections that targets layer I.

A second observation is that several connections show a gradient-like distribution, which parallels that of *RBP*. The most suggestive may be amygdalo-cortical connections (Fig. 5A and B). In area V1, these terminations are sharply limited to layer I, where they might target distal apical dendrites of neurons in layer II or other layers (Freese and Amaral, 2005) and in early visual areas and visual inferotemporal cortex, the terminations have a similar distribution, terminating in layers I and V (Freese and Amaral, 2005). In more anterior areas, amygdalo-cortical projections terminate more in layer II and upper III, with some involvement of layer V (Fig. 5A). These connections originate from the basal nucleus, including its magnocellular subdivision and this subdivision is known to contain a large population of *RBP*-expressing neurons (Komatsu et al., 2005).

Feedback connections also have laminar features reminiscent of *RBP* expression, and variably terminate in mainly layer I or in all layers except layer IV (Felleman and Van Essen, 1991). According to a ‘‘distance rule,’’ if one area projects to multiple other areas, more layers – both of origin and termination – will be involved for those areas that are physically closer together (Kennedy and Bullier, 1985; Rockland, 1997; Douglas and Martin, 2004). Thus, feedback connections from area TEO terminate densely in area V4, where they occur in all layers except layer IV (Fig. 5D); but TEO also projects to areas V2 and V1, and these terminations are more limited to layer I (Fig. 5E).

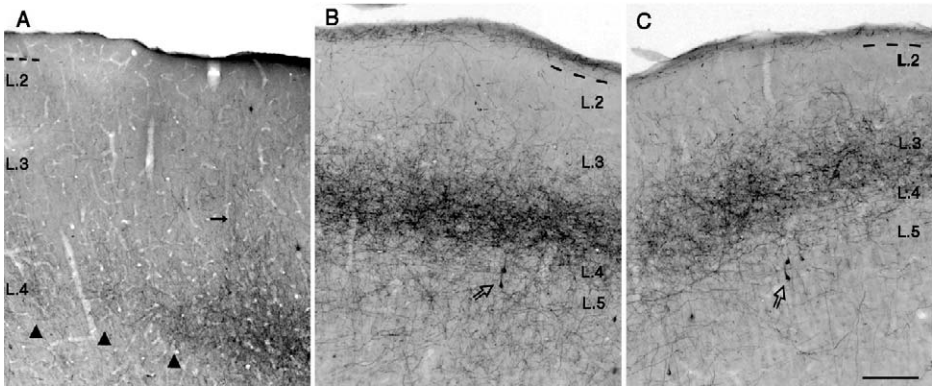


Fig. 4. Feedforward corticocortical and pulvinocortical connections terminate heavily in the middle layers. (A) Cortical terminations, anterogradely labeled by an injection of fluoro-ruby (FR) in area TEO. Terminations are mainly in layer IV, but extend in a columnar fashion toward the pia (solid arrow). Three distinct terminal patches (arrowheads) can be discerned medially. (B) Pulvinocortical terminations in layers I, IIIC, and upper IV of area TE, anterogradely labeled by an injection of biotinylated dextran amine (BDA) in the medial pulvinar. A few corticopulvinar neurons (hollow arrow) have been retrogradely labeled by the tracer. (C) Pulvinocortical terminations in area V4, from the same injection as in (A). Note the similar, characteristic laminar distribution. Scale bar = 100 μm (same for A–C).

