Perspectives on the developmental origins of cortical interneuron diversity.

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Abstract

Cortical gabergic interneurons in mice are largely derived from the subpallium. Work from our laboratory and others over the past five years has demonstrated that a developmental logic in space and time underlies the emergence of specific cortical interneuronal subtypes. Following on the seminal work of the Rubenstein laboratory (Anderson et al., 1997a, b), we set out to fate map the output of the subpallial ganglionic eminences. Our initial approach utilized ultrasound backscatter microscopy to perform homotopic and heterotopic transplants of genetically marked progenitors from the lateral, medial and caudal ganglionic eminences (LGE, MGE and CGE respectively) to unmarked host brains (Wichterle et al., 2001; Nery et al., 2002, Butt et al., 2005). The LGE at least in the context of our transplant studies did not appear to generate cortical interneurons. By contrast, we found that that approximately eighty percent of cortical interneurons arise from the MGE, while the remaining twenty percent was generated by the CGE. Hence, the majority of interneuron subtypes, including all fast spiking parvalbumin-positive basket cells and somatostatin-positive Martinotti cells appear to arise from the MGE. A more restricted set of cortical interneurons seems to be generated in the CGE, the majority of which are bipolar calretinin/VIP-positive interneurons. Complementing these results, we have recently demonstrated using inducible genetic fate mapping that the MGE produces specific cortical interneuron subtypes at discrete timepoints during development (Miyoshi et al., 2007). These studies demonstrate that cortical interneurons arise from a precise developmental program that acts in both space and time. Beyond this however, it seems likely that postmitotic events influence the specific function of subclasses of cortical interneurons. A primary challenge in the future will be determining what aspects of interneuron diversity are determined by intrinsic genetic programs within each lineage versus those properties imposed by the local environment in the cortex.

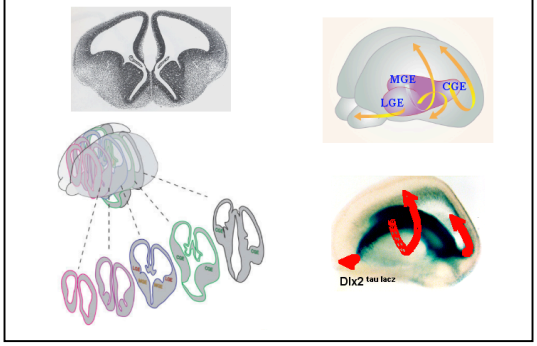
Since the original descriptions by Ramon y Cajal a hundred years ago, cortical interneurons have been recognized to be a remarkably diverse population (Molnar et al., 2006). Although they make up only a fifth of the neurons within the cerebral cortex, their function is thought to be central to learning and their dysfunction is correlated with disease. A starting point for understanding their role in both normal and abnormal contexts is determining how cortical interneuron diversity is generated. Work from my laboratory and others over the past five years have revealed that the place and time of origin of cortical interneurons predicts their intrinsic physiological properties. Here I will review findings that suggest that the broad classes of cortical interneurons are specified at the place and time of their generation. Moreover, I will argue that this is achieved through the action of transcriptional codes within the ventral progenitor zones that give rise to them. Understanding the logic of this transcriptional code holds the promise of both unraveling the molecular means by which different cortical interneurons subtypes are generated and providing genetic tools for their prospective identification and manipulation.

Cortical Interneurons are generated within the Subpallium.

The realization that cortical interneurons originate within the subpallium provided the first clue that understanding how cortical interneurons are generated would require looking beyond the cortex (Anderson et al, 1997a, 1997b). In a series of landmark papers, the Rubenstein laboratory revealed that a massive ventral to dorsal migration of

Figure 1:

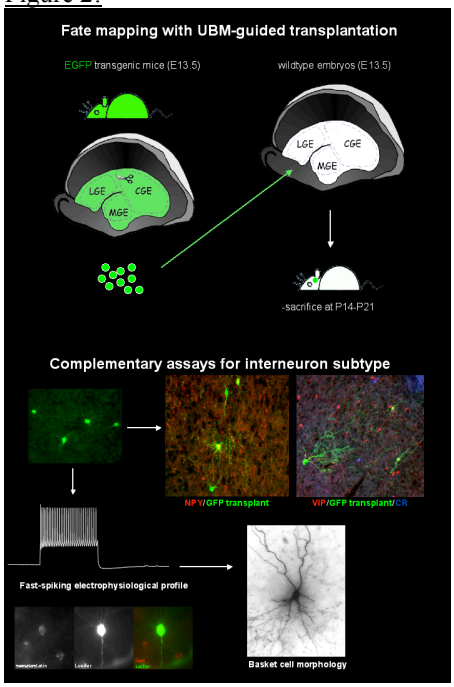
The Spatial Temporal Origins of Cortical Interneurons:



