The maturation of cortical interneuron diversity: how multiple developmental journeys shape the emergence of proper network function

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If the classical functional attribute of cortical GABAergic interneurons is to mediate synaptic inhibition in the adult cortex, it is becoming evident that their major task is instead to shape the spatio-temporal dynamics of the network oscillations that support most brain functions. This complex function involves a division of labour between morpho-physiologically diverse interneuron subtypes. Both the central network function and the bewildering heterogeneity of the interneuron population are especially emphasized during cortical development: at early postnatal stages, a single GABAergic neuron can efficiently pace the activity of hundreds of other cells, whereas some interneuron subtypes are still poorly developed. Given the role of coherent activity in brain development, this confers to GABAergic interneurons a major role in the proper maturation of cortical networks.

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Introduction
It is now becoming increasingly evident that a selective disruption of cortical GABAergic interneuron development, resulting from either genetic or epigenetic factors, is related to many neurological disorders like epilepsy, mental retardation, autism or even schizophrenia [1–7,8•]. Interestingly, the developmental loss of restricted interneuron subpopulations [6,9] or subtle functional alterations of interneuron physiological properties [4] were shown to have dramatic consequences often leading to the initiation of seizure activity at early postnatal stages. Since epilepsy can be easily conceived as the direct outcome of an inhibition deficit due to interneuron loss, understanding other more complicated brain disorders certainly indicates more elaborate cellular mechanisms and interpretations.

Two nonexclusive explanations account for the multiple impacts on brain operation of an altered development of GABAergic neurons. First, in addition to providing inhibition, GABAergic interneurons are the substrate of several nonlinear network operations required to support high brain functions. To this aim, GABAergic interneurons come in many flavors, each of them designed to carry a specific circuit task and bear the variety of network oscillations generated by mature cortical networks [10]. The second explanation for the multiple consequences of an abnormal maturation of subpopulations of GABAergic cells is that aberrant development is not restricted to the affected microcircuits but rather affects the entire network. Indeed, during brain development, there is an almost continuous crosstalk between GABAergic interneurons and the networks they integrate into, whereby the same population that supports adult network function also controls the generation of early network patterns which in turn contribute to network development creating a feedback loop.

Until recently, investigating the functional maturation of GABAergic microcircuits was seriously hampered for one major reason: developing interneuron subtypes cannot be readily identified and classified as they have not yet reached their mature neurochemical and morpho-physiological attributes (Figure 1). The advance in novel imaging and genetic strategies to dissect the functional organization of developing GABAergic neurons has opened a new era for the investigation of GABA neuron development. We will review recent work aiming at understanding how the functional diversity of this major neuronal population develops in parallel with the maturation of coherent network patterns.