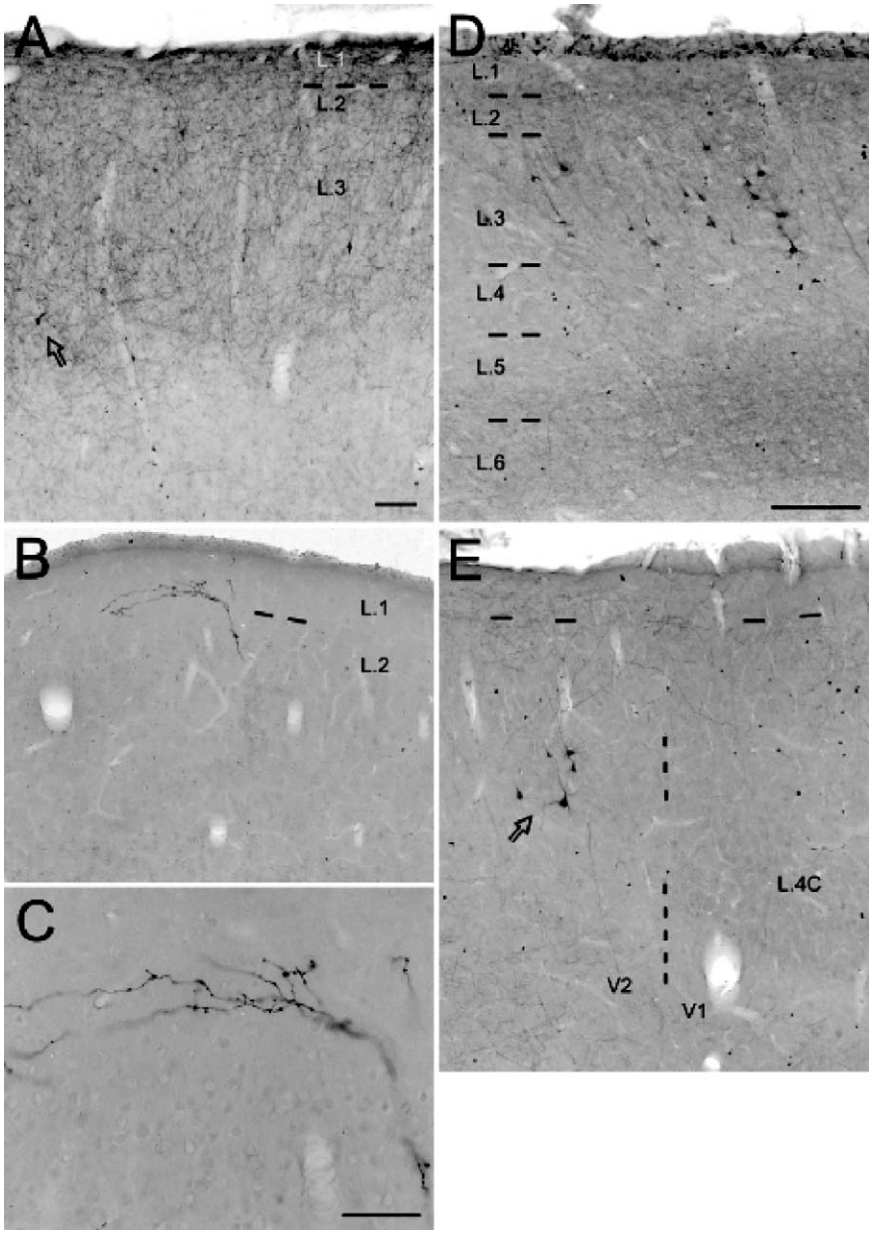


Fig. 5. Feedback corticocortical and amygdalocortical connections avoid layer IV. (A) Dense projections to orbitofrontal cortex, anterogradely labeled by a BDA injection in the lateral nucleus (photo is courtesy of Dr. Toshio Miyashita). (B) Higher magnification. (C) A single amygdalocortical axon terminating in area V4 at the border of layers I and II (labeled by the same injection as in (A)). (D) Dense projections to area V4, anterogradely labeled by an FR injection in area TEO. (E) Lighter terminations, from the same injection as in (D), mainly to layer I of areas V1 and V2. Dashed lines indicate laminar borders; smaller dashed lines in E indicate border between areas V1 and V2. Hollow arrows in (A) and (E) indicate neurons retrogradely labeled by the injected tracer. Scale bars = 100 μm in A and D (B, E are same as D); 50 μm in C.

Pulvinocortical projections terminate rather uniformly in layers I, deeper III, and upper layer IV throughout association cortex (Fig. 4B and C). This would seem less similar to the progressively increasing laminar expression pattern of *RBP*.

Third, we remark that *RBP* distribution parallels the distribution of glutamatergic terminations that use the neuromodulator zinc as co-factor (Ichinohe and Rockland, 2005). These are likely to originate from subsets of cortico-cortical and/or amygdalo-cortical connections. In early visual areas, layer II has a high concentration of $zinc^+$ terminations and within the occipitotemporal region (or ''ventral visual pathway''), the distribution of $zinc^+$ terminations shows a progressive increase in density and layers. Notably, zinc signals are consistently absent from layer IV in all cortical areas (Fig. 3 and Ichinohe and Rockland, 2005). The progressive increase of zinc levels, in some contrast with *RBP* expression, is more gradual through V1, V2, and V4.

