Published in final edited form as:

Brain Res. 2019 March 01; 1706: 13–23. doi:10.1016/j.brainres.2018.10.024.

Thalamic inhibitory circuits and network activity development

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Abstract

Inhibitory circuits in thalamus and cortex shape the major activity patterns observed by electroencephalogram (EEG) in the adult brain. Their delayed maturation and circuit integration, relative to excitatory neurons, suggest inhibitory neuronal development could be responsible for the onset of mature thalamocortical activity. Indeed, the immature brain lacks many inhibition-dependent activity patterns, such as slow-waves, delta oscillations and sleep-spindles, and instead expresses other unique oscillatory activities in multiple species including humans. Thalamus contributes significantly to the generation of these early oscillations. Compared to the abundance of studies on the development of inhibition in cortex, however, the maturation of thalamic inhibition is poorly understood. Here we review developmental changes in the neuronal and circuit properties of the thalamic relay and its interconnected inhibitory thalamic reticular nucleus (TRN) both *in vitro* and *in vivo*, and discuss their potential contribution to early network activity and its maturation. While much is unknown, we argue that weak inhibitory function in the developing thalamus allows for amplification of thalamocortical activity that supports the generation of early oscillations. The available evidence suggests that the developmental acquisition of critical thalamic oscillations such as slow-waves and sleep-spindles is driven by maturation of the TRN. Further studies to elucidate thalamic GABAergic circuit formation in relation to thalamocortical network function would help us better understand normal as well as pathological brain development.

Keywords

Thalamic reticular nucleus; EEG development; spindle-bursts; delta-brush; slow wave; sleep-spindle

1. Introduction

a. TRN and thalamocortical circuits

Most of the major activity patterns observed in the adult EEG result from a complex interaction between thalamic relay nuclei, the inhibitory thalamic reticular nucleus (TRN),

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and cortex (Crunelli et al., 2018; Steriade, 2005). The combined presence of low-voltage-activated T-type calcium channels and hyperpolarization-activated sodium currents (I_h) provides adult TRN and thalamic relay neurons with bursting and intrinsic pacemaker properties. The unique properties of thalamic neurons incorporated in a nested loop with connected cortex to form an integrated ‘thalamocortex’ facilitate the generation of sleep-spindles and slow-waves during quiet sleep as well as alpha waves during dissociated awake states (Barthó et al., 2014; Crunelli et al., 2015; David et al., 2013; Fuentealba and Steriade, 2005; Halassa et al., 2011; Lewis et al., 2015; Vijayan and Kopell, 2012). The regulation of these adult thalamic circuit properties by neuromodulatory and cortical inputs contributes to cortical arousal state control through global sleep/wake cycles as well as by selective attention (Crick, 1984; Halassa et al., 2014; McCormick et al., 2015; Wells et al., 2016). Corruption of these properties is the mechanistic basis of absence seizures (Fogerson and Huguenard, 2016).

We focus here on the TRN, a thin structure surrounding the dorsal thalamus composed almost exclusively of inhibitory neurons (Houser et al., 1980). TRN provides the totality of thalamic inhibition to most thalamic relay nuclei (excluding dLGN) in rodents (Arcelli et al., 1997; Fogerson and Huguenard, 2016). TRN receives collaterals from both corticothalamic and thalamocortical axons, acting as an inhibitory hub between cortex and thalamus (Pinault, 2004). TRN is not a diffuse circuit but rather organized into modality-specific sectors. Vision occupies the dorsal sector, sensorimotor is in the medial, and auditory is in the medial and ventral part of TRN (Guillery and Harting, 2003; Pinault, 2004). Each sector of TRN is differentially innervated by axon collaterals of primary and secondary cortex, and by first- and higher- order thalamus, suggesting the presence of anatomical, and possibly functional, subdivisions within TRN sectors (Coleman and Mitrofanis, 1996; Deschênes et al., 1998; Wimmer et al., 2010). Functional subdivision by neuron type, as identified by the markers parvalbumin (PV) and somatostatin (SOM), has recently become apparent (Ahrens et al., 2015; Clemente-Perez et al., 2017; Csillik et al., 2005; Hou et al., 2016).

The centrality of the TRN-relay neuron complex to adult thalamocortical activity generation leads logically to the conclusion that its maturation must be a critical timer of the emergence of thalamocortical function during development. Here we review the development of thalamic inhibition with a focus on its relationship to the generation of immature activity and the emergence of mature activity patterns. This review gives a précis of cortical activity development, summarizes existing knowledge on the maturation of thalamic inhibitory circuits, and discusses the few results testing the role of thalamic inhibition in developing thalamocortical activity *in vivo* (Figures 1, 2). We argue the following two points: (1) the absence of strong and reliable thalamic inhibition during early development contributes to a functional configuration of thalamocortical circuits that is substantially different than mature circuits; and (2) the integration and establishment of inhibition within thalamus drives the development of mature cortical activity patterns, particularly sleep-spindles.

b. Development of activity in thalamocortex *in vivo*

The reader is directed to several recent reviews that describe the development of thalamocortical activity in multiple brain regions (Cirelli and Tononi, 2015; Clawson et al.,

2016; Colonnese and Phillips, 2018; Khazipov et al., 2013a; Luhmann and Khazipov, 2018; Yang et al., 2016), as only a sketch of activity development can be attempted here. Unless otherwise specified, discussion of cellular and circuit neurophysiology refers to rodent data, where most of the recent work involving thalamus has been conducted. Human EEG development is discussed alongside this work to highlight potential clinically relevant development of brain activity.

