from seafloor spreading[12], and they shed new light on its mechanical behaviour and strength, and on earthquake physics. ■

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BRAIN DEVELOPMENT

# The neuron family tree remodelled

**The discovery of different classes of neuronal progenitor cell, destined to give rise to neurons in specific layers of the cerebral cortex, could presage the revision of a 50-year-old model of brain development.**

OSCAR MARÍN

The neocortex, the mammalian brain's most recent evolutionary acquisition, controls the aspects of behaviour that make us human, from the fine-scale finger movements of a virtuoso pianist to the complex syntactic processing required for language. Its highly regular structure contains a complex matrix of excitatory and inhibitory neurons organized into distinct layers and columns. Neurons in any one cortical layer share general patterns of connectivity, whereas neurons in the same column are typically interconnected across layers and function as the basic unit of cortical operations[1]. Over the past 100 years, analysis of the developing brain has provided fundamental insights into the functional organization of the neocortex[2]. However, Franco *et al.*[3], writing in *Science*, provide evidence that puts a radically new perspective on the link between brain development and neuronal function.

A fascinating aspect of cortical development is that excitatory neurons (also known as pyramidal cells) are 'born' in sequential order, with those located in deep layers of the neocortex being generated first and subsequently generated neurons being positioned in progressively more superficial layers. It is usually assumed that pyramidal cells in all layers of the neocortex originate from a single type of progenitor cell, and that a progenitor's ability to generate distinct classes of neuron decreases with time. That is, progenitors during early embryonic development can give rise to any class of pyramidal cell (they are 'multipotent') but are progressively restricted to producing superficial neurons later on[4–6]. New neurons, originating from transient amplifying cells that become detached from the ventricular zone (the inner layer of the cortex, where progenitors reside), migrate to their final position by following the radial fibres of progenitor cells (Fig. 1a). These fibres serve as a scaffold that links the ventricular zone and the cortical surface, just like spokes connecting the centre of a wheel to its outer edge.

According to this classical view, the 'birth date' of a neuron largely determines its fate, and sibling neurons are vertically aligned through the radial axis of the neocortex. This model has been highly influential, because it relates the concept of ontogenetic columns (vertical arrangements of sibling neurons born from a common progenitor) with the notion of functional columns — the long-sought fundamental unit of cortical computation. Indeed, recent studies suggest that sibling neurons are more likely to respond to the same sensory stimuli than a random subset of neighbouring neurons[7,8].

Franco *et al.* report that the gene-regulatory protein Cux2 is expressed by a small subset of progenitor cells in the developing cortex of mice, and that this subset increases over time. These findings are unexpected, because Cux2 expression was previously thought to be restricted to pyramidal cells in the superficial layers of the cortex. The authors then hypothesized that the Cux2-expressing progenitor cells might be fated to generate superficial pyramidal cells. To test this possibility, they generated and studied a mouse strain in which a fluorescent protein was produced exclusively in cells


## 50 Years Ago

It is now fifty years since, with the creation of the former Medical Research Committee, Great Britain took the lead in setting up central organizations for research ... The Medical Research Council conceives its function as: to watch over the whole fields of medical and related biological research so as to foresee, to the best of its ability, the needs and opportunities to give support to any promising research in these fields irrespective of the agent concerned; to work in partnership with the universities and professions on one hand and the various Government departments on the other, so that new knowledge may be made available as the need arises.
**From *Nature* 13 October 1962**

## 100 Years Ago

Coming out from Queenstown on September 10 on her way toward Boston, the ss. *Arabic* was accompanied for some hours by a large flock of gulls. For the most part these birds were visibly working, flapping their wings, but occasionally a few would cease flapping and merely sail along for considerable distances … An explanation of the ability of the birds to sail, under the conditions described above, is, I believe, found in the upward course of the wind which has struck the weather side of the ship and must rise in order to pass over it … As the trail of smoke marks the direction of the wind with respect to the moving ship, the bird must, in order to sail with the same velocity and direction as the ship, have a motion relative to the air equal and opposite to the motion of the smoke relative to the ship. Accordingly, the bird's axis is kept parallel to, and opposite to, the course of the smoke as indicated by its train from the funnel.
**From *Nature* 10 October 1912**