Finally, we can consider the laminar distribution not of terminations but rather of their parent neurons. Some projecting neurons have markedly specific laminar patterns. In areas V2 and V4, neurons in layer II and upper III are a source of feedback connections (along with neurons in layer VI). The laminar coincidence with the thin band of *RBP*-expressing layer II neurons, especially in areas V1 and V2 is conspicuous. Since

RBP is secreted and bound to retinol, both pre- and postsynaptic cells may take it up together with retinol, and a postsynaptic association may be possible. Additional evidence concerning the specialized properties of neurons in layer II is from physiological recordings in area V2, which report responses in this layer as being more generalized, in terms of directional, orientation, and spectral sensitivity, than those in underlying layer III (Shipp and Zeki, 2002). This generalizing feature seems appropriate to cortical processing beyond the primary areas.

Concerning laminar position of parent neurons, it is important to keep in mind, however, that projection neurons are very likely to consist of a heterogeneous population. This is most evident in the case that projections have a bilaminar origin, which is very common. Feedback projecting neurons are situated in layer VI, but also layers II, and can occur as well in upper layer III and scattered in layer V. Feedforward projecting neurons in association areas occur in layers III and V, with possible contributions from neurons in layers II and VI. Within layers, finer analysis techniques are likely to reveal further subclassifications.

As this brief review shows, the association of genes and connections is sure to be complex, especially in association areas. Factors that need to be taken into account are: (1) the coincidence between a gene profile and a given population may be only partial because connections often originate from neurons in several layers and even within the same layer, parent neurons may have significantly different properties (Rockland and Pandya, 1979; Felleman and Van Essen, 1991; Salin et al., 1993). (2) Interactions and convergence of different connections are only poorly understood, especially in the association areas. Studies using double anterograde tracer injections provide some hint of the complexity of connectional interactions even at just the anatomical level. For example, inputs from dorsolateral prefrontal and posterior parietal cortices converge to 15 cortical areas (Selemon and Goldman-Rakic, 1988). In some of these common target areas, inputs were arranged in interdigitating columns, in layers I–VI; but in others, there was laminar interdigitation. Similarly, combinations of both overlapping and nonoverlapping projections have been reported, from four pairs of injected areas, in the superior temporal sulcus (Seltzer et al., 1996). (3) Previously, inactivation studies were used to assess the influence of connections on area function. Cooling experiments, for example, suggested that neurons in the ventral visual pathway (areas V2, V4, TEO, and TE) are dependent on active inputs from area V1, but those in the dorsal visual pathway (areas V3a, MT, MST, FST, and POa) or in multimodal area STP are not (Bullier et al., 1994; but see Collins et al., 2005). More recently, connectional influences have been addressed by reversible blocking of receptor proteins (Liu et al., 2004), by evidence of BDNF upregulation during tasks involving memory formation (Tokuyama et al., 2000), and by stimulus driven dual-activity maps for *zif268* mRNA (short time course) and zif268 protein (longer time course; Zangenehpour and Chaudhuri, 2005). The pre- and postsynaptic anatomical substrates of receptive field properties and area specializations are much less well-investigated in association cortices than is the case for thalamo-cortical connections in primary areas. For association cortex, the specific roles of particular connections remain to be determined, as does the genetic profiles of cells of origin and termination.

6. Area-specific genes in postnatal development

The expression of both *RBP* and *occ1* is significantly altered in postnatal development. In newborn monkeys, *occ1* is expressed faintly but clearly in V1 and strongly enhanced in postnatal development, suggesting that *occ1* expression is controlled by thalamocortical projections and activity. For *RBP*, there are several observations (Komatsu et al., 2005 and Fig. 6). First, *RBP*-expression in both V1 and V2 of neonatal monkeys is broader than in the adult, in that signals extend into deeper layer III. In area V2 in the adult, *RBP*-expression is more strictly limited to layer II, and in area V1 it is expressed in only a thin line of cells in upper layer II. Second, the laminar expression in higher order association areas involves fewer layers than in the adult. In prefrontal area 11, *RBP* expression is strong in layers II and III, and much weaker in layer V. In fact, in newborns, the layer distribution of *RBP* expression is rather similar in both area V2 and prefrontal area 11, and does not show the characteristic adult regional gradation. Thus, the specific expression of *RBP* is developed gradually through postnatal development, by processes that enhance its laminar distribution in higher-order association areas but diminish this in early sensory areas. Thalamocortical projections may be supposed to have some role in controlling *RBP* expression. Almost certainly, this will be in combination with other factors and/or projections, since the laminar coincidence between *RBP* expression and any one projection system is only partial.