Interneurons have a crucial early network function that spans throughout an extended developmental period
At adult stages it is now well established that the major function of cortical GABAergic interneurons is to organize in time and space the generation of most network oscillations associated with behavioural and cognitive brain functions [10,11•,12••]. This central network function of the GABAergic interneuron population is emphasized during cortical development in several ways. First, the
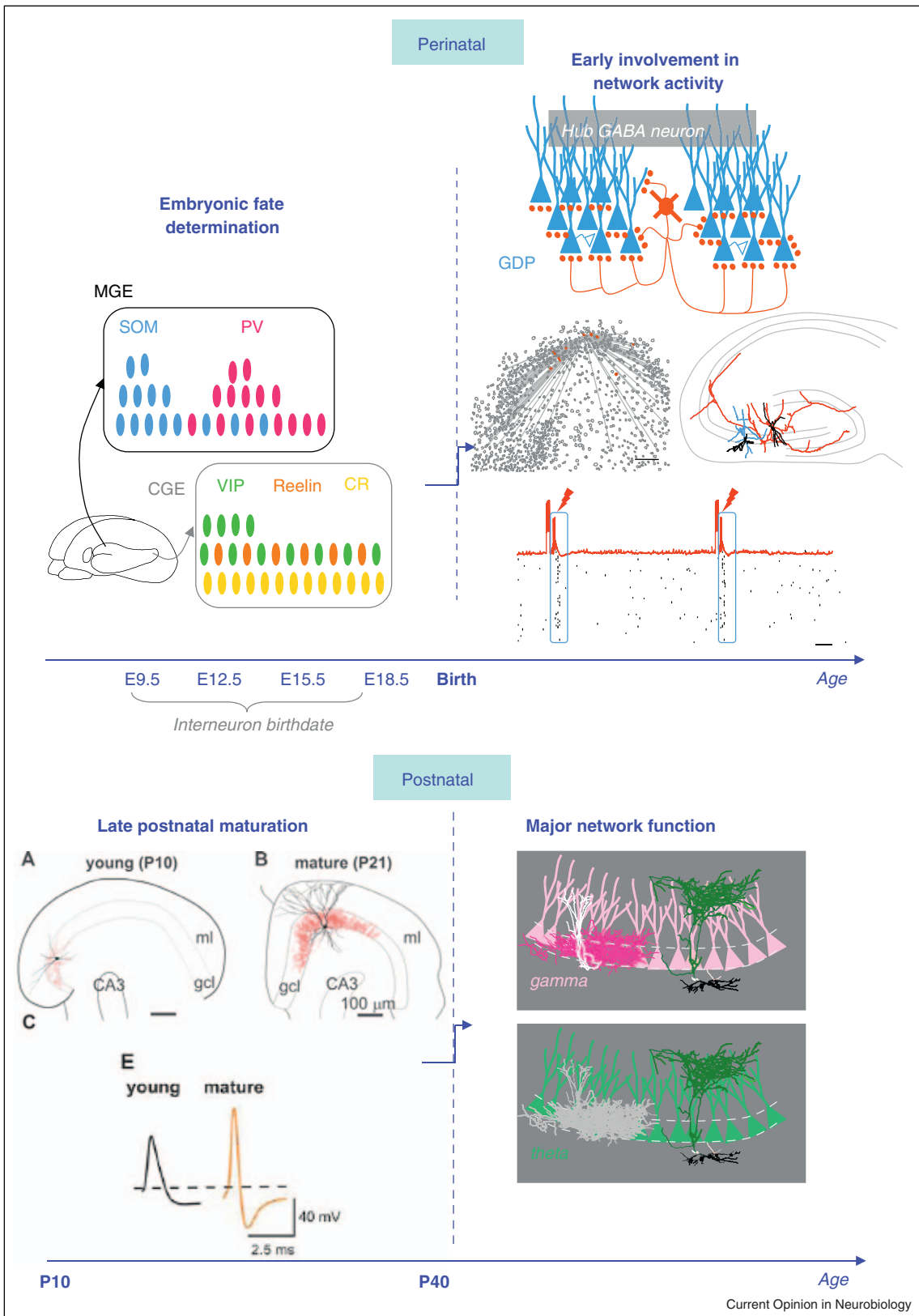
Figure 1
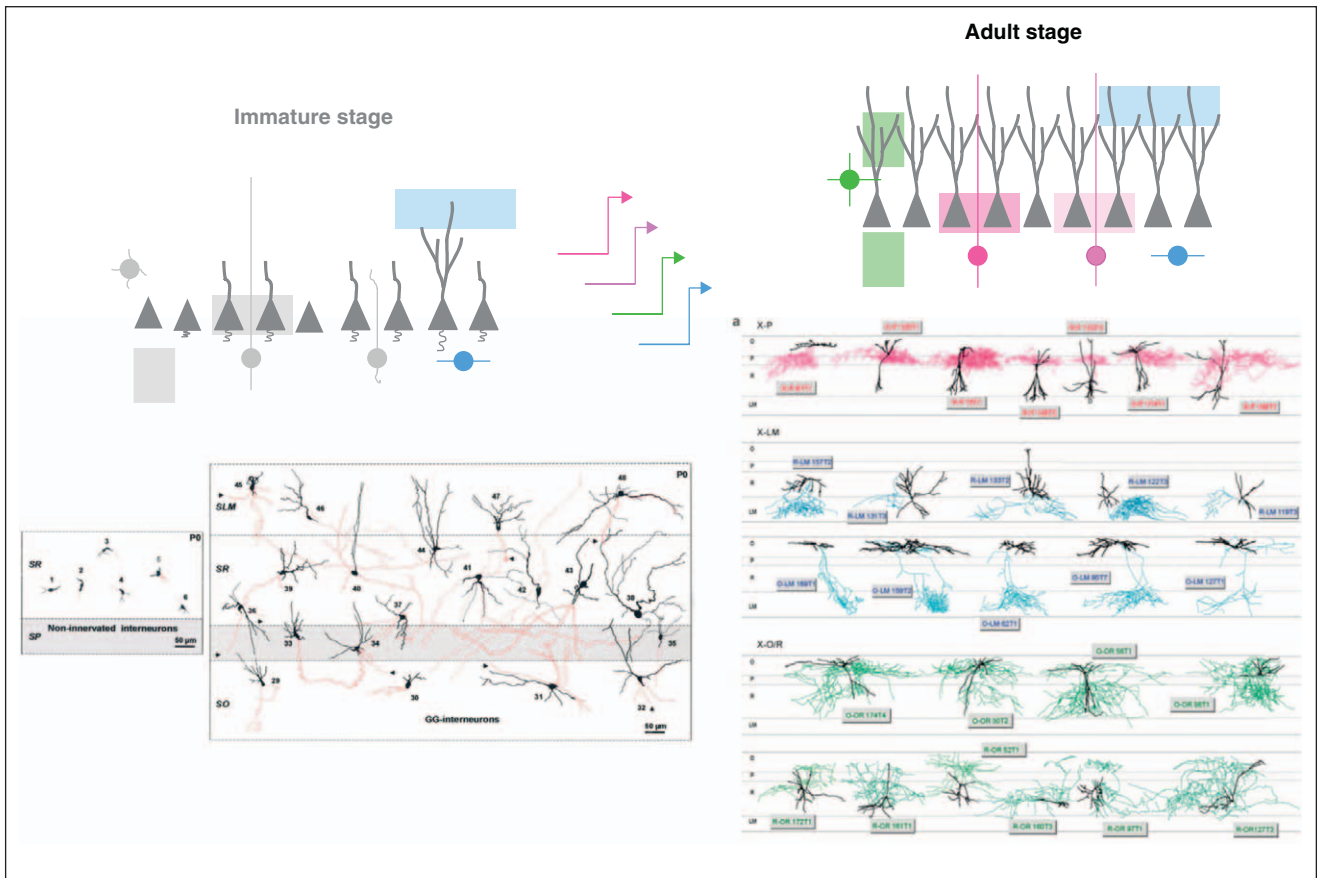
Bewildering diversity of the developing interneuron population. Schematic comparison between an immature developmental stage (left) for cortical interneuron networks (i.e. around birth in the rodent hippocampus) and the adult stage (right). At early stages of development, the developing interneuron network comprises (i) well-developed interneurons almost already displaying their adult morphological and neurochemical features (blue); (ii) interneurons with developed anatomical features but that do not express yet their characteristic neurochemical properties (gray future pink cell); (iii) neurochemically and morphologically immature interneurons. Interneurons that belong to the same family (like pink cells) may develop differently. Well developed interneurons already receive both GABAergic and glutamatergic inputs (GG-interneurons) whereas poorly developed cells are still not innervated as illustrated in the panels below taken with permission from [19]. Note that none of the reconstructed interneurons filled at P0 displays a recognizable morphology as compared to interneurons in the adult hippocampus (right panel) where different interneuron subtypes can be easily identified and classified according to their axonal arborisation (taken with permission from Cossart *et al.* Hippocampus 2006).

