Title

Network state transitions during cortical development

Authors

Wu, Michelle W
Kourdougli, Nazim
Portera-Cailliau, Carlos

Publication Date

2024-05-23

DOI

10.1038/s41583-024-00824-y

Peer reviewed

Network state transitions during cortical development

Michelle W. Wu[1,2,3,5], Nazim Kourdougli[1,5] and Carlos Portera-Cailliau[1,4,†]

[1]Department of Neurology, David Geffen School of Medicine at the University of California Los Angeles, Los Angeles, CA, USA
[2]Neuroscience interdepartmental graduate program, University of California Los Angeles, Los Angeles, CA, USA
[3]UCLA-Caltech Medical Scientist Training Program, David Geffen School of Medicine at the University of California Los Angeles, Los Angeles, CA, USA
[4]Department of Neurobiology, David Geffen School of Medicine at the University of California Los Angeles, Los Angeles, CA, USA

[5] These authors contributed equally: Michelle W. Wu, Nazim Kourdougli
[†] email: cpcailliau@mednet.ucla.edu

Abstract| Mammalian cortical networks are active before synaptogenesis begins in earnest, before neuronal migration is complete, and well before an animal opens their eyes and begins to actively explore their surroundings. This early activity undergoes several transformations during development. The most significant of these is a transition from episodic synchronous network events, which are necessary for patterning the neocortex into functionally related modules, to desynchronized activity that is computationally more powerful and efficient. Network desynchronization is perhaps the most dramatic and abrupt developmental event in an otherwise slow and gradual process of brain maturation. In this Review we summarize what is known about the phenomenology of developmental synchronous activity in the rodent neocortex and speculate on the mechanisms that drive its eventual desynchronization. We argue that desynchronization of network activity is a fundamental step through which the cortex transitions from passive, bottom-up detection of sensory stimuli to active sensory processing with top-down modulation.

[H1] Introduction

The development of cortical structures has fascinated neuroscientists since the time of Santiago Ramón y Cajal. The principal insights made in the 20th century about neocortical development (including the discoveries of axonal pathfinding, radial cortical neuronal migration and critical periods of plasticity) were initially all related to anatomical observations about the structure of the brain. Our understanding of early patterns of network activity was delayed, relative to these discoveries, because the development of techniques to record from large numbers of neurons in intact circuits lagged behind those used to reveal neuronal structure. Although electrophysiological techniques enabling recording from populations of neurons in the mature cortex have been available for more than 100 years, it was not until the 1990s that scientists began to use electrophysiological approaches and **calcium imaging** to record activity from populations of neurons in the developing brain. These pioneering studies revealed that the earliest forms of spontaneous activity in the neonatal rodent cortex are characterized by bursts of synchronous firing across large cohorts of neighboring neurons[1-6].

Over the last three decades, numerous studies have contributed a wealth of information about developmental network activity in different species. This led to two principal discoveries. First, that activity is highly synchronous during the earliest stages of brain development, but undergoes some transformations during this time. And second, that activity eventually transitions into a desynchronized network state, in which the number of neurons that participate in each network event is drastically reduced. This desynchronization coincides with major milestones in the animal's behavior (such as eye opening or the onset of exploration in rodents)[7] and transforms the neocortex from a passive detector of sensory inputs to a sophisticated agent that processes these inputs to affect behavior.

The first goal of this Review is to summarize what is known about the different patterns of synchronous neuronal firing during development, building on other excellent reviews[8-18] and providing our own interpretation of the state of the field. The second, and perhaps more important, goal is to discuss the mechanisms that bring about developmental transitions between different network states, focusing on the rather abrupt desynchronization and **sparsification** of cortical network activity. We will also speculate about the roles that synchronous activity may play during development and how changes in the developmental timing or extent of desynchronization could lead to neurological or psychiatric symptoms.

One of the challenges when approaching this topic is making sense of the terminology that is used to describe developmental network activity. Many terms are used to describe similar patterns of network activity during development, including **early network oscillations** (ENOs), **giant depolarizing potentials** (GDPs) and **spindle bursts**, creating unnecessary confusion. This

situation has arisen because of the use of different experimental preparations (such as brain slices versus in vivo recordings) and different recording techniques (such as electrophysiology versus calcium imaging), or because studies have focused on different brain regions or animal species. Here, we make a concerted effort to simplify and clarify the matter. First, we focus on a single brain region, the neocortex, and on events that take place in early postnatal rodents. Although much pioneering research on developmental network activity was carried out in the hippocampus, recent in vivo studies in the neocortex have investigated the important relationship between sensory inputs and early network activity. Second, we incorporate the results of different studies into a single, cohesive narrative about developmental changes in network activity. This requires some interpretation of the available data and, inevitably, some readers may disagree with our take; however, we hope that this will lead to a healthy debate. Third, we propose a new unifying term to refer to neuronal activity during early development (that is, prior to desynchronization): **synchronous network activity** (SNA). Because prolonged periods of silence between synchronous events are a prominent characteristic of this developmental pattern, some might prefer to use qualifiers, such as intermittent SNA or episodic SNA. It is important to note that it is difficult to reach a consensus when choosing a term to describe a complex and varied phenomenon. Although developmental network activity presents in different ways (especially when measured using different techniques), we believe that a unifying term is useful because there is one prominent feature of this developmental activity that is shared: the activity is synchronous.

Although much of the research on cortical SNA during development has been carried out in brain slices (**BOX 1**), in vitro imaging of early network activity has limitations. For example, the intermittent synchronous network events that are characteristic of the developing brain in vivo cannot be detected in acute brain slices from mice or rats older than postnatal day (P)7[3-5]. This suggests that basic circuits in vitro are capable of generating some avtivity spontaneously. However, the natural evolution of SNA likely requires intact long-range connectivity and brainstem neuromodulator inputs, which are disrupted by slicing the brain. In support of the need for neuromodulation, pharmacological manipulations of acetylcholine can induce synchronous network events in vitro[19]. Additionally, more recent in vivo studies have identified transitions between different patterns of activity that had not been observed in slices. Thus, in this review we emphasize in vivo studies of SNA and discuss how it is modulated by peripheral inputs and brainstem neuromodulation, both of which are absent in slices.

[H1] SNA in neonatal cortical circuits

[H2] What is meant by synchronous activity?

To help explain our proposed use of the unifying term SNA to describe developmental network activity, it is important first to consider what the term synchrony means. At short time scales, synchrony refers to the notion that individual spikes (action potentials) are being produced by two or more neurons at approximately the same time (or phase, if their activity follows a rhythmic oscillation), typically within a few milliseconds of each other. This is usually defined as spike synchrony. At longer time scales (for example, the behavioural time scales at which neonatal mice respond to stimuli as they explore their surroundings), synchrony is often defined as an elevated pairwise correlation between the spike trains of two or more neurons. The correlation of their spike trains, defined as rate synchrony, is calculated by binning recording data into certain time windows: that is, grouping the values of continuous data into a smaller number of 'bins' (for example, by averaging across 100 ms of recordings).

Studies of early network activity have consistently documented a high degree of rate synchrony during early postnatal cortical development, which is why we favour the term 'synchronous' to refer to this activity over terms like GDPs or ENOs, which fail to convey this important characteristic.

[H2] SNA recorded in vivo

The first recordings of SNA were independently obtained using two distinct approaches: calcium imaging, and electrophysiology. The former has been extremely useful in characterizing the changes in pairwise correlations between neurons throughout development, the spatial characteristics of SNA, and the contribution of specific interneuron subclasses to these correlations, while the latter technique has given us valuable information about how brain oscillations at different frequency bands change across development.

The first in vivo recordings of SNA with cellular resolution were achieved in newborn mice using 2-photon calcium imaging at P5[6]. The field of view was restricted because imaging was done through a small fiber optic implant, but synchronous firing of large ensembles of neurons could clearly be resolved. The temporal dynamics of these network events were similar to those of the cortical ENOs previously described in vitro[3]. Since then, many in vivo calcium imaging studies have investigated SNA in early postnatal mice across different cortical areas and layers[7,20-27]. These studies described periodic calcium transients that are synchronous across most neurons in the field of view and occur in one of two distinct patterns (**Fig. 1a**). In the first

postnatal week, SNA manifests as brief, intermittent, synchronous calcium transients that are spatially restricted within clusters of neurons, with the greatest degree of correlation occurring between neurons that are located within 100 μm of each other[20]. Then, in the second postnatal week, SNA appears as larger and less circumscribed calcium events that involve partially overlapping neuronal ensembles. This progression of SNA is discussed in more detail below.

Using in vivo electrophysiology in the primary somatosensory cortex (S1) of unanesthetized newborn rats, early network activity appears as spindle bursts[28]. These are brief (lasting <2 s) spindle-shaped **neural oscillations** in the local field potential that have a frequency within the theta range (4-20 Hz) and are nestled within delta waves (slow, intermittent depolarizations occurring every 10 secs). Spindle bursts occur infrequently, being separated by several seconds-long periods of inactivity (**Fig. 1b**). Nearly identical spindle bursts were later observed in the neonatal primary visual cortex (V1)[29-31]. It is noteworthy that cortical neurons in culture also show synchronous bursting when recorded by electrophysiology[32-34]. This suggests that synchronous bursting activity of cortical neurons is a characteristic of immature networks.

Based on electrophysiological recordings, several different stages of network activity in neonatal rodents have been described[10,13,15]. First, at P0-P2, activity is dominated by slow delta waves. This is followed at P3-P8 by the appearance of spindle bursts nestled within the delta waves. A third stage (P8-P11) is still characterized by spindle bursts, but these now co-exist with short bouts of GABA-driven early gamma oscillations (EGOs), which have a much higher frequency (30-50 Hz) and are more prominent in superficial cortical layers[13,14]. EGOs can be observed as early as P2 in rodents and are initially driven by feedforward excitatory input from the thalamus[35]; when interneurons later become integrated into the cortical microcircuit (by the end of the first postnatal week), EGOs are mediated by GABAergic inhibition [36-38]. More recent findings suggest that the development of network activity is a continuous (rather than step-wise) process in which network events gradually increase in both frequency and amplitude as development proceeds[39]. In support of this, the long-range synchrony of spindle bursts across both hemispheres increases gradually during the first postnatal week[35].

The similarities between SNA recorded with calcium imaging or with electrophysiology in neonatal cortical neurons suggest that they represent the same phenomenon. Indeed, later studies that combined in vivo extracellular recordings with two-photon calcium imaging confirmed that spindle bursts are the electrophysiological correlates of synchronous calcium events in the developing neocortex[24,40].

[H2] GABAergic contributions to SNA

Early in vitro calcium imaging studies suggested that interneurons participate in SNA[3] and subsequent studies in vivo confirmed the interplay of excitatory and inhibitory neuronal activity during development[22,41-45], although the specific contributions of different subclasses of inhibitory interneurons remained a mystery. A recent study characterized the synchronous activity of inhibitory cells between P4 and P9 as **GABAergic calcium events** (GCEs)[46] and showed that interneurons of the major subclasses manifest GCEs with different characteristics. For example, between P7 and P9, precursors of parvalbumin (PV) neurons derived from the medial ganglionic eminence (MGE) tend to segregate into spatially clustered assemblies of neurons with synchronous activity to a greater extent than other subclasses derived from the caudal ganglionic eminence[46]. In contrast, somatostatin (SST) interneurons, which also derive from the MGE and are the first subclass of interneurons to establish functional synapses with cortical pyramidal cells[47,48], do not form such assemblies and the frequency of their GCEs is lower[46]. Elucidating the unique roles of different subclasses of inhibitory neurons in generating SNA and shaping mature circuit dynamics is an area of active research.

[H2] Activity patterns in the embryonic rodent neocortex

In recent years, recording activity in vivo in the embryonic rodent brain with cellular resolution has finally become achievable[49-51]. Using an ingenious approach for para-uterine calcium imaging of individual mouse embryos, it was possible to record from cortical neurons as early as embryonic day (E) 13.5[51]. This revealed that activity of embryonic cortical excitatory neurons manifests in two phases: a transient phase of sparse activity that takes place at E14.5 and is followed by two days of little or no spontaneous activity, and then a second, more stable phase of activity after E17.5[51], in which activity is synchronous across different neurons. This matches well the results of earlier studies that used transcranial calcium imaging in mouse embryos and revealed that spontaneous activity in S1 manifests as distinct patches of synchronously active neurons[52].

[H2] Developmental sequence of network activity

Taking into consideration all the available in vivo data, we can now infer the developmental sequence of SNA in the rodent brain and can speculate on the mechanisms that mediate the specific activity patterns seen at each stage and their functional contributions (discussed in more detail in later sections) (**Fig. 1**). Although we have focused on evidence from rodents to generate this sequence, it is important to note that SNA is highly conserved across species (**BOX 2**).

Importantly, although we have split this sequence into discrete stages for the purposes of this article, the reader should recognize that the transitions between these patterns are gradual.

Stage 1 takes place roughly between E14 and E17. The earliest pattern of network activity in the embryonic brain, seen at E14.5, is sparse and non-synchronous[51]. Additional in vivo studies will be necessary to determine whether the scattered activity of individual neurons in the embryonic brain at this stage is dependent on gap junctions. At present, the mechanisms and role of this activity remain a mystery.

Stage 2 takes place between E18 and P8. Beginning between E17.5 and E18.5, synchronous network events become apparent. These take the form of localized, well-circumscribed events that tend to be brief (lasting <2 s) and are interspersed between sustained periods (>5 s) of no activity[20,23,51]. This SNA is uniquely patchy, as well-demarcated, non-overlapping clusters (patches) of neurons fire synchronously. These patches correspond to individual cortical columns (groups of neurons that are arranged in a cylindrical structure and span the cortical thickness)[53]. Stimulation of the whisker pad at E18.5 triggers localized calcium events in layer 4[52] of S1 that are reminiscent of this patchwork pattern[23]. This implies that these patches represent functional protomaps (primitive patterning of the neocortex that eventually corresponds topographically to functional units responsible for processing different sensory modalities[54]) and reflect the synchronous firing of thalamic neurons that project to sensory cortices. In other words, passive whisker movements in utero may generate peripheral inputs that shape protomaps in S1. During the first postnatal week, similar patches of synchronous neurons are also apparent in cortical layers 2 and 3[20,25]. At the electrophysiological level, this pattern of activity manifests as spindle bursts and EGOs[28,36]. EGOs may enable spatiotemporal thalamus–cortex synchronization across the entire sensory processing hierarchy from the thalamus to the sensory cortex [36]. Borrowing from the terminology used by Mizuno et al.[25], we suggest that this stage be referred to as **patchwork SNA**. We propose that the term ENO be reserved to describe the similar events observed in vitro. This SNA pattern, which peaks between P5 and P7, seems critical for patterning the neocortex into functional assemblies of neurons subserving similar roles. Although V1 lacks the striking anatomical segregation of functionally-related neurons that is seen in S1, in vivo calcium imaging also reveals clusters of co-active neurons (so-called low participation events) in this cortical region[21].

Stage 3 takes place between P8 and P11. Patchwork activity is eventually replaced by more diffuse, partially overlapping events that spread beyond anatomical boundaries (such as columns or barrels)[20,25]. Such synchronous events can propagate locally over short distances in a halting, chaotic fashion, reminiscent of lightning flashes. Although this SNA does not demonstrate a

sustained directional vector, it has historically been referred to as **wave-like SNA**[6,25,55]. At the electrophysiological level, these network events still manifest as spindle bursts and EGOs (with the latter reflecting an increasing role of GABAergic inhibition). Interestingly, the synchronous activity of inhibitory interneurons in S1 undergoes a similar transition from small barrel-sized patches to larger wave-like events, as GCEs more than double in size between P4-6 and P7-9[46]. Both patchwork SNA and wave-like SNA may reflect bottom-up influences on cortical activity, which is important for both patterning of circuits at the structural level and for simple detection of sensory stimuli[23,52](**Fig. 2; Fig. 3**). However, the synchronous nature of the activity precludes the discrimination of inputs or other more sophisticated sensory processing.

Stage 4 begins at P12 and continues through adulthood. By the end of the 2nd postnatal week, and with the maturation of glutamatergic neurotransmission and the increasing influence of GABAergic inhibition within cortical circuits, the activity of cortical neurons becomes desynchronized and sparse (as the proportion of cells participating in a given spontaneous network event decreases drastically)[7,20]. We propose the term **sparse network activity** to describe this final mature stage of network activity. The exact mechanisms driving this network transition are not yet known. At a time that coincides with rhythmic whisking and eye opening, this developmental desynchronization allows for the rapid refinement of sensory-evoked responses[56-58]. Furthermore, sparse activity of neurons is essential for coding information and is more efficient from an energy expenditure standpoint [59-61].

[H1] Mechanisms of SNA

Despite our growing understanding of the phenomenology of the various developmental patterns of cortical network activity, many of the mechanisms responsible for SNA and its subsequent desynchronization remain a mystery. In this section we first consider whether SNA is generated intrinsically in the cortex or triggered by bottom-up inputs and then review the potential mechanisms that bring about network synchrony during development (**Fig. 3**). Notably, most of the pharmacological experiments that have informed current hypotheses have only been carried out in acute brain slices. Thus, it is presently unknown whether the proposed mechanisms also apply in vivo. Because SNA involves bursts of neuronal firing, we believe that it may be helpful to consider these synchronous network events as an early manifestation of **Up states**[7,62] (**BOX 3**) and thus, although not discussed here, the mechanisms involved in generating Up and Down states may also be pertinent to SNA.