Thalamocortical activity can be roughly divided into three stages (Colonnese and Phillips 2018): [1] The embryonic period, [2] the immature (pre-sensory) activity period, and [3] the mature (sensory) activity period. The stages are defined by large scale transitions in activity, though fine scale maturation occurs within each.

[1] Embryonic period. During the prenatal period in rodents, when thalamocortical axons are entering subplate and thalamic and cortical regions are forming (López-Bendito and Molnár, 2003), spontaneous thalamic calcium waves propagated through gap-junctions in relay neurons set up initial regional identity within thalamus and cortex (Moreno-Juan et al., 2017).

[2] Immature activity period. Beginning near birth when thalamic axons begin to enter the just forming cortical layers, bursts of thalamic firing, generated in response to input from the sense organ (for thalamic relay nuclei) or hippocampus (for midline thalamic nuclei), drive topographically restricted activity in cortex (Khazipov et al., 2013b; Lindemann et al., 2016). None of the major activity patterns observed in the adult EEG (slow-waves, sleep-spindles, hippocampal theta, cortical layer2/3 gamma) are present during this period, despite robust synaptic activity in cortex and thalamus. Cortical activity is poorly modulated by sleep and waking states (Jouvet-Mounier et al., 1970; Seelke and Blumberg, 2008; Vanhatalo and Kaila, 2006). Activity is largely restricted to the thalamic bursts, which have a unique oscillatory structure that depends on the size and nature of the input. The most prominent and universal of these oscillations are “spindle-bursts”, which synchronize firing within all layers of cortex (including subplate) in 8–20Hz oscillations. Spindle-bursts have been observed in visual (Colonnese and Khazipov, 2010; Colonnese et al., 2010; Hanganu et al., 2006; Kirmse et al., 2015; Kummer et al., 2016), somatosensory (Khazipov et al., 2004; Minlebaev et al., 2007; Yang et al., 2009), motor (An et al., 2014), and prefrontal/prelimbic cortex (Bitzenhofer et al., 2015; Brockmann et al., 2011). They occur in response to spontaneous (as well as evoked) activity in the relevant sense organ (or hippocampus for pre-frontal cortex), but can also persist at a reduced rate in its absence, suggesting they are an intrinsic thalamocortical oscillation triggered by the input. Another early thalamocortical oscillation, the ‘early gamma oscillation’ or EGO, is similar to spindle-bursts but faster (30–60Hz), largely restricted to the input and superficial layers, and occurs only in response to input that is very topographically restricted (e.g. single whisker or toe) or only during the initial sensory response (before lateral connections allow interactions between cortical columns) (Khazipov et al., 2013b). Both patterns are generated in thalamus, and their appearance in cortex largely reflects this input, with little contribution from intracortical amplification (Luhmann and Khazipov, 2018; Valiullina et al., 2016).

[3] Mature activity period. After the emergence of all cortical layers and the establishment of topography, and a couple days before the onset of active sensation (eg., whisking in barrel cortex, eyeopening in visual), the long-lasting silent periods and immature oscillations characteristic of the immature period disappear. They are replaced by spontaneous and evoked activity that is qualitatively similar to the adult in many respects (Colonnese and Phillips, 2018). This transition from immature to mature activity occurs simultaneously in thalamus and cortex (Murata and Colonnese, 2018). In particular, bistability in the thalamocortical network emerges, allowing for the generation of up-down state transitions during sleep and stable depolarization during waking (Colonnese 2014), which in turn causes switching between desynchronized and synchronized states by arousal (Hoy and Niell, 2015) and the emergence of sleep/wake EEG patterns (Blumberg et al., 2014; Frank and Heller, 1997; Frank et al., 2017; Gramsbergen, 1976; Jouvett-Mounier et al., 1970). These cortical activities, fundamentally based on the corticocortical and thalamocortical interactions generating the desynchronized state, undergo further stabilization, and new activity patterns, such as layer 2/3 gamma and sleep-spindles, are added during the next 2–3 weeks (Chen et al., 2015; Shen and Colonnese, 2016).

Evidence for an immature period with a rapid switch to the mature period has been identified in every mammalian species examined (Jouvett-Mounier et al., 1970). Most clinically relevant, human infants appear to transition between the immature and mature stages around or just prior to term. An oscillatory pattern resembling spindle-bursts in its appearance and capacity to be evoked by sensory input, called the delta-brush, has been identified in the EEG of preterm human infants during the third trimester (with the highest occurrence and amplitude around 28–34 weeks of gestation) (André et al., 2010; Whitehead et al., 2017). Human infants undergo a change in their sensory evoked responses in auditory, somatosensory and visual regions around 36 weeks of gestation consistent with a shift from immature to mature activity at this time (Chipaux et al., 2013; Colonnese et al., 2010; Fabrizi et al., 2011). Temporally this coincides with the initial emergence of strong modulation of the EEG by sleep-wake states. The development of truly adult cortical activity patterns continues through the next 2–3 months after birth, when sleep-spindles and continuous slow-waves emerge (Dereymaeker et al., 2017; Scher, 2008).

