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

types were pyramidal, Lorente also described dozens of different types of interneurons and argued that the morphological details of the axons were key to help distinguish subtypes of neurons. This work provided an alternative explanation to the mental superiority of "higher" mammalian species: humans could have more mental abilities than mice, not because they have more different types of neurons, but because they may have more copies of a basic structural circuit module, one that could be essentially the same in rodents and primate.

Since this work, several new techniques have greatly enriched our understanding of interneurons. Besides the continuing tradition of Golgi studies (Fairen et al., 1984; Szentagóthai, 1978), the introduction of electron microscopy has provided information about synaptic targets (Peters et al., 1976), demonstrating that interneurons can be extremely specific in the choice of postsynaptic target, down to the specific part of the neuron they contact (Somogyi et al., 1982). Also, the development of molecular markers and specific antibodies has became a reliable method for identifying interneurons (DeFelipe, 1993), and the introduction of brain slices has enabled high-quality intracellular electrophysiological studies of their intrinsic electrophysiological properties (McCormick et al., 1985). Finally, developmental studies have discovered that many interneurons originate in the ganglionic eminence and migrate into the cortical plate (Anderson et al., 1997; Wichterle et al., 1999).

Nevertheless, in spite of a hundred years of research, the basic question of which are the different types of interneurons, or whether subtypes actually exist at all, is still unresolved. A major problem lies in the terminological confusion that exists in interneuron research. The irruption of novel techniques and the increasing number of laboratories has generated a rich data set revealing a tremendous diversity in every aspect of the phenotype of an interneuron. This has created a plethora of studies that use different nomenclatures to classify interneurons or their phenotypic features. Not only is it commonplace for different laboratories to use different nomenclatures, but even sometimes researchers from the same laboratory use different terms to describe the same type of interneurons. Thus, this essentially qualitative field has given rise to a series of subjective criteria that are not universally accepted, making it difficult to compare results and to assess exactly what types of interneurons were studied. Because there are many alternative classification schemes being proposed, what constitutes a cell class to one investigator does not to another, and laboratories work in isolation without being able to capitalize on the work of other colleagues. This atomization of research is particularly inappropriate when considering the magnitude of the common goal, the understanding of cortical circuits, a daunting task that should humble all researchers. In the midst of this situation there are skeptics that argue that there are no defined groups of interneurons, but instead a continuum of anatomical or physiological subtypes (Parra et al., 1998). In this extreme view, the diversity is the ultimate reality, and the efforts to classify this diversity are bound to fail. The subtypes of neocortical interneurons would be meaningless, because they would arise as the result of combining all possible anatomical, physiological, or molecular features of interneurons.

To tackle this nomenclature problem, a group of 39 interneuron researchers recently met in the birthplace of Cajal, Petilla de Aragón (Navarra, Spain), with the aim of standardizing the nomenclature of interneuron features. This group agreed on the use of a common list of terms that describe the anatomical, physiological, and molecular features of neocortical interneurons (http://www.columbia.edu/cu/biology/faculty/yuste/petilla/). The idea is that using common terms to describe the same features of interneurons will make it easier to arrive at an eventual consensus with respect to the classification of neocortical interneurons and their nomenclature. In fact, the "Petilla convention" formed a committee, with morphological, electrophysiological, and molecular experts, to work toward a unified terminology of subtypes of interneurons. The participants of this Petilla meeting were convinced that there are indeed distinct classes of interneurons and that their different anatomical, molecular, and physiological features are but reflections of one unique reality. Like the four blind men encountering an elephant, many researchers today may not realize that the very specific features of a particular interneuron could reflect a more basic constellation of phenotypic features. Although it could be argued that classifying and naming is a purely academic exercise, it currently seems essential for further progress, particularly given the infusion of molecular researchers with backgrounds in different fields. It is difficult to imagine how anyone could attempt to decipher a circuit without clear knowledge of its components.

There are good reasons to expect that interneuron subtypes exist and are of functional importance. Some of the best arguments come from recent work on spinal cord development, where *Hox* transcription factors specify the fate of different subtypes of neurons (Dasen et al., 2005). In fact, the expression of a particular transcription factor is correlated with specific dendritic and axonal morphologies and also with a specific synaptic connectivity. Moreover, changing transcription factor expression induces phenotypic switches between subtypes of cells, complete with changes of morphologies and other molecular markers. Importantly, in the spinal cord there does not appear to exist a continuum of cell types, but the expression of particular morphogens and the widespread use of negative-feedback mechanisms generates clear diversity of few cell types. In the spinal cord, therefore, it is becoming possible to define neuronal cell types by their transcription factor specification.