[H2] Is cortical SNA intrinsically generated or triggered by bottom-up inputs?

An ongoing debate in the field concerns whether SNA in the cortex is spontaneous and generated intrinsically or is a response to external inputs from the periphery or from other brain regions. The available evidence suggests that some developmental cortical activity recorded in vivo is triggered by bottom-up inputs from the thalamus, which in turn could be driven by peripheral sensory inputs (such as myoclonic twitches in the pup[28]) or spontaneous activity in peripheral sensory organs (such as retinal waves[55] or spontaneous activity in the cochlea[63]). Nevertheless, the neocortex is certainly capable of producing synchronous events in the absence of external inputs. Indeed, organotypic neonatal brain slice cultures that are completely deprived of sensory inputs manifest bursts of synchronous firing[34].

At least some of the SNA observed in the developing sensory cortices is inherited in a bottom-up manner from their respective thalamic relay nuclei (the lateral geniculate nucleus (LGN) for V1 and the ventral posteromedial nucleus (VPM) for S1)[18]. Spontaneous correlated activity in the developing retina is present long before the onset of vision[64,65] and propagates across the entire visual processing hierarchy[55,66,67]. Similarly, correlated activity in the cochlea is relayed to the neurons of the inferior colliculus and eventually to the auditory cortex[63]. Finally, in the somatosensory system, many synchronous events in S1 reflect the propagation of tactile inputs from the periphery[28]. It is also possible that the thalamus could generate spontaneous activity, even in the absence of sensory inputs, and transmit it to sensory cortices. Voltage dye imaging has shown that most cortical SNA is preceded by thalamic activity, and stimulation of the VPM triggers spindle bursts in S1[38,68]. Thalamocortical loops are already present and functional in the neonatal brain[52], meaning that synchronous events within the thalamus can propagate all the way to the cortex[69]. As peripheral inputs travel up the sensory processing hierarchy, there is evidence that thalamocortical circuits amplify these signals [67], and this is thought to aid in sensory detection[13].

Experimental manipulations of bottom-up inputs also support the notion that peripheral sensory inputs contribute to SNA. Injecting lidocaine into the whisker pad of mice greatly diminishes patchwork events in L4 of S1 at P1[23]. Lesioning thalamic barreloids also reduces spontaneous activity in S1[38]. Likewise, acutely reducing thalamic activity at P4-5 with chemogenetics in mice abolishes patchwork SNA, but the same manipulation done later (at P9) does not significantly affect SNA frequency, suggesting that sensory inputs are less involved in shaping the wave-like SNA that occurs at that age[23]. Additionally, direct thalamic stimulation in rodent pups can trigger bursts of activity in S1[38], as can whisker movements[70]. Furthermore, spindle bursts recorded in S1 or V1 are reliably associated with spontaneous myoclonic jerks (muscle twitches)[28] and spontaneous retinal waves[29,55], respectively. Thus, there is evidence that

synchronous activity originating in the periphery can spread all the way to the cortex in a bottom-up manner.

On the other hand, it could be argued that embryonic cortical circuits may rely more on internally generated spontaneous activity than on bottom-up inputs to shape their early connectivity, because of the relative absence of sensory stimulation in utero. Furthermore, there is evidence that spontaneous SNA in the newborn rodent brain can occur independently of peripheral sensory inputs, although the events are less frequent. For example, spindle bursts in S1 that are typically associated with hindlimb motor twitches can persist after spinal cord transection[28]. In vibrissal S1 (barrel cortex), synchronous network events in L4 neurons are either unchanged or somewhat less frequent after the infraorbital nerve that transmits whisker inputs from the mystacial pad is severed[25,70]. Similarly, repeated whisker plucking starting at P2 either has no effect on the early postnatal synchronous activity of excitatory neurons in S1[20,26] or causes a modest decrease in the frequency of synchronous interneuron activity[46]. Activity also persists in the mouse visual cortex after the surgical removal of one eye, albeit at lower rates[21,71], and in ferret visual cortex after optic nerve transection[72].

Taken together, the available data suggests that the neocortex is intrinsically capable of generating SNA and that such activity is not solely a reflection of external sensory information passed on by thalamic relay nuclei (**Fig. 2**). Developing neocortical circuits are nevertheless primed to receive an array of bottom-up inputs, including retinal waves and sensorimotor inputs arising from myoclonic twitches, spontaneous whisker movements or passive tactile stimulation by the dam and littermates[73]. This sensory experience shapes SNA into functional modules designed for optimal detection of sensory inputs, which ultimately influence cortical patterning. Hence, blocking thalamic waves in the auditory nucleus causes an expansion in the barrel field in S1[69], while attenuating thalamic activity leads to an enlargement of barrels and impairs whisker discrimination[26].

[H2] Electrical synapses via gap junctions

Gap junctions, which form direct conduits between adjacent cells[74-77], often come to mind as potential mediators of synchronous calcium events involving clusters of neurons. During patch-clamp recordings in early postnatal mice or rats, the dye tracers used for subsequent morphological reconstruction of neuronal processes tend to spread to neighboring neurons, revealing the presence of gap junctions[78,79]. Neuronal domains observed in vitro are sensitive to gap junction blockers[79]. Preferential electrical coupling via gap junctions between sister excitatory neurons (those generated from consecutive asymmetric divisions of a single radial glial

progenitor) promotes their synchronous firing in ontogenetic columns at P1-P2, but not after P6[80], which could help ensure that they eventually have similar feature selectivity[81]. In an in vivo study, administration of the gap junction blocker carbenoxolone at P8-10[21] reduced the frequency of synchronous events with high neuronal participation (>80% of cells) in V1, which represents only a fraction of all SNA. However, because carbenoloxone can affect neuronal membrane conductance independently of its effects on gap junctions[82], additional in vivo studies with more specific pharmacology will be needed to determine the role of gap junctions in generating and/or propagating SNA.

[H2] Excitatory and inhibitory chemical synapses

Pharmacological experiments have demonstrated that glutamatergic neurotransmission is critical for SNA. In neonatal rat cortical slices, ENOs are blocked by antagonists of AMPA, Kainate and NMDA receptors[4,83]. In the intact neocortex of P3-P6 rats, spontaneous and sensory-evoked spindle bursts rely on AMPA receptors[84]: the AMPA receptor specific antagonist, CNQX, suppresses the fast oscillatory component of the spindle bursts. By contrast, antagonists of both NMDA and AMPA receptors are necessary to eliminate the slower delta component of spindle bursts[85].

GABAergic synaptic activity also plays a significant role in modulating SNA. In one in vitro study, the $GABA_A$ receptor antagonist bicuculline modestly reduced the frequency (and increased the amplitude) of cortical ENOs in slices from newborn rats[4]. However, subsequent in vivo studies demonstrated that the role of GABAergic transmission in SNA is complex. In the rat barrel cortex at P2-6, blockade of $GABA_A$ receptors with gabazine nearly doubled the occurrence of spontaneous spindle bursts, whereas the $GABA_A$ modulator diazepam reduced their frequency[84]. Other studies confirmed the effects of gabazine using widefield calcium imaging in P3-4 mice in hippocampus and visual cortex but observed only a negligible impact of diazepam on SNA[40,86]. Interestingly, there is some evidence that GABA signaling could be important for the spatial compartmentalization of SNA, as spindle bursts spread over a larger cortical area in the presence of gabazine[84].

Knockdown of *Gabrb3*, which encodes the $\beta 3$ subunit of the $GABA_A$ receptor, in cortical excitatory neurons led to significant increases in the percentage of neuron pairs exhibiting correlated firing and the percentage of neurons participating in synchronous network events in mice at P7 and P14[41]. Similar increases in network synchrony were obtained by deleting the $\gamma 2$ subunit of $GABA_A$ receptors, suggesting that these receptors limit the spread of synchronous network events in early postnatal mice.

The effects of GABA on postsynaptic cortical neurons are depolarizing at early postnatal ages, but later switch to become hyperpolarizing[87,40,88,89]. This begs an obvious question: are the effects of GABAergic transmission on SNA during early cortical development caused by GABA's depolarizing or hyperpolarizing effects? In L4 of mouse S1 the GABA polarity switch occurs at the end of the first postnatal week[90], which coincides with the transition from patchwork to wave-like SNA. However, pharmacological studies do not support a role of depolarizing GABA in SNA. Bumetanide, an antagonist of the NKCC1 chloride co-transporter that negatively shifts GABA polarity so that it becomes less depolarizing, has no effect on spindle bursts or synchronous calcium events[40,84,86]. Moreover, deleting NKCC1 from telencephalic glutamatergic neurons has no effect on network activity in visual cortex in vivo, despite significantly attenuating the depolarizing actions of GABA[86]. In fact, chronic neonatal bumetanide treatment does not seem to negatively impact the developmental trajectory or behavior of mice[91,92].

We also do not fully understand which subclass of inhibitory neurons mediates GABA's effects on SNA. SST neurons are the first MGE-derived interneurons to differentiate and assume their identity (in late embryonic development)[93]. Interestingly, transient thalamocortical inputs to SST neurons form in the first postnatal week but disappear at later stages[93,94]. Thus, SST neurons might be implicated in the transition from patchwork SNA to larger wave-like SNA. Indeed, suppressing SST neuron activity in mice leads to larger spread of SNA in the second postnatal week, at least in V1[44].

[H2] Acetylcholine and other neuromodulators

The neocortex is always under the influence of neuromodulation by noradrenaline (NA), acetylcholine (ACh), serotonin (5HT) and dopamine[95]. Cholinergic and catecholaminergic projections massively innervate the mouse neocortex after birth[96]. In the context of SNA, ACh has been well studied, although the mechanisms through which it is thought to influence SNA are complex and depend on whether it acts via muscarinic or nicotinic receptors[19,97]. Repetitive stimulation of the cholinergic basal forebrain at 10 Hz in P5-6 rats induces ipsilateral spindle bursts in V1, while intracortical injections of the muscarinic antagonist atropine reduce their occurrence[30]. Whether other brainstem neuromodulators play any role in SNA is largely unexplored; however, in one study, application of NA directly to the cortical surface of rats desynchronized activity in V1 and eliminated light-evoked bursts[31].

[H1] Function of SNA

Several hypotheses have been put forth regarding the roles of SNA[12,15,98,99]. The most compelling of these proposes that SNA provides a means for co-active neurons that will eventually belong to the same functional unit (those that respond to stimuli from the same eye or from the same whisker, for example) to establish a blueprint of their future connectivity, a functional protomap of sorts[100]. A growing number of studies support this appealing and intuitive model, which appears to take place in several stages that coincide with transitions in SNA types throughout development. Importantly, changes in the developmental trajectory of SNA, whether environmental or genetic, are also likely to impact higher cognitive function and behaviors that emerge later in life, as seen in various neurodevelopmental conditions (**Box 4**).

[H2] Patchwork SNA patterns topographic maps

In vivo calcium imaging studies in S1 of P4-P7 mice[20,23,25] as well as voltage dye imaging in P3-P6 rats[73] have shown that the clusters of neurons involved in synchronous network events have diameters that correspond to the size of columns or individual barrels. Based on this, a Hebbian 'fire together - wire together' process — whereby SNA provides an instructive signal for the arealization of the neocortex into functional domains — has been proposed. This 'constructionist' view argues that synchronous activity in lower brain regions patterns developing circuits in higher-order areas[99]. Importantly, this activity need not be triggered by sensory inputs; it can be spontaneous and internally generated. With ongoing maturation of the sense organs and greater motor activity of the animal, the neocortex may increasingly rely on sensory experience to refine an initially crude map based on a 'best guess'[99].

One prediction of this model is that SNA shapes structural connectivity to match the functional domains of the neocortex. For example, thalamocortical axons from the LGN to V1 are initially diffuse; after birth, their exuberant branching in L4 undergoes a pruning process that restricts their arbors to a single column[101]. The same is true for axonal projections from VPM to S1[102,103]. Bottom-up signals from thalamocortical axons trigger de novo cortical SNA (or pace spontaneous SNA), providing an instructive role in this sculpting, and thus in cortical arealization. This process begins a few days before birth, at the time that thalamocortical projections reach the subplate (**Fig. 3**)[104,105]. Blocking synaptic activity in S1 for several weeks after birth disrupts the topographic refinement of thalamocortical connectivity and columnar organization into barrels[106]. On the flip side, electrical stimulation of adjacent regions of the VPM in slices from E18.5 mice triggers patchwork SNA in distinct columnar regions in S1, as does mechanical stimulation of adjacent areas of the whisker pad in vivo[52]. In the auditory system, blockade of spontaneous thalamic

waves from E14.5 onwards led to a reduction in the size of auditory cortex (with a corresponding increase in the size of S1), suggesting that late embryonic thalamic activity regulates cortical arealization[69]. Because these manipulations do not change the size of thalamic nuclei, this regulation is likely to occur in a bottom-up manner. Interestingly, at P2-3 in vivo, the horizontal spread of SNA across the cortex is significantly more extensive in VPM-inactivated mice than it is in controls and, strikingly, barrels are no longer anatomically evident at P4[52]. This illustrates how bottom-up tactile information (conveyed by the axons of VPM relay neurons) influences patchwork SNA and the importance of this in creating the topography of barrel protomaps. Similarly, spontaneous retinal waves[107] are important for patterning along the entire visual pathway hierarchy[65,108]. Not only are they required for the refinement of both retinogeniculate and geniculocortical projections[109-111], they are also necessary for shaping activity in higher visual areas[112]. Spontaneous retinal activity passes to V1 via the LGN, but also to higher-order visual areas in a parallel, modular fashion via the superior colliculus and higher-order thalamic nuclei. Only later are corticocortical connections established.

[H2] Wave-like SNA shapes long-range connectivity

The evidence discussed in the previous section suggests that patchwork SNA that matches bottom-up synchronous activity within the thalamus, whether spontaneous or sensory-evoked, is vital for the maturation of thalamocortical projections and cortical arealization in the first postnatal week in rodents. As neocortical networks transition to larger wave-like events later in development (**Fig. 2**), the thalamus must lose some of its protagonism in shaping cortical SNA to allow for top-down modulation of this information. Indeed, a lesser influence of bottom-up activity on the cortex after P8 would also be necessary for more complex intracortical computations to emerge (including those that require context from higher-order cortical areas), as the brain prepares to transition from sensory detection to sensory processing. Interestingly, after the second postnatal week, activity from the retina does not drive V1 as strongly as it does in the first postnatal week[113].

We favor a model in which patchwork SNA first establishes the local functional connectivity of a cortical unit (such as a barrel), but larger wave-like SNA later drives more diffuse and/or broad functional connectivity, such as that underlying the salt-and-pepper distribution of neurons that respond to surround whiskers[114]. The onset of rhythmic whisking, together with the sudden increase in the density of SST inhibitory synapses during the second postnatal week[115], could be responsible for this transition. Interestingly, the inhibitory tone from SST neurons to pyramidal cells decreases in V1 after eye opening, while perisomatic inhibition mediated by PV interneurons increases[116]. Subsequently, the wave-like activity would promote long-range connectivity across

functionally related areas. For example, twitch-associated activity that spreads from S1 to motor cortex[68] may be a blueprint for reciprocal sensory-motor connections[117]. As attractive as this model may seem, it has not been thoroughly tested in vivo and, in particular, a role for SNA at older ages (P8-P11) has not yet been confirmed. Nevertheless, recent modeling studies lend support to the notion that different patterns of spontaneous activity during development could refine network connectivity via different activity-dependent plasticity mechanisms[118]. Specifically, they predict that local low-synchronicity events in V1 (which originate from the retina[21]) refine the topographic map (by providing coincident thalamic pre-synaptic and cortical post-synaptic activity under Hebbian covariance rules); by contrast, high-synchronicity events (which arise within V1) homeostatically regulate connection strength by scaling their amplitude in an activity-dependent manner[118]. Further experimental work will be needed to support these predictions and expand them to other sensory cortical areas.

[H2] SNA regulates developmental neuronal cell death

The participation of both excitatory and inhibitory cortical neurons in SNA is known to be important for their survival[119]. A significant proportion of cortical pyramidal neurons and GABAergic interneurons succumb to a wave of apoptosis during early postnatal development. The excitatory neuron population decreases by approximately 12% between P2 and P5, while the inhibitory neuron population decreases by approximately 30% between P5 and P8[120-123]. Increasing pyramidal cell firing during this period prevents interneuron apoptosis, resulting in a higher density of interneurons in adulthood[120]. Increasing activity of interneurons also increases their survival[121,122]. Interestingly, it has been shown that the interneurons that eventually die previously exhibited slightly less correlated activity than those that survive[22] and that increasing network synchrony can prevent interneuron apoptosis. Thus, SNA that mediates coupling between excitatory and inhibitory neurons during early brain development ensures the survival of neurons[43,124], while those neurons whose firing is uncorrelated with the network undergo apoptosis.

[H1] Desynchronization of network activity

As important as SNA is for cortical patterning, synchronous firing of neurons is grossly inadequate for neural coding, as complex computations cannot be produced from all-or-none firing of large groups of neurons. Ultimately, sparse, decorrelated activity is necessary for the neocortex to perform the sophisticated data processing required to encode sensory information and to generate complex behaviors. In 2009, two studies demonstrated that such

desynchronization takes place by the end of the second postnatal week[7,20]. Subsequent studies confirmed both the timing and extent of this dramatic network transition in rodent S1[23,25,56,125] and V1[21,126,127].