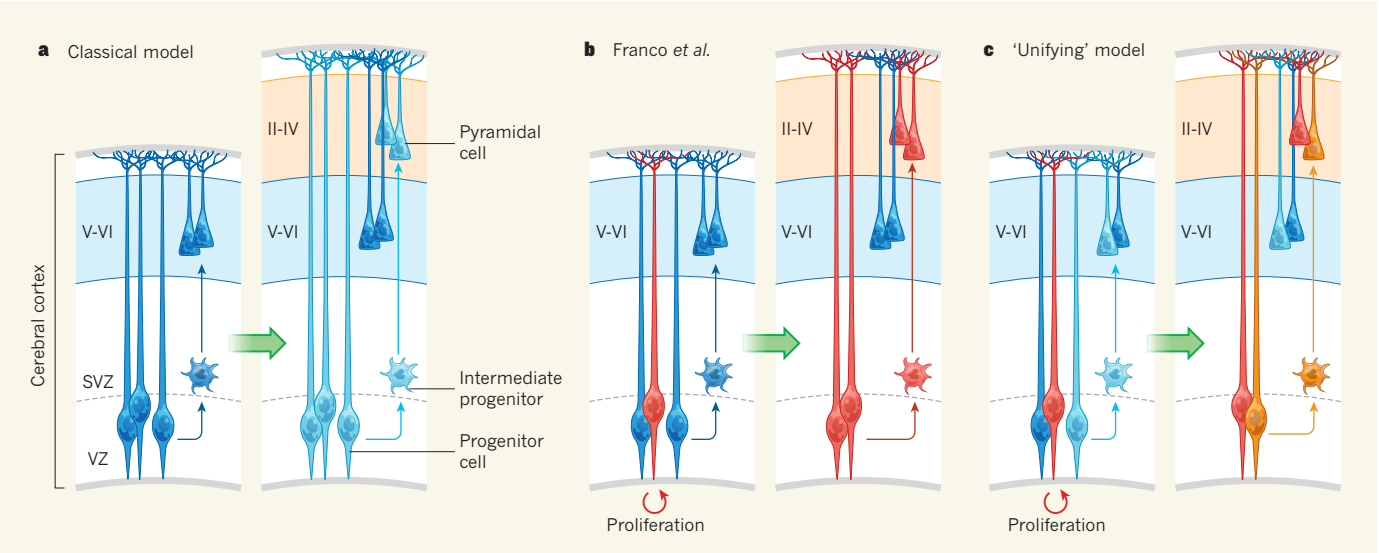


**Figure 1 | Adding layers of complexity to the brain.** Several models have been proposed to explain the formation of neural layers (II to VI) during the development of the cerebral cortex. **a**, The classical model suggests that there is a homogeneous population of multipotent progenitor cells in the ventricular zone (VZ) of the cortex that produce intermediate, transient, dividing progenitors located in the subventricular zone (SVZ), which in turn give rise to different classes of pyramidal cell (a type of neuron) in sequential order. According to this model, progenitors can generate any class of pyramidal cell during early development, but are progressively restricted to producing superficial neurons at later stages. **b**, Franco and colleagues' findings[3] indicate that there are two classes of progenitor cell, each with a defined fate: one class gives rise to deep pyramidal cells (layers V and VI), whereas the other generates superficial pyramidal cells (layers II to IV). During early development, only a few progenitor cells exist that are destined to form superficial layers; but these progenitors proliferate before they begin producing neurons. **c**, In a unifying hypothesis that attempts to reconcile different sets of observations, several progenitor lineages exist. Progenitor cells are fate-restricted to generate deep- or superficial-layer neurons, but, within each lineage, intrinsic or extrinsic factors modulate the production of distinct classes of pyramidal cell (dark and light colours), which are vertically aligned in progressively more superficial positions.

that either expressed Cux2 ($Cux2^+$ cells) or were derived from Cux2-expressing cells. Using this lineage-tracing technique, the researchers found that most neurons generated from $Cux2^+$ progenitor cells settle in the superficial layers of the cortex (layers II to IV), whereas those derived from $Cux2^-$ progenitors end up in the deep cortical layers (layers V and VI).

To gain further support for their hypothesis, the authors created a second mouse strain in which the fluorescent labelling of $Cux2^+$ cells could be triggered by the injection of a specific compound (tamoxifen) into pregnant mice at different times during embryonic development. This approach allowed Franco *et al.* to observe the unequivocal labelling of $Cux2^+$ progenitor cells at very early stages of brain development, and to confirm that $Cux2^+$ progenitor cells give rise almost exclusively to pyramidal cells located in the superficial layers of the cortex.

Taken together, the results show that at least two classes of progenitor cell exist in the neocortex: $Cux2^-$ progenitors generate deep-layer pyramidal cells, whereas $Cux2^+$ progenitors primarily produce pyramidal cells for the superficial layers. Franco and colleagues' results therefore indicate that cortical progenitor cells are programmed to produce specific classes of excitatory neuron (Fig. 1b), a finding that is at odds with the classical view that multipotent progenitor cells exist in the neocortex. According to the authors' findings, distinct classes of pyramidal cell are produced at different times during development because fate-restricted progenitor cells begin to produce neurons at different stages, and not because the potential of the progenitor cells becomes more limited with time. This model is consistent with recent research suggesting that progenitor cells in the cortex are much more diverse than previously thought[9].

However, the model is in conflict with several previous studies. For example, single progenitor cells isolated from the embryonic cortex, or embryonic stem cells that are induced to become cortical progenitors *in vitro*, are multipotent and generate excitatory neurons in the normal *in vivo* order[10,11]. One possible explanation for the conflict is that these older observations reflect the potential of cortical progenitor cells before they become fate-locked at a certain stage of development. In addition, *in vivo* studies using other lineage-tracing methods have shown that pyramidal cells derived from a single progenitor cell are typically arranged in vertical clusters, although mostly within adjacent layers[6,7]. These observations are consistent with a hybrid, 'unifying' model of cortical neurogenesis (also suggested by Franco and colleagues), in which intrinsic or extrinsic factors affect the potential of fate-restricted progenitors to generate specific classes of neuron during brain development (Fig. 1c).

Our current view of the mechanisms that control the assembly of cortical circuits may also need adjustment. For example, if most pyramidal cells from deep and superficial layers are derived from different progenitors, it is unlikely that many pyramidal cells are connected across layers according to lineage relationship[7,8]. Inhibitory interneurons, which modulate the function of pyramidal cells and are derived from progenitor cells outside the cortex[12], have also been suggested to be arranged in relation to the columnar organization of pyramidal cells[13]. However, if Franco and colleagues' results reflect a general property of cortical development, interneuron progenitors might instead be fate-restricted to preferentially match the laminar pattern of the neocortex. Whatever the answers to these questions, I believe that this study marks a major shift in our understanding of cortical development. ■

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