A comprehensive mechanistic understanding of cortical activity development should include at least the following: 1) the transitions between developmental stages, 2) the generative mechanisms of early oscillations, and 3) the emergence and maturation of adult oscillations. For this review, we ask what changes in thalamic inhibitory circuitry are occurring that might underlie these. In the following three sections, we first review the developmental timeline of inhibition in thalamus as assayed anatomically and functionally *ex vivo*, then review the few functional studies of thalamic inhibition *in vivo*.

2. Embryonic development of thalamocortical and thalamic inhibitory circuits

In rodents, the majority of TRN neurons are generated in the prethalamus at E13–15 (Altman and Bayer, 1988; Martinez-Ferre and Martinez, 2012). DiI-labeled TRN axons are

observed in dorsal relay nuclei at E14, thalamocortical axons are observed in TRN at E15, and cortical axons in TRN at E16 in rats (Mitrofanis and Baker, 1993). Thus, initial axonal projections to and from TRN develop embryonically. Corticothalamic axons pause in perireticular nucleus, an area lateral to TRN, or in TRN for one or two days before passing through it and reaching the border of the thalamic relay nuclei (Mitrofanis and Guillery, 1993). Thus, pre-reticular nucleus and TRN are the sites of convergence of thalamocortical and corticothalamic axons in early development and potentially act as an anatomical hub for establishing reciprocal connections between cortex and thalamus (Grant et al., 2012).

During this time of initial axon ingrowth, spontaneous calcium waves cross multiple thalamic regions (Moreno-Juan et al., 2017). In slices from E14.5 up to P2, this activity emerges in the primary sensory thalamic nuclei, mostly in VPM (ventral posterior medial nucleus, somatosensory) but also in dLGN (dorsal lateral geniculate nucleus, visual) and MGv (ventro medial geniculate nucleus, auditory); and spreads within and across nuclei including the higher-order thalamic relay nuclei. These calcium waves are impaired by the general gap junction blocker Carbenoxolone as well as the voltage-dependent sodium channel blocker TTX, suggesting that electrical synapses and membrane depolarization are involved in the initiation and/or propagation of early thalamic activity. Blockade of waves within a specific thalamic relay nucleus reduced the relative size of the associated cortex, suggesting an important role for thalamic waves in regulating connectivity and arealization in thalamocortical circuits. TRN was not examined; thus, it remains an open question whether the waves propagate to TRN and, if so, how they regulate inhibitory circuit formation in the developing thalamus. Investigation of perinatal thalamic waves *in vivo* and their electrophysiological properties would be interesting for future study.

3. Early postnatal development of thalamic inhibitory circuits and their relation to immature oscillations

a. Intra-TRN circuitry

One of the unique physiological features of TRN circuits is their extensive gap junction coupling throughout the lifespan (Landisman et al., 2002; Niculescu and Lohmann, 2014). In adults, TRN neurons with the same axonal targets are preferentially coupled, thus forming local anatomical and functional clusters (Coulon and Landisman, 2017; Lee et al., 2014). The probability of electrical coupling among TRN neurons is 60–80% at birth and does not change significantly with age. However, gap-junction conductance at birth is relatively low, increasing by 6–10 fold in the second postnatal week (Parker et al., 2009). This increase likely offsets the developmental reduction in membrane resistance, thus maintaining a relatively stable effectiveness of electrical coupling during development. Membrane resistance and electrical synapse development are causally linked. Knockout of connexin 36, which reduces the effectiveness of electrical coupling by 85%, also delayed the developmental drop in membrane resistance without affecting cell morphology (Zolnik and Connors, 2016). This pattern of increasing functional electrical connectivity in TRN is opposite to that found in relay neurons. For example, electrical coupling probability in VBN (ventrobasal nucleus, nociception) is around 30% in the first postnatal weeks but drops after P5 in mice and at P9 in rats; and completely disappears in the late second postnatal week in

both species (Lee et al., 2010). This roughly coincides with the developmental disappearance of early calcium waves in thalamic relay nuclei which depends, at least partially, on electrical synapses (Moreno-Juan et al., 2017). However, there have not, to our knowledge, been any comparative tests of the network roles for gap-junctions in TRN throughout development. During a limited time period (P12–15) electrical coupling of TRN neurons is critical for the generation of synchronous activity around 10Hz (5–15Hz) in rat slices. This rhythmic activity can be induced by internal capsule stimulation or by membrane depolarization of TRN neurons by the metabotropic glutamate receptor agonist ACPD. This activity persists even when ionotropic glutamate receptors or GABA_A receptors are blocked, suggesting its independence from fast chemical synaptic transmission (Long et al., 2004). It remains unknown if this activity is present before P11.

While electrical connectivity increases over development, synaptic connections within TRN may actually decrease. TRN neurons express GABA receptors from early in development (Bentivoglio et al., 1991; Pangratz-Fuehrer et al., 2016). The presynaptic sources of GABA in TRN include extrathalamic inputs such as long-range inhibitory projections from the globus pallidus in basal ganglia (Asanuma, 1989; Clemente-Perez et al., 2017; Gasca-Martinez et al., 2010), although their detailed developmental timelines remain to be fully characterized. Intra-TRN GABAergic synapses are prevalent during the first two postnatal week and less likely to be observed thereafter (Deleuze and Huguenard, 2006; Lam et al., 2006; Landisman et al., 2002; Parker et al., 2009; Sun et al., 2011). Importantly, a recent study using optogenetics and transgenic mice shows that parvalbumin (PV)-positive TRN neurons form intra-TRN GABAergic synapses until P14, but not after (Hou et al., 2016). In fact, conditional elimination of GABA transporters from PV-positive neurons (using PV-Vgat^{-/-} mice) fails to reduce miniature IPSCs in TRN neurons at P15–P18, suggesting that GABA can be provided by PV-‘negative’ TRN neurons and/or extrathalamic GABAergic projections. In either case, it suggests that synaptic coupling between TRN neurons decreases in counterpoint to strengthening of electrical coupling. Future studies determining the presynaptic source of GABA in TRN especially in adults, as well as the functional significance of GABAergic synapses in TRN across development, will be very informative.