The transition to sparse, desynchronized activity is dramatic because of the sheer magnitude of change in correlation coefficients (50-75% decrease, depending on the study) and because it occurs over just a few days, which is remarkable considering the lifespan of the animal (2 years). Calcium imaging in mouse S1 revealed that the transition happens at around P11-P15[20,125], while multiunit recordings in rat pups revealed that the firing of pyramidal cells in V1 undergoes this change overnight between P11 and P12[31].

In many ways, P10-P12 represents a crucial age for development in rodents. Eye opening and several other important behavioral milestones occur at this age (**Fig. 3**). In the rodent whisker system, vibrissa movements undergo a transformation from uncoordinated, brief unilateral whisker movements (predominantly retractions) before P11 to oriented and purposeful rhythmic whisking at ~8-12 Hz when scanning object surfaces (palpation whisking) after P14[128,129]. After P12, mice and rats begin to leave the comfort and protection of their dam to explore their surroundings[127]. The second postnatal week is also a time of massive growth in the neocortex, as synapse density nearly quadruples between P10 and P15[130]. This would be expected to cause an increase in network events (Up states).

[H1] Mechanisms of desynchronization

The mechanisms responsible for desynchronization are not well understood. Some potential candidates can be ruled out. For instance, massive synaptogenesis during the 2nd postnatal week should not, by itself, drive decorrelation of network activity because it is rather gradual (although sudden phase transitions can happen as a result of more gradual changes in a single parameter [131]). Similarly, although the changes in sensory experience at approximately P12 are more abrupt, desynchronization happens nonetheless in the absence of such inputs[71].

Desynchronization requires excitatory neurons not to fire during every surge of depolarization that occurs in the cortex (**Fig. 1b**). This could be accomplished via changes in the intrinsic excitability of the neurons, by increases in inhibition or by the disappearance of signals that synchronize network activity.

[H2] Changes in intrinsic excitability

One main difference between activity before and after desynchronization is that neurons in the adult neocortex fire more sparsely than those in the neonatal cortex[7]. As described in **Box 3**,

mature cortical neurons no longer fire with every Up state. The simplest way to lower the probability that a neuron will fire in an Up state is to decrease its intrinsic excitability. The input resistance of excitatory neurons, which governs their intrinsic excitability, remains constant (at approximately 5 GΩ) during late embryonic development, but there is a substantial drop after P2[132], followed by additional drops at P8-P10 and P14-P16[20]. What drives these changes? Increases in leak conductances, as a result of increased expression of a potassium channel or an increase in the hyperpolarization induced current, I_h, for example, would be sufficient. Indeed, in brain slices, I_h in cortical neurons becomes more prominent after birth[132]. However, to our knowledge, experimental manipulations of I_h to deliberately affect the timing of desynchronization have not been performed.

[H2] Changes in GABAergic activity

There are several ways by which changes in inhibition during development could contribute to neuronal desynchronization and sparsification. The end of the second postnatal week is a period of major changes in inhibition at the cellular level. One of these is the gradual increase in the number of both GABAergic interneurons[133] and their inhibitory synapses[47,130]. Although the first synapses in the rat neocortex are observed at E16[134], it is not until P5 that most cortical pyramidal cells show evidence of inhibitory post-synaptic currents[135] and the connection probability between fast-spiking interneurons and pyramidal cells is low before P8-P10 [37]. The relative number of PV-expressing interneurons also increases dramatically between P5 and P16, as does the number of their perisomatic synapses onto pyramidal cells between P7 and P14[47]. A prominent role of inhibition in desynchronization is supported by experimental manipulations. Selective optogenetic stimulation of inhibitory neurons in the prefrontal cortex of early postnatal mice triggers a decrease in network synchrony[42]. Similar results were observed when PV interneurons were activated with optogenetics at P10[43] or with chemogenetics at P11[136]. Interestingly, chronic chemogenetic inhibition of SST interneurons from P8 to P10 also leads to a decrease in correlation coefficients, suggesting that these two subclasses of interneurons may work synergistically to promote network desynchronization[136].

After approximately P10-P12, PV neurons both gradually activate their *Pvalb* promoter[137] and begin to express Kv3.1b channels[138], a subclass of voltage-gated potassium channels that enables their fast-spiking behavior[139,140]. Thus, PV neurons assume their fast-spiking identity (and exert a more potent inhibition on pyramidal cells) around the time that cortical networks desynchronize. By contrast, SST interneurons assume their identity much earlier, expressing *Sst*

in late embryonic development[93,141], and their density increases more gradually[142], making them less likely to be involved in desynchronization.

The decorrelating effect of inhibition on network activity could also occur indirectly via oxytocin. A recent in vivo calcium imaging study demonstrated that oxytocin can decorrelate network activity in mouse V1 at P9-P13 (though surprisingly not in S1) by activating interneurons[27]. Earlier in vitro experiments had reported that oxytocin increased the firing of fast-spiking interneurons[143,144]. Knowing that the related neuropeptide arginine vasopressin also increases interneuron firing and mediates similar network desynchronization in the hippocampus in vitro[145], it will be interesting to decipher the role of these and other neuromodulators in developmental network state transitions.

Another potential mechanism for desynchronization is the developmental change in GABA polarity, from depolarizing to hyperpolarizing[146]. Studies have demonstrated that, as early as P3-P4, $GABA_A$ receptor-mediated responses are depolarizing in vivo; however, these responses appear to be sub-threshold and to result predominantly in inhibitory effects (via shunting)[40,147,148]. Additional studies are needed to establish whether these depolarizing effects of GABA have an excitatory influence on the network in vivo. Excitatory actions of GABA have been reported in the hippocampus (though not in V1) before P3, but GABA subsequently becomes inhibitory [89,149]. These findings therefore suggest that the developmental GABA polarity shift occurs a few days before network desynchronization[31,89,90]. Developmental changes in the expression of NKKC1 and KCC2, the main potassium and/or chloride co-transporters responsible for GABA's actions, also precede the timing of desynchronization[150-152]. Thus, the GABA polarity switch is unlikely to be the main driver of network desynchronization.

[H2] The disappearance of Cajal-Retzius neurons

The second postnatal week is also when the density of Cajal-Retzius (CR) neurons in the cortex decreases dramatically. These neurons, a subclass of GABAergic interneurons, are the earliest generated neurons in the brain (born at around E11[153]) and eventually populate the marginal zone (future L1)[154]. They eventually all but disappear due to programmed cell death and by P12 only 3% of the original CR neurons remain[155]. Interestingly, CR neurons make synapses with the apical dendritic tufts of pyramidal cells in deeper layers[156] and CR neurons themselves manifest synchronous firing during early postnatal development[157]. Thus, their disappearance might represent the loss of one of the principal synchronous inputs that excitatory neurons receive during early development. It would be interesting to test whether optogenetic activation of CR

neurons in vivo can trigger SNA in pyramidal cells and whether chemogenetically silencing them might trigger premature desynchronization.

[H2] Changes in the subplate

The subplate, located below the cortical plate during embryonic development[158,159], eventually becomes cortical L6b[160]. Subplate neurons are believed to play temporary roles in cortical maturation before they disappear by the end of the first postnatal week in rodents[161]. They are the first cortical neurons to receive thalamocortical axons and to respond to sensory stimuli[162]. Indeed, the subplate serves as a transient relay station for thalamic information reflecting peripheral stimuli to cortical L4 long before L4 receives inputs directly from the thalamus[163]. The subplate also sends feedback projections to higher order thalamic nuclei, and the ensuing thalamus–subplate–thalamus circuit loops[164] are likely to help amplify peripheral inputs[163]. These early thalamocortical loops may also serve to produce spontaneous cortical activity that mimics sensory information as a way to 'rehearse' such patterns in the absence of inputs. Eventually, with the increasing influence of the sensory periphery, direct connections from the thalamus to L4 replace the connections to subplate neurons, and this culminates in the death of most subplate neurons by P21[159].

Some in vitro data supports a model in which, at early postnatal ages, much of the neuronal activity within a cortical column originates in the subplate and spreads via gap junctions, whereas a few days later (between P5 and P7), after subplate neurons begin to disappear [165], similar events are synaptic and mediated by NMDA receptors[19]. Future in vivo studies in late embryonic stage rodents[51] could test how the subplate contributes to SNA and whether its disappearance contributes to desynchronization.

[H1] Future directions

We still know relatively little about the phenomenology of SNA and the different network transitions. Despite exciting new evidence revealing what activity looks like in the embryonic rodent brain[51], we do not fully understand how it emerges or the influence of bottom-up sensory inputs (not just in neocortex but in other brain regions as well). Because recording neuronal activity in the human brain in utero is not presently possible, it will be important to determine whether organoid and/or assembloid technology will eventually produce the major network state transitions mentioned herein. Recent studies suggest that cortical organoids, over the course of 10 months, can mature to generate intermittent synchronous activity that is reminiscent of SNA observed in vivo[166,167].

Although the role of bottom-up inputs and the thalamus in driving SNA has been established (**Fig. 2; Fig. 3**), how activity can be intrinsically generated in the absence of such inputs remains a mystery. For instance, is SNA in primary motor cortex different because this region does not receive sensory inputs via thalamic relay nuclei? Additional electrophysiological studies that permit the simultaneous recording of thalamic and cortical neurons could help fill this knowledge gap in ways that calcium imaging (which suffers from limited temporal resolution and is restricted to upper cortical layers) could not.

What determines which neurons participate in SNA and when they desynchronize? Optogenetics experiments could test whether activating transient neurons in the developing neocortex (such as CR neurons and sublate neurons) is sufficient to unleash synchronous network events. The same applies to 'hub' cells, a minority of GABAergic interneurons with a high functional degree of connectivity that allows them to orchestrate network activity during development[168,169]. Intriguingly, targeted holographic photostimulation of single cortical hub cells in vivo can desynchronize spontaneous network bursts at P8-P11, while inhibition of these cells increases local synchrony in response to sensory stimulation[45].

The mechanisms driving the major network state transitions, and in particular desynchronization, also remain largely unknown. In vivo studies could take advantage of optogenetic and chemogenetic manipulations of specific subclasses of inhibitory interneurons (as has been done recently[43,136]) to further explore their role in these transitions, or use pharmacological manipulations to test the role of brainstem neuromodulators or neuropeptides like oxytocin. It would also seem important to use gain or loss of function manipulations of gene expression for candidate molecules that could mediate desynchronization. Transcriptomic studies could help identify candidate genes whose expression changes drastically around the time of desynchronization. A recent study revealed that the onset of vision selectively drives the specification of excitatory neurons in upper layers of V1, but not of other cell types[170]. Because much of the brain development that occurs during the second postnatal week is orchestrated by brain-derived neurotrophic factor (BDNF)[171], including the maturation of GABAergic interneurons[172], it could contribute to desynchronization. It would be interesting to explore whether manipulations of BDNF or its receptor TrkB have an impact on desynchronization.

Finally, a useful approach to understand network transitions will be to use computational frameworks to model SNA and make testable predictions of which parameters can desynchronize activity. Early efforts have pointed to inhibitory interneurons as potential mediators of this network transition[42,173] and shown that adaptation of global high-synchronicity events to levels of recent cortical activity could also contribute to developmental sparsification of network activity[118].

Clearly, the next decade will bring exciting new information about the evolution of cortical network activity throughout postnatal development. This will undoubtedly help us understand how differences in the trajectory of this activity can lead to symptoms of neurodevelopmental conditions (**Box 4**).

REFERENCES

1 Yuste, R., Peinado, A. & Katz, L. C. Neuronal domains in developing neocortex. *Science* **257**, 665-669, doi:10.1126/science.1496379 (1992).

2 Leinekugel, X., Medina, I., Khalilov, I., Ben-Ari, Y. & Khazipov, R. Ca2+ oscillations mediated by the synergistic excitatory actions of GABA(A) and NMDA receptors in the neonatal hippocampus. *Neuron* **18**, 243-255, doi:10.1016/s0896-6273(00)80265-2 (1997).

3 Garaschuk, O., Hanse, E. & Konnerth, A. Developmental profile and synaptic origin of early network oscillations in the CA1 region of rat neonatal hippocampus. *J Physiol* **507 (Pt 1)**, 219-236, doi:10.1111/j.1469-7793.1998.219bu.x (1998).

4 Garaschuk, O., Linn, J., Eilers, J. & Konnerth, A. Large-scale oscillatory calcium waves in the immature cortex. *Nat Neurosci* **3**, 452-459, doi:10.1038/74823 (2000).

5 Corlew, R., Bosma, M. M. & Moody, W. J. Spontaneous, synchronous electrical activity in neonatal mouse cortical neurones. *J Physiol* **560**, 377-390, doi:10.1113/jphysiol.2004.071621 (2004).

6 Adelsberger, H., Garaschuk, O. & Konnerth, A. Cortical calcium waves in resting newborn mice. *Nat Neurosci* **8**, 988-990, doi:10.1038/nn1502 (2005).

7 Rochefort, N. L. *et al.* Sparsification of neuronal activity in the visual cortex at eye-opening. *Proc Natl Acad Sci U S A* **106**, 15049-15054, doi:0907660106 [pii]
10.1073/pnas.0907660106 (2009).

8 Feller, M. B. Spontaneous correlated activity in developing neural circuits. *Neuron* **22**, 653-656, doi:10.1016/s0896-6273(00)80724-2 (1999).

9 Ben-Ari, Y. Developing networks play a similar melody. *Trends Neurosci* **24**, 353-360, doi:10.1016/s0166-2236(00)01813-0 (2001).

10 Khazipov, R. & Luhmann, H. J. Early patterns of electrical activity in the developing cerebral cortex of humans and rodents. *Trends Neurosci* **29**, 414-418, doi:10.1016/j.tins.2006.05.007 (2006).

11 Allene, C. & Cossart, R. Early NMDA receptor-driven waves of activity in the developing neocortex: physiological or pathological network oscillations? *J Physiol* **588**, 83-91, doi:jphysiol.2009.178798 [pii]
10.1113/jphysiol.2009.178798 (2010).

12 Leighton, A. H. & Lohmann, C. The Wiring of Developing Sensory Circuits-From Patterned Spontaneous Activity to Synaptic Plasticity Mechanisms. *Front Neural Circuits* **10**, 71, doi:10.3389/fncir.2016.00071 (2016).
13 Colonnese, M. T. & Phillips, M. A. Thalamocortical function in developing sensory circuits. *Curr Opin Neurobiol* **52**, 72-79, doi:10.1016/j.conb.2018.04.019 (2018).
14 Luhmann, H. J. & Khazipov, R. Neuronal activity patterns in the developing barrel cortex. *Neuroscience* **368**, 256-267, doi:10.1016/j.neuroscience.2017.05.025 (2018).
15 Khazipov, R. & Milh, M. Early patterns of activity in the developing cortex: Focus on the sensorimotor system. *Semin Cell Dev Biol* **76**, 120-129, doi:10.1016/j.semcdb.2017.09.014 (2018).
16 Molnar, Z., Luhmann, H. J. & Kanold, P. O. Transient cortical circuits match spontaneous and sensory-driven activity during development. *Science* **370**, doi:10.1126/science.abb2153 (2020).
17 Iannone, A. F. & De Marco Garcia, N. V. The Emergence of Network Activity Patterns in the Somatosensory Cortex - An Early Window to Autism Spectrum Disorders. *Neuroscience* **466**, 298-309, doi:10.1016/j.neuroscience.2021.04.005 (2021).
18 Martini, F. J., Guillamon-Vivancos, T., Moreno-Juan, V., Valdeolmillos, M. & Lopez-Bendito, G. Spontaneous activity in developing thalamic and cortical sensory networks. *Neuron* **109**, 2519-2534, doi:10.1016/j.neuron.2021.06.026 (2021).
19 Dupont, E., Hanganu, I. L., Kilb, W., Hirsch, S. & Luhmann, H. J. Rapid developmental switch in the mechanisms driving early cortical columnar networks. *Nature* **439**, 79-83, doi:10.1038/nature04264 (2006).
20 Golshani, P. *et al.* Internally mediated developmental desynchronization of neocortical network activity. *J Neurosci* **29**, 10890-10899, doi:29/35/10890 [pii]
10.1523/JNEUROSCI.2012-09.2009 (2009).
21 Siegel, F., Heimel, J. A., Peters, J. & Lohmann, C. Peripheral and central inputs shape network dynamics in the developing visual cortex in vivo. *Curr Biol* **22**, 253-258, doi:10.1016/j.cub.2011.12.026 (2012).
22 Duan, Z. R. S. *et al.* GABAergic Restriction of Network Dynamics Regulates Interneuron Survival in the Developing Cortex. *Neuron* **105**, 75-92 e75, doi:10.1016/j.neuron.2019.10.008 (2020).
23 Nakazawa, S., Yoshimura, Y., Takagi, M., Mizuno, H. & Iwasato, T. Developmental Phase Transitions in Spatial Organization of Spontaneous Activity in Postnatal Barrel Cortex Layer 4. *J Neurosci* **40**, 7637-7650, doi:10.1523/JNEUROSCI.1116-20.2020 (2020).
24 Kummer, M. *et al.* Column-like Ca(2+) clusters in the mouse neonatal neocortex revealed by three-dimensional two-photon Ca(2+) imaging in vivo. *Neuroimage* **138**, 64-75, doi:10.1016/j.neuroimage.2016.05.050 (2016).
25 Mizuno, H. *et al.* Patchwork-Type Spontaneous Activity in Neonatal Barrel Cortex Layer 4 Transmitted via Thalamocortical Projections. *Cell Rep* **22**, 123-135, doi:10.1016/j.celrep.2017.12.012 (2018).
26 Che, A. *et al.* Layer I Interneurons Sharpen Sensory Maps during Neonatal Development. *Neuron* **99**, 98-116 e117, doi:10.1016/j.neuron.2018.06.002 (2018).