cortical interneurons occurred during late embryonic development. Near coincident work from the laboratory of Arturo Alvarez-Buylla suggested that the medial ganglionic eminence (MGE) might be the source of these interneurons (Wichterle et al., 1999). This idea came from studies showing that MGE explants are remarkably migratory and perinatal transplants of embryonic day (E) 13.5 MGE to postnatal day (P) 0 recipients, resulted in the wide dispersion of cells within the telencephalon.

In an attempt to explore this issue further, I was approached by Arturo Alvarez Buylla with the suggestion of using *in utero* ultrasound backscatter microscopy (UBM)-guided transplantation to fate map the MGE and LGE (lateral ganglionic eminence). My laboratory had used this method as a means of doing gain of function viral experiments (Gaiano et al., 1999), after Daniel Turnbull had pioneered this method several years earlier (Olsson et al., 1997). Lacking however was a precise method to introduce the nanoliter quantities of cells required for these transplants, a difficulty overcome through the innovative adaptation of a X-directional micromanipulator as a microinjector by Arturo Alvarez-Buylla. Our collaborative effort provided the first definitive proof that large numbers of cortical interneurons arose from the MGE, while the striatum and olfactory bulb neurons were derived from the LGE (Wichterle et al., 2001, Figure 1). Importantly, this work also showed that the site of origin of the donor tissue

Figure 2:



and not the site of transplantation predicted the fate of the transplanted tissue. Specifically LGE donor tissue transplanted into the MGE was indistinguishable from homotopic transplants of LGE progenitors. This provided the first strong evidence that the fates of progenitors within the ventral eminences were cell autonomously specified in their respective proliferative zones.

The success of this approach encouraged Susanna Nery and Joshua Corbin, a student and postdoctoral fellow in my laboratory, to examine the caudal ganglionic eminence (CGE). While the MGE and LGE are distinct progenitor zones within the subpallium, it had been observed by us and others (Anderson et al., 2000) that the posterior aspect of these eminences are fused. First referred to as the CGE by Anderson and colleagues (2001), it was unclear whether this was a posterior extension of the MGE and/or the LGE, or an entirely distinct structure in and of itself. The purpose of our study was to determine which structures within the mature telencephalon the CGE contributed to and indeed whether in fact it should be considered a separate progenitor zone. While the MGE can be distinguished from the CGE and LGE by its expression of *Nkx2.1,* there are no molecular markers to distinguish between CGE and LGE. Indeed, other than their differences in fate, the best evidence to date that the LGE and CGE are genetically distinct comes from the observation that in *Gsh2* null mutants, pallial genes such as *Ngn2* encroach on the LGE but not the CGE (Nery et al., 2002).

MGE and CGE Progenitors give rise to Distinct Populations of Cortical Interneurons.

Our original goal in fate mapping the CGE, MGE and LGE was to determine the contribution of these eminences to structures in the telencephalon. While ultimately this