interneuron population pioneers cortical development, as the peak of genesis for GABAergic cells takes place a couple of days before that of their glutamatergic counterparts in rodents [13]. Cortical GABAergic neurons, at least in nonprimate vertebrates, are generated in the subpallium, mainly from two transient structures, the medial and caudal ganglionic eminences [14–16] but also from the preoptic area [17•]. Among them, some GABAergic neurons are postmitotic and start migrating tangentially towards the cortex as early as embryonic day 10 [13,18•]. Probably mostly because they constitute an older cell population, the morpho-physiological properties and firing activity of interneurons are globally more developed than those of glutamatergic cells within the same network during each stage of development. Hence the GABAergic network is already operative *in utero* in the CA1 hippo-

campal region at a time when glutamatergic cells are poorly developed morphologically and barely receive any synaptic input [19•,20]. Regarding the maturation of their intrinsic excitability, it was recently shown that neocortical interneurons display a lower threshold for action potential generation than pyramidal cells at early postnatal stages [21] which confers them a higher probability to be recruited at the early phases of network synchronization [22]. Interestingly, the firing of immature hippocampal interneurons was also shown to be maintained at a high rate through specific regulatory mechanisms [23]. On the postsynaptic side, cortical GABAergic synapses mature on average before glutamatergic ones in most cell types ranging from pyramidal neurons and interneurons [19•,24,25••] to oligodendrocyte precursors [26], indicating a very general sequence