27 Maldonado, P. P. *et al.* Oxytocin Shapes Spontaneous Activity Patterns in the Developing Visual Cortex by Activating Somatostatin Interneurons. *Curr Biol* **31**, 322-333 e325, doi:10.1016/j.cub.2020.10.028 (2021).
28 Khazipov, R. *et al.* Early motor activity drives spindle bursts in the developing somatosensory cortex. *Nature* **432**, 758-761, doi:10.1038/nature03132 (2004).
29 Hanganu, I. L., Ben-Ari, Y. & Khazipov, R. Retinal waves trigger spindle bursts in the neonatal rat visual cortex. *J Neurosci* **26**, 6728-6736, doi:10.1523/JNEUROSCI.0752-06.2006 (2006).
30 Hanganu, I. L., Staiger, J. F., Ben-Ari, Y. & Khazipov, R. Cholinergic modulation of spindle bursts in the neonatal rat visual cortex in vivo. *J Neurosci* **27**, 5694-5705, doi:10.1523/JNEUROSCI.5233-06.2007 (2007).
31 Colonnese, M. T. *et al.* A conserved switch in sensory processing prepares developing neocortex for vision. *Neuron* **67**, 480-498, doi:10.1016/j.neuron.2010.07.015 (2010).
32 Maeda, E., Robinson, H. P. & Kawana, A. The mechanisms of generation and propagation of synchronized bursting in developing networks of cortical neurons. *J Neurosci* **15**, 6834-6845, doi:10.1523/JNEUROSCI.15-10-06834.1995 (1995).
33 Mohajerani, M. H. & Cherubini, E. Spontaneous recurrent network activity in organotypic rat hippocampal slices. *Eur J Neurosci* **22**, 107-118, doi:10.1111/j.1460-9568.2005.04198.x (2005).
34 Johnson, H. A. & Buonomano, D. V. Development and plasticity of spontaneous activity and Up states in cortical organotypic slices. *J Neurosci* **27**, 5915-5925, doi:10.1523/JNEUROSCI.0447-07.2007 (2007).
35 Yang, J. W., Hanganu-Opatz, I. L., Sun, J. J. & Luhmann, H. J. Three patterns of oscillatory activity differentially synchronize developing neocortical networks in vivo. *J Neurosci* **29**, 9011-9025, doi:10.1523/JNEUROSCI.5646-08.2009 (2009).
36 Minlebaev, M., Colonnese, M., Tsintsadze, T., Sirota, A. & Khazipov, R. Early gamma oscillations synchronize developing thalamus and cortex. *Science* **334**, 226-229, doi:10.1126/science.1210574 (2011).
37 Daw, M. I., Ashby, M. C. & Isaac, J. T. Coordinated developmental recruitment of latent fast spiking interneurons in layer IV barrel cortex. *Nat Neurosci* **10**, 453-461, doi:10.1038/nn1866 (2007).
38 Yang, J. W. *et al.* Thalamic network oscillations synchronize ontogenetic columns in the newborn rat barrel cortex. *Cereb Cortex* **23**, 1299-1316, doi:10.1093/cercor/bhs103 (2013).
39 Bitzenhofer, S. H., Popplau, J. A. & Hanganu-Opatz, I. Gamma activity accelerates during prefrontal development. *Elife* **9**, doi:10.7554/eLife.56795 (2020).
40 Kirmse, K. *et al.* GABA depolarizes immature neurons and inhibits network activity in the neonatal neocortex in vivo. *Nat Commun* **6**, 7750, doi:10.1038/ncomms8750 (2015).
41 Babij, R. *et al.* Gabrb3 is required for the functional integration of pyramidal neuron subtypes in the somatosensory cortex. *Neuron* **111**, 256-274 e210, doi:10.1016/j.neuron.2022.10.037 (2022).
42 Chini, M., Pfeffer, T. & Hanganu-Opatz, I. An increase of inhibition drives the developmental decorrelation of neural activity. *Elife* **11**, e78811, doi:10.7554/eLife.78811 (2022).

43 Kourdougli, N. *et al.* Improvement of sensory deficits in fragile X mice by increasing cortical interneuron activity after the critical period. *Neuron* **111**, 2863-2880, doi:10.1016/j.neuron.2023.06.009 (2023).
44 Leighton, A. H. *et al.* Somatostatin interneurons restrict cell recruitment to retinally driven spontaneous activity in the developing cortex. *Cell Rep* **36**, 109316, doi:10.1016/j.celrep.2021.109316 (2021).
45 Bollmann, Y. *et al.* Prominent in vivo influence of single interneurons in the developing barrel cortex. *Nat Neurosci* **26**, 1555-1565, doi:10.1038/s41593-023-01405-5 (2023).
46 Modol, L. *et al.* Assemblies of Perisomatic GABAergic Neurons in the Developing Barrel Cortex. *Neuron* **105**, 93-105 e104, doi:10.1016/j.neuron.2019.10.007 (2020).
47 Gour, A. *et al.* Postnatal connectomic development of inhibition in mouse barrel cortex. *Science* **371**, doi:10.1126/science.abb4534 (2021).
48 Picardo, M. A. *et al.* Pioneer GABA cells comprise a subpopulation of hub neurons in the developing hippocampus. *Neuron* **71**, 695-709, doi:10.1016/j.neuron.2011.06.018 (2011).
49 Yuryev, M. *et al.* In vivo two-photon imaging of the embryonic cortex reveals spontaneous ketamine-sensitive calcium activity. *Sci Rep* **8**, 16059, doi:10.1038/s41598-018-34410-x (2018).
50 Huang, Q. *et al.* Intravital imaging of mouse embryos. *Science* **368**, 181-186, doi:10.1126/science.aba0210 (2020).
51 Munz, M. *et al.* Pyramidal neurons form active, transient, multilayered circuits perturbed by autism-associated mutations at the inception of neocortex. *Cell* **186**, 1930-1949, doi:10.1016/j.cell.2023.03.025 (2023).
52 Anton-Bolaños, N. *et al.* Prenatal activity from thalamic neurons governs the emergence of functional cortical maps in mice. *Science* **364**, 987-990, doi:10.1126/science.aav7617 (2019).
53 Mountcastle, V. B. Modality and topographic properties of single neurons of cat's somatic sensory cortex. *J Neurophysiol* **20**, 408-434, doi:10.1152/jn.1957.20.4.408 (1957).
54 Rakic, P. Specification of cerebral cortical areas. *Science* **241**, 170-176, doi:10.1126/science.3291116 (1988).
55 Ackman, J. B., Burbridge, T. J. & Crair, M. C. Retinal waves coordinate patterned activity throughout the developing visual system. *Nature* **490**, 219-225, doi:10.1038/nature11529 (2012).
56 Ikezoe, K., Tamura, H., Kimura, F. & Fujita, I. Decorrelation of sensory-evoked neuronal responses in rat barrel cortex during postnatal development. *Neurosci Res* **73**, 312-320, doi:10.1016/j.neures.2012.05.009 (2012).
57 Stern, E. A., Maravall, M. & Svoboda, K. Rapid development and plasticity of layer 2/3 maps in rat barrel cortex in vivo. *Neuron* **31**, 305-315, doi:10.1016/s0896-6273(01)00360-9 (2001).
58 Dorrn, A. L., Yuan, K., Barker, A. J., Schreiner, C. E. & Froemke, R. C. Developmental sensory experience balances cortical excitation and inhibition. *Nature* **465**, 932-936, doi:10.1038/nature09119 (2010).
59 Shadlen, M. N. & Newsome, W. T. Noise, neural codes and cortical organization. *Curr Opin Neurobiol* **4**, 569-579, doi:10.1016/0959-4388(94)90059-0 (1994).

60 Zohary, E., Shadlen, M. N. & Newsome, W. T. Correlated neuronal discharge rate and its implications for psychophysical performance. *Nature* **370**, 140-143, doi:10.1038/370140a0 (1994).
61 Olshausen, B. A. & Field, D. J. Sparse coding of sensory inputs. *Curr Opin Neurobiol* **14**, 481-487, doi:10.1016/j.conb.2004.07.007 (2004).
62 Colonnese, M. T. Rapid developmental emergence of stable depolarization during wakefulness by inhibitory balancing of cortical network excitability. *J Neurosci* **34**, 5477-5485, doi:10.1523/JNEUROSCI.3659-13.2014 (2014).
63 Babola, T. A. *et al.* Homeostatic Control of Spontaneous Activity in the Developing Auditory System. *Neuron* **99**, 511-524 e515, doi:10.1016/j.neuron.2018.07.004 (2018).
64 Maffei, L. & Galli-Resta, L. Correlation in the discharges of neighboring rat retinal ganglion cells during prenatal life. *Proc Natl Acad Sci U S A* **87**, 2861-2864, doi:10.1073/pnas.87.7.2861 (1990).
65 Meister, M., Wong, R. O., Baylor, D. A. & Shatz, C. J. Synchronous bursts of action potentials in ganglion cells of the developing mammalian retina. *Science* **252**, 939-943, doi:10.1126/science.2035024 (1991).
66 Weliky, M. & Katz, L. C. Correlational structure of spontaneous neuronal activity in the developing lateral geniculate nucleus in vivo. *Science* **285**, 599-604, doi:10.1126/science.285.5427.599 (1999).
67 Murata, Y. & Colonnese, M. T. An excitatory cortical feedback loop gates retinal wave transmission in rodent thalamus. *Elife* **5**, doi:10.7554/eLife.18816 (2016).
68 McVea, D. A., Mohajerani, M. H. & Murphy, T. H. Voltage-sensitive dye imaging reveals dynamic spatiotemporal properties of cortical activity after spontaneous muscle twitches in the newborn rat. *J Neurosci* **32**, 10982-10994, doi:10.1523/JNEUROSCI.1322-12.2012 (2012).
69 Moreno-Juan, V. *et al.* Prenatal thalamic waves regulate cortical area size prior to sensory processing. *Nat Commun* **8**, 14172, doi:10.1038/ncomms14172 (2017).
70 Akhmetshina, D., Nasretdinov, A., Zakharov, A., Valeeva, G. & Khazipov, R. The Nature of the Sensory Input to the Neonatal Rat Barrel Cortex. *J Neurosci* **36**, 9922-9932, doi:10.1523/JNEUROSCI.1781-16.2016 (2016).
71 Riyahi, P., Phillips, M. A. & Colonnese, M. T. Input-Independent Homeostasis of Developing Thalamocortical Activity. *eNeuro* **8**, doi:10.1523/ENEURO.0184-21.2021 (2021).
72 Chiu, C. & Weliky, M. Spontaneous activity in developing ferret visual cortex in vivo. *J Neurosci* **21**, 8906-8914, doi:10.1523/JNEUROSCI.21-22-08906.2001 (2001).
73 Tiriac, A., Uitermarkt, B. D., Fanning, A. S., Sokoloff, G. & Blumberg, M. S. Rapid whisker movements in sleeping newborn rats. *Curr Biol* **22**, 2075-2080, doi:10.1016/j.cub.2012.09.009 (2012).
74 Kandler, K. & Katz, L. C. Coordination of neuronal activity in developing visual cortex by gap junction-mediated biochemical communication. *J Neurosci* **18**, 1419-1427, doi:10.1523/JNEUROSCI.18-04-01419.1998 (1998).
75 Bennett, M. V. *et al.* Gap junctions: new tools, new answers, new questions. *Neuron* **6**, 305-320, doi:10.1016/0896-6273(91)90241-q (1991).

76 Kumar, N. M. & Gilula, N. B. The gap junction communication channel. *Cell* **84**, 381-388, doi:10.1016/s0092-8674(00)81282-9 (1996).
77 Sohl, G., Maxeiner, S. & Willecke, K. Expression and functions of neuronal gap junctions. *Nat Rev Neurosci* **6**, 191-200, doi:10.1038/nrn1627 (2005).
78 Montoro, R. J. & Yuste, R. Gap junctions in developing neocortex: a review. *Brain Res Brain Res Rev* **47**, 216-226, doi:10.1016/j.brainresrev.2004.06.009 (2004).
79 Peinado, A., Yuste, R. & Katz, L. C. Gap junctional communication and the development of local circuits in neocortex. *Cereb Cortex* **3**, 488-498, doi:10.1093/cercor/3.5.488 (1993).
80 Yu, Y. C. *et al.* Preferential electrical coupling regulates neocortical lineage-dependent microcircuit assembly. *Nature* **486**, 113-117, doi:10.1038/nature10958 (2012).
81 Li, Y. *et al.* Clonally related visual cortical neurons show similar stimulus feature selectivity. *Nature* **486**, 118-121, doi:10.1038/nature11110 (2012).
82 Tovar, K. R., Maher, B. J. & Westbrook, G. L. Direct actions of carbenoxolone on synaptic transmission and neuronal membrane properties. *J Neurophysiol* **102**, 974-978, doi:10.1152/jn.00060.2009 (2009).
83 Allene, C. *et al.* Sequential generation of two distinct synapse-driven network patterns in developing neocortex. *J Neurosci* **28**, 12851-12863, doi:10.1523/JNEUROSCI.3733-08.2008 (2008).
84 Minlebaev, M., Ben-Ari, Y. & Khazipov, R. Network mechanisms of spindle-burst oscillations in the neonatal rat barrel cortex in vivo. *J Neurophysiol* **97**, 692-700, doi:10.1152/jn.00759.2006 (2007).
85 Minlebaev, M., Ben-Ari, Y. & Khazipov, R. NMDA receptors pattern early activity in the developing barrel cortex in vivo. *Cereb Cortex* **19**, 688-696, doi:10.1093/cercor/bhn115 (2009).
86 Graf, J. *et al.* A limited role of NKCC1 in telencephalic glutamatergic neurons for developing hippocampal network dynamics and behavior. *Proc Natl Acad Sci U S A* **118**, doi:10.1073/pnas.2014784118 (2021).
87 Ben-Ari, Y., Cherubini, E., Corradetti, R. & Gaiarsa, J. L. Giant synaptic potentials in immature rat CA3 hippocampal neurones. *J Physiol* **416**, 303-325, doi:10.1113/jphysiol.1989.sp017762 (1989).
88 Ben-Ari, Y. The GABA excitatory/inhibitory developmental sequence: a personal journey. *Neuroscience* **279**, 187-219, doi:10.1016/j.neuroscience.2014.08.001 (2014).
89 Murata, Y. & Colonnese, M. T. GABAergic interneurons excite neonatal hippocampus in vivo. *Sci Adv* **6**, eaba1430, doi:10.1126/sciadv.aba1430 (2020).
90 He, Q., Nomura, T., Xu, J. & Contractor, A. The developmental switch in GABA polarity is delayed in fragile X mice. *J Neurosci* **34**, 446-450, doi:10.1523/JNEUROSCI.4447-13.2014 (2014).
91 Deidda, G. *et al.* Early depolarizing GABA controls critical-period plasticity in the rat visual cortex. *Nat Neurosci* **18**, 87-96, doi:10.1038/nn.3890 (2015).
92 Marguet, S. L. *et al.* Treatment during a vulnerable developmental period rescues a genetic epilepsy. *Nat Med* **21**, 1436-1444, doi:10.1038/nm.3987 (2015).
93 Tuncdemir, S. N. *et al.* Early Somatostatin Interneuron Connectivity Mediates the Maturation of Deep Layer Cortical Circuits. *Neuron* **89**, 521-535, doi:10.1016/j.neuron.2015.11.020 (2016).