A potential role for early GABAergic synapses in TRN is in the generation of spontaneous activity. During the first postnatal weeks, slices of TRN exhibit thalamic giant depolarizing potentials (tGDP) (Pangratz-Fuehrer et al., 2007). GDPs have been described in slices of multiple developing brain regions; their defining feature is a large scale activation of local synaptic activity dependent on excitatory GABA (Allène et al., 2008; Ben-Ari et al., 1989). The incidence of tGDPs peaks around P7 but their amplitude and duration sharply decrease after P4. Antagonists of AMPA and NMDA glutamate receptors reduce tGDP amplitudes by about 30%, while GABA_A receptors antagonists nearly eliminate tGDPs, suggesting that excitatory GABAergic action is a driver of tGDPs in the developing TRN *in vitro* (see section 3c for excitatory GABA *in vitro* and *in vivo*).

It is still unclear how internally generated spontaneous tGDPs in one week old slices, and input- and gapjunction-dependent synchronization in two week old slices are related to each other; and how these activities interact with afferent inputs to generate activity *in vivo*. However, the presence of tGDPs in TRN suggests that the circuit structure possesses the

capacity to spontaneously generate rhythmic activity during early development, and that this changes in counterpoint to the development of adult circuitries including mature gap-junctions and reciprocal connectivity with thalamic relay nuclei (see below). If the downregulation of synaptic connectivity and increase in electrical connections between TRN neurons is true *in vivo*, it suggests the following developmental periods for intra-TRN connections: (1) a perinatal (and possibly fetal) period of weak electrical, but strong synaptic, intercoupling contemporaneous with the period of early thalamocortical oscillations; (2) strengthening of TRN electrical coupling but weakening of synaptic coupling as early oscillations disappear and the slow-waves and sleep-spindles emerge.

b. Neuromodulatory systems in TRN

In adults, neuromodulatory systems play central roles in state modulation (Lee and Dan, 2012). A wide range of neuromodulatory systems, including acetylcholine, noradrenaline, serotonin, and dopamine, send axonal projections to TRN and thalamus and control their activity pattern (McCormick, 1989; Pinault, 2004; Rodríguez et al., 2011; Vertes et al., 2015). Acetylcholine may be the most characterized for its function in TRN *in vivo*. TRN receives strong cholinergic innervations from both basal forebrain and brainstem, whereas the relay and other thalamic nuclei receive innervation mostly from brainstem (Hallanger et al., 1987). Optogenetic stimulation of cholinergic projections to TRN in slices evokes biphasic responses, an initial excitation driven by nicotinic receptors with subsequent inhibition by muscarinic receptors (Sun et al., 2013). It can also induce synchronous activity that resembles spindle oscillations between TRN and VBN (Pita-Almenar et al., 2014). *In vivo*, optogenetic stimulation of cholinergic axons in TRN induces excitatory currents via nicotinic receptors, generates sleep spindles and promotes non-REM (rapid eye movement) sleep in adult ChAT-ChR2 mice (Ni et al., 2016), demonstrating a strong influence of cholinergic afferents in modulating TRN capability to generate oscillations in a stimulation-dependent and state-dependent manner (Halassa et al., 2011; Lewis et al., 2015).

The development of cholinergic projections to TRN were recently measured anatomically and physiologically by expressing channelrhodopsin in the terminals of all cholinergic neurons (i.e. both basal forebrain and brainstem) (Sokhadze et al., 2018). Cholinergic fibers gradually innervate the non-visual (somatosensory and auditory) sector of TRN during the first two postnatal weeks and reach the adult level around P14, whereas cholinergic innervation of the visual sector of TRN is delayed for almost a week and is complete by P21. Optogenetic stimulation of cholinergic projections confirms that functional connectivity develops in a similar manner. It is clear that further developmental and functional studies of other neuromodulatory inputs to TRN will be important to determine their role in maturation of thalamocortical activity.

c. Connectivity between TRN and thalamic relay neurons

In adults, the role of thalamic inhibition in the generation of cortical rhythms, particularly sleep-spindles and delta-waves, comes largely from the recurrent connectivity of TRN with relay nuclei (Crunelli et al., 2018; Fogerson and Huguenard, 2016). Thus, understanding the development of this connectivity is important to determine its contribution to the emergence of these mature oscillations and if it is sufficiently functional to be involved in the generation

of spindle-bursts and EGOs. While reciprocal synaptic connections between TRN and VPM are detectable at birth in the somatosensory pathways of the rat (Evrard and Ropert, 2009), these connections are very immature, with lower conductance and higher failure rate at both the TRN to VPM synapse and vice-versa, until P5. At P6–9, the conductance increases by 3–5 fold and the failure rate decreases from 10–30% to almost 0% in both nuclei. The dendritic branching pattern of TRN and VPN (ventral posterior nucleus) neurons grows between P3 and P7 when reciprocal connections become strong and also between P10 and P14 when multi-spike bursting appears (Warren and Jones, 1997). In the nociceptive system, di-synaptic inhibitory transmission (VBN to TRN to VBN) triggered by electrical stimulation in VBN is absent until P5. It first appears on P6, and the probability of di-synaptic inhibitory connectivity improves from around 5% at P6 to 11% at P10–P14 (Lee et al., 2010), coinciding with the morphological development of GABAergic synaptic terminals in VBN (De Biasi et al., 1997). In the visual system, developmental changes in physiological connections between TRN and dLGN have not been fully documented in rodents, possibly due to technical difficulties obtaining slices containing both structures and the presence of local interneurons in rodent dLGN.

