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Cortical developmental death: Selected to survive or fated to die

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Running Title: Developmental death in the cerebral cortex

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Abstract

The mature cerebral cortex only contains a fraction of the cells that are generated during embryonic development. Indeed some neuronal populations are produced in excess and later subjected to partial elimination whereas others are almost completely removed during the first two postnatal weeks in mice. Although the identity of cells that disappear, the time course and mechanisms of their death are becoming reasonably well established, the meaning of producing supernumerary cells still remains elusive. In this review, we focus on recent data that shed a new light on the mechanisms involved in adjusting cell numbers and discuss the significance of refinement versus complete elimination of cell populations in the developing cortex.

Introduction

Programmed cell death (PCD) is a biological process which serve crucial functions in the body. It is used to match numbers of distinct cell types in tissue homeostasis, to remove aberrant cells, to eliminate transient structures or to shape organ morphogenesis [1]. In the nervous system PCD fine-tunes the density of neuronal populations and their targets. The so-called trophic theory states that neurons compete for target-derived survival factors available in limited amounts, leading to the elimination of up to 50% of neurons [2-5]. Although this theory is largely supported by experimental evidences in the peripheral nervous system, it remains to be demonstrated in the central nervous system (CNS) where survival has not been linked formally to growth factor(s). Furthermore, in the cerebral cortex several populations of cells exist that almost completely disappear during the first two postnatal weeks. This seems to be a unique characteristic of the mammalian neocortex not reported in other territories of the nervous system and used in different organs to fully eliminate embryonic or unwanted structures such as patterning centers or sex-specific primordia [1].

Processes of cell death in the developing nervous system have been extensively reviewed elsewhere [4-8]. Here we will especially focus on the cerebral cortex and survey recent data shedding light on cell populations either subjected to partial elimination or complete removal during development and discuss the potential relevance of their disappearance in the construction of functional and dysfunctional neural circuits.

Refinement of neuronal numbers versus complete removal in the developing cortex

In the cerebral cortex, the existence of exuberant neurons and projections and their role during development has been studied for many years. Notably, an increase in transient axonal and cell populations has been suggested to correlate with the complexification of cortical circuits in primates [9]. While cellular processes like neurogenesis, migration, synaptogenesis or myelination are recognized building bricks for circuit formation, the role of transient cells and their PCD in the assembly of nascent cortical networks is still poorly understood. Both glutamatergic projection neurons and more recently GABAergic interneurons were shown to undergo significant cell death at early postnatal stages in mice, leading to the disappearance of 30-40% of both cell types [10*,11*] (Figure 1a, d and Table 1). In addition, four populations identified so far massively disappear at the end of cortical development: Cajal-Retzius neurons (CRs), subplate

neurons (SPs), cortical plate transient neurons (CPTs) and the first wave of embryonic oligodendrocyte precursors (firstOPCs) [12[•],13[•],14,15[•]] (Figure 1a-c and Table 1).

Characterizing the lifespan of populations which disappear is not an easy task. Earlier works heavily relied on histological hallmarks of cell death – most notably pyknosis and DNA fragmentation - which did not allow assessing cell identity. Activated Caspase-3 immunodetection has also been used extensively but given the short interval between Caspase cleavage and phagocytosis by macrophages (estimated to a few hours [16]) it is suitable only for studying populations which are either very large or that die synchronously over a short period of time. In addition, one should keep in mind the emerging roles of Caspase activation beyond apoptosis as well as Caspase-3 independent cell death [17-19]. On the contrary, lineage analysis in flies and nematodes, but also in mice thanks to genetic tracing, allows following cells throughout their life and unequivocally proving their absence or transformation during adulthood.

Mechanisms of refinement

It is well established that the neurotrophins NGF and NT-3 are required for the survival of most peripheral neurons. In the CNS, BDNF, which is the most expressed neurotrophin, does not display the same activity [5,20]. A very appealing explanation came with the discovery that both receptors for NGF and NT-3, TrkA and TrkC, but not the BDNF receptor TrkB, behave as “dependence receptors”, triggering cell death unless bound to their respective ligands [21,22]. Other growth factors such as IGF-1 and TGF- β 1 were proposed to regulate cortical neuronal survival since their loss results in increased cell death [23,24]. However, their precise contribution to the selective elimination of cortical interneurons and projection neurons remains to be assessed. Southwell et al. [10] proposed that interneurons death is not mediated by competition for trophic factors but rather by an intrinsic program following the observation that upon heterochronic grafts, interneurons die according to their own birthdate and not that of their environment. Yet, our global understanding of developmental cell death in the cortex remains fragmentary, reflecting either the existence of multiple cell-type specific extracellular and intracellular pathways (reviewed by [8]) and/or the implication of alternative mechanisms that do not fit with the classical neurotrophic theory.