Recent results give credence to the possibility that the mammalian cortex could also be endowed with clearly defined subtypes of interneurons. There has been increasing awareness of the reliable correlations between morphological, molecular, and electrophysiological features of interneurons (Cauli et al., 1997; Kawaguchi and Kubota, 1993). As an example, a systematic correlation has been found between the morphologies of many neocortical interneurons and the details of the neuronal intrinsic firing patterns, when stimulated with pulses of somatic current (Gupta et al., 2000). Also, a recent study has uncovered a multidimensional correlation matrix between the expression of particular genes and fine details of the firing pattern of interneurons (Toledo-Rodriguez et al., 2004). Thus, subtypes of neocortical interneurons

can be identified by a constellation of anatomical, physiological, and molecular features.

The work of Butt et al., published in this issue (Butt et al., 2005), together with a previous paper from another group (Xu et al., 2004), make this argument even stronger. These studies describe clear correlations between the developmental origin of interneurons and their anatomical, electrophysiological, and molecular properties. Both studies used fate mapping of embryonic cells from EGFP donor cells into wild-type animals to understand the fate of interneurons originating from the medial and caudal ganglionic eminence (MGE and CGE). After transplantation into cultures or in utero, they characterized the developmental phenotype of MGE and CGE-derived cells in the relatively mature circuit. Xu et al. found that parvalbumin and somatostatin-expressing interneurons originated in the MGE, whereas the CGE gave rise to calretinin-expressing interneurons. Butt et al. used the intrinsic electrophysiological properties of the neuron to classify interneurons into seven classes and found that, whereas E13 MGE cells gave rise to "fast-spiking" cells, E13 CGE neurons produced "regular-spiking" cells. Interestingly, CGE cells transplanted at a later developmental stage generated other subtypes of regular-spiking cells.

Essential for the analysis and interpretation of the data is the definition of different interneuron cell types and the criteria used for this classification. For example, the seven subtypes chosen by Butt et al. may not have been the ones chosen by other investigators, and their nomenclature makes it difficult for other investigators that use different criteria and terms to describe the same neurons to fully understand the scope of the work. This is not a problem unique to this study, but a symptom of the generalized and acute problem in the field. But regardless of this nomenclature/classification problem, the data stand on their own, uncovering a pattern by which different subtypes of interneurons are generated at different spatial positions and, in some cases, also at different developmental stages. Thus, like in the spinal cord, the spatiotemporal patterning, presumably by regional differences in transcription factor expression, could result in the specification of different subtypes of cells. Also, the sequential generation of different subtypes of cells from presumably similar progenitor data also could imply that different subtypes of neocortical interneurons might be related in their developmental lineage, in an interneuron family tree.

Besides demonstrating an orchestrated generation and migration of different subtypes of interneurons, these studies provide us with light at the end of the tunnel with respect to the problem of classification of interneurons. The fact that subtypes of interneurons have different developmental histories provides a new method to classify neocortical interneurons: by their origin. Because the mechanisms underlying this spatiotemporal specification are likely to be due to transcription factor patterning, interneurons could be classified by the transcription factor (TF) or combination of TFs, that specify them. In doing so, researchers would be using the internal instructions of the system to classify it. All the other phenotypic features could be directly or indirectly specified by the TFs and the mysterious correlations between anatomical, physiological, and molecular features would merely result from this common cause. Not only does this criteria seem more natural than using accidental phenotypic features to classify neurons, but it also appears that it could be the definite final classification, assuming that interneurons subtypes are genetically hardwired. Moreover, using the TF expression as the classification criteria could be something very practical, because molecular tools will be generated to take advantage of this TFs specificity in order to enable the genetic manipulation of each individual subtype of cortical interneuron. Thus, molecular genetics may help provide definite causal evidence as to what is the exact role that each class of interneuron plays in the circuit.

In finishing, it is ironic to note that, in the spinal cord, axonal morphology appears to be the phenotypic characteristic that best correlates with the earlier TF expression and specification. If this holds true in the neocortex, we could reinterpret Lorente's qualitative anatomical work, 83 years later, and argue that, unbeknownst to him, what he and others were really doing with their careful classifications based on axonal morphologies was scoring differences in TFs. It would be a beautiful confirmation of the exceptional powers of observation and intuition of the early anatomists. As Elliot put it, "... and the end of all our exploring will be to arrive where we started and know the place for the first time" (Eliot, 1944).

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A Rose by Any Other Code

In this issue of *Neuron*, Mazor and Laurent demonstrate that the internal representation of an odor in the antennal lobe of locusts is broadly distributed across the population of projection neurons and is formatted in a manner that requires deciphering of response transients rather than steady-state activity patterns.

