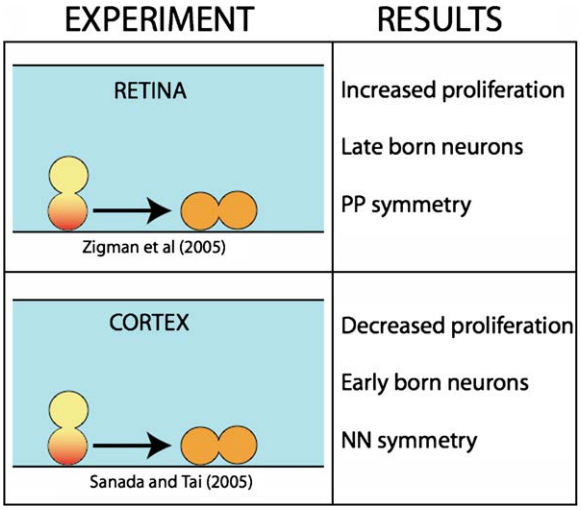

Figure 1. Different Symmetries from Similar Experiments

The top panel shows the Zigman et al. (2005) experiment in the mouse retina where the apical complex (red) is compromised by RNA interference with mInsc, and the Sanada and Tsai (2005) experiment in the mouse cortex where the apical complex is compromised by RNAi to ASG3 is shown below. In both cases, there is a reduction in apicobasal divisions in favor of divisions in the horizontal plane. The effect of this is a change of fate in both cases, but in the retina it is an increase in PP symmetry, while in the cortex it is an increase in NN symmetry.

cells to remain in a progenitor sate (Petersen et al., 2002). Studies in the rat retina late in neurogenesis, however, show that the inheritance of numb does not favor cells remaining in the cell cycle. In horizontal divisions, where both daughters inherit numb, they often both differentiate into the same type of cells, such as photoreceptors, a fate that is also promoted by overexpression of numb, whereas the asymmetric distribution of numb in the these cells correlates with different postmitotic fates (Cayouette and Raff, 2003). Numb is only one of many determinants that could be symmetrically or asymmetrically partitioned according to the orientation of cell division. Thus, it is not much of a leap to imagine that the symmetric versus asymmetrical inheritance of numb, or perhaps other determinants, might have very different consequences in the retinal versus neocortical lineages. The key point here is that the featured studies show that the orientation of division does have a role in determining cell fate in the developing mammalian nervous system, as it does in *Drosophila*. But that role is different in different lineages. Thus, decreasing apicobasal division increases symmetrical fates, even though these fates might be very different in distinct regions of the nervous system that are undergoing different (Danny DeVito- or Hulk Hogan-generating) lineage programs.

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Local Axon Guidance in Cerebral Cortex and Thalamus: Are We There Yet?

Normal brain function requires the development of precise connections between thalamus and cerebral cortex. In this issue of *Neuron*, Cang et al. and Tori and Levitt argue that EphA/ephrin-A signaling in the target tissue guides sensory thalamic axons to the correct cortical area, and sensory cortical axons to precise thalamic targets. Although EphA/ephrin-A signaling organizes sensory maps within areas, and thalamocortical axons in the internal capsule, both papers argue that each developmental event is dissociable from the others.

Higher functions of the mammalian brain, including perception, planned movement, and cognition, rely on a complex interaction between cerebral cortex and the thalamus. Still unanswered is the question of how the anatomical substrate for this interaction, a highly patterned reciprocal innervation, is established in development.

In this issue of *Neuron*, two studies make significant advances toward an answer (Torii and Levitt, 2005; Cang et al., 2005). Torii and Levitt conclude that axons from sensory cortex find a precise target in the thalamus by responding to local levels of ephrin-A5. Cang and colleagues provide evidence that ephrin-A2, -A3, and -A5 are required to position primary visual cortex (V1) in the cortical plate as well as to direct formation of a visuotopic map in V1. Perhaps just as significant, the latter investigation exemplifies a new type of study, combining genetic manipulation of development with optical imaging of an altered cortical area map.

The development of connections between cortex and thalamus has been studied for decades (Lopez-Bendito and Molnar, 2003). An early hypothesis was that pioneer axons forge the way, as in invertebrates. In cats and ferrets, a breakthrough observation was that the subplate, a transient cell layer in the developing cortex, sent pioneer projections to the thalamus, defining a pathway that thalamic axons could follow to the cortex (McConnell et al., 1989). In rats and mice, however, thalamocortical and corticothalamic axons begin to grow almost simultaneously toward their targets. Tracing studies indicated that axons from parts of the cortex and thalamus that will ultimately connect meet in the internal capsule (IC). Based on these observations, the "handshake" hypothesis was proposed, in which cortical and thalamic axons contact and then guide one another to their respective targets (Lopez-Bendito and Molnar, 2003; Molnar et al., 1998).