The expression shifts in *occ1* and *RBP* are not surprising, since the early postnatal period is a time of major structural and functional changes. There is significant increase of synaptic density (see for example, Rakic et al., 1986; Granger et al., 1995; Huttenlocher and Dabholkar, 1997; Lewis, 1997; Levitt, 2003), and extensive maturational changes in neurochemical systems such as transmitter phenotypes, transmitter receptors, and specific calcium binding proteins (parvalbumin, calretinin, calbindin) (see Akil and Lewis, 1992; Lewis et al., 2005). Many maturational processes show laminar and/or topographic gradients; for example, in marmoset area V1 (Bourne et al., 2005), non-phosphorylated neurofilament protein (NPNP) appears earliest in layer VI (P0), in contrast with upper layers (PD 7 for layer IIIC, and PD 28 for layer IIIBa [or layer IVB of Brodmann]). In marmoset, NPNP appears first in primary areas and extrastriate MT, and only later in association cortices (Bourne and Rosa, 2005).

Considerable work will be necessary to elucidate how maturational changes in cortical connectivity are influenced by molecular events, and under what degree of genetic and/or epigenetic control (Crair, 1999; Pallas, 2001; Sur and Leamey, 2001; Grubb and Thompson, 2004). Here we give four examples of changes in cortical connectivity during early postnatal development, which might be addressed in this