Figure 2

Perinatal

Early involvement in network activity

Hub GABA neuron

GDP

Embryonic fate determination

MGE

SOM   PV

CGE   VIP   Reelin   CR

E9.5   E12.5   E15.5   E18.5   **Birth**   *Age*

Interneuron birthdate

Postnatal

Late postnatal maturation

Major network function

A   young (P10)   B   mature (P21)

ml   ml

CA3   gcl   gcl   CA3

100 μm

C

E

young   mature

gamma

40 mV

2.5 ms

theta

P10   P40   *Age*

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for the maturation of receptors. Given that this developmental sequence also holds for newborn neurons maturing in an adult environment [27], it likely reveals a mostly cell autonomous intrinsic sequence for receptor maturation. Along these lines, a direct inductive action of GABAergic transmission on AMPA-receptor development was recently demonstrated [25••,28,29] Pfeffer, 2009 15126/id. However, it is important to stress that a differential maturation of GABAergic synapses is likely to occur along the somato-dendritic domain with probably a delayed development of somatic GABAergic synapses [24,30–32]. Therefore at least part of the GABAergic interneuron network starts operating a couple of days before the glutamatergic one, conferring a crucial network function to the interneuron population. Nevertheless, it is important to temper this statement by taking into account interneuron diversity since it is very likely that only specific subtypes of cortical GABAergic interneurons display an early functional maturation endowing them network function (see below).

The second major support for a key early network function of the developing interneuron population stems from the fact that GABAergic transmission depolarizes and excites neurons at early developmental stages due to a higher intracellular chloride content. Obviously, within a given developing structure, some neurons may be excited while others inhibited by GABAergic transmission depending on their intrinsic chloride load, as supported by the heterogeneity of intracellular chloride concentrations observed using chloride imaging techniques [33]. This observation is a very robust phenomenon observed throughout developing structures and species, resulting from a delayed maturation of chloride extruding transporters compared to importers [34]. Regarding depolarizing GABA actions it is important again to consider the developmental and morpho-physiological complexities of the interneuron population (Figure 1). First, the action of GABAergic transmission on a given pyramidal neuron is very likely to be highly dependent not only on the age of the postsynaptic neuron, but also on the type of presynaptic interneuron, even at nearby synapses [35–37]. Also, in agreement with an advanced stage of maturation, it is possible that older interneurons display a lower intracellular chloride concentration than pyramidal cells resulting in hyperpolar-izing GABAergic inputs [38] while younger interneurons will still be depolarized by GABAergic transmission [39••,40]. This probably stems from the general increased expression of the chloride exporter KCC2 as a function of age in interneurons [41•]. Particular interneuron subtypes, like NPY hilar interneurons, may even display a specific chloride homeostasis that further extends into adulthood [42].

A firm evidence in support of a central role of specific GABAergic microcircuits in synchronizing early neuronal activity is the recent finding that a few exceptional interneurons act as network 'hubs' that is high connectivity nodes gating information flow, through a dense axonal arborisation (Figure 2) and high intrinsic and synaptic excitabilities [43••]. Modifying the activity of a single hub neuron can synchronize (Figure 2) or desynchronize network dynamics depending on the type of hub neuron and on the state of the network. This indicates that the network function of hub neurons relies on a more complex chain of neuronal activation than a mere direct excitatory action of GABA. In fact, it remains to be determined whether excitatory GABAergic transmission is indeed a mandatory condition to hub function.

We have reviewed recent data indicating that the early maturation of GABAergic networks will endow some interneurons a unique early network function hence electing them as major contributors to activity-dependent development processes. However, it is probably equally important to stress that a reason for the particular susceptibility of the interneuron population to developmental insults, linking them to many brain disorders, is the long time span of interneuron development from *in utero* stages to puberty. Until when do interneurons continue developing? The critical period for GABAergic neuron maturation extends towards late postnatal stages in rodents maybe even after the stabilization of glutamatergic networks [44]. Hence, the electrophysiological properties of fast-spiking cortical interneurons develop until 40 postnatal days ([45•,46] and Figure 2) while on the postsynaptic side, the structural and functional determinants of GABAergic synaptic transmission continue developing for similar time periods [47,48•,49]. The continuous postnatal maturation of part of GABAergic networks may explain the late postnatal emergence of