Synaptic transmission has long been suggested to play a key role in controlling the balance between cortical cell survival and elimination [5,7,25]. Accordingly, cortical cell death peaks during the first two postnatal weeks, coinciding with the emergence of chemical synapses (Figure 1b-d). Three elegant studies recently formally demonstrated that *in vivo* electrical activity regulates the extent of apoptosis in both excitatory neurons and interneurons. Comparison between primary motor and somatosensory areas indicated that the density of apoptotic cells is more important in the former whereas electrical activity is higher in the latter. Consistent with the idea that electrical activity favours survival, kainate-stimulated animals display decreased apoptosis in the motor cortex whereas sensory-deprivation results in increased apoptosis in primary somatosensory areas [26^{••}]. Interneurons targeted genetically to express ion channels that either decrease or increase neuronal excitability are prone to elimination or survival respectively [27^{••}]. Consistently, interneurons expressing a DREADD (designer receptor exclusively activated by designer drug) that increases activity better survive when grafted in an early postnatal cortex [28^{••}]. Together these results

highlight the general role of electrical activity as a mean for functional selection and refinement of cortical networks.

Transient populations in the developing cortex

The cerebral cortex appears to be original with respect to other parts of the nervous system as at least four populations massively (>90%) disappear: CRs, SPs, CPTs and *first*OPCs [12•,13•,14,15•] (Figure 1a).

SPs comprise several neuron types and are essential for correct circuit assembly as transient targets of thalamocortical axons [14]. While earlier studies proposed that SPs massively disappear from the cortex [29], several reports suggest that at least part of them may persist in the postnatal brain [30-32] and/or merely diluted by increasing number of incoming axons in primates [33]. Given the heterogeneity of SPs and above all the lack of genetic tools to follow them throughout cortical development it remains unknown whether SPs undergo cell death.

By contrast, the disappearance of CRs, CPTs and *first*OPCs has been formally proven by genetic tracing in mice. This allowed identifying the CPTs, a novel glutamatergic population which are present during embryonic life, participate in the radial growth of the neocortex in a non-cell autonomous manner and massively die during the first postnatal week in mice [13•,34]. Genetic tracing was also instrumental in revealing that cortical OPCs are generated and eliminated with specific spatio-temporal patterns. A first wave, called *first*OPCs, disappear by postnatal day 10 in mice when the oligodendrocyte production and myelination process have not started yet and were considered dispensable elements for cortical circuit formation [12•]. However, recent reports showed that *first*OPCs contribute to the blood vessel network formation and stabilization during late embryonic stages [35]. The evidence that these can survive when OPCs derived from the two following waves are ablated [12•] argues against the possibility that their elimination is solely controlled by an intrinsic and timely regulated program and suggests that in a competition for survival factors *first*OPCs are less performing than other OPCs. The mechanisms underlying the massive disappearance of CPTs and *first*OPCs still remain uncharacterized.

CRs disappearance has been extensively studied. These are generated at three main sources at the borders of the developing pallium, the cortical hem, septum and pallium-subpallium boundary (PSB). From these focal sites CRs migrate tangentially to cover the entire cortical surface (the future layer 1) and influence the organization of the developing cortex at multiple stages by releasing signals affecting the underlying neurons [36]. Within the first two postnatal weeks the layer 1 in the neocortex becomes almost completely depleted of CRs in rodents, to an extent which cannot be explained by simple dilution of these neurons in the growing cortex [37] (Figure 1a, c). Beyond confirming the global loss of 94-97% of CRs [38,39], the use of mouse models in which CR subtypes were permanently labeled by genetic tracing allowed to exclude the hypothesis raised by Parnavelas [40] of CRs transfating into non-pyramidal neurons [15•,41]. Tracing distinct subtypes [15•] also revealed specific differences in the dynamics of CR death (PSB-derived CR die earlier) as well as in the molecular pathways involved. Indeed, conditional inactivation of the pro-apoptotic factor *Bax* gene in both hem- and septum-derived CRs could partially prevent their death whereas hem-specific *Bax* deletion had no effect on

survival, suggesting that septum- but not hem-CR die in a *Bax*-dependent manner in the neocortex [15^{*}]. Other death subroutines such as necroptosis or autophagy [18] may be active in cortical-hem derived CRs. This massive neural cell death is specific to CRs, while all GABAergic subtypes disappear in a *Bax*-dependent manner and with similar rate in layer 1 compared to other cortical layers [10^{*},42] suggesting that layer 1 is not merely a hostile environment.