How is the odor of a rose represented by neural activity patterns within the first few stages of our olfactory system? What are the neural mechanisms through which we can distinguish that rose's odor from one of a different variety? Issues related to olfactory coding have inspired a great deal of recent experimental and theoretical research and have yielded a host of significant insights into mechanisms underlying population coding of complex stimuli. However, several fundamental questions related to olfactory coding have recently been raised that are the focus of considerable debate. Two questions of particular interest relate to the density and the dynamics of the olfactory representation. How broadly distributed is the trace of a particular odor across the population of principal neurons of the first olfactory processing stage? Can the identity of an odor be "read out" from a static steady-state activity pattern that develops across this population during a "sniff," or is the information about the odor formatted into some aspect of the population's dynamic activity patterns during the sniff? Mazor and Laurent report the results of a spectacular set of experiments that provide definitive, quantitative answers to these questions: they demonstrate that the odor representations are very broadly distributed in the first processing stage and that they are, indeed, "dynamically formatted" (Mazor and Laurent, 2005).

The experiments were carried out on the locust, which is one of several invertebrate and vertebrate preparations Laurent and colleagues (and researchers at several other institutions) have been studying over the past decade. The specific targets of the study were the projection neurons (PNs) in the animal's antennal lobe (AL), which functions as an "encoding machine" to transform the olfactory input in a manner that enables the formation of olfactory memories within the next processing stage (the mushroom body). (The PNs and AL are functionally equivalent to the mitral cells and olfactory bulb in vertebrates.) There are only about 830 PNs in the locust's entire antennal lobe. These PNs receive direct input from the animal's array of olfactory receptors and interact with one another through a group of local interneurons in the AL. The focus of this study was on a complex and unresolved issue: what is the precise nature of the coding scheme established at these early stages? Specifically, the goals were to determine (1) how many of the 830 PNs were activated over one single oscillation cycle of a long-lasting response, (2) how reliably the spikes were produced by individual PNs, (3) how rapidly the representations (i.e., the population activity patterns) for single odors evolved, (4) if these representations eventually stabilized to a fixed pattern, and if so, (5) whether or not those stabilized patterns were optimally discriminable.

The experiments designed to answer these questions were very straightforward, though technically a tour de force: different odors were presented to a group of test animals, and the fully resolved spike-train responses of 99 out of the 830 PNs were recorded. This represents 12% of the entire PN population. For some of the experiments, local field potentials were recorded simultaneously. Although this sample of 99 PNs was drawn from 10 different animals, population data could be assembled by combining sets of simultaneously recorded PNs across experiments, as described in earlier experiments (Stopfer et al., 2003). The authors characterized the population's responses to five different odors, presented for durations ranging from 0.3 to 10 s, with enough repetitions of all stimuli to get quantitative statistical assessments of pattern discriminability.

The results, in a nutshell, were as follows. In the resting initial state, in the absence of any odor, only 1% of the PNs were highly active, 23% were silent, and the remaining 76% were "flickering" on and off. Upon presentation of the odor, the PN population activity became much more structured: about 10% of the PNs became reliably active and highly correlated with one another in their firing, 60% became inactive, and the remaining 30% "flickered" unreliably (i.e., without any significant correlation to the stimulus). After approximately 50 ms, this 10-60-30 pattern was re-established, but with a somewhat different set of PN cells in each of the three activity categories. (Each one of these 50 ms epochs partially correlated activity corresponded to one of cycle of the 20 Hz LFP oscillations.) During maintained odor presentations, this characteristic decorrelation and recorrelation of different sets of PN cells continued for 1–2 s, after which the pattern stabilized to a fixed set of active, inactive, and unreliable PNs. By the end of the 1–2 s period of transient dynamical activity, approximately half of the 830 PN cells had participated in one of the "10%" (reliably active and highly correlated) groups.

A simple analogy might help illustrate this complex scenario. Imagine that 832 PN cells are configured as a low-resolution Palm-Pilot-like screen, having only 26 × 32 pixels. Before the odor presentation, eight to ten of the pixels scattered throughout the array are latched up to full brightness, about 190 are blacked out, and the remaining 630 are flickering on and off like "snow" on a video monitor. The overwhelming impression would be of totally unpatterned activity. Upon odor presentation, however, a spatio-temporal pattern emerges: 500 of the pixels go black, and about 80 go bright at nearly the same instant. The remaining 250 pixels flicker on and off with no apparent correlation to either the bright or dark pixel groups. The screen image then starts to throb at 20 Hz: upon every cycle, a new pattern is established