An implication is that axons are sorted in the forming IC, so that corresponding sets of cortical and thalamic axons readily find one another. Recent studies in mouse indicate how this may be achieved. Subcortical cues organize thalamic axons in the IC well before the axons approach the cortex. EphA/ephrin-A signaling gradients position thalamic axons in the growing IC (Dufour et al., 2003). Neurogenin2 controls the responsiveness of thalamic axons and is required for anterior-to-posterior sorting in the IC (Seibt et al., 2003). Thalamocortical axons are therefore, at least hypothetically, organized in the IC in a pattern that reflects the topography of their projection onto the cortex. Additional positional cues are found at the telencephalic/diencephalic junction. Genetic defects affecting this region can halt axons traveling in either direction, or lead to misrouting (Garel and Rubenstein, 2004; Hevner et al. 2002).

A general conclusion drawn from these results is that subcortical positional cues provide sufficient information for thalamocortical axons to find their target cortical area. This idea was encapsulated in a review, subtitled "it's not where you go, but how you get there"(Marin, 2003). However, once axons leave the IC they must still travel some distance to the correct part of the cortex or thalamus. Subcortical cues might be alternatively described as dropping off axons in the right neighborhood. The papers by Torii and Levitt and Cang and colleagues shed light on how thalamic and cortical axons travel from the drop-off point to "where they go." Conspicuously, in both studies, the guidance of axons to particular targets is mediated by ephA/ephrin-A signaling.

An important feature of the study by Torii and Levitt is a focus on the guidance of cortical axons to thalamic targets. The corticothalamic projection has received too little recent attention relative to its importance. The choice turns out to have additional significance. Interesting differences appear between the mechanisms that guide cortical axons to thalamic targets and those proposed to guide the thalamocortical projection.

Torii and Levitt note that patterns of ephA7 and ephrin-A5 in cortex and thalamus match up in a way that suggests that ephA7-positive cortical axons are repelled by ephrin-A5 into correct target zones. They then determine what happens to corticothalamic targeting if levels of ephA7 are increased or decreased in the cortex. In an elegant series of experiments, electroporation-mediated gene transfer is used to manipulate cortical levels of ephA7 in living mouse embryos and, at the same time, to introduce axon tracers. Two distinguishable tracers are used, one red, and one yellow, mixed at high and low concentrations, respectively. Coelectroporation has been found to give qualitatively similar levels of expression. Thus, bright-yellow axons in the thalamus are likely to belong to the cortical neurons with the highest expression of ephA7. The investigators can, with a single manipulation, alter ephA7 levels in a specific region of cortex, trace cortical axons to the thalamus, and compare the thalamic distribution of axons arising from cells that misexpress ephA7 a little, or a lot.

Results support the hypothesis that ephA/ephrin-A signaling directs corticothalamic innervation. Just as important, however, was a mismatch that developed between thalamocortical and corticothalamic projections. Although targeting of cortical axons in the thalamus was changed, there was no alteration in the targeting of thalamic axons to the cortex. Further, there was no change in the position of either corticothalamic or thalamocortical axons in the IC. The two sets of axons intermingled normally. The handshake, therefore, had not in this case led to an exchange of precise positional information. Thalamus projected to the cortex as usual, but the projection back from the cortex was now directed toward the wrong part of thalamus. Given that feedback from the cortex is essential for normal thalamic function, Torii and Levitt speculate on the functional consequences such a mismatch could have.

The projections under study are those between sensory cortex and sensory relay nuclei of the thalamus. An investigation of somatosensory cortex and thalamus in rat indicates the importance of corticothalamic feedback (Temereanca and Simons, 2004). In the somatosensory whisker barrel system, activity in the corticothalamic projection regulates how strongly thalamic neurons respond to the deflection of their preferred whisker versus a nonpreferred whisker (Temereanca and Simons, 2004). This means of regulating response to the environment would presumably be unavailable to Torii's and Levitt's mice.