The signals that trigger CRs death represent still an open question. Seminal studies from Del Rio [43] highlighted the role played by electrical activity on CRs' survival. Opposite to what described for cortical neurons (reviewed in [7]) global silencing of neural activity using TTX, a voltage-gated sodium channels blocker, decreased CRs death *in vitro*. Therefore the same biological process, i.e. integration in neural networks, is essential for cortical neuron survival and has detrimental effects on CRs [44^{*}], underlying that intrinsic differences specific to each neural population contribute to the program triggering cell death. An intriguing explanation may reside in the fact that CRs remain in "a state of persistent immaturity" in a mature circuits, thereby failing to adapt to the new postnatal environment as other cortical neurons do. One modification occurring in cortical neurons after birth and which is not observed in CRs is the shift of GABAergic response from depolarizing toward hyperpolarizing. The excitatory action of GABA on CRs is due to the persistence of the chloride inward transporter NKCC1 and absence of chloride outward transporter KCC2, resulting in an elevated intracellular Cl⁻ concentration in CRs. Interestingly, GABA activity was shown to be deleterious for CR survival and pharmacological inhibition or genetic deletion of NKCC1 reduced CR death.

It should also be considered the special case of the CRs residing in the hippocampus that derive mostly from the cortical hem [45] and behave differently from those found in the neocortex. Indeed, in the hippocampus CR death is delayed, it seems independent from Caspase-3 activity [46^{*}] and at late postnatal stages almost the double of CRs are found in this region compared to the neocortex [41]. Furthermore, exposure to an enriched environment increased CRs survival in the hippocampus but not in the neocortex, likely due to increased neurogenesis, hence highlighting the role played by the environment in determining the lifespan of CRs [41].

Significance of developmental cell death in the neocortex

Interfering with PCD results in severe brain malformations, as seen in Caspase knockout mice [47,48]. However, depending on the genetic background, such modifications may also remain almost silent [49], blurring our understanding of the physiological significance of removing a large fraction of neurons generated during development. Although highly unlikely regarding populations that completely disappear, the possibility exists that what we refer to as a "refinement in neuronal numbers" might actually reflect, in part, the elimination of abnormal cells (Figure 2a). It has been estimated that up to a third of embryonic cortical neuroblasts exhibit aneuploidy and that the fate of such cells is probably death [50], indicating that the number of abnormal cells generated during brain development is perhaps more important than one can anticipate.

With an evolutionary perspective, it would be surprising that the cost of generating entire populations or even supernumerary cells is not balanced by some kind of advantage for the developing organism.

Circuit maturation is an obvious explanation. It is perhaps more efficient to generate larger networks than needed and subsequently select the most appropriate components (Figure 2). With this prism, the fact that glutamatergic neurons and inhibitory interneurons undergo similar reductions in their numbers should be remarked. However, this does not apply to populations that completely disappear, the death of which may rather reflect a transient function. One example could be the need to remove signals that are no longer needed (Figure 2c).

In support of this, the anterior neural ridge (ANR) acts as an organizing center releasing FGF8 which is essential to early regionalization. The ANR is also a highly apoptotic region and it was proposed that the removal of morphogen-secreting cells allows to shape the spatial and temporal FGF8 gradient in order to ensure correct cortical patterning [51]. Through the secretion of Reelin, CRs control radial neuronal migration, a process that is achieved at the time of their elimination [52]. In addition, both CRs and CPTs behave as transient signaling units [53], releasing a variety of diffusible signals that control progenitor proliferation and neuronal differentiation [34,54,55]. Beyond patterning centers, intermediate targets for growing axons and migrating neurons are also sources of signals and serve as “waiting” zones (Figure 2d). Indeed, transient neuronal populations were shown to serve as guidepost for crossing of callosal axons at the midline [56] and SPs for thalamocortical axons [14]. Similarly, both SPs and CRs are strategically located in the close vicinity of migrating interneurons incoming from the ganglionic eminences before they enter the cortical plate or connect with them. Moreover, CRs were shown to influence interneuron migration [57], a function that becomes obsolete once interneurons have settled in the cortical plate. Incidentally, cell elimination provides extra space to neighbor neurons (Figure 2e). For instance the marginal zone is massively depleted of cell bodies after CRs disappear, allowing the terminal dendritic arborization of pyramidal neurons to expand. Complete elimination of these transient populations could thus reflect the necessity to stabilize cortical networks by removing signals that influence their establishment or an intermediate target which could represent a functional or physical “barrier” to circuit maturation.