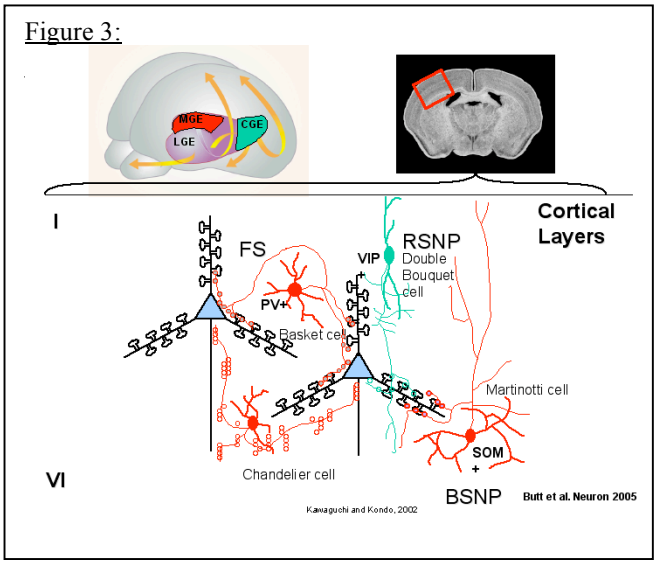
focused on the cortical interneuron population, it is important to remember that a significant proportion of neurons derived from these eminences contribute to subpallial structures, including the striatum, the nucleus accumbens and the amygdaloid complex (Nery et al., 2002). Importantly, as with our previous study, the fate of transplanted MGE and CGE progenitors appeared to be cell autonomous restricted: the pattern of integration and differentiation of MGE-derived cells was the same regardless of whether the graft was targeted to the MGE or the CGE. The resulting fate mapping study (which also reexamined the fate of LGE-progenitors for comparison) revealed that the three ganglionic eminences each contributed neurons to distinct and largely non-overlapping structures within the telencephalon. For instance, while the CGE-derived neurons populated the shell of the nucleus accumbens, LGE-derived neurons contributed to the core of this structure. Alternatively, while the CGE gave rise to neurons in the medial amygdala nuclei, the MGE contributed primarily to the lateral amygdala nuclei. In the cortex however, the areal distribution of MGE and CGE neurons largely overlapped. Moreover, in both cases all neurons within the cortex derived from these structures were gabaergic and hence inhibitory interneurons. However, in both their laminar distribution and their morphology, the interneurons derived from the MGE and CGE were markedly different. It was these observations that first focused my laboratory on the question of cortical interneuron diversity.

At the time we did our MGE/CGE fate mapping experiments, the literature describing the diversity of cortical interneurons was divided into the groupers (such as Kawaguchi, 1993) and the dividers (such as Markram et al., 2004). The groupers divided interneurons into five basic categories, while the dividers posited the existence of at least

a hundred distinct cortical interneuronal subtypes. These subdivisions were based largely on three criteria, morphology, marker expression and intrinsic physiological properties. Notably absent from the debate was a clear notion as to how this diversity was generated. Our results suggested that at least some aspects of cortical interneuron diversity are established by their place and time of origin. While the work presented in Nery et al (2002) demonstrated that the distribution, morphology and immunomarkers from interneurons originating in the MGE and CGE differed, the extent to which specific subtypes are generated in space and time was less certain. Studies from the Anderson laboratory published shortly afterward (Xu et al., 2003), clarified these divisions by showing how specific interneuron populations, identified on the basis of their marker expression, arose from the CGE and MGE. By studying the intrinsic properties of these cells, such as firing rate, adaptation, as well as their morphological characteristics (Figure 2), we were able to relate an cortical interneuron's site of origin to their physiological subclass.

In 2001, shortly before we published our CGE fate map study, the first of a series of cortical development meetings was held in Delphi. In discussing our data with Arnold Kriegstein at this meeting, I asked whether they were interested in helping us explore the physiological properties of interneurons originating from the MGE and the

Figure 3:



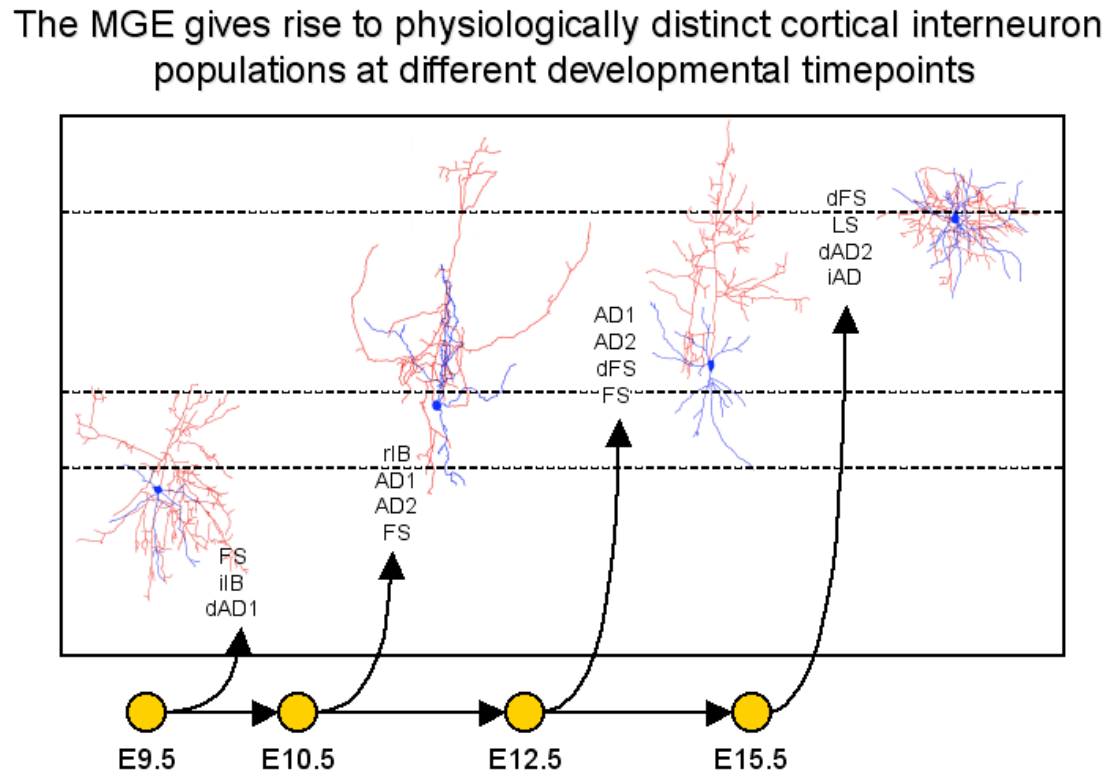
CGE. This began an extremely fruitful collaboration between our laboratories initiated by Susanna Nery from my laboratory and Steven Noctor from the Kriegstein laboratory. The proof of principle for this work came from UBM-guided transplants of GFP labeled donor MGE or CGE cells done at NYU medical center, with the postnatal patch clamp analysis being done at Columbia medical center. However, transferring animals between laboratories proved cumbersome and Susanna Nery shortly departed my laboratory for a postdoctoral fellowship in England. The work was continued in my laboratory by a postdoctoral physiologist Simon Butt and a graduate student Marc Fuccillo. Working together they refined the protocols for both the transplants and the physiological analysis of cortical interneurons in P14-P24 slice preparations (Butt et al., 2005). Broadly speaking our classification schemes were based on those outlined by Kawaguchi and Kubota in their analysis of frontal cortex (1997), as well as Cauli et al. (1997) in their analysis of sensory and motor cortex. This was greatly aided by our interactions with Bernardo Rudy, who guided us in developing meaningful protocols for examining the intrinsic physiological properties of cortical interneurons. Moreover, Bernardo Rudy's focus on the biophysical functions of specific ion channels (Rudy and McBain, 2001; Goldberg et al., 2005) led us to consider how developmentally expressed transcription factors could control interneuron function through modifying their membrane properties.

Our studies revealed that at E13.5 while the twenty percent of cortical interneurons that are bipolar Calretinin and VIP-expressing interneurons came from the CGE, the remaining eighty percent of cortical interneurons arose from the MGE (Figure 3). Within this later population were included both the parvalbumin (PV)-positive, fast-spiking (FS), basket cell population, as well as the somatostatin (Sst)-positive, burst-

spiking (BS) Martinotti cells. Therefore, the populations arising from these structures are distinct, demonstrating that the CGE and the MGE gave rise to entirely non-overlapping populations of cortical interneurons. Furthermore, through repeating the heterotopic transplantation of MGE progenitors to the CGE, we were able to demonstrate that the morphology and intrinsic physiological properties of cortical interneurons is also cell autonomously specified within the progenitor domains.

Different MGE-derived Interneuron Subtypes are Generated at Distinct Developmental Timepoints.

Figure 4



The recognition that distinct subsets of cortical interneurons arise from the MGE and CGE only partially addresses the question of how the diversity in this population is generated. This is particularly pertinent with regards to the MGE from which 80% of all

cortical interneuronal subtypes originate. The E13.5 transplant studies described above indicated that at this timepoint approximately half of all cortical interneurons derived from the MGE are FS basket cells or chandelier cells. An additional twenty percent are of the BS Martinotti interneuron subtype. While together these account for a majority of the interneuronal subtypes that arise from the MGE at E13.5, the remaining MGE-derived populations are quite diverse. In our longitudinal analysis of MGE-derived interneurons described below, we found that between E9 and E15.5 an additional eight subclasses of cortical interneurons are generated. Taken together this suggests that the MGE generates ten distinct interneuronal subtypes. In principle, two broad developmental strategies could underlie the generation of different cortical interneuron subtypes from the MGE. Different interneuron classes might be generated within the MGE from discrete spatial subdomains. Alternatively, they might be generated through a shifting developmental fate of the MGE to sequentially give rise to discrete interneuron subtypes over time.