94 Marques-Smith, A. *et al.* A Transient Translaminar GABAergic Interneuron Circuit Connects Thalamocortical Recipient Layers in Neonatal Somatosensory Cortex. *Neuron* **89**, 536-549, doi:10.1016/j.neuron.2016.01.015 (2016).
95 Lee, S. H. & Dan, Y. Neuromodulation of brain states. *Neuron* **76**, 209-222, doi:10.1016/j.neuron.2012.09.012 (2012).
96 Riffault, B. *et al.* A quantitative cholinergic and catecholaminergic 3D Atlas of the developing mouse brain. *Neuroimage* **260**, 119494, doi:10.1016/j.neuroimage.2022.119494 (2022).
97 Peinado, A. Traveling slow waves of neural activity: a novel form of network activity in developing neocortex. *J Neurosci* **20**, RC54, doi:10.1523/JNEUROSCI.20-02-j0002.2000 (2000).
98 Cossart, R. & Garel, S. Step by step: cells with multiple functions in cortical circuit assembly. *Nat Rev Neurosci* **23**, 395-410, doi:10.1038/s41583-022-00585-6 (2022).
99 Katz, L. C. & Shatz, C. J. Synaptic activity and the construction of cortical circuits. *Science* **274**, 1133-1138, doi:10.1126/science.274.5290.1133 (1996).
100 Willshaw, D. J. & von der Malsburg, C. How patterned neural connections can be set up by self-organization. *Proc R Soc Lond B Biol Sci* **194**, 431-445, doi:10.1098/rspb.1976.0087 (1976).
101 LeVay, S., Stryker, M. P. & Shatz, C. J. Ocular dominance columns and their development in layer IV of the cat's visual cortex: a quantitative study. *J Comp Neurol* **179**, 223-244, doi:10.1002/cne.901790113 (1978).
102 Senft, S. L. & Woolsey, T. A. Growth of thalamic afferents into mouse barrel cortex. *Cereb Cortex* **1**, 308-335, doi:10.1093/cercor/1.4.308 (1991).
103 Rebsam, A., Seif, I. & Gaspar, P. Refinement of thalamocortical arbors and emergence of barrel domains in the primary somatosensory cortex: a study of normal and monoamine oxidase a knock-out mice. *J Neurosci* **22**, 8541-8552, doi:10.1523/JNEUROSCI.22-19-08541.2002 (2002).
104 Higashi, S., Molnar, Z., Kurotani, T. & Toyama, K. Prenatal development of neural excitation in rat thalamocortical projections studied by optical recording. *Neuroscience* **115**, 1231-1246, doi:10.1016/s0306-4522(02)00418-9 (2002).
105 Miller, B., Chou, L. & Finlay, B. L. The early development of thalamocortical and corticothalamic projections. *J Comp Neurol* **335**, 16-41, doi:10.1002/cne.903350103 (1993).
106 Fox, K., Schlaggar, B. L., Glazewski, S. & O'Leary, D. D. Glutamate receptor blockade at cortical synapses disrupts development of thalamocortical and columnar organization in somatosensory cortex. *Proc Natl Acad Sci U S A* **93**, 5584-5589, doi:10.1073/pnas.93.11.5584 (1996).
107 Feller, M. B., Wellis, D. P., Stellwagen, D., Werblin, F. S. & Shatz, C. J. Requirement for cholinergic synaptic transmission in the propagation of spontaneous retinal waves. *Science* **272**, 1182-1187, doi:10.1126/science.272.5265.1182 (1996).
108 Seabrook, T. A., Burbridge, T. J., Crair, M. C. & Huberman, A. D. Architecture, Function, and Assembly of the Mouse Visual System. *Annu Rev Neurosci* **40**, 499-538, doi:10.1146/annurev-neuro-071714-033842 (2017).

109 Stryker, M. P. & Harris, W. A. Binocular impulse blockade prevents the formation of ocular dominance columns in cat visual cortex. *J Neurosci* **6**, 2117-2133, doi:10.1523/JNEUROSCI.06-08-02117.1986 (1986).
110 Shatz, C. J. & Stryker, M. P. Prenatal tetrodotoxin infusion blocks segregation of retinogeniculate afferents. *Science* **242**, 87-89, doi:10.1126/science.3175636 (1988).
111 Cang, J. *et al.* Development of precise maps in visual cortex requires patterned spontaneous activity in the retina. *Neuron* **48**, 797-809, doi:10.1016/j.neuron.2005.09.015 (2005).
112 Murakami, T., Matsui, T., Uemura, M. & Ohki, K. Modular strategy for development of the hierarchical visual network in mice. *Nature* **608**, 578-585, doi:10.1038/s41586-022-05045-w (2022).
113 Gribizis, A. *et al.* Visual Cortex Gains Independence from Peripheral Drive before Eye Opening. *Neuron* **104**, 711-723 e713, doi:10.1016/j.neuron.2019.08.015 (2019).
114 Clancy, K. B., Schnepel, P., Rao, A. T. & Feldman, D. E. Structure of a single whisker representation in layer 2 of mouse somatosensory cortex. *J Neurosci* **35**, 3946-3958, doi:10.1523/JNEUROSCI.3887-14.2015 (2015).
115 Favuzzi, E. *et al.* Distinct molecular programs regulate synapse specificity in cortical inhibitory circuits. *Science* **363**, 413-417, doi:10.1126/science.aau8977 (2019).
116 Guan, W. *et al.* Eye opening differentially modulates inhibitory synaptic transmission in the developing visual cortex. *Elife* **6**, doi:10.7554/eLife.32337 (2017).
117 Sato, T. R. & Svoboda, K. The functional properties of barrel cortex neurons projecting to the primary motor cortex. *The Journal of neuroscience : the official journal of the Society for Neuroscience* **30**, 4256-4260, doi:10.1523/JNEUROSCI.3774-09.2010 (2010).
118 Wosniack, M. E. *et al.* Adaptation of spontaneous activity in the developing visual cortex. *Elife* **10**, doi:10.7554/eLife.61619 (2021).
119 Warm, D., Bassetti, D., Schroer, J., Luhmann, H. J. & Sinning, A. Spontaneous Activity Predicts Survival of Developing Cortical Neurons. *Front Cell Dev Biol* **10**, 937761, doi:10.3389/fcell.2022.937761 (2022).
120 Wong, F. K. *et al.* Pyramidal cell regulation of interneuron survival sculpts cortical networks. *Nature* **557**, 668-673, doi:10.1038/s41586-018-0139-6 (2018).
121 Priya, R. *et al.* Activity Regulates Cell Death within Cortical Interneurons through a Calcineurin-Dependent Mechanism. *Cell Rep* **22**, 1695-1709, doi:10.1016/j.celrep.2018.01.007 (2018).
122 Denaxa, M. *et al.* Modulation of Apoptosis Controls Inhibitory Interneuron Number in the Cortex. *Cell Rep* **22**, 1710-1721, doi:10.1016/j.celrep.2018.01.064 (2018).
123 Southwell, D. G. *et al.* Intrinsically determined cell death of developing cortical interneurons. *Nature* **491**, 109-113, doi:10.1038/nature11523 (2012).
124 Contractor, A., Ethell, I. M. & Portera-Cailliau, C. Cortical interneurons in autism. *Nat Neurosci* **24**, 1648-1659, doi:10.1038/s41593-021-00967-6 (2021).
125 He, C. X., Arroyo, E. D., Cantu, D. A., Goel, A. & Portera-Cailliau, C. A Versatile Method for Viral Transfection of Calcium Indicators in the Neonatal Mouse Brain. *Front Neural Circuits* **12**, 56, doi:10.3389/fncir.2018.00056 (2018).
126 Smith, G. B. *et al.* The development of cortical circuits for motion discrimination. *Nat Neurosci* **18**, 252-261, doi:10.1038/nn.3921 (2015).

127 van der Bourg, A. *et al.* Layer-Specific Refinement of Sensory Coding in Developing Mouse Barrel Cortex. *Cereb Cortex* **27**, 4835-4850, doi:10.1093/cercor/bhw280 (2017).
128 Arakawa, H. & Erzurumlu, R. S. Role of whiskers in sensorimotor development of C57BL/6 mice. *Behav Brain Res* **287**, 146-155, doi:10.1016/j.bbr.2015.03.040 (2015).
129 Grant, R. A., Mitchinson, B. & Prescott, T. J. The development of whisker control in rats in relation to locomotion. *Dev Psychobiol* **54**, 151-168, doi:10.1002/dev.20591 (2012).
130 Micheva, K. D. & Beaulieu, C. Quantitative aspects of synaptogenesis in the rat barrel field cortex with special reference to GABA circuitry. *J Comp Neurol* **373**, 340-354, doi:10.1002/(SICI)1096-9861(19960923)373:3<340::AID-CNE3>3.0.CO;2-2 (1996).
131 Brochini, L. *et al.* Phase transitions and self-organized criticality in networks of stochastic spiking neurons. *Sci Rep* **6**, 35831, doi:10.1038/srep35831 (2016).
132 Picken Bahrey, H. L. & Moody, W. J. Early development of voltage-gated ion currents and firing properties in neurons of the mouse cerebral cortex. *J Neurophysiol* **89**, 1761-1773, doi:10.1152/jn.00972.2002 (2003).
133 Lim, L., Mi, D., Llorca, A. & Marin, O. Development and Functional Diversification of Cortical Interneurons. *Neuron* **100**, 294-313, doi:10.1016/j.neuron.2018.10.009 (2018).
134 Konig, N., Roch, G. & Marty, R. The onset of synaptogenesis in rat temporal cortex. *Anat Embryol (Berl)* **148**, 73-87, doi:10.1007/BF00315564 (1975).
135 Owens, D. F., Liu, X. & Kriegstein, A. R. Changing properties of GABA(A) receptor-mediated signaling during early neocortical development. *J Neurophysiol* **82**, 570-583, doi:10.1152/jn.1999.82.2.570 (1999).
136 Modol, L., Moissidis, M., Selten, M., Oozeer, F. & Marin, O. Somatostatin interneurons control the timing of developmental desynchronization in cortical networks. *Neuron* **112**, 1-18, doi:https://doi.org/10.1016/j.neuron.2024.03.014 (2024).
137 del Rio, J. A., de Lecea, L., Ferrer, I. & Soriano, E. The development of parvalbumin-immunoreactivity in the neocortex of the mouse. *Brain Res Dev Brain Res* **81**, 247-259, doi:10.1016/0165-3806(94)90311-5 (1994).
138 Du, J., Zhang, L., Weiser, M., Rudy, B. & McBain, C. J. Developmental expression and functional characterization of the potassium-channel subunit Kv3.1b in parvalbumin-containing interneurons of the rat hippocampus. *J Neurosci* **16**, 506-518, doi:10.1523/JNEUROSCI.16-02-00506.1996 (1996).
139 Rudy, B. & McBain, C. J. Kv3 channels: voltage-gated K+ channels designed for high-frequency repetitive firing. *Trends Neurosci* **24**, 517-526, doi:10.1016/s0166-2236(00)01892-0 (2001).
140 Kaczmarek, L. K. & Zhang, Y. Kv3 Channels: Enablers of Rapid Firing, Neurotransmitter Release, and Neuronal Endurance. *Physiol Rev* **97**, 1431-1468, doi:10.1152/physrev.00002.2017 (2017).
141 Elbert, A. *et al.* CTCF Governs the Identity and Migration of MGE-Derived Cortical Interneurons. *J Neurosci* **39**, 177-192, doi:10.1523/JNEUROSCI.3496-17.2018 (2019).
142 Gonchar, Y., Wang, Q. & Burkhalter, A. Multiple distinct subtypes of GABAergic neurons in mouse visual cortex identified by triple immunostaining. *Front Neuroanat* **1**, 3, doi:10.3389/neuro.05.003.2007 (2007).

143 Muhlethaler, M., Charpak, S. & Dreifuss, J. J. Contrasting effects of neurohypophysial peptides on pyramidal and non-pyramidal neurones in the rat hippocampus. *Brain Res* **308**, 97-107, doi:10.1016/0006-8993(84)90921-1 (1984).
144 Owen, S. F. *et al.* Oxytocin enhances hippocampal spike transmission by modulating fast-spiking interneurons. *Nature* **500**, 458-462, doi:10.1038/nature12330 (2013).
145 Spoljaric, A. *et al.* Vasopressin excites interneurons to suppress hippocampal network activity across a broad span of brain maturity at birth. *Proc Natl Acad Sci U S A* **114**, E10819-E10828, doi:10.1073/pnas.1717337114 (2017).
146 Ben-Ari, Y. Excitatory actions of gaba during development: the nature of the nurture. *Nat Rev Neurosci* **3**, 728-739, doi:10.1038/nrn920 (2002).
147 Tyzio, R. *et al.* Postnatal changes in somatic gamma-aminobutyric acid signalling in the rat hippocampus. *Eur J Neurosci* **27**, 2515-2528, doi:10.1111/j.1460-9568.2008.06234.x (2008).
148 van Rheede, J. J., Richards, B. A. & Akerman, C. J. Sensory-Evoked Spiking Behavior Emerges via an Experience-Dependent Plasticity Mechanism. *Neuron* **87**, 1050-1062, doi:10.1016/j.neuron.2015.08.021 (2015).
149 Valeeva, G., Tressard, T., Mukhtarov, M., Baude, A. & Khazipov, R. An Optogenetic Approach for Investigation of Excitatory and Inhibitory Network GABA Actions in Mice Expressing Channelrhodopsin-2 in GABAergic Neurons. *J Neurosci* **36**, 5961-5973, doi:10.1523/JNEUROSCI.3482-15.2016 (2016).
150 Kurki, S. N. *et al.* Expression patterns of NKCC1 in neurons and non-neuronal cells during cortico-hippocampal development. *Cereb Cortex* **33**, 5906-5923, doi:10.1093/cercor/bhac470 (2023).
151 Rivera, C. *et al.* The K+/Cl- co-transporter KCC2 renders GABA hyperpolarizing during neuronal maturation. *Nature* **397**, 251-255, doi:10.1038/16697 (1999).
152 Ludwig, A., Li, H., Saarma, M., Kaila, K. & Rivera, C. Developmental up-regulation of KCC2 in the absence of GABAergic and glutamatergic transmission. *Eur J Neurosci* **18**, 3199-3206, doi:10.1111/j.1460-9568.2003.03069.x (2003).
153 Hevner, R. F., Neogi, T., Englund, C., Daza, R. A. & Fink, A. Cajal-Retzius cells in the mouse: transcription factors, neurotransmitters, and birthdays suggest a pallial origin. *Brain Res Dev Brain Res* **141**, 39-53, doi:10.1016/s0165-3806(02)00641-7 (2003).
154 Bielle, F. *et al.* Multiple origins of Cajal-Retzius cells at the borders of the developing pallium. *Nat Neurosci* **8**, 1002-1012, doi:10.1038/nn1511 (2005).
155 Chowdhury, T. G. *et al.* Fate of cajal-retzius neurons in the postnatal mouse neocortex. *Front Neuroanat* **4**, 10, doi:10.3389/neuro.05.010.2010 (2010).
156 Radnikow, G., Feldmeyer, D. & Lubke, J. Axonal projection, input and output synapses, and synaptic physiology of Cajal-Retzius cells in the developing rat neocortex. *J Neurosci* **22**, 6908-6919, doi:10.1523/JNEUROSCI.22-16-06908.2002 (2002).
157 Aguilo, A. *et al.* Involvement of cajal-retzius neurons in spontaneous correlated activity of embryonic and postnatal layer 1 from wild-type and reeler mice. *J Neurosci* **19**, 10856-10868, doi:10.1523/JNEUROSCI.19-24-10856.1999 (1999).
158 Kostovic, I. & Rakic, P. Developmental history of the transient subplate zone in the visual and somatosensory cortex of the macaque monkey and human brain. *J Comp Neurol* **297**, 441-470, doi:10.1002/cne.902970309 (1990).

159 Allendoerfer, K. L. & Shatz, C. J. The subplate, a transient neocortical structure: its role in the development of connections between thalamus and cortex. *Annu Rev Neurosci* **17**, 185-218, doi:10.1146/annurev.ne.17.030194.001153 (1994).
160 Marx, M. *et al.* Neocortical Layer 6B as a Remnant of the Subplate - A Morphological Comparison. *Cereb Cortex* **27**, 1011-1026, doi:10.1093/cercor/bhv279 (2017).
161 Kanold, P. O. & Luhmann, H. J. The subplate and early cortical circuits. *Annu Rev Neurosci* **33**, 23-48, doi:10.1146/annurev-neuro-060909-153244 (2010).
162 Wess, J. M., Isaiah, A., Watkins, P. V. & Kanold, P. O. Subplate neurons are the first cortical neurons to respond to sensory stimuli. *Proc Natl Acad Sci U S A* **114**, 12602-12607, doi:10.1073/pnas.1710793114 (2017).
163 Kerschensteiner, D. Spontaneous Network Activity and Synaptic Development. *Neuroscientist* **20**, 272-290, doi:10.1177/1073858413510044 (2014).
164 Tolner, E. A., Sheikh, A., Yukin, A. Y., Kaila, K. & Kanold, P. O. Subplate neurons promote spindle bursts and thalamocortical patterning in the neonatal rat somatosensory cortex. *J Neurosci* **32**, 692-702, doi:10.1523/JNEUROSCI.1538-11.2012 (2012).
165 Ghezzi, F. *et al.* Non-canonical role for Lpar1-EGFP subplate neurons in early postnatal mouse somatosensory cortex. *Elife* **10**, doi:10.7554/eLife.60810 (2021).
166 Trujillo, C. A. *et al.* Complex Oscillatory Waves Emerging from Cortical Organoids Model Early Human Brain Network Development. *Cell Stem Cell* **25**, 558-569 e557, doi:10.1016/j.stem.2019.08.002 (2019).
167 Sharf, T. *et al.* Functional neuronal circuitry and oscillatory dynamics in human brain organoids. *Nat Commun* **13**, 4403, doi:10.1038/s41467-022-32115-4 (2022).
168 Bonifazi, P. *et al.* GABAergic hub neurons orchestrate synchrony in developing hippocampal networks. *Science* **326**, 1419-1424, doi:326/5958/1419 [pii]
10.1126/science.1175509 (2009).
169 Marissal, T. *et al.* Pioneer glutamatergic cells develop into a morpho-functionally distinct population in the juvenile CA3 hippocampus. *Nat Commun* **3**, 1316, doi:10.1038/ncomms2318 (2012).
170 Cheng, S. *et al.* Vision-dependent specification of cell types and function in the developing cortex. *Cell* **185**, 311-327 e324, doi:10.1016/j.cell.2021.12.022 (2022).
171 Huang, E. J. & Reichardt, L. F. Neurotrophins: roles in neuronal development and function. *Annu Rev Neurosci* **24**, 677-736, doi:10.1146/annurev.neuro.24.1.677 (2001).
172 Hensch, T. K. Critical period plasticity in local cortical circuits. *Nat Rev Neurosci* **6**, 877-888, doi:nrn1787 [pii]
10.1038/nrn1787 (2005).
173 Romagnoni, A., Colonnese, M. T., Touboul, J. D. & Gutkin, B. S. Progressive alignment of inhibitory and excitatory delay may drive a rapid developmental switch in cortical network dynamics. *J Neurophysiol* **123**, 1583-1599, doi:10.1152/jn.00402.2019 (2020).
174 Milh, M. *et al.* Rapid cortical oscillations and early motor activity in premature human neonate. *Cereb Cortex* **17**, 1582-1594, doi:10.1093/cercor/bhl069 (2007).
175 Destexhe, A., Hughes, S. W., Rudolph, M. & Crunelli, V. Are corticothalamic 'up' states fragments of wakefulness? *Trends in neurosciences* **30**, 334-342, doi:10.1016/j.tins.2007.04.006 (2007).