Lastly, PCD has been proposed to act as a signal *per se* (Figure 2f; see reviews [58,59]). Non-autonomous apoptosis-induced apoptosis has been described but its existence in the brain remain to be demonstrated. Apoptosis-induced proliferation on the other hand has been described in the cerebral cortex, and could represent a compensatory mechanism following injury. We have highlighted such processes by which cortical progenitors can change their behavior in response to major neuronal loss [60]. Thus, the possibility that the massive and synchronous death of transient cells at early postnatal stages is instructive for cortical development should perhaps not be ruled out.

Future perspectives

The persistence of CRs during postnatal life has been detected in pathological conditions such as temporal lobe epilepsy and polymicrogyria and that of SPs in pharmaco-resistant epilepsy, thereby highlighting that the lack of disappearance of transient populations might also contribute to the

dysfunction of cortical circuits [15,61]. Interestingly, the abnormal presence of neurons in the white matter and aberrant circuits in the prefrontal cortex of schizophrenic patients has also been attributed to alterations in the pattern of PCD [62]. Notably, oligodendrocytes derived from embryonic ventral precursors, including *first*OPCs, display a reduced capacity to produce myelin than those from postnatal dorsal regions and this difference mainly emerges in demyelinating lesions [63]. An abnormal survival of *first*OPCs could thus also participate to pathologies related to myelin disorders.

Interestingly, if early born CRs in human appear to be transient, later waves, possibly specific to humans, were suggested to persist in the adult and their location correlated with the bottom of small sulci and ingrowing vasculature opening the intriguing possibility that increase number and lifespan might be needed in primates to serve specific evolutionary function ([64]. Similarly, the width of the subplate is most prominent in association areas whose size has specifically increased during cortical evolution [33].

While the requirement of transient cell populations during early cortical development is well accepted, it remains unknown whether their death at a precise postnatal age is necessary for late aspects of cortical maturation. Animal models rescuing death of specific populations, as those obtained for CRs, will help addressing the functional relevance of their complete removal.

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Conflict of interest statement

Nothing declared

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Figure Legends

Figure 1

Cell populations subjected to postnatal developmental death. **(a)** Cajal-Retzius cells (CRs, orange), cortical plate transient neurons (CPTs, purple), the first wave of oligodendrocyte precursors (*first*OPCs, yellow) and subplate cells (SPs, green) are almost completely eliminated whereas cortical interneurons (INs, red) and glutamatergic projection neurons (GPNs, blue) are subjected to partial elimination. **(b)**, **(c)** and **(d)** Extrapolated temporal windows of cell death and dynamics of disappearance of these populations are indicated with the same color code. Subtle differences might exist between populations, however they all undergo cell death within the first two postnatal weeks. Dashed lines for SPs and *first*OPCs indicate the absence of precise time course.

Figure 2

Significance of cell death in the developing cortex. Apoptosis could reflect the elimination of cells which are abnormal **(a)**, inappropriately embedded in cortical networks **(b)**, that have become unnecessary or detrimental **(c)** and **(d)**, but could also be used to provide additional space **(e)** or deliver a last signal **(f)** to neighbor cells. Populations that are subjected to partial or complete removal may fit in one or several of the situations depicted.