To date there is little evidence for the existence of subdomains within the MGE akin to those observed in the spinal cord. Recently Goichi Miyoshi and Simon Butt in my laboratory have explored the alternative possibility that the MGE produces different interneuron subtypes at discrete developmental timepoints (Miyoshi et al., 2007). They did this using a genetic fate mapping method developed by our colleague Alexander Joyner (Zervas et al., 2004; Joyner and Zervas, 2006). This method relies on two components, a driver allele, coupled with a reporter allele (reviewed in Miyoshi and Fishell, 2006). In our case we combined the use of an *Olig2*^{CreER} driver (Takebayashi et al., 2002) with the *Z/EG* reporter (Novak et al., 2000). Fortuitously, we discovered that when *Olig2*^{CreER}*;Z/EG* mice are induced using 4 milligrams of tamoxifen it results in the

labeling of nascent neurons as they exit the MGE. Hence, in effect this provides a genetic method for fate mapping MGE neurons based on their birthdate. From this analysis we found that each of the ten classes of interneurons are born with a distinct temporal signature (Figure 4). Some classes such as the Martinotti neurons are born only at early times during development (E9.5-E13.5), while others such as the delayed FS interneurons are only born at late times during neurogenesis (~E15.5) (for details of this analysis see Miyoshi et al. 2007). While this work demonstrates that within the MGE the production of different cortical interneuronal subtypes are linked to their time of generation, it says nothing of the molecular means by which this diversity is created. Indeed, our preliminary analysis of conditional *Olig2* loss of function mice indicate that this gene is not required for the generation of different MGE-derived interneuronal subclasses within the MGE.

Developmental Genes involved in the Development of Cortical Interneurons.

What then is the developmental genetic basis by which cortical interneuron diversity is generated? Work over the past fifteen years has identified a number of transcription factors that are required for the generation of cortical interneurons, most notably the *Dlx* family of genes, *Mash1, Nkx2.1, Lhx6* and *Lhx7* (reviewed in Corbin et al., 2001; Cobos et al., 2006; Wonders and Anderson, 2006). While analysis of null alleles of each of these genes supports that they play a role in the development of cortical interneurons, it is less clear how they are causal in the diversification of this population. A chief impediment to interpreting the phenotypes of these knockouts is that loss of many of these genes leads to lethality. Hence although the numbers of cortical interneurons seen at birth in *Dlx1/2* compound mutants is reduced by 60% (Anderson et al., 1997b), and by

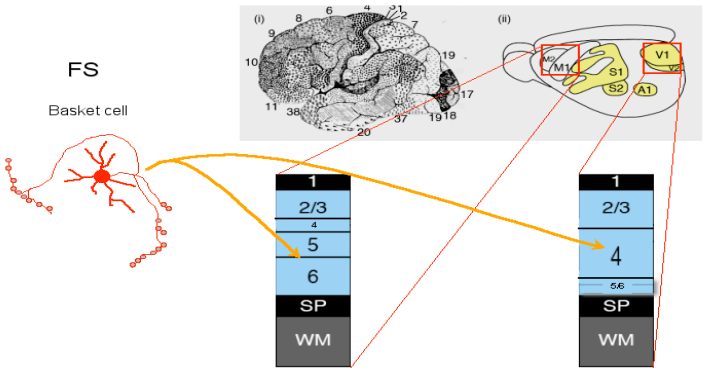
40% in either *Nkx2.1* (Sussel et al., 1999) or *Mash1* mutants (Casarosa et al, 1999), the fact that these animals do not survive postnatally makes assessing their contribution to subtype diversity difficult to gauge. The increasing availability of conditional alleles, as well as driver lines to genetically fate map these populations provides an attractive approach to begin addressing the role of these genes in generating cortical interneuron diversity. In addition, it is clear that many of the genes involved in this process have yet to be identified. To this end, Renata Brito in my laboratory has begun a microarray screen for genes expressed in cortical interneurons as a whole. We have achieved this by using a Dlx5/6^{EGFP} transgenic allele generated by Kenneth Campbell (Stenman et al., 2003). While in accordance with the normal expression of the *Dlx5* and *Dlx6* genes, there is widespread expression of EGFP within the subpallium, it appears to selectively label the entire cortical interneuron population. By isolating embryonic cortex at E13.5 and E15.5 and FACS sorting EGFP positive cells, we have succeeded in isolating large numbers of cortical interneuron precursors. Our preliminary microarray analysis of these cells fortifies our confidence that we have been successful in this endeavor, as *GAD1, Dlx2, Lhx6, NPY* and *Sst* are all highly enriched in this population. We are currently examining the expression of candidate genes in the hope they will provide clues as to the identity of specific determinants that control the fate of interneuron subpopulations.