In addition to synaptic strength, the development of GABAergic transmission is affected by chloride reversal potential, which determines whether GABA_A receptors act in an inhibitory or excitatory fashion (Ben-Ari et al., 2012). In many brain regions, intracellular chloride concentration [Cl⁻] is higher during early development, leading to excitatory, or less inhibitory, GABAergic action. Adult function is achieved by changes in expression and function of chloride transporters NKCC1 and KCC2 (Kaila et al., 2014). In the mouse VPN, the reversal potential of GABA_A currents is around -45mV at P4 and then gradually decreases and stabilizes around -75mV after P12 (Warren and Jones, 1997). Resting membrane potential decreases only mildly from around -52mV at P4 to -60mV at P12 (Warren and Jones, 1997), thus GABA shifts from depolarizing to hyperpolarizing between the first and second postnatal weeks. Another study shows a similar developmental change in chloride reversal potential in VPM: around -55mV at P5 and -70mV at P15 (Glykys et al., 2009). Together these studies suggest that in addition to synaptic strengthening, the inhibitory drive from TRN becomes stronger in the second and third week. It is possible that, in the first few postnatal days, the chloride reversal potential is high enough that GABAergic transmission is actually excitatory in relay neurons. In general it appears that the development of inhibitory GABA occurs in thalamus before cortex, a finding also observed in the visual system (MacLeod et al., 1997).

A potential excitatory role for GABA in slices is supported by functional assays, as GABA is the driving force for giant depolarizing potentials in TRN at P4–P7 (Pangratz-Fuehrer et al., 2007). GABAergic IPSCs are observed at P11–P15 (Deleuze and Huguenard, 2006; Hou et al., 2016), suggesting that GABAergic action in TRN slices may shift from excitatory to inhibitory early in the second week. One caveat to these slice studies is that *in vivo* studies have revealed somewhat divergent and equivocal results regarding excitatory GABA and its roles in the immature brain (Ben-Ari, 2015; Bregestovski and Bernard, 2012; Khakhalin, 2011; Khazipov et al., 2015; Kirmse et al., 2015, 2017; Valeeva et al., 2016; Zilberter, 2016). Therefore, *in vivo* examination of GABA-mediated transmission, both its excitatory or

inhibitory actions, as well as interneuron circuit function, will be needed to truly understand the role of GABA in the development of network activity and brain function.

Overall, these slice results predict that during the immature period, TRN influence on relay neurons is likely to be weak both because of weak synaptic strength as well as a relatively depolarized GABA_A reversal potential. The implications for immature rhythm generation are discussed below (section 3e).

d. Local interneurons in thalamic relay nuclei

In addition to TRN, some thalamic nuclei contain local GABAergic interneurons. The distribution of local GABAergic neurons in the adult thalamus differs between species. In general, local interneurons are present more broadly in dorsal sensory thalamic nuclei in non-rodent mammals, with particularly high density in humans (Arcelli et al., 1997; Sherman, 2004). The dLGN is the only dorsal nucleus that contains local GABAergic interneurons in all mammalian species, though they constitute only 5.6% of total dLGN neurons in mouse (Benson et al., 1992; Evangelio et al., 2018). GABAergic neurons in TRN and the dorsal thalamus have different developmental origins. While TRN neurons originate in prethalamus (Altman and Bayer, 1988), local GABAergic interneurons in mouse dLGN originate outside the thalamus, in the ventral wall of the third ventricle (Golding et al., 2014) and midbrain tectum (Jager et al., 2016). These local inhibitory neurons migrate into dLGN in the first postnatal week in an activity-dependent manner. However, they do not become well integrated into the feedforward circuit until late in the second week; Optic nerve stimulation elicits a second order inhibitory potential in only about 20% of relay neurons at P7–11, increasing to 40% at P12–15 and to 80% after P16 (Bickford et al., 2010).

Local interneurons in dLGN receive direct inputs from multiple retinal ganglion neurons in early development but also in adulthood (Seabrook et al., 2013a), suggesting a lack of pruning and tuning during development. Local dLGN interneurons form both typical axonal and atypical dendritic presynaptic terminals onto relay neurons (Sherman, 2004), and make retina-driven feedforward circuits, which contribute to gain control in dLGN (Sherman, 2004; Williams et al., 1996). While it is tempting to assume that local interneurons participate in visual processing while TRN organizes thalamocortical oscillations, it appears that both structures actually play important roles in visual processing (Hirsch et al., 2015). An interesting area to explore is the roles of thalamic inhibition in developmental plasticity. A recent study showed GABAergic inhibition in dLGN is necessary for ocular dominance plasticity in both thalamus and cortex (Sommeijer et al., 2017).

e. Early oscillations and thalamic inhibition

EGOs in the whisker somatosensory system.—EGOs are thought to originate in the thalamic relay nuclei because (1) similar oscillations are observed in both VPM and barrel cortex, (2) each phase of gamma in VPM precedes cortex by 7 ms (Minlebaev et al., 2011), and (3) electrolytic lesion reduces cortical EGOs (Yang et al., 2013). Cortical EGOs are not eliminated by blockade of GABA_A receptors (Minlebaev et al., 2011). By contrast, intrathalamic blockade of GABA_A receptors at P2–4 increases the whisker-triggered LFP

response in cortex and reduces gamma oscillations within EGOs, suggesting a possible involvement of thalamic GABAergic circuits in EGOs (Minlebaev et al., 2011).