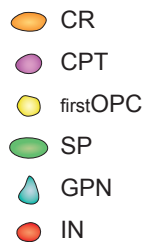
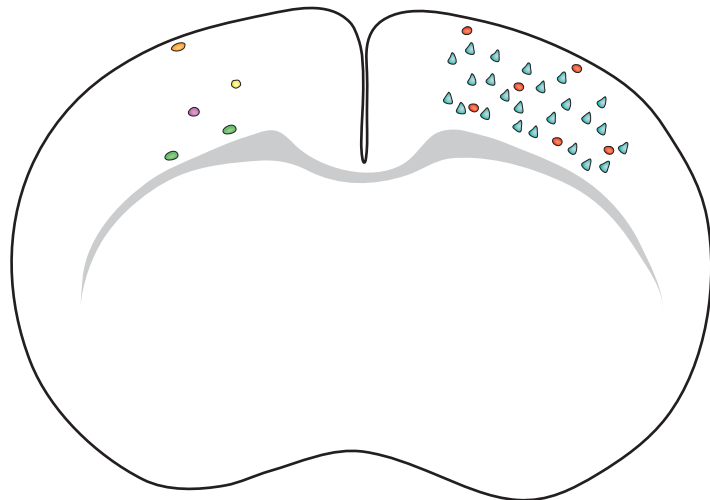
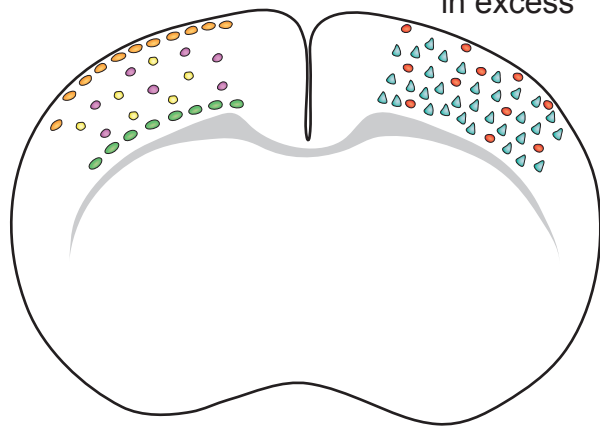
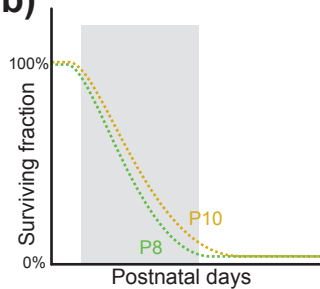
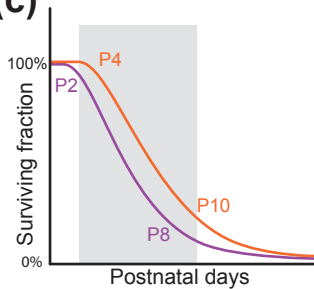
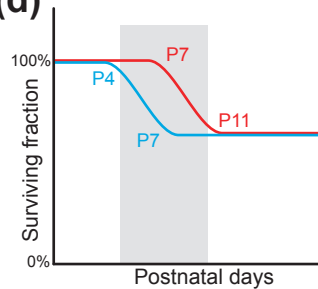
(a)