What aspects of Cortical Interneuron Identity are Specified in the Ganglionic Eminences?

As noted above, the central issue surrounding cortical interneuron diversity is the question of how many subclasses of this cell type exist. At its essence, an interneuron's identity is defined by it connectivity coupled with its input/output function. Even within

the confines of cortical interneurons that share morphology, immunomarkers and intrinsic physiological properties, one can imagine that depending on their precise afferent input and efferent targets, they function quite differently. Similarly relatively subtle changes in their firing-threshold, firing-rate or adaptation could allow very similar cortical interneuron populations to function quite differently within the cortical network (e.g. Goldberg et al., 2005). Which of these properties are controlled by the developmental genetic history of the progenitors that give rise to them? For the foreseeable future, this question will at some level remain one of "nature versus nurture".

Figure 5:



Our analyses to date demonstrate that at least with regard to broad subclass, specification of cortical interneurons is established in the progenitor zones. However the extent to which an interneuron's subsequent interactions with its environment further shape its identity remains an open question. In the spinal cord, studies of motor neurons have to date provide us with our best understanding of the means by which specific neuronal subclasses in vertebrates are generated (Dasen et al., 2003). Motor neurons while derived from a relative small progenitor region soon diverge into specific "pools" as a result of their combinatorial gene expression (e.g. Dasen et al., 2003, 2005). This lends itself to the idea that neuronal diversity in motor neurons is established very early

in development, prior to the functional innervation of targets. However, the data as yet have failed to reveal a similar precision of gene expression in the MGE and CGE. While it is appealing to think that the logic used to create this phylogenically older spinal cord population would be maintained in the brain, the selective pressures refining these populations are likely quite distinct. Notably, the primary function of motor neurons is execution, while the central role of cortical interneurons is the filtering and processing of "complex sensory" information. The necessity of precisely innervating a well-defined set of peripheral muscles may demand a fidelity that is neither required nor desirable in the structuring of cortical circuits. Also consistent with the idea that strategies vary between motor neurons is the observation that their final position of specific neuronal subtypes in the spinal cord is stereotyped, while that of cortical interneurons are not. Indeed, although the laminar fate of cortical interneurons is predicted by their birthdate, we as yet see little evidence that cortical interneurons derived at a given position within the subpallium are destined to occupy a precise cortical area. If one then imagines that a particular FS basket cell might stochastically "choose" to reside in layer four of the visual cortex or layer five of motor cortex (Figure 5), one can see significant pressure for the precise wiring of a given cortical interneuron to be shaped by its environment. At present, I suspect that cortical interneurons while relegated to a broad class, such as Martinotti cell or basket cell, retain significant plasticity to adapt to cues within the region of cortex to which they ultimately contribute. I envision that their specification beyond the adoption of a particular shape and firing pattern, amounts to a "look up table" of hardwired responses that dictate how they will react to the particular cues they might encounter during their migration and integration into the developing cortex.

At present our understanding of the mechanisms that control the fate of cortical interneurons is too rudimentary to distinguish between these possibilities. Nonetheless, it would seem that sorting out the level of specification of cortical interneurons in the progenitor zones is a prerequisite to understanding the subsequent influences of their postmitotic environment. Furthermore, as parallel understanding of the means by which interneuron diversity is generated in the spinal cord, it will be interesting to compare how local inhibitory neurons are generated in these two systems.

The role of Cortical Interneurons in the refinement of the Cortical Cell Assembly.