(Figure 2 Legend) The long developmental journey of cortical GABAergic interneurons. (1) Schematic representation of different steps in the development of cortical GABAergic neurons from embryonic to adult stages. Top panel: Perinatal development from late embryonic to early postnatal stages. Left: Interneuron phenotypes are largely predetermined by their spatial and temporal embryonic origins with somatostatin (SOM) and parvalbumin (PV)-expressing cells mostly originating from the medial ganglionic eminences (MGE) whereas VIP, calretinin and Reelin-containing neurons are preferentially born in the caudal ganglionic eminences (CGE) as established in [18,63]. Right: Coherent network activity patterns emerge around birth and interneurons are central for the synchronization of neuronal activity. For example stimulation of hub GABA neurons, with a widespread axonal morphology (red) as compared to other interneurons at the same developmental stage (blue), synchronizes the activity of hundreds of cells as shown in the rasterplot below (adapted with permission from [43]). Bottom panel: Postnatal development of interneurons. Left: The morpho-physiological properties of dentate gyrus basket-cells continue developing at late postnatal stages (taken with permission from [45]). Right: Schematic representation showing that in adult networks, different types of interneurons are differentially involved in the generation of network oscillations like gamma or theta rhythms.

adult patterns of network dynamics [50,51] given the major contribution of GABAergic inputs in the emergence of sparse network spikes [52]. It also explains why some interneuron subtypes are particularly prone to postnatal environmental insults (see below). In fact, it may even well be that specific interneuron populations continue being generated throughout adulthood since the SVZ was shown to continue producing GABAergic interneurons postnatally [53].

The strong genetic predetermination of interneuron subtypes facilitates interneuron developmental studies

Given the major role of GABAergic networks in cortical development it is surprising that the morpho-physiological development of different GABAergic microcircuits as well as the emergence of their respective network function remains largely unknown. This is because the organization of the GABA neuron population is complex and even more difficult to study during development than adulthood (Figure 1). As extensively commented before [54], the connectivity of GABAergic microcircuits is amazingly organized. Although heterogeneous and complex, a general wiring diagram for adult cortical GABAergic networks can now be pictured as a result of a combined effort of several groups worldwide [10].

The description of similar functional connectivity maps in immature GABAergic microcircuits was until recently almost impossible because developing interneurons have not yet acquired the characteristic adult features used to classify them [55] (Figure 1); and they display an heterogeneous development as discussed above. One possible way to challenge this limitation is to use imaging approaches to map functional connectivity patterns [37,56–58]. Using a pairwise description of multineuron calcium activity combined to electrophysiology to reconstruct online the connectivity of developing hippocampal networks in mice where GABAergic neurons were GFP-labelled, the functional organization of the developing hippocampus was recently described [43••]. It was shown that the early postnatal CA3 region of the hippocampus displayed a scale-free mode of organization that is that the distribution of connections between neurons followed a power law [59] where 'hub' neurons were GABAergic interneurons displaying a widespread axonal arborisation, on average four times longer than the axonal length of other interneurons in the developing CA3 region of the hippocampus (Figure 2). It is important to stress how concepts from graph theory and statistical physics provide several useful models for the interpretation of imaging data to study the organization of complex dynamical systems such as developing neuronal networks. Still, if imaging approaches allow studying the general functional connectivity of developing GABAergic microcircuits without any a priori assumption regarding the importance of a particular interneuron subtype, they cannot easily address the development of precisely defined morpho-physiologically interneuron families. However, this is now possible using 'genetic fate mapping' approaches.