Transient populations

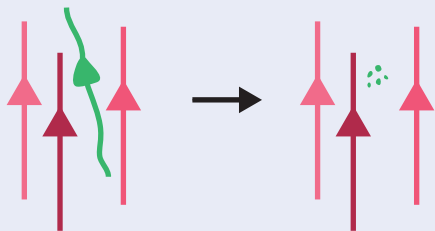
Neurons produced
in excess

Elimination

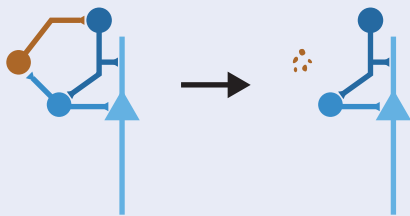
Refinement

**(b)****(c)****(d)**

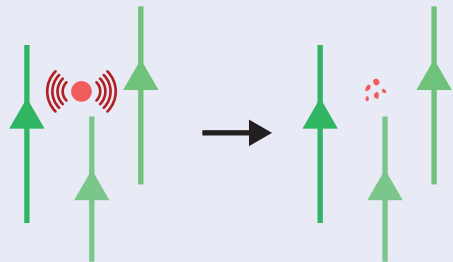
(a) Removal of abnormal cells



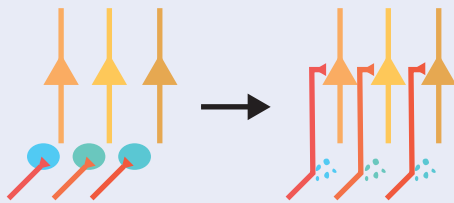
(b) Circuit maturation



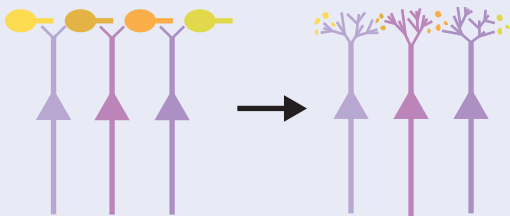
(c) Signal removal



(d) Intermediate target removal



(e) Clear extra space



(f) Death as a signal

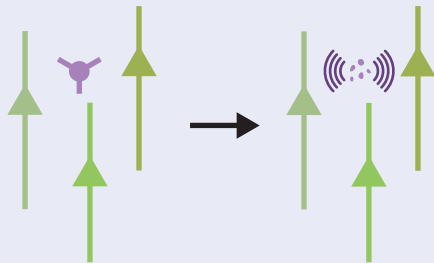


Table 1

Studies that characterized naturally occurring cell death of specific populations in the cerebral cortex				
Cell population	Reference	Method	Stages	notes
IN	[10•]	Casp3 ⁺ /GAD67-GFP ⁺ cells	Peak of death at P7-P11	
IN	[10•]	Total GAD67-GFP ⁺ cells	40% decline between P5 and P20	
IN	[27••]	Casp3 ⁺ /5HT3aR ^{eGFP+} cells	Peak of death at P9	Only CGE-derived IN are labeled
IN	[27••]	Total 5HT3aR ^{eGFP+} cells	20% decline between P5 and P21	Only CGE-derived IN are labeled
Cortical neurons (mostly glutamatergic)	[26••]	Casp3 ⁺ and TUNEL ⁺ cells in the primary motor cortex	Peak of death at P4-P7	
Cortical cells	[11•]	TUNEL ⁺ cells in the primary and secondary somatosensory cortex	Peak of death at P4-P6	
CR	[15•]	Genetic tracing using $\Delta Np73^{Cre};Tau^{nlsLacZ}$, $Dbx1^{Cre};Tau^{nlsLacZ}$ and $Wnt3a^{Cre};Tau^{nlsLacZ}$	Most CR disappear between P4 and P10 95% loss at P21	Regions/subpopulations differences
CR	[39]	Ebf2-GFP ⁺ /Reelin ⁺ cells in the somatosensory cortex	60% loss between P2 and P6 80% loss between P2 and P13	Not all CR subtypes are labeled
CR	[39]	Time-lapse imaging of Ebf2-GFP ⁺ cells using cranial windows	Most CR disappear between P7-P15	Not all CR subtypes are labeled
CR	[38]	CxCR4-EGFP	CR nearly completely disappeared at P14 in the neocortex	No quantification
CR	[38]	Genetic tracing using $Wnt3a^{Cre};Rosa26^{Tomato}$ and $PDE1c^{Cre};Rosa^{Tomato}$	50% loss between P7 and P14	Around 20% of CR cells are not labeled
CR	[42]	Reelin ⁺ /GAD67-GFP ⁺ cells in primary motor, somatosensory and visual areas	Around 50 % reduction in CR density between P4 and P6. Almost complete loss at P14	Minor differences between areas
CPT	[13•]	Genetic tracing using $Dbx1^{Cre};Tau^{nlsLacZ}$	Most CPT disappear between P0 and P8 95% loss in adults	
first OPC	[12•]	Genetic tracing using $Nkx2.1-Cre;Rosa26R-GFP$ in the motor cortex combined with Sox10 immunostaining	Almost complete loss between P0 and P10	
SP	[3]	Cells labeled with BrdU between E10.5 and E12.5	Almost complete loss between P0 and P8	

SP	[32]	Cells labeled with BrdU between E10.5 and E12.5 combined with immunostaining for SP markers Lpar1-GFP, Cplx3 and Nurr1	BrdU-labeled neurons mostly disappear during the first postnatal week whereas marker-labelled cells mostly remain
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Studies focusing on the disappearance of cortical interneurons (IN), glutamatergic projection neurons, Cajal-Retzius cells (CR), cortical plate transient cells (CPT), the first wave of oligodendrocyte precursors (_{first}OPC) and subplate cells (SP). A brief description of the labeling techniques as well as the mouse strains used by the authors is indicated. Most of these cells disappear during the first two postnatal weeks, with variations between and among populations.