As discussed in section 3c, reciprocal connections between VPM and TRN are likely insufficient to generate such high-frequency, coordinated oscillations as observed during EGOs. Furthermore, the developmental elimination of EGOs is correlated with the development of strong synaptic interactions within thalamus. Surprisingly, this development of reciprocal connectivity between TRN and VPM occurs at the same time as the development of feedforward inhibition in somatosensory cortex (Daw et al., 2007; Minlebaev et al., 2007, 2011). Thus, the disappearance of EGOs around the end of the first postnatal week coincides with maturation of inhibitory circuits in both somatosensory thalamus and cortex. This suggests that the role of inhibition during EGOs is not to generate gamma oscillations, but rather to provide general inhibition, the absence of which leads to over-excitation in thalamus and loss of fast oscillations.

Spindle-bursts in the somatosensory and visual systems.—Spindle-bursts in both systems occur simultaneously in sensory thalamic nuclei and cortex, and thalamic silencing eliminates this (and almost all) cortical activity, suggesting a thalamic origin of spindle-bursts (Murata and Colonnese, 2016; Yang et al., 2013). Like EGOs, corticothalamic connections are not necessary for the generation of spindle-burst oscillations in thalamus at P0–1 in VPM or P5–7 in dLGN, suggesting that these oscillations are generated in thalamus, and not by recurrent activity in the thalamocortical loop, at least during the early stage of the immature period. In the visual system, spindle-burst oscillations accelerate in the second postnatal week, a process that is dependent on corticothalamic connections (Murata and Colonnese, 2016; Shen and Colonnese, 2016). Furthermore, rapid optogenetic stimulation of visual cortex *in vivo* during the second postnatal week, but not the first, can drive phase-locked activity in dLGN (Murata and Colonnese, 2016). Thus, it is possible that the mechanisms of rhythmogenesis change even within the immature period.

More importantly, cortical silencing strongly reduces activity in dLGN at P5–7 and P9–11 (but only mildly in VPM at P0–1), suggesting that cortical projections exert strong excitatory actions on the developing thalamus, which is a sharp contrast to its net inhibitory action in the adult dLGN (Olsen et al., 2012). Recruitment of feedforward inhibition in dLGN by cortical stimulation (which is mostly mediated by TRN in adults (Olsen et al., 2012; Reinhold et al., 2015)) does not begin until P13, one day before eye-opening (Murata and Colonnese, 2016). This is the same developmental time that sensory-evoked and spontaneous spindle-bursts are eliminated. Together, these results suggest that a lack of functional feedforward inhibition from cortex to the thalamus is intimately associated with the production of early thalamocortical oscillations. This is likely at least in part because the lack of this inhibition allows the recurrent excitatory corticothalamic connections to form a feedback excitatory loop that amplifies thalamic input. Such early corticothalamic amplification may compensate for a lack of mature connectivity and ensure reliable transmission from the sensory organ to the cortex, which is crucial for circuit formation (Ackman and Crair, 2014; Huberman et al., 2008; Kirkby et al., 2013).

The current evidence suggests that delayed onset of functional thalamic inhibition during development is relevant to normal brain development because it permits immature thalamocortical oscillatory activity. Weak synaptic connectivity and ineffective inhibition provided by GABA_A receptors causes a lack of inhibition and thus allows the early excitatory circuits to create unique emergent network properties critical for development. Development of functional connections between TRN and thalamic relay neurons at the end of the first week in the whisker somatosensory system and the end of the second week in the visual system may terminate these immature oscillations and provide the substrate for the emergence of mature activity patterns. This development of functional TRN inhibition appears to be part of a widespread development of functional inhibition, as feedforward inhibition in thalamus from intrinsic dLGN interneurons and feedforward inhibition in cortex driven by thalamocortical inputs both develop at the end of the second postnatal week (Bickford et al., 2010; Colonnese, 2014).

This theory raises the question of how early thalamus might generate correlated local oscillations without an inhibitory component. One possibility is that the early excitatory thalamo-cortico-thalamic loop entrains thalamic oscillations. As discussed above, this is unlikely in the first postnatal week because silencing cortex does not eliminate thalamic oscillations, but possible in the second week. Another possible contributor to spindle activity is intrinsic thalamic neuronal properties. Developing dLGN neurons can produce long-lasting depolarizations, called plateau potentials, in response to optic nerve stimulation in slices (Dilger et al., 2011). Plateau potentials depend on L-type calcium channels and are prevalent until strong GABAergic inhibition develops in the thalamus around P14 (Dilger et al., 2011). The contribution of plateau potentials to spindle bursts *in vivo* has not been determined, but a lack of plateau potentials in knockout mice of the β_3 subunit of the L-type calcium channel impairs refinement of retino-genicular projections (Dilger et al., 2015), suggesting they play some developmental role. In summary, although the generative mechanisms of spindle oscillations remain to be fully characterized, developing thalamo-cortico-thalamic circuitry likely possesses unique inhibition-independent mechanisms for generating early oscillations.