As other developmental processes, the maturation of GABAergic functional microcircuits results from the interplay between intrinsic genetic programs and neuronal activity. Recent studies clearly indicate that the morpho-physiological identity of GABA neurons is strongly predetermined by their embryonic origin [15,18•,60••,61–65]. In other words, the adult phenotype of a given interneuron is largely dependent on where and when in the ganglionic eminences it was born (Figure 2). Hence, the cortical interneuron subtypes arising from the MGE and CGE are different [60••,61,66], the MGE producing mostly the parvalbumin-containing and somatostatin-containing neocortical interneurons while the CGE gives rise to calretinin-expressing and VIP-expressing cells [15,18•,60••,63]. It was also recently shown that two considered distinct hippocampal interneuron subtypes, Ivy and nitric oxide synthase positive neurogliaform cells are both derived from MGE progenitors under the control of Nkx2-1 [67•]. The strong embryonic predetermination of cortical interneuron identity carries implications that extend beyond the mere genetic analysis of interneuron development. Indeed, it can be applied as a tool to study different interneuron subtypes at an immature stage when they do not appear morpho-physiologically and neurochemically different yet using inducible genetic fate-mapping approaches [68]. Moreover, this spatio-temporal embryonic stamp is so robust that it could almost be proposed as a complementary way to reach a compelling classification of adult interneuron types, an even now problematic issue [55].

When and how activity may influence interneuron maturation

If interneuron diversity is largely predetermined by genetic programs, it is also well established that activity and environmental factors are equally important at every step of interneuron development, from early migration [69•,70], postnatal cortical layer sorting [41•], to late network integration [30,41•]. Developing interneurons are particularly well designed to be directly influenced by activity. Hence, it was recently shown that action-potential-independent release of GABA originating from developing cerebellar interneurons could be sensed by the presynaptic cells themselves in the form of 'preminis' [71], thus providing developing interneurons with a feedback 'private' source of GABA possibly serving their own maturation [30]. In addition, as discussed above, the development of cortical GABAergic microcircuits is a prolonged process, extending well into the postnatal period in rodents, a time window more likely to involve action-potential-dependent-neuronal activity. Indeed, the earliest forms of network electrical activity patterns appear postnatally in rodents [72,73•]. Accordingly, it was

recently shown that early environmental stimulation accelerates the postnatal development of GABAergic neurotransmission and in particular the developmental decrease of intracellular chloride concentration [74•].

What type of activity may mostly contribute to GABA-ergic interneuron development? Activity in developing neurons is usually correlated between cells, in the form of spontaneous and recurrent calcium rises [75,76]. As reviewed elsewhere [76], a bewildering diversity of network dynamics and mechanisms have been described so far in developing neuronal structures. One possible way to simplify the picture is to classify early synchronous activity patterns according to the developmental stage at which they dominate cortical networks. Indeed, the maturation of coordinated activity patterns appears to follow a precise and coordinated developmental sequence, common to many developing structures. Hence, in both the hippocampus [73•] and neocortex [77], correlated neuronal activity emerges around birth. It first synchronizes restricted gap-junction-coupled neuronal assemblies producing membrane potential oscillations associated with long-lasting calcium plateaus (Synchronous Plateau Assemblies — SPAs). Later, it involves large neuronal populations synchronized by synaptic transmission (Giant Depolarizing Potentials — GDPs; Figure 2). Given their specific spatial dynamics and associated calcium plateaus, SPAs could be proposed as playing a role in the consolidation of functional GABA-ergic microcircuits. Several observations indeed suggest that sustained elevations of intracellular calcium concentration encode a specific trigger signal to pathways regulating gene transcription [78•].

Given its postnatal emergence, electrical activity is certainly more likely to influence the development of late-developing rather than early-developing interneurons [41•,79]. This may explain why the late maturing [20,24,45•], parvalbumin-containing perisomatic targeting interneurons are frequently pointed out in numerous developmental disorders [5,9,48•,80,81].

Conclusion
A new era for interneuron developmental studies has recently opened thanks to the combination of novel genetic and imaging approaches as well as to the increasing evidence that interneuron diversity may be embryonically predetermined. It is now possible to foresee interneuron diversity even at the earliest stages of cortical development. Developing interneurons support network function, maybe even more stronger than in adulthood. Their engagement in early network patterns is the seed for a proper development of cortical networks. But interneurons do not mature as a uniform unit; diversity also prevails upon their developmental journey. Hence the early maturation of some interneuron subtypes will endow them a crucial role in activity-dependent processes

while the late maturation of others could confer them with a particular susceptibility to environmental and activity-dependent insults. Along these lines, it may well be that GABAergic hub neurons are born earlier than other interneuron subtypes, a hypothesis that could be addressed using fate-mapping approaches. A better understanding of interneuron functional diversity will certainly help the interpretation of their various maturation patterns. In any case, the diverse and long developmental journey of cortical interneurons largely explains the intimate links between determinants of GABA neuron proper development and brain disorders.

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