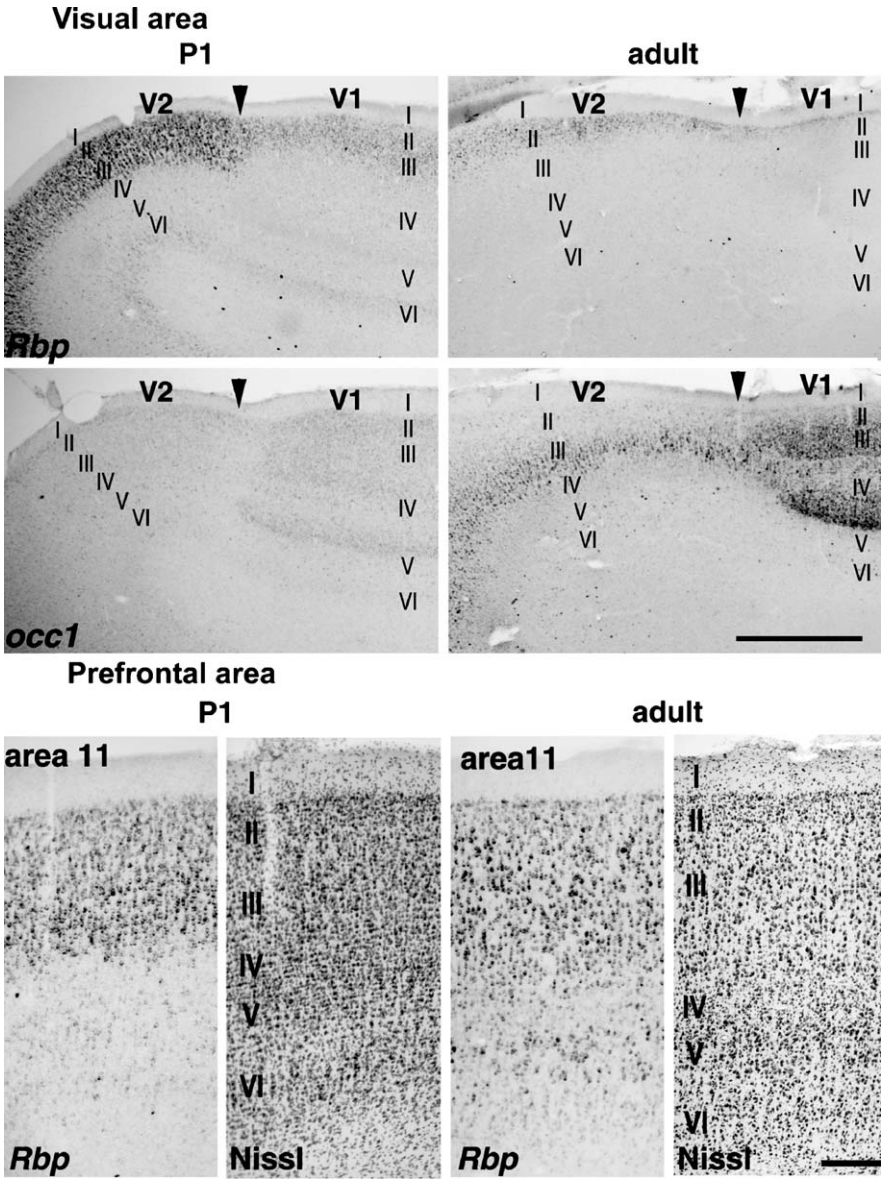


Fig. 6. Developmental change of *RBP* and *occ1* expression. (A) The expression patterns of *RBP* and *occ1* are shown around the border of areas V1 and V2 of postnatal day 1 (P1) and adult monkeys, (B) *RBP* expression in frontal area 11 of P1 and adult monkeys. Nissl staining of lamination patterns are also shown at the right of each panel. The figure is taken from Fig. 8 in Komatsu et al. (2005).

context. One is active remodeling of connectional systems. Exuberant callosal connections occur in many species (Innocenti, 1981, 1995; LaMantia and Rakic, 1990), and transitory connections to ''inappropriate'' targets are common (Clarke and Innocenti, 1986). In the early visual cortical system, several studies have demonstrated preferential remodeling of intrinsic (Coogan and Van Essen, 1996) or feedback cortical connections. In the adult monkey, feedback connections typically originate from neurons mainly in layer VI and in the uppermost supragranular layers (layers II and upper III; Rockland and Pandya, 1979); but in the fetal monkey (E122), there are more supragranular neurons and more involvement of deeper layer III (Meissirel et al., 1991). The developmental decline of the ''excessive'' supragranular component is complete by one month postnatal (Barone et al., 1995). This greater involvement of the supragranular layers in development is in striking parallel with neonatal *RBP* expression. As remarked above, however, these connectional changes are likely to reflect multiple interacting complex processes and one might wish for further data at younger ages to help in identifying different components.

Second, connectional systems develop according to different stages and rates. In visual cortex, feedback connections mature later than the reciprocal feedforward projections. In humans, feedforward projections from V1 to V2 are described as having mature laminar characteristics at 4 months, but at this stage, feedback connections do not yet have terminations in layer I (Burkhalter, 1993). In mice, feedforward connections from V1 to extrastriate area LM show the mature laminar pattern by P14, but the feedback connections were dense only in layer VI at this age and continued to increase in density in this and other layers until P120 (Dong et al., 2004).

Third, dramatic changes occur for intrinsic connections, both intra- and interlaminar (Callaway, 1998). The typical adult pattern of horizontal intrinsic connections (which originate from local collaterals of pyramidal neurons in layers II, III, and V) is thought to emerge by pruning of inappropriately targeted axons and to be dependent on visual activity (Callaway and Katz, 1990; Katz, 1991). For vertical, interlaminar intrinsic connections, experiments in slice preparations of ferret visual cortex suggest instead that the mechanisms regulating layer-specific axonal targeting differ depending on the layers targeted and the type of parent pyramidal neuron (Butler et al., 2001). That is, layer V neurons, but not those in layer VI, develop correct laminar specificity (respectively, to layers II, III, and V, and layer IV) in the presence of TTX; but neurons in layers II and III fail to form any layer-specific connections even without TTX.

Fourth, dramatic changes are associated with pre- and postsynaptic components of the glutamatergic cortico- and thalamocortical pathways at the synaptic level (Lujan et al., 2005). There are differential influences of glutamate, depending on cortical layers. In monkey area V1, the major geniculo-recipient layers and CO patches, in contrast with the upper and lower layers, have low levels of GluR2, presumably favoring synaptic transmission via calcium-permeable glutamate receptors (Wong-Riley and Jacobs, 2002). At E139, unlike in the adult, there is no patchiness of GluR2 in layers II or III, but there is a transitory expression GluR2 in a layer IVA honeycomb (Wong-Riley and Jacobs, 2002). There are significant developmental changes in the levels of synaptic zinc, a neuromodulator that in the adult is localized in a subset of non-thalamic glutamatergic projections. In the rat, where this has been better studied than in monkey, the granular retrosplenial cortex is a zinc-dense region until P18, but a zinc-poor region in the adult (Miro-Bernie et al., in press). In somatosensory barrel cortex, barrels in layer IV are darkly zinc reactive early in life, but then lose much of their synaptic zinc during postnatal weeks 2–4 (Land and Shamalla-Hannah, 2002). We note that in both adult rodent and monkey, zinc levels are dynamically reorganized during sensory manipulation (whisker trimming or monocular enucleation). A brief period of up-regulation is followed by longer term down-regulation (Dyck, 1994; Brown and Dyck, 2002).