4. Development of mature oscillations and thalamic inhibition

a. Slow/delta-waves and desynchronized activity

The elimination of immature oscillations occurs in lockstep with the emergence of continuous background activity and the organization of this activity into slow-waves (the synchronized state) during sleep and desynchronized activity during wakefulness, suggesting they result from the same circuit maturation (Colonnese and Phillips, 2018). In humans, ultradian (primitive shorter sleep/wake) cycles along with delta oscillations appear around 37 weeks of gestation (Dereymaeker et al., 2017; Dreyfus-Brisac, 1970; Whitehead et al., 2018). The circuit changes underlying these changes have been studied at the circuit level in the visual cortex of rodents, where P13–14 appears to be the functional equivalent of term in humans (Colonnese et al., 2010). Early primitives of delta oscillations emerge during quiet sleep around P10–11 in frontal and visual cortex (Colonnese and Khazipov, 2010; Seelke and Blumberg, 2008; Shen and Colonnese, 2016), but these are largely isolated bursts of

activity rather than constant slow-waves as observed during adult sleep. Slow-waves lasting tens of seconds during sleep are first observed by P12–13, becoming fully continuous within a few days in both dLGN and visual cortex (Murata and Colonnese, 2018). Intracellular recordings reveal that balanced inhibition and excitation, which is required for the production of stable depolarization during waking, and REM sleep and bistability during slow-wave sleep, emerge in cortex at P13 (Colonnese, 2014). These changes in thalamocortical circuit properties likely underlie the simultaneous emergence of slow-wave activity during sleep as well as stable depolarization during wakefulness at P13.

As discussed in the last section, TRN-relay synapses strengthen along the same timeline as the development of slow-waves and desynchronized activity *in vivo*. It is generally acknowledged that thalamic relay nuclei and TRN play crucial roles in generating adult slow-waves and delta-oscillations (Crunelli et al., 2015; Lemieux et al., 2014; McCormick et al., 2015) and their transition to desynchronized activity (Poulet et al., 2012), though there are species and experimental variables that are incompletely understood (Constantinople and Bruno, 2011). A recent study showed that 30 second excitation of TRN can induce local production of slow-waves in cortex (Lewis et al., 2015), possibly by increasing the activation of I_h and low-threshold T-type calcium currents (David et al., 2013). In rat VPN, thalamic relay neurons are immature until P10, as characterized by a relatively depolarized resting membrane potential, slower action potentials, and a poor ability to generate low-threshold calcium spikes (Warren and Jones, 1997). At P12, they acquire the basic characteristics of adult neurons including the capability to sustain multispikes bursts (though full adult bursting is not acquired until weeks later). Slice recordings of mouse dLGN show a similar developmental time course (MacLeod et al., 1997). In addition, the development of cholinergic modulation of TRN follows the same timeline as the development of slow-waves and arousal modulation (Sokhadze et al., 2018). Functionally this leads to a desynchronization of mouse thalamic relay neuron firing between P10 and P14 *in vivo* (Colonnese et al., 2017). In rats *in vivo* the acquisition of adult-like arousal modulation emerges between P11 and P13, with significant bursting of relay neurons 2–3 days later (Murata and Colonnese, 2018).

While thoroughly understudied, the above data allow us to propose that cortical slow and delta waves, and their state-dependent modulation, result from strengthening of TRN to relay synapses that allow for inhibition of thalamic relay neurons under appropriate behavioral circumstances (eg. sleep), followed by the development of burst firing in TRN and thalamic relay neurons. This capacity of TRN is likely further supported by maturation of neuromodulatory inputs, particularly acetylcholine, and possibly cortical and thalamic inputs as well.

b. Development of sleep spindles

Thalamocortical oscillations with the best-described circuit origin are the sleep spindles, prevalent during early stages of non-REM sleep (McCormick and Bal, 1997). Sleep spindles are generated through the back and forth interaction of excitatory relay neurons and inhibitory reticular thalamus (Steriade and McCarley, 2005). Burst firing in TRN induces strong hyperpolarization of relay neurons, which in turn activates I_h , the hyperpolarization-

activated rectification current. I_h depolarizes the neuron, activating a low-threshold calcium conductance, causing burst firing in the relay neuron which in turn drives burst firing in TRN (Crunelli et al., 2015; Fogerson and Huguenard, 2016). Sleep-spindles, along with strong synchronized activity during slow-wave sleep, are the last EEG grapho-elements to emerge during development. Sleep-spindles do not appear until 2–3 months of age in humans (Eisermann et al., 2013; Plouin et al., 2013). This pattern is repeated in carnivores and rodents, with sleep-spindles emerging well after eye-opening and the initial development of slow-waves during non-REM sleep (Domich et al., 1987). Despite their name, sleep-spindles appear functionally distinct from spindleburst/delta-brush patterns of early development. This is most evident in the clear developmental gap between the disappearance of delta-brushes and the appearance of sleep-spindles, indicating that one does not simply shift into the other (Tiriac and Blumberg, 2016).