176 Crepel, V. *et al.* A parturition-associated nonsynaptic coherent activity pattern in the developing hippocampus. *Neuron* **54**, 105-120, doi:S0896-6273(07)00203-6 [pii]
10.1016/j.neuron.2007.03.007 (2007).
177 Grienberger, C., Giovannucci, A., Zeiger, W. & Portera-Cailliau, C. Two-photon calcium imaging of neuronal activity. *Nat Rev Methods Primers* **2**, doi:10.1038/s43586-022-00147-1 (2022).
178 Mire, E. *et al.* Spontaneous activity regulates Robo1 transcription to mediate a switch in thalamocortical axon growth. *Nat Neurosci* **15**, 1134-1143, doi:10.1038/nn.3160 (2012).
179 Dard, R. F. *et al.* The rapid developmental rise of somatic inhibition disengages hippocampal dynamics from self-motion. *Elife* **11**, doi:10.7554/eLife.78116 (2022).
180 Leprince, E. *et al.* Extrinsic control of the early postnatal CA1 hippocampal circuits. *Neuron* **111**, 888-902 e888, doi:10.1016/j.neuron.2022.12.013 (2023).
181 Valeeva, G. *et al.* Emergence of Coordinated Activity in the Developing Entorhinal-Hippocampal Network. *Cereb Cortex* **29**, 906-920, doi:10.1093/cercor/bhy309 (2019).
182 Leinekugel, X. *et al.* Correlated bursts of activity in the neonatal hippocampus in vivo. *Science* **296**, 2049-2052, doi:10.1126/science.1071111 (2002).
183 Inacio, A. R., Nasretdinov, A., Lebedeva, J. & Khazipov, R. Sensory feedback synchronizes motor and sensory neuronal networks in the neonatal rat spinal cord. *Nat Commun* **7**, 13060, doi:10.1038/ncomms13060 (2016).
184 Dehorter, N. *et al.* Onset of Pup Locomotion Coincides with Loss of NR2C/D-Mediated Cortico-Striatal EPSCs and Dampening of Striatal Network Immature Activity. *Front Cell Neurosci* **5**, 24, doi:10.3389/fncel.2011.00024 (2011).
185 Ferrari, D. C. *et al.* Midbrain dopaminergic neurons generate calcium and sodium currents and release dopamine in the striatum of pups. *Front Cell Neurosci* **6**, 7, doi:10.3389/fncel.2012.00007 (2012).
186 Akin, O., Bajar, B. T., Keles, M. F., Frye, M. A. & Zipursky, S. L. Cell-type-Specific Patterned Stimulus-Independent Neuronal Activity in the Drosophila Visual System during Synapse Formation. *Neuron* **101**, 894-904 e895, doi:10.1016/j.neuron.2019.01.008 (2019).
187 Bajar, B. T. *et al.* A discrete neuronal population coordinates brain-wide developmental activity. *Nature* **602**, 639-646, doi:10.1038/s41586-022-04406-9 (2022).
188 Xu, H., Khakhalin, A. S., Nurmikko, A. V. & Aizenman, C. D. Visual experience-dependent maturation of correlated neuronal activity patterns in a developing visual system. *J Neurosci* **31**, 8025-8036, doi:10.1523/JNEUROSCI.5802-10.2011 (2011).
189 Suarez, R. *et al.* Cortical activity emerges in region-specific patterns during early brain development. *Proc Natl Acad Sci U S A* **120**, e2208654120, doi:10.1073/pnas.2208654120 (2023).
190 Steriade, M., Nunez, A. & Amzica, F. A novel slow (< 1 Hz) oscillation of neocortical neurons in vivo: depolarizing and hyperpolarizing components. *J Neurosci* **13**, 3252-3265, doi:10.1523/JNEUROSCI.13-08-03252.1993 (1993).
191 Jercog, D. *et al.* UP-DOWN cortical dynamics reflect state transitions in a bistable network. *Elife* **6**, doi:10.7554/eLife.22425 (2017).
192 Soldado-Magraner, S., Seay, M. J., Laje, R. & Buonomano, D. V. Paradoxical self-sustained dynamics emerge from orchestrated excitatory and inhibitory homeostatic plasticity rules. *Proc Natl Acad Sci U S A* **119**, e2200621119, doi:10.1073/pnas.2200621119 (2022).

193 Hoffman, K. L. *et al.* The upshot of up states in the neocortex: from slow oscillations to memory formation. *J Neurosci* **27**, 11838-11841, doi:10.1523/JNEUROSCI.3501-07.2007 (2007).
194 Sanchez-Vives, M. V. & McCormick, D. A. Cellular and network mechanisms of rhythmic recurrent activity in neocortex. *Nat Neurosci* **3**, 1027-1034, doi:10.1038/79848 (2000).
195 Constantinople, C. M. & Bruno, R. M. Effects and mechanisms of wakefulness on local cortical networks. *Neuron* **69**, 1061-1068, doi:S0896-6273(11)00162-0 [pii]
10.1016/j.neuron.2011.02.040 (2011).
196 Goncalves, J. T., Anstey, J. E., Golshani, P. & Portera-Cailliau, C. Circuit level defects in the developing neocortex of Fragile X mice. *Nature neuroscience* **16**, 903-909, doi:10.1038/nn.3415 (2013).
197 Namiki, S. *et al.* Layer III neurons control synchronized waves in the immature cerebral cortex. *J Neurosci* **33**, 987-1001, doi:10.1523/JNEUROSCI.2522-12.2013 (2013).
198 Shen, J. & Colonnese, M. T. Development of Activity in the Mouse Visual Cortex. *J Neurosci* **36**, 12259-12275, doi:10.1523/JNEUROSCI.1903-16.2016 (2016).
199 Dreyfus-Brisac, C. & Larroche, J. C. in *Société d'EEG et de Neurophysiologie Clinique de Langue Française*
200 Iyer, K. K. *et al.* Cortical burst dynamics predict clinical outcome early in extremely preterm infants. *Brain* **138**, 2206-2218, doi:10.1093/brain/awv129 (2015).
201 Bitzenhofer, S. H., Popplau, J. A., Chini, M., Marquardt, A. & Hanganu-Opatz, I. L. A transient developmental increase in prefrontal activity alters network maturation and causes cognitive dysfunction in adult mice. *Neuron* **109**, 1350-1364 e1356, doi:10.1016/j.neuron.2021.02.011 (2021).
202 Cheyne, J. E., Zabouri, N., Baddeley, D. & Lohmann, C. Spontaneous Activity Patterns Are Altered in the Developing Visual Cortex of the Fmr1 Knockout Mouse. *Front Neural Circuits* **13**, 57, doi:10.3389/fncir.2019.00057 (2019).
203 Kourdougli, N. & Portera-Cailliau, C. aGABRacadabra: A surprising new role for GABA(A) receptors in cortical development. *Neuron* **111**, 146-149, doi:10.1016/j.neuron.2022.12.019 (2023).
204 La Fata, G. *et al.* FMRP regulates multipolar to bipolar transition affecting neuronal migration and cortical circuitry. *Nat Neurosci* **17**, 1693-1700, doi:10.1038/nn.3870 (2014).
205 Samarasinghe, R. A. *et al.* Identification of neural oscillations and epileptiform changes in human brain organoids. *Nat Neurosci* **24**, 1488-1500, doi:10.1038/s41593-021-00906-5 (2021).
206 Penagarikano, O. *et al.* Absence of CNTNAP2 leads to epilepsy, neuronal migration abnormalities, and core autism-related deficits. *Cell* **147**, 235-246, doi:10.1016/j.cell.2011.08.040 (2011).

Acknowledgments: We are grateful to M. Colonnese, M. Dipoppa and C. Lohmann for feedback on earlier versions of this manuscript. When citing papers, we attempted to be as inclusive as possible in acknowledging the many investigators whose work has helped shape our ideas; however, we recognize that we have probably missed attributing credit in some cases, and we

apologize for any inadvertent oversights. This work was supported by the following grants: Department of Defense (DOD, 13196175), R01NS117597 (NIH-NINDS), R01HD108370 and R01HD054453 (NIH-NICHD) awarded to C.P-C, by a fellowship grant from the FRAXA research foundation to N.K., and by the Training Grant in Neurobehavioral Genetics (T32NS048004; NIH, NINDS) and the UCLA-Caltech Medical Scientist Training Program (T32 GM008042; NIH, NIGMS) to M.W.W.

Author contributions

The authors contributed equally to all aspects of the article.

Competing interests

The authors declare no competing interests.

Fig. 1: In vivo cortical network state transitions across development **a**, In vivo calcium imaging in mice reveals four different patterns of cortical network activity throughout development: sparse embryonic activity, patchwork activity, wave-like activity and sparse and decorrelated activity. The schematics depict the spatial organization of each of these patterns of activity and the appearance of typical calcium traces from excitatory pyramidal neurons at different postnatal ages. At the embryonic stage, calcium events are initially sparse and decorrelated across neurons[51]. At late embryonic stages (from embryonic day (E)18) calcium transients become longer and are highly synchronous across clusters of neurons that correspond to cortical columns; they can be triggered by activity that originates in the thalamus or emerge spontaneously[27,52]. This patchwork pattern persists throughout the first postnatal week but then evolves into longer calcium events that appear to flicker across the cortex in a wave-like manner[20,23,25]. Eventually, after postnatal day (P)10-12, cortical activity becomes desynchronized and calcium transients are smaller in amplitude and more frequent[7,20]. An approximate timeline for each of these activity patterns in mice and humans is provided[174]. **b**, In vivo electrophysiology recordings also reveal an evolution of network activity across development. Schematic illustrations of typical extracellular recordings (top) of the local field potential (LFP, which reflects the firing of hundreds of neurons) show that activity is discontinuous during the first week of postnatal development. Neurons fire in infrequent bursts (asterisks) separated by long periods of electrical silence[31]. When the LFP is recorded via an extracellular electrode or via electroencephalography (EEG, trace in blue insett),

this activity appears as spindle bursts on top of a slower delta wave, as illustrated in the schematic[28]. Toward the end of the first postnatal week these spindle bursts evolve into early gamma oscillations[13]. After P10-P12, the network events become smaller in amplitude and more frequent. The decrease in the silent periods has given rise to the term 'continuous' activity to describe activity at this stage[13]. Schematic illustrations of typical intracellular patch-clamp recordings reveal that synchronous network events in the first postnatal week are akin to large Up states, a term used to describe transient depolarizations associated with slow wave sleep[175]. Action potentials generated by different neurons participating in these Up states coincide with the peaks of the spindle burst oscillation. After P10-P12, neurons fire more sparsely and only in a subset of the Up state-like network events, giving rise to desynchronization of network activity. **c** In mice, the end of the second postnatal week in mice marks an abrupt turning point in cortical development from synchronous activity that is largely driven by bottom-up sensory information and is important for developmental patterning of circuits and for sensory detection, to desynchronized activity that is dominated by intrinsic activity and is increasingly driven by top-down inputs (from higher-order regions), which is important for sensory processing.

Fig. 2: Thalamocortical influences on cortical network activity during development.
Cartoons of a generic thalamocortical circuit, showing the evolving influence of sensory inputs through thalamic relay nuclei, as well as interneuron connectivity, on cortical network activity at three different postnatal ages in mice. During the first postnatal week (based on studies in animals between postnatal day (P) 0 and P2), subplate (SP) neurons, as the major cortical recipients of thalamic afferents at this stage, have a transient role in the regulation of network activity. Somatostatin (SST)-expressing interneurons also receive thalamic inputs and are the first to synapse onto excitatory pyramidal neurons (with the GABA that they release having a depolarizing effect)[40,89]. At this stage, sensory inputs primarily reflect spontaneous activity in sensory organs (retina and cochlea) and myoclonic twitches. Early in the 2nd postnatal week (P8), parvalbumin (PV)-expressing neurons and spiny-stellate neurons in layer (L)4 begin to receive direct sensory inputs via thalamic relay neurons. These include inputs generated as a result of spontaneous whisker movements (eyes are still closed). In turn, spine stellate neurons project to pyramidal neurons in L2/3 for further sensory processing. The disappearance of the subplate along with developmental apoptotic death of SST and PV neurons (as well as Cajal-Retzius neurons in the marginal zone (MZ)) might play a role in the transition to larger wave-like events

at this stage. Surviving SST neurons continue to target dendrites of Pyr cells. Finally, toward the end of the second postnatal week (P14), as more PV interneurons assume their identity and exert an even greater inhibitory influence in the cortex, they help to drive the desynchronization of network activity. SST inhibition of Pyr cell dendrites also strengthens at this stage. By then, cortical activity increasingly reflects top-down modulation from higher order brain regions. LGN: lateral geniculate nucleus; VPM: ventral posteromedial nucleus.

Fig. 3: Mechanisms of desynchronization and other network transitions

Changes in cortical network activity are illustrated in the context of developmental events at the synaptic, cellular, and circuit levels, as well as within the framework of major behavioral milestones. At the synaptic level, the main events driving desynchronization are the disappearance of gap junctions, a switch in the polarity of GABA signalling (from depolarizing to hyperpolarizing), changes in input resistance, a massive increase in glutamatergic and GABAergic (first SST then PV) synapse density and the stabilization of dendritic spines (excitatory synapses). At the cellular level we highlight the elimination of Cajal-Retzius and subplate neurons, which could play transient roles in the intrinsic generation or pacing of SNA at earlier stages, the arrival of thalamocortical (TC) axons in the cortex and their arborization/pruning and the period of developmental apoptosis of interneurons. At the circuit-level, we indicate the transitions between the main patterns of activity observed with calcium imaging or electrophysiology, how this activity changes from synchronous (and discontinuous) to desynchronized (and continuous), the increasing influence of brainstem neuromodulation, the relative switch from bottom-up to top-down modulation, and the important shift in cortical circuit function from developmental patterning to sensory processing. Finally, at the behavioral level, we highlight the unique events that take place at around P12 (such as eye opening and rhythmic whisking). The arrow at the bottom indicates how these developmental processes are initially driven primarily by genetic programs, then require neuronal activity, and eventually require sensory experience.

CR: Cajal-Retzius neurons; L: layer; LGN: lateral geniculate nucleus; MZ: marginal zone; PV: parvalbumin interneuron; SP: subplate; SST: somatostatin interneuron; TC: thalamocortical; VPM: ventral posteromedial nucleus.

Box 1: In vitro studies of developmental cortical network activity

Synchronous neuronal events were first described in vitro, where calcium imaging in acute cortical slices from rats aged between postnatal day (P) 0 and P7 revealed small clusters of neurons that simultaneously exhibit calcium transients (rapid changes in the fluorescence

intensity of a calcium indicator molecule)[1]. Originally termed neuronal domains[1], these calcium events are mediated by gap junctions between neighboring neurons, but not by synaptic activity (as they were insensitive to tetrodotoxin (TTX), a sodium channel blocker that prevents action potentials) (see the schematic representations of these events in the figure, part **a**)**.** A related network phenomenon has been observed in vitro in the neonatal rat hippocampus[176] and mouse neocortex[83] and was termed a synchronous plateau assembly (SPA). It is important to note that, although calcium imaging is typically used by neuroscientists to record neuronal activity (fluorescence intensity changes are considered a surrogate for action potential firing[177]), calcium transients can also reflect increases in the intracellular concentration of calcium ions that are unrelated to neuronal spiking[177]. Furthermore, to our knowledge, activity akin to neuronal domains or SPAs has only been observed in vitro. As such, the significance of SPAs or neuronal domains and their potential role in cortical maturation remain unclear.

Several groups later discovered a different pattern of network activity in the developing cortex, known as an early network oscillation (ENO). ENOs are synchronous calcium transients that reflect action potential firing (they are sensitive to TTX) and rely on both excitatory and inhibitory synaptic transmission (see the schematic representations of these events in the figure, part **b**) [2-5]. Subsequently, a study in early postnatal rat cortical slices proposed a developmental sequence in which ENOs appear first but are then followed by giant depolarizing potentials (GDPs)[83]. GDPs had been originally discovered in electrophysiological studies of hippocampal slices and are synchronous network events that are driven by depolarizing GABAergic transmission[87]. The main differences between ENOs and GDPs lie in their spatiotemporal dynamics — with ENOs being slightly longer and much less frequent — and in their sensitivity to the $GABA_A$-receptor antagonist bicuculline (ENOs are not sensitive)[83].