The cell assembly hypothesis proposed by Donald Hebb (1949) in the 1940's suggested that the CNS was comprised of a well-order circuitry with intrinsic function independent of sensory input. He suggested that learning was accomplished through the activity dependent reorganization of this cell assembly. The realization that inhibitory cells originate within the ventral telencephalon and enter the cortex en masse perinatally raises the question of how their integration into the developing cortex is regulated. Understanding this process, is particularly pressing, as shortly after their arrival, activity dependent refinement results in the reorganization of (third order) sensory afferents. Moreover it has been recently shown that this so called "critical period" of remodeling is dependent on cortical interneurons and can be delayed through genetic or pharmacological interference with their normal function (Fagiolini et al., 2004; Hench and Stryker, 2005; Hensch, 2005). Studies where the cortex has been genetic deprived of all afferents demonstrates that the areal organization of the cortex is intrinsically encoded (Miyashita-Lin et al., 1999; Nakagawa et al., 1999). Therefore, cortical interneurons

while not obviously predestined to occupy a particular functional region of cortex are required soon after their arrival for refinement. Taken together I hypothesize that a "handshaking" occurs during development where pyramidal neurons bestow positional information onto cortical interneurons. Hence, insights into the initial interactions between these two populations during development will be central to understanding how the cortical cell assembly is established.

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Figure Legends:

Figure 1: Cortical interneurons arise from the three progenitor zones within the subpallium, the lateral, the medial and the caudal ganglionic eminences. The brain section on the top left, shows a coronal section through the telencephalon at the level of the MGE and LGE. This is equivalent to the center section in the series shown below on the bottom left (this is taken from Danglot et al., 2006: with permission). On the top right is a schematic showing the three ganglionic eminences and the general paths of migration from each of them, with tangentially migrating neurons from the LGE going to the olfactory bulb, while the CGE and the MGE send their progeny to the cortex. The saggital section below this shows a *Dlx2*^{tauLacZ} brain histochemically stained for beta galactosidase. The labeled cells can be seen tangentially dispersing along the paths shown in the figure above it.

Figure 2: Schematic showing the procedure used to do ultrasound backscatter microscopy (UBM) guided injection *in utero* and the subsequent analysis of the genetically marked donor cells within the cerebral cortex. In the upper panel, donor tissue is dissected from one of the three ganglionic eminences from an EGFP-transgenic mouse. The EGFP-positive donor cells are introduced into an embryonic recipient host brain using UBM-guided transplantation. The animals receiving grafts are allowed to give birth and brain sections from these animals are analyzed between P14 and P24 days postnatally. Donor cells that have entered the cortex and become mature cortical interneurons are visualized and examined for their expression of neural markers either

immediately (top right panels in lower part of this figure) or following electrophysiological analysis (three panels at the bottom left). Shown in the bottom panel is a trace of the firing pattern of a typical FS basket cell and its appearance after Lucifer yellow fill and immuno-visualization.

Figure 3: The MGE and CGE gives rise to distinct subsets of cortical interneurons. This figure shows a summary of the transplantation study by Butt et al. (2005). In the schematic shown in the top left in red is shown the MGE as it appears at E13.5. The boxed area of cortex shown at the top right is schematically shown in the figure below. In this schematized view of the cortex (adapted from Kubota and Kawaguchi, 1997) is shown a basket, a chandelier cell and a Martinotti cell (in red), all of which are derived from the MGE at this timepoint. The turquoise region in the schematic at the top left, shows the CGE. In the cortical schematic shown below is turquoise labeled double bouquet cell, representative of the CGE-derived bipolar cortical interneuron population.

Figure 4: Schematized results of the findings of Miyoshi et al. (2007), where the cortical interneurons derived from the MGE were genetically determined by fate mapping the *Olig2*-expression population (see Miyoshi et al, 2007 for details). In this study we found that the 10 different MGE-derived populations are born at precise developmental timepoints between E9.5 and E15.5. Their position in this schematic of cortex reflects their laminar position within the cortex. As interneurons, like pyramidal neurons, are born and populate the cortex in an inside out manner, the earliest born neurons are found in the deep layers, while the latest born neurons are found in the superficial layers.

Figure 5: Do specific cortical interneuron subtypes vary their function integration depending on the area of cortex into which they integrate? (FS schematic adapted from Kawaguchi and Kubota, 1997). Our results suggest that the areal position of interneurons within the cortex is stochaistically determined. This raises the intriguing question of whether the function of particular subclass of cortical interneuron (such as the basket cell shown in this figure) varies according to whether it ends up in layers 5 or 6 of the motor cortex versus layer 4 of the visual cortex.

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