How similar are developmental processes in rodents, non-human primates, and human? On the one hand, in thalamic nuclei of mouse and monkey, the expression of regulatory genes during development is reported to be very similar. Each thalamic nucleus was distinguished by expression of a combination of genes, and homologous nuclei in mouse and monkey exhibited the same combination (Jones and Rubenstein, 2004). On the other hand, the larger primate neocortex, in comparison with rodent brains, requires a prolonged temporal developmental cycle (see for example Levitt, 2003; Northcutt and Kaas, 1995; Krubitzer and Huffman, 2000). This is poorly understood, since there are serious practical difficulties in studying the earlier, prenatal stages in primates (Levitt, 2003). Moreover, the association areas, so well-developed in the primate, are not particularly delineated by the markers that have been useful in rodent brains (Cadherins, Ephs, etc.). In the mouse neocortex, these correspond only to regions, rather than to Brodmann areas (see Rubenstein et al., 1999; O'Leary and Nakagawa, 2002). Thus, the full complement of mechanisms contributing to the formation of these complex cytoarchitectonic areas is still undetermined. In considering these questions, the search for genes that are expressed in specific areas of the adult primate neocortex is an essential prerequisite.

While the basic framework of cortical development may make use of the same mechanisms in human and non-human, for the human cortex, dynamic postnatal developmental changes may be more necessary, and these may be area-specific. For example, in humans, maximum synaptic density is reached at about postnatal 3 months in the auditory cortex, but not until after 15 months of age in middle frontal gyrus (Huttenlocher and Dabholkar, 1997).

7. Summary and future directions

A small number of genes are expressed in the macaque neocortex specific to primary areas (*occ1*) or association areas (*RBP*). For *occ1*, its dense expression in area V1 accords well with accepted views on the specialization and importance of this area and of its thalamocortical connections. For *RBP*, the more complex expression pattern raises intriguing questions. Does this correlate with one set of connections, and if so, which? Is the expression related to functional processing or to some other quality, perhaps related to plasticity processes? Is the expression pattern best viewed as area-specific or gradient?

We conclude by considering three avenues for future directions. One obvious direction is continued work on the relation of particular genes and combinations of genes to cortical area identity. A second is comparative cortical gene expression in different species. In nonprimate mammals, some specific molecules such as latexin and LAMP have been identified, but these seem to be broadly region-specific. Fascinating inter-species anatomical differences and specializations are well-known (e.g., interneuron diversity, as Yanez et al., 2005; greater collateralization of mouse projection neurons, Mitchell and Macklis, 2005). The next step is to look for phenotypic features that might be correlated with specific features of gene expression, and to elucidate how genetic and epigenetic interactions influence the establishment, maturation, and plasticity of cortical connections.

Third is what gene expression profiles might reveal about cell types, especially as this concerns pyramidal projection neurons. For inhibitory neurons, earlier subtypes are now being further refined on the basis of molecular and gene expression profiles (Gupta et al., 2000; Markram et al., 2004; Toledo-Rodriguez et al., 2004). Comparably fine classification of pyramidal cells has lagged behind, although some reports have suggested a large diversity of pyramidal cells as well (Kozloski et al., 2001). Cellular level gene expression analysis (single or double), and double labeling for gene expression and connectivity or other characteristics offers a new approach to the classification problem.

Many aspects of human cognition are likely to emerge from organizational properties that allow for enhanced plasticity and efficient learning (Oldham and Geschwind, 2005). It will be increasingly possible to address these properties by probing correlations between relevant phenotypic and genetic phenomena, and by combined analyses for area-specific and cell-type specific gene expression (Sugino et al., 2006).

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