Box 2: SNA in other brain regions and other species

The occurrence of synchronous network activity (SNA) during development is not unique to the sensory cortices or even to rodents or other mammals. Similar patterns of correlated network activity have been observed in the thalamus, hippocampus and the spinal cord. Correlated firing of developing thalamic neurons has been documented as early as E14.5 in

in vitro mouse preparations[69,178]. Several studies have suggested that SNA within the cortex originates in the thalamus, where synchronous events may be triggered by peripheral sensory inputs or may occur spontaneously[18,36,38]. SNA in the hippocampal CA1 region or the entorhinal cortex of neonatal mice has been documented in vivo[179-182]. Bursts of neuronal activity have also been recorded in the neonatal rat spinal cord and were closely linked to spontaneous hindlimb myoclonic twitches [183]. Whether SNA also occurs in the neonatal amygdala, striatum, cerebellum or other brain regions remains to be determined, but there is no reason to believe that early patterns of activity in those regions would not be synchronous. For example, in vitro studies have revealed synchronous activity patterns in the embryonic and neonatal striatum[184,185]. Future studies using silicon probes should aim to record SNA in these deep brain regions that are not accessible to conventional two-photon calcium imaging.

Synchronous activity has been found across the animal kingdom, from invertebrates to mammals. In *Drosophila melanogaster* larvae, activity is synchronous and is referred to as patterned stimulus-independent neuronal activity[186,187]. Correlated activity has also been described in the tectum of the tadpoles of *Xenopus* species [188]. More recently, SNA was reported during cortical development in dunnarts (a marsupial species) as early as Stage 23 (equivalent of E15 in mice)[189]. Owing to their unique maturation in the pouch, these non-placental mammals may be particularly well suited to uncover the mechanisms that mediate different synchronous activity patterns, such as patches in the developing somatosensory cortex and waves in the visual cortex[189].

Box 3 – Can developmental synchronous network events be considered Up states?

In neonatal rodents, synchronous network activity (SNA) manifests as brief (lasting less than 2 s), non-rhythmic bursts of firing across groups of neighboring neurons, separated by long periods (lasting up to tens of seconds) of no activity. During anesthesia or slow wave sleep in healthy adult animals, the dominant electroencephalography (EEG) rhythm is the slow oscillation (0.1 Hz). Patch-clamp recordings have shown that the electrophysiological signature of this slow oscillation is the Up and Down state transition[190]. During an Up state, the resting membrane potential (V_m) is in a stable depolarized state, during which action potentials may occur. By contrast, a Down state features a more hyperpolarized V_m, and action potentials are unlikely to occur[190]. This definition is consistent with computational models of bistable networks that exhibit Up and Down transitions and function in an inhibition

stabilized regime[191,192]. During sleep or quiet wakefulness (and during anesthesia) the V_m continuously undergoes Up–Down state transitions [193]. By contrast, during attentive wakefulness, it has been argued that neurons are persistently in the Up state[175,194,195], even as early as P14 in rodents[196].

We speculate that the synchronous network events observed during development, a time when animals are mostly inactive and often asleep, can be viewed as 'primitive' versions or precursors of Up states. In support of this argument, both in vivo and in vitro whole-cell recordings during early postnatal development (including experiments involving simultaneous calcium imaging and electrophysiological recording) have shown network events that are very reminiscent of Up states[7,44,57,62,197,198]. These synchronous network events involve depolarizations lasting 1-2 seconds, during which neurons fire action potentials (like Up states), as well as prolonged periods when activity is absent (like Down states). Nevertheless, we acknowledge that the mechanisms underlying SNA and Up states could differ; for example, SNA can be generated intrinsically in the cortex or can be triggered by bottom-up signals from the thalamus or the periphery, whereas Up states in the adult brain are mainly self-generated intracortical events[195]. As the brain matures and the number of synaptic connections grows rapidly, the frequency of Up states also increases (**Fig. 1b**)[7,13]. However, the probability of action potential firing during any Up state decreases dramatically in rodent neocortex at around P12[7], leading to a sudden decrease in pairwise correlation coefficients in the spiking of different neurons. Hence, even though many more depolarizing events (Up states) occur in the neocortex after P12, neurons are much less likely to participate in each of these events, leading to desynchronization.

Box 4: Network synchrony and neurodevelopmental conditions

Synchronous bursting activity has been reported in the electroencephalogram (EEG) of preterm human neonates at 24-27 weeks gestational age[199]. Infrequent periodic bursts of activity (with a frequency below 1 Hz, in the slow delta wave range) were separated by periods of prolonged electrical silence (lasting up to 20 s). The EEG of extremely preterm infants also showed discontinuous bursting activity[200]. During quiet sleep, these bursts tended to be synchronous over large cortical areas, if not the whole brain[10]. Each event, lasting between 1 and 5 s, was characterized by rapid oscillatory activity in a delta brush pattern (with a frequency between 8 and 25 Hz), similar to the spindle bursts observed in rodents. A minority

of these bursts closely follow spontaneous myoclonic twitches of the limbs[174], just as in rodents. In full term human babies, network desynchronization occurs around the time of birth[31].

The study of cortical network state transitions is relevant not just to human brain maturation but also to the emergence of neurotypical behavior and of neurodevelopmental conditions. Given the importance of SNA for patterning functional connectivity within and across cortical areas, one would assume that mutations in genes associated with neurodevelopmental conditions, environmental insults or exposure to CNS-acting drugs or medications that affect SNA could negatively impact map formation. In turn, alterations in SNA and the ensuing changes in circuit assembly, could have implications for behavior. Indeed, manipulating the activity of pyramidal neurons in the medial prefrontal cortex of neonatal mice by optogenetically inducing rhythmic activity impaired their subsequent performance on an array of working memory tasks and impaired social interactions later in adulthood[201]. It is also conceivable that subtle changes in the timing or magnitude of network transitions, especially desynchronization, could occur in neurological or psychiatric conditions. Indeed, seizures in humans frequently manifest for the first time soon after birth. The highly correlated neuronal activity in developing cortical circuits is a network regime that could predispose neonates and infants to seizures and epilepsy because, under certain circumstances (such as fever, infection or intracranial hemorrhage), it could switch to a more unstable regime in which synchrony propagates in a runaway fashion. Furthermore, EEG patterns in premature infants correlate with neurodevelopmental outcome[200].

Autism and intellectual disability are also first recognized in infants or toddlers. Several studies have shown changes in cortical network synchrony in various animal models of these and related conditions. For example, the *Fmr1* knockout mouse model of fragile X syndrome shows atypically high network synchrony in vivo[196,202,203] and in vitro[204]. Likewise, fusion organoids derived from patients with Rett syndrome show hypersynchronous network activity[205]. By contrast, however, cortical neurons in the *Cntnap2* knockout mouse model of cortical dysplasia-focal epilepsy syndrome show reduced correlation coefficients[206]. Neuropsychiatric conditions with a later age of onset, like schizophrenia, may also be associated with differences in SNA; the prefrontal cortex of a ‘dual-hit’ genetic-environmental mouse model of schizophrenia exhibits reduced network synchrony at P4-P10[42].

GLOSSARY OF TERMS

Synchronous network activity (SNA): Synchronous activity occuring during development that is mediated by chemical synapses and involves most of the neurons within a local network, manifesting either as brief (< 3 s) bursts of activity within clusters of neighboring cells or as larger events that propagate locally within a cortical region.

Early network oscillations (ENOs): Synchronous network events recorded in vitro using calcium imaging in the hippocampus and neocortex during the first postnatal week and driven by glutamatergic neurotransmission.

GABAergic calcium events (GCEs): Synchronous calcium events specifically involving GABAergic interneurons.

Giant depolarizing potentials: Spontaneous network-mediated synaptic events observed in vitro in the developing hippocampus that are driven by GABAergic neurotransmission.

Patchwork SNA: The predominant pattern of synchronous network activity (SNA) seen between E18 and P7 in the rodent neocortex. In patchwork SNA, largely non-overlapping well-circumscribed clusters or patches of neurons fire synchronously, with their firing being separated in time by long periods of quiescence.

Neuronal domains: Gap junction-mediated calcium signals that appear synchronously across small clusters of neighboring neurons in acute brain slices from neocortex; they are not mediated by action potentials, and it is unclear whether they occur in vivo.

Sparsification: Process occurring alongside desynchronization, in which the network activity transitions to a state in which relatively few neurons within the population are firing at any given time.

Wave-like SNA: The main pattern of SNA observed in rodent neocortex during the second postnatal week. Wave-like SNA involves large, partially overlapping neuronal ensembles and the activity propagates haltingly, between short periods of quiescence.

Neural oscillations: Emergent phenomena of brain circuits that reflect the rhythmic or repetitive firing patterns of groups of neurons. Oscillations can occur spontaneously or in response to sensory stimuli, and often reflect the interaction between excitation and inhibition.

Spindle bursts: A specific pattern of spontaneous neural activity observed in the immature cortex using electrophysiology that is characterized by a fast oscillatory component (approximately 4-20 Hz) occurring on top of a slower delta wave. Spindle bursts are brief (<2 s) and reflect the synchronous firing of many neurons.

Up state: A stable depolarized state of the resting membrane potential (V_m) during which action potentials may occur. They are brief (< 2 s) and separated by periods when the V_m is more hyperpolarized (Down state) and action potentials are unlikely to occur. Transitions between Up and Down states are seen during sleep or quiet wakefulness.

Gap junctions: Structures consisting of heterameric connexin channels in the plasma membrane that form direct conduits between adjacent cells and allow the rapid exchange of small molecules between neighboring neurons during; they are responsible for the dye coupling phenomenon observed in whole cell patch-clamp recordings in acute brain slices.

Highlighted references

Adelsberger, H., Garaschuk, O., and Konnerth, A. (2005). Cortical calcium waves in resting newborn mice. Nat Neurosci 8, 988-990

- First in vivo recordings of spontaneous calcium waves (synchronous network events) using two-photon imaging through an optical fiber.

Anton-Bolaños, N., Sempere-Ferrandez, A., Guillamon-Vivancos, T., Martini, F.J., Perez-Saiz, L., Gezelius, H., Filipchuk, A., Valdeolmillos, M., and Lopez-Bendito, G. (2019). Prenatal activity from thalamic neurons governs the emergence of functional cortical maps in mice. Science 364, 987-990.

- Demonstration of patches of activity in S1 corresponding to thalamocortical events

Ben-Ari, Y., Cherubini, E., Corradetti, R., and Gaiarsa, J.L. (1989). Giant synaptic potentials in immature rat CA3 hippocampal neurones. J Physiol 416, 303-325.

- First in vitro evidence for the depolarizing action of GABA in newborn rats

Chini, M., Pfeffer, T., and Hanganu-Opatz, I. (2022). An increase of inhibition drives the developmental decorrelation of neural activity. Elife 11:e78811

- A computational model makes predictions about the role of GABAergic inhibition in driving desynchronization and optogenetic experiments provide evidence supporting those predictions.

Colonnese, M.T., Kaminska, A., Minlebaev, M., Milh, M., Bloem, B., Lescure, S., Moriette, G., Chiron, C., Ben-Ari, Y., and Khazipov, R. (2010). A conserved switch in sensory processing prepares developing neocortex for vision. Neuron 67, 480-498.

- In vivo spindle bursts are conserved in the preterm human and desynchronization occurs in both rats and humans (around birth in human)

Duan, Z.R.S., Che, A., Chu, P., Modol, L., Bollmann, Y., Babij, R., Fetcho, R.N., Otsuka, T., Fuccillo, M.V., Liston, C.*, et al.* (2020). GABAergic Restriction of Network Dynamics Regulates Interneuron Survival in the Developing Cortex. Neuron 105, 75-92 e75.

- Co-occurrence of in vivo calcium SNA observed in immature interneurons and pyramidal neurons

Golshani, P., Gonçalves, J.T., Khoshkhoo, S., Mostany, R., Smirnakis, S., and Portera-Cailliau, C. (2009). Internally mediated developmental desynchronization of neocortical network activity. J Neurosci 29, 10890-10899.

- First in vivo evidence of abrupt desynchronization in S1 in the second postnatal week provided using two-photon calcium imaging. Evidence for the persistence of SNA after whisker deprivation also shown, suggesting the intrinsic ability of cortical neurons to generate SNA independent of sensory inputs.

Gonçalves, J.T., Anstey, J.E., Golshani, P., and Portera-Cailliau, C. (2013). Circuit level defects in the developing neocortex of Fragile X mice. Nature neuroscience 16, 903-909.

- First in vivo demonstration of cortical network hypersynchrony and delayed desynchronization in a mouse model of fragile X syndrome.

Khazipov, R., Sirota, A., Leinekugel, X., Holmes, G.L., Ben-Ari, Y., and Buzsaki, G. (2004). Early motor activity drives spindle bursts in the developing somatosensory cortex. Nature 432, 758-761

- First in vivo evidence of spindle bursts mediated by myoclonic twitches using electrophysiological recordings with silicon probes.

Kourdougli, N., Suresh, A., Liu, B., Juarez, P., Lin, A., Chung, D.T., Graven Sams, A., Gandal, M.J., Martinez-Cerdeño, V., Buonomano, D.V.*, et al.* (2023). Improvement of sensory deficits in fragile X mice by increasing cortical interneuron activity after the critical period. Neuron, 111(18):2863-2880

- Shows that interneurons and pyramidal neurons co-participate in SNA during development, as well as the first all-optical in vivo evidence that activation of putative PV interneurons mediates network desynchronization during development.

Modol, L., Bollmann, Y., Tressard, T., Baude, A., Che, A., Duan, Z.R.S., Babij, R., De Marco Garcia, N.V., and Cossart, R. (2020). Assemblies of Perisomatic GABAergic Neurons in the Developing Barrel Cortex. Neuron 105, 93-105 e104.

- Coined the term GABAergic calcium events (GCE) to describe the co-occurrence of synhronous events in interneurons and excitatory neurons.

Munz, M., Bharioke, A., Kosche, G., Moreno-Juan, V., Brignall, A., Rodrigues, T.M., Graff-Meyer, A., Ulmer, T., Haeuselmann, S., Pavlinic, D.*, et al.* (2023). Pyramidal neurons form active, transient, multilayered circuits perturbed by autism-associated mutations at the inception of neocortex. Cell, 186(9):1930-1949

- First para-uterine in vivo two-photon calcium imaging recordings of cortical neurons at early embronic stages (E13.5-E18.5) in mice.

Murata, Y., and Colonnese, M.T. (2020). GABAergic interneurons excite neonatal hippocampus in vivo. Sci Adv 6, eaba1430.

- Using in vivo electrophysiological recordings coupled with optogenetics, the first in vivo confirmation of the excitatory actions of GABA in developing mice.

Picardo, M.A., Guigue, P., Bonifazi, P., Batista-Brito, R., Allene, C., Ribas, A., Fishell, G., Baude, A., and Cossart, R. (2011). Pioneer GABA cells comprise a subpopulation of hub neurons in the developing hippocampus. Neuron 71, 695-709.

- A description of early born GABAergic hub cells, which are SST-interneurons that are highly connected to pyramidal neurons and are throught to play a crucial role in developmental synchrony.

Nakazawa, S., Yoshimura, Y., Takagi, M., Mizuno, H., and Iwasato, T. (2020). Developmental Phase Transitions in Spatial Organization of Spontaneous Activity in Postnatal Barrel Cortex Layer 4. J Neurosci 40, 7637-7650.

- Shows developmental transitions in spontaneous activity of layer 4 neurons of the barrel cortex: first from patchwork SNA to wave-like SNA and then to desynchronized activity, as well as the dependence of only patchwork SNA on thalamic activity.

Rivera, C., Voipio, J., Payne, J.A., Ruusuvuori, E., Lahtinen, H., Lamsa, K., Pirvola, U., Saarma, M., and Kaila, K. (1999). The K+/Cl- co-transporter KCC2 renders GABA hyperpolarizing during neuronal maturation. Nature 397, 251-255

- Evidence that the GABA polarity shift depends on the developmental expression of the K-Cl co-transporter KCC2 in the developing hippocampus.

Rochefort, N.L., Garaschuk, O., Milos, R.I., Narushima, M., Marandi, N., Pichler, B., Kovalchuk, Y., and Konnerth, A. (2009). Sparsification of neuronal activity in the visual cortex at eye-opening. Proc Natl Acad Sci U S A 106, 15049-15054.

- First evidence for sparsification of neuronal activty during the 2nd postanatal week in V1 using in vivo two-photon calcium imaging.

Yuste, R., Peinado, A., and Katz, L.C. (1992). Neuronal domains in developing neocortex. Science 257, 665-669

- First report of synchronous network events in acute slices of the developing neocortex at P0-P7 (neuronal domains), which were insensitive to TTX and therefore independent of synaptic activity.

Box 1

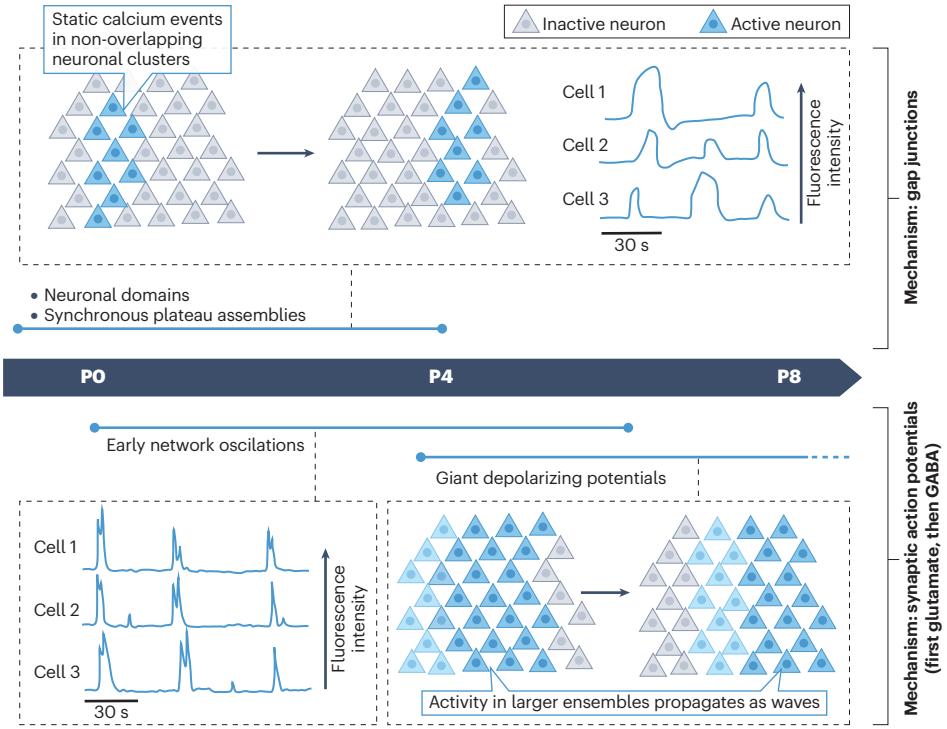

Static calcium events in non-overlapping neuronal clusters
Inactive neuron
Active neuron
Cell 1
Cell 2
Cell 3
Fluorescence intensity
30 s
Mechanism: gap junctions
• Neuronal domains
• Synchronous plateau assemblies
P0
P4
P8
Early network oscilations
Giant depolarizing potentials
Cell 1
Cell 2
Cell 3
Fluorescence intensity
30 s
Activity in larger ensembles propagates as waves
Mechanism: synaptic action potentials (first glutamate, then GABA)

Fig 1

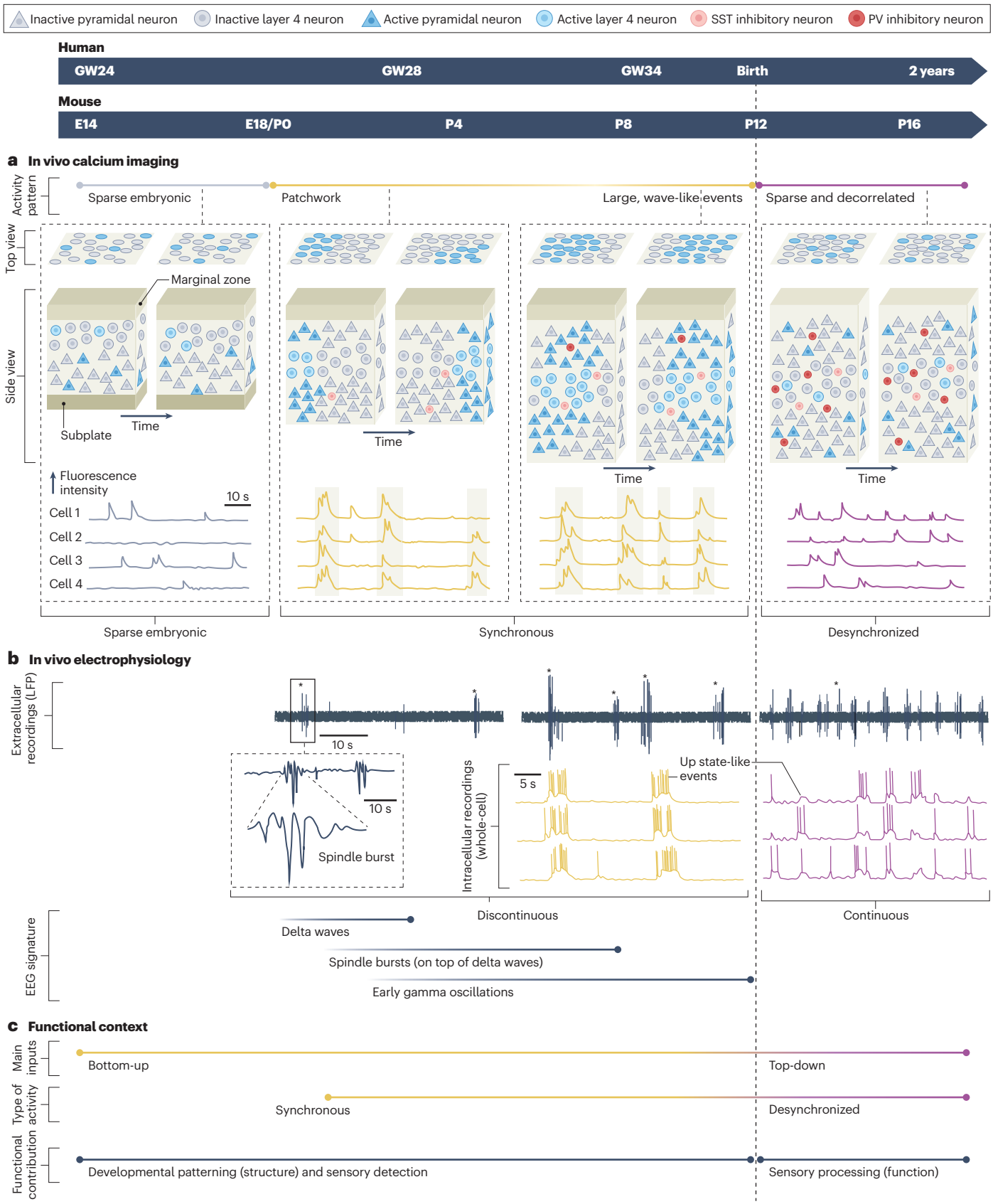

Inactive pyramidal neuron
Inactive layer 4 neuron
Active pyramidal neuron
Active layer 4 neuron
SST inhibitory neuron
PV inhibitory neuron
Human
GW24
GW28
GW34
Birth
2 years
Mouse
E14
E18/P0
P4
P8
P12
P16
a In vivo calcium imaging
Activity pattern
Sparse embryonic
Patchwork
Large, wave-like events
Sparse and decorrelated
Top view
Side view
Marginal zone
Subplate
Time
Fluorescence intensity
10 s
Cell 1
Cell 2
Cell 3
Cell 4
Sparse embryonic
Synchronous
Desynchronized
b In vivo electrophysiology
Extracellular recordings (LFP)
10 s
Spindle burst
Intracellular recordings (whole-cell)
5 s
Up state-like events
Discontinuous
Continuous
EEG signature
Delta waves
Spindle bursts (on top of delta waves)
Early gamma oscillations
c Functional context
Main inputs
Bottom-up
Top-down
Type of activity
Synchronous
Desynchronized
Functional contribution
Developmental patterning (structure) and sensory detection
Sensory processing (function)

Fig 2

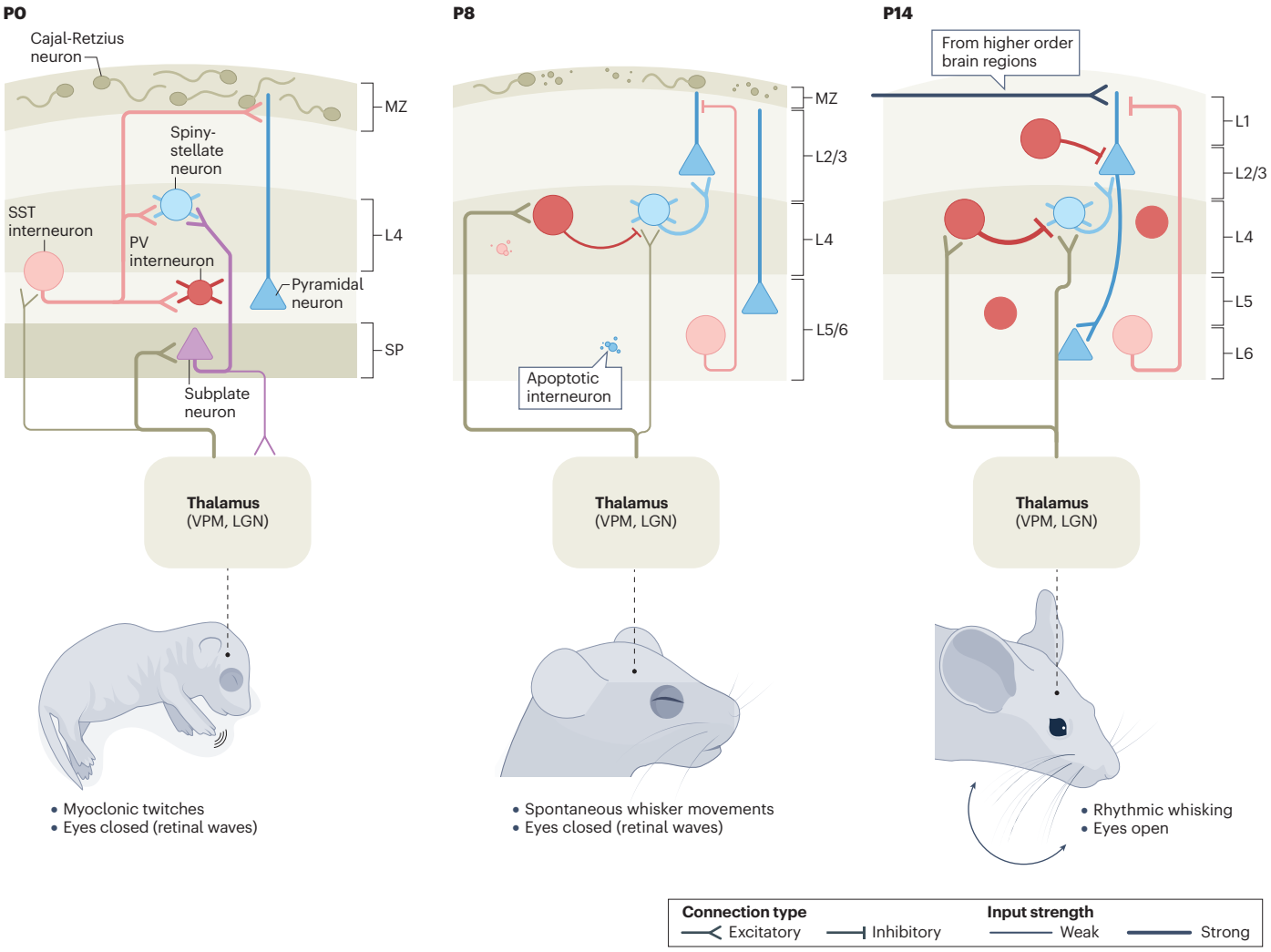
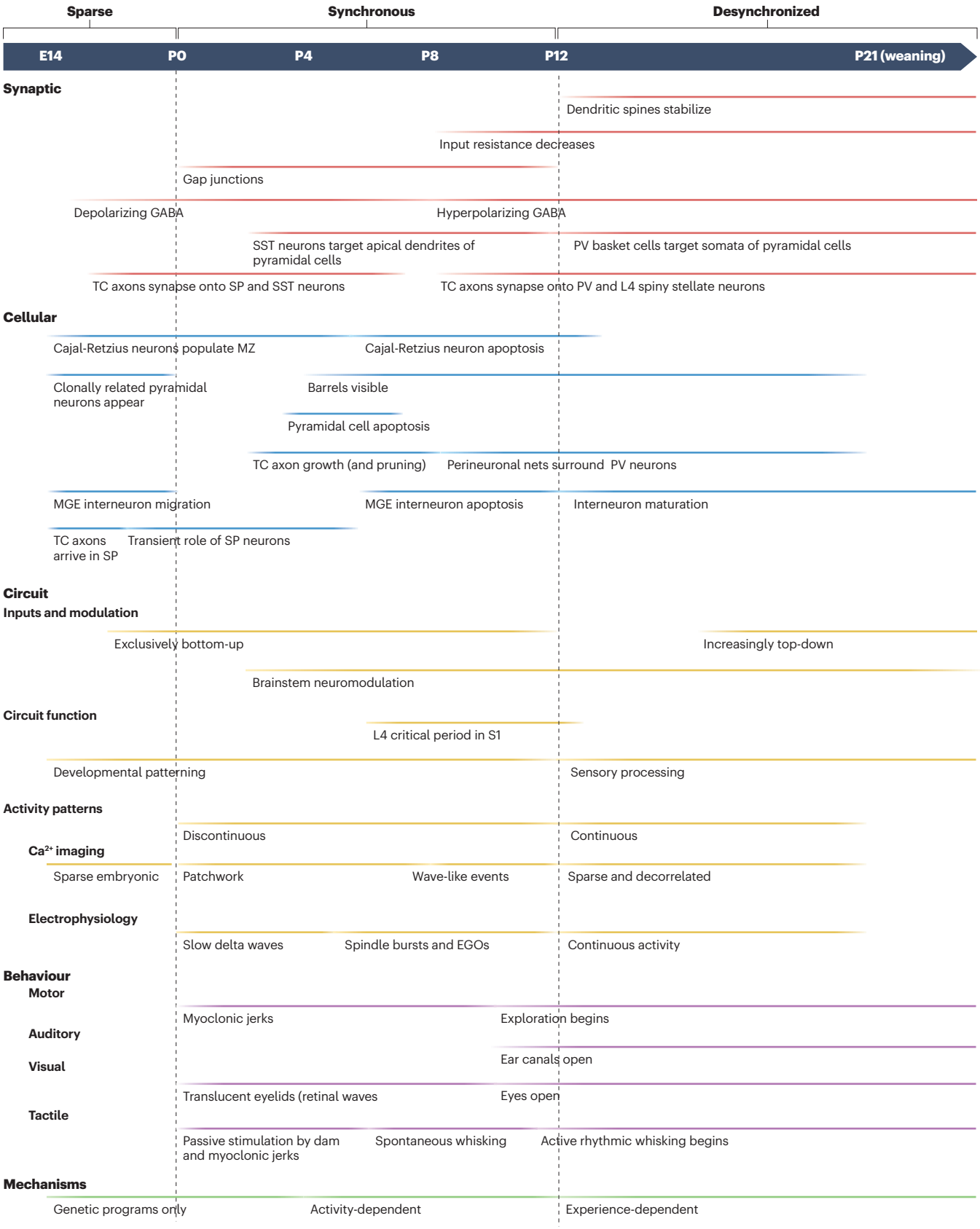

P0
Cajal-Retzius neuron
MZ
Spiny-stellate neuron
SST interneuron
PV interneuron
L4
Pyramidal neuron
SP
Subplate neuron
Thalamus (VPM, LGN)
• Myoclonic twitches
• Eyes closed (retinal waves)
P8
MZ
L2/3
L4
L5/6
Apoptotic interneuron
Thalamus (VPM, LGN)
• Spontaneous whisker movements
• Eyes closed (retinal waves)
P14
From higher order brain regions
L1
L2/3
L4
L5
L6
Thalamus (VPM, LGN)
• Rhythmic whisking
• Eyes open
Connection type
Excitatory
Inhibitory
Input strength
Weak
Strong

Fig 3


Sparse
Synchronous
Desynchronized
E14
P0
P4
P8
P12
P21 (weaning)
Synaptic
Dendritic spines stabilize
Input resistance decreases
Gap junctions
Depolarizing GABA
Hyperpolarizing GABA
SST neurons target apical dendrites of pyramidal cells
PV basket cells target somata of pyramidal cells
TC axons synapse onto SP and SST neurons
TC axons synapse onto PV and L4 spiny stellate neurons
Cellular
Cajal-Retzius neurons populate MZ
Cajal-Retzius neuron apoptosis
Clonally related pyramidal neurons appear
Barrels visible
Pyramidal cell apoptosis
TC axon growth (and pruning)
Perineuronal nets surround PV neurons
MGE interneuron migration
MGE interneuron apoptosis
Interneuron maturation
TC axons arrive in SP
Transient role of SP neurons
Circuit
Inputs and modulation
Exclusively bottom-up
Increasingly top-down
Brainstem neuromodulation
Circuit function
L4 critical period in S1
Developmental patterning
Sensory processing
Activity patterns
Discontinuous
Continuous
Ca2+ imaging
Sparse embryonic
Patchwork
Wave-like events
Sparse and decorrelated
Electrophysiology
Slow delta waves
Spindle bursts and EGOs
Continuous activity
Behaviour
Motor
Myoclonic jerks
Exploration begins
Auditory
Ear canals open
Visual
Translucent eyelids (retinal waves
Eyes open
Tactile
Passive stimulation by dam and myoclonic jerks
Spontaneous whisking
Active rhythmic whisking begins
Mechanisms
Genetic programs only
Activity-dependent
Experience-dependent