The circuit and synaptic correlates of sleep-spindle development have been extensively examined in the dLGN of ferrets. The factor most relevant to the emergence of sleep-spindle oscillations is the capacity of TRN and relay neurons to generate strong bursts containing multiple action potentials (McCormick et al., 1995; Ramoa and McCormick, 1994). The development of this capacity develops along a similar time course, though TRN appears to lag dLGN by some weeks, suggesting the functional capacity of inhibitory bursting is the limiting factor for sleep-spindle development. The same pattern is observed in relay neurons of cats and mice, with strong low-threshold calcium currents and multiple action potentials in bursts emerging only well after eye-opening (Adrien and Roffwarg, 1974; MacLeod et al., 1997; Murata and Colonnese, 2018; Pirchio et al., 1990, 1997). The TRN of rats shows similar maturation, but only at the end of third week (Warren and Jones, 1997). Thus there appears to be a similar developmental timeline for the acquisition of sleep-spindles and for the bursting ability of neurons in thalamic relay nuclei and TRN.

While to our knowledge, no specific *in vivo* tests have correlated development of sleep-spindles and the development of specific circuits, the *in vitro* data suggest the following hypothesis. Immature oscillations disappear in tandem with the emergence of slow-waves and the desynchronized state by a mechanism that involves the development of functional synaptic connections between TRN and thalamic relay neurons, as well as the establishment of modulatory connections to TRN (and probably relay neurons as well). These connections, however, are not sufficient for the production of sleep-spindles, largely because bursting remains weak in both TRN and relay neurons. As the number of spikes within each burst increases, particularly in TRN, the power of bursts to entrain the thalamic circuit increases, leading to the gradual emergence and strengthening of sleep-spindles, perhaps the final stage of thalamocortical activity maturation.

5. Medical relevance: Absence seizures and neurodevelopmental disorders

The ability of thalamocortical circuits to generate robust brain-wide oscillations means their perturbation can lead to neurological disorders. Most notably, TRN and thalamocortical circuits are implicated in absence seizures, which are childhood-onset (4–14 years old),

sudden, brief seizures causing a partial or complete loss of consciousness. In animal models, disruption of intrinsic neuronal properties or connectivity within TRN can induce spike-and-wave discharges, hypersynchronous thalamocortical oscillations at 3–8 Hz, and result in absence seizure symptoms (Fogerson and Huguenard, 2016; Makinson et al., 2017; Paz et al., 2011; Timofeev and Steriade, 2004).

TRN has long been implicated in schizophrenia because of substantial overlap between TRN function and schizophrenic symptoms, including sleep, sensory gating, and attention (Ferrarelli and Tononi, 2011). TRN abnormalities have been reported in animal models. Importantly, parvalbumin (PV)-positive TRN inhibitory neurons, a neuronal population accounting for 58% of all human TRN neurons, are reduced by 71% in patients with schizophrenia and by 66% in bipolar disorders (Pratt and Morris, 2015; Steullet et al., 2017a). In addition, several genes related to autism spectrum disorder (ASD) and schizophrenia are highly and selectively expressed in the developing TRN, and TRN dysfunction has been shown to underlie some ASD symptoms (Krol et al., 2018; Wells et al., 2016).

Brain insult during pregnancy or infancy has also been implicated in these psychiatric and neurodevelopmental disorders. Hypoxic-ischemic encephalopathy (HIE) and subsequent seizure is prevalent in preterm and neonatal infants (Abend et al., 2018; Jensen, 2009), and perinatal HIE can cause maldevelopment or death of GABAergic neurons in TRN along with cortex and hippocampus (Failor et al., 2010; Komitova et al., 2013; McQuillen et al., 2003). Furthermore, a wide range of risk factors including maternal stress, inflammation, virus infection, alcohol and drug exposure, affects GABAergic, especially PV-positive, neurons (Steullet et al., 2017b).

Thus, disturbed development of GABAergic neurons and subsequent dysfunction of TRN could underlie some common symptoms of neurodevelopmental disorders. Understanding how neuronal and circuit abnormalities arise in the developing TRN and how early TRN anomaly may impair acquisition of mature network activity would advance our understanding of the circuit-level etiology of mental disorders.

6. Summary and future perspectives

We reviewed the development of thalamic inhibitory circuits and their relationship to thalamocortical network activity, aiming to address fundamental questions about the cellular and circuit mechanisms underlying the expression of immature cortical oscillations and the developmental acquisition of mature EEG grapho-elements.

The available evidence suggests that the intrinsic physiological properties of TRN and relay neurons, as well as the synaptic connectivity between them, are extremely weak during the time-period when developmental thalamocortical oscillations such as EGOs and spindle bursts are prevalent. This poor inhibitory function of TRN at a time when the excitatory efferents and afferents of thalamic relay neurons are functional is likely the circuit mechanism that allows formation of a developmentally-transient excitatory thalamo-cortico-thalamic loop that amplifies early thalamic input. One caveat to this hypothesis is that

functional effectiveness *in vivo* is often poorly correlated with anatomical and synaptic development. For example, corticothalamic feedback is critical to dLGN function *in vivo* even at ages where terminal density is low (Brooks et al., 2013; Grant et al., 2016; Seabrook et al., 2013b), and thalamocortical connections are capable of supporting rapid oscillations in cortex during a similar period of low density and weak synaptic strength (Luhmann and Khazipov, 2018).

Regardless of the functional state of TRN-relay circuits during the time of immature oscillations, the timing of many developmental changes of cellular properties (eg., resting membrane potential, chloