the computational abilities of the nervous system well beyond previous calculations. Could certain neural pathologies be caused by an overworked neuron performing the wrong job at the wrong time? And is it possible for a neuron to perform multiple tasks simultaneously? At first glance, the AII cell's duties appear to be functionally and temporally distinct; it passes single-photon signals at night and enables detection of an approaching falcon during the day. Perhaps future experiments will explain what happens when an owl swoops in under the moonlight, while the AII cell is busy working the night shift.

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Regional control of cortical lamination

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Laminar neuronal density varies between cortical areas; thus, the developmental specification of areas and layers needs to be coordinated. AP2γ turns out to be an important regulator of upper layer development in occipital cortex.

The largest portion of the cerebral cortex, the neocortex, is characterized by a six-layered organization. The neocortex is also organized into areas, each of which exhibit distinct connectivity and carry out specific functions such as motor control or visual processing. Not only are the cortical areas functionally distinct, but they differ in their cytoarchitecture and laminar neuronal density[1]. The primate visual cortex, for example, contains 50% more pyramidal neurons in its upper layers (layers II/III) than neighboring cortical areas[1]. Molecular mechanisms that regulate the development of distinct cortical areas[2] as well as laminar identity[3] have recently been the subject of extensive investigation. However, the manner in which these two processes are integrated remains unclear.

In this issue, Pinto *et al.*[4] provide evidence that the transcription factor AP2γ is required for correct laminar development exclusively in the occipital (visual) cortex. Specifically, AP2γ is necessary and sufficient for the correct number of pyramidal neurons to be produced in layers II/III of the visual cortex. Indeed, Pinto *et al.* found that pyramidal neurons in layers II/III of the visual cortex, as marked by Cux1/2 staining or retrograde labeling from the opposite cortical hemisphere, were severely reduced in *AP2γ* (also known as *Tcfap2c*) conditional knockout mice (**Fig. 1**). In contrast, *AP2γ* loss did not affect the numbers of upper layer neurons in rostral cortical regions (**Fig. 1**). Neuronal density in the deep cortical layers V/VI, as identified by the markers Er81 and Tbr1, was normal in the *AP2γ* mutant cortex at both rostral and caudal levels.

Recent studies[1,3,5–8] indicate that the neurons that occupy different cortical layers are generated from distinct progenitors in the cortical germinal zone. Deep-layer neurons arise largely from progenitors such as radial glia that divide at apical locations in the ventricular zone at early stages of corticogenesis, whereas the upper layer neurons are generated from intermediate progenitors that divide at the basal margin in the subventricular zone (SVZ) at later time points (**Fig. 1a**). These two progenitor types have also been termed apical and basal progenitors, respectively. The basal (intermediate) progenitors arise from radial glia and usually divide symmetrically in the SVZ to produce two neurons destined for the upper cortical layers (**Fig. 1a**). Because the upper layers of the occipital cortex in *AP2γ* mutants are specifically affected, Pinto *et al.*[4] examined the generation of basal progenitors in the mutant cortical germinal zone. They found dividing cells at basal positions in caudal regions of the *AP2γ* mutant cortex and even found that the numbers of these cells were slightly increased at mid-neurogenesis stages. However, these cells lacked some typical features of basal progenitors and instead appeared to retain characteristics of the radial glial (apical) progenitors (**Fig. 1c**). A number of transcription factors such as Tbr2 (refs. 9,10), Insm1 (ref. 11) and Cux2 (ref. 12) have recently been shown to be required for the normal generation and neurogenic function of basal progenitors. These factors function broadly in the production of neurons from basal progenitors throughout the developing cortex, as no area-specific laminar defects have been reported in mice that are deficient for any of these factors[9–12]. Pinto *et al.*[4] found that the expression of many of these factors, including Tbr2 and Tis21 (refs. 7–10), was reduced or missing in caudal basal progenitors of the *AP2γ* mutant cortex (**Fig. 1c**).

Pinto *et al.*[4] found that AP2γ uniquely differs from other regulators of basal progenitors in a couple of ways. First, unlike Tbr2, Insm1 and Cux2 expression, AP2γ expression was restricted to the radial glial (apical) progenitors and was not maintained in the basal progenitors. Second, AP2γ only regulated the specification of basal progenitors in caudal portions of the developing cerebral (visual) cortex. Nevertheless, Pinto *et al.*[4] observed the reduced neurogenic capacity of basal progenitors reported in Tbr2 (refs. 9,10) and Insm1 (ref. 11) mutants in the developing *AP2γ* mutant visual cortex. In addition, at mid-stages of cortical neurogenesis (embryonic day 14, E14), when upper-layer neurons commence generation, the number of basally dividing cells was increased in the *AP2γ* mutant cortex[4], similar to observations in *Cux2* mutants[12]. Indeed, both *Tbr2* and *Cux2* were severely downregulated in the caudal cortical germinal zone of *AP2γ* mutants. At late stages of cortical neurogenesis (E17), the basal progenitors were severely reduced in the *AP2γ* mutant visual cortex as a result of increased cell death (**Fig. 1c**).

Thus, it appears likely that an initial misspecification of caudal basal progenitors leads to the reduced production of layer II/III neurons in the visual cortex of *AP2γ* mutants (**Fig. 1c**), indicating that AP2γ is required for the correct specification and/or generation of neurogenic basal progenitors in the caudal cortical germinal zone. Furthermore, Pinto *et al.*[4]

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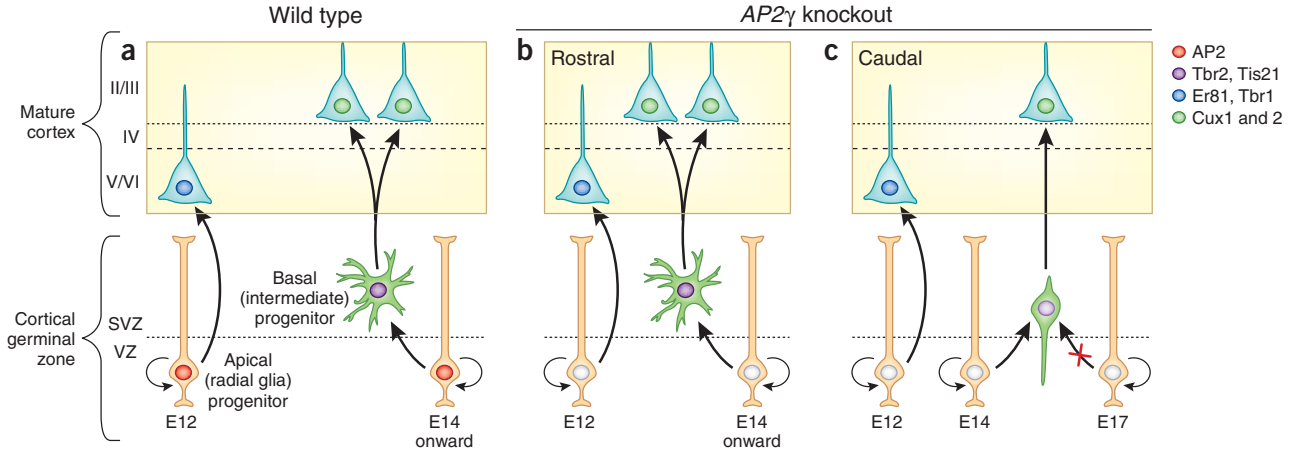

Figure 1 Regional laminar defects in the cortex of *AP2γ* conditional knockout mice. (**a**) Schematic diagram illustrating the cellular generation of deep-layer (marked by Er81 and Tbr1) and upper-layer cortical neurons (marked by Cux1 and 2) from apical (radial glial) and basal (intermediate) progenitors, respectively, in wild-type cortex. Basal progenitors express Tbr2 and Tis21 and normally divide to generate two upper-layer neurons. (**b**) AP2γ is not required in rostral cortical regions for the correct generation of deep-layer neurons or for the correct specification of basal progenitors and upper-layer neurons. (**c**) In caudal (that is, occipital) cortical regions of the *AP2γ* mutants, intermediate progenitors are not correctly generated. These progenitors exhibit certain radial glial characteristics such as a process contacting the apical surface and have severely reduced or missing expression of basal progenitor regulators such as Tbr2 and Tis21. Moreover, by later stages (E17), many basal progenitors undergo cell death. These alterations in the mutant basal progenitors probably lead to the generation of fewer upper-layer cortical neurons in the occipital cortex.

provide, to the best of our knowledge for the first time, evidence that areal and laminar identity in the developing cortex may be controlled by a single molecule; for the visual cortex, this appears to be AP2γ.

One major question that remains to be resolved relates to the specific mechanism that could restrict AP2γ function to the generation of upper-layer neurons in only the occipital cortex. *AP2γ* expression itself is not restricted to the caudal portions of the cortical ventricular zone; rather, Pinto *et al.*[4] found it throughout the cortical ventricular zone. Moreover, at least at early stages, *AP2γ* appeared to be expressed at slightly lower levels in the caudal versus rostral cortex. It seems possible, therefore, that AP2γ interacts with one or several other factors that would be enriched in or restricted to caudal portions of the cortical ventricular zone. The transcription factor Emx2 is a potential candidate, as it has a high caudal–to–low rostral gradient of expression in the developing cortical ventricular zone[2]. Furthermore, *Emx2* is required for correct area patterning of the visual cortex[2]. Thus, one can envision a model in which a specific threshold for *AP2γ* and *Emx2* expression in radial glial progenitors would specify the correct production of basal progenitors in the developing occipital cortex. Unfortunately, *Emx2* mutants do not survive after birth[2] and whether they have occipital cortex laminar defects that might resemble those seen in the *AP2γ* mutants remains unknown.

Alternatively, the region-specific requirements for *AP2γ* in the forming visual cortex could be the result of a local lack of compensation by another factor. The paired homeobox gene *Pax6* is required for the correct specification of rostral cortical areas and developmental markers of caudal cortical areas expand rostrally in its absence[2]. Accordingly, *Pax6* is expressed in a decreasing rostral to caudal gradient in the developing cortex[2]. Pinto *et al.*[4] found that Pax6 directly promotes the expression of both *AP2γ* and the basal progenitor regulator *Tbr2*. Thus, the higher levels of *Pax6* in rostral cortical regions could compensate for the lack of *AP2γ* in the specification and/or generation of basal progenitors.

Pinto *et al.*[4] also found that AP2γ is required to specify basal progenitors only from E14 onward, when the generation of upper-layer neurons' from basal progenitors begins[3]. Accordingly, viral overexpression of *AP2γ* at E14 increased the numbers of basal progenitors and, subsequently, neurons in visual cortex layer II/III[4], whereas similar overexpression initiated at E12 had no effect on basal progenitors in either rostral or caudal cortex. These results are consistent with a previous study[13] that found restricted developmental potential of late-stage (that is, E15 and onward) cortical progenitors compared with mid-stage (E12) progenitors, with the restriction being dependent on cell-intrinsic (that is, transcription) factors[13].

Thus, in addition to region-specific restrictions on AP2γ's function in the specification of basal progenitors, temporal constraints are also active in this process. It may be, however, that temporal restrictions of developmental potential are not a region-specific phenomenon, but rather a telencephalon-wide one. Recently, we found that even when dorsal telencephalic (cortical) progenitors are ventralized at later stages of development, they remain limited to generating late, ventral telencephalic, neuronal fates[14].

The laminar defects observed in the *AP2γ* mutant visual cortex lead to impairments in visual acuity[4]. Moreover, the adult *AP2γ* mutant visual cortex had increased plasticity, suggesting a degree of immaturity. Thus, correct neuronal density in layers II/III may be required for full functional maturation of the visual cortex. Pinto *et al.*[4] also found that AP2γ was expressed in the germinal zone of the developing primate visual cortex, suggesting that it might be involved in the generation of the particularly large numbers of upper-layer neurons that characterize the visual cortex of higher mammals[1]. Future studies will help to uncover whether the coupling of area- and lamina-specific development by one transcription factor is unique to the visual cortex or whether analogous factors perform similar functions in other areas of the developing cortex.

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