In the paper by Cang and colleagues, experiments move directly from genetic manipulation to the impact on brain function. In mice with severely deficient ephrin-A signaling, changes in the shape and position of V1 were observed by intrinsic signal optical imaging. These mice lacked all three of the ephrins, ephrin-A2, -A3, and -A5, normally expressed in the cortex, and in particular, in posteromedial neocortex. Strikingly, in the triple knockout, primary visual cortex (V1) was shifted medially in the area map, rotated, and compressed. Activity in V1 indicated that axons from the dorsal lateral geniculate nucleus (dLGN) were able to follow altered guidance cues. That the lack of ephrin signaling in the cortex was responsible for the changes in V1 was supported by electroporating *ephrin-A5* into the cortical primordium. V1 shifted away from the site of overexpression. These observations indicate that V1 is positioned in part by repulsive ephrin-A signaling from neighboring cortex.

It has been suggested that ephrins and other guidance molecules in the cortex may not be involved in establishing area boundaries, but are critical for the internal organization of an area (Dufour et al., 2003). Results obtained by Cang and colleagues do not support

the first proposal, but do support the second. Different ephrin-A manipulations were able to shift V1 and to alter the retinotopic map, and the effects were dissociable.

The two new studies are therefore in accord with previous reports, proposing that a basic signaling mechanism—eph/ephrin signaling—can mediate several highly related developmental processes. These include sorting thalamocortical axons in the IC, guiding corticothalamic projections to their targets, regulating the position of thalamic afferents within the cortical plate, and directing the organization of thalamic innervation within an area. Both papers published in this issue of *Neuron* argue, however, that these developmental events remain independently regulated.

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Origin and Classification of Neocortical Interneurons

Neocortical interneurons are very diverse in morphological, physiological, molecular, and developmental characteristics. Recent work is discovering strong correlations between these phenotypic features, confirming the intuition of Cajal and Lorente that distinct classes of interneurons exist, each presumably mediating a different circuit function. A paper by Butt et al. in this issue of *Neuron* describes correlations between the developmental origin of interneurons and their anatomical, electrophysiological, and molecular properties. An effort to standardize the nomenclature of interneurons is underway. Because different interneuron subtypes have different ontogenic origin, they could be classified based on their developmental specification by transcription factors.

> …The opinion generally accepted at that time that the differences between the brain of non-mammals (cat, dog, monkey, etc.) and that of man are only quantitative, seemed to me unlikely and even a little offensive to the human dignity. But do not the existence of articulate language, the capability of abstraction, the ability to create concepts, and, finally, the art of inventing ingenious instruments, appear to indicate (even admitting fundamental structural correspondences with the animals) the existence of original resources, of something qualitatively new, which justifies the psychological nobility of *Homo sapiens*? My investigations showed that the functional superiority of the human brain is intimately bound up with the prodigious abundance and unusual wealth of forms of the so-called neurons with short axon…
>
> —S. Ramón y Cajal,
> Recuerdos de mi vida, 1917

> That which has a name exists.
>
> —Basque proverb

In the mammalian neocortex, interneurons are a heterogeneous group of nonpyramidal, GABAergic cells, which traditionally have been considered to project locally (hence the term "short-axon cells") and appear to be mostly inhibitory in their postsynaptic action. Interneurons are also distinct from pyramidal cells in that they migrate into the cortical mantle during development from territories elsewhere in the telencephalon. Most studies of cortical circuits have focused on pyramidal neurons, because they amount to 80%–90% of the neurons in the neocortex and have long-range axons, which probably makes them the sole output of the circuit. Pyramidal cells have been traditionally considered the backbone or skeleton of the cortex, whereas interneurons have been thought to play an auxiliary role, such as to prevent epilepsy generated by runaway excitation of the pyramidal cells. Nevertheless, many investigators, starting with Cajal, have been drawn to the interneurons and have considered that they are the ones likely to be responsible for the richness of cortical processing. In Cajal's own words, interneurons were the "butterflies of the soul," and he argued that they were particularly abundant in higher primates and therefore were likely to be responsible for higher brain functions (Ramón y Cajal, 1923).

Lorente de Nó trained with Cajal and, like a great disciple, proceeded to challenge many of his master's assumptions. At the early age of 20, while still a medical student at the University of Madrid, Lorente performed a systematic Golgi study of the cerebral cortex of the mouse and published a monograph that still today is one of the most complete accounts of cell types in the neocortex ever published (Lorente de Nó, 1992). In this paper, Lorente argued that the mouse, the same species that Cajal had used to exemplify simpler circuits, is endowed with at least 70 classes of neocortical cells, more that Cajal described in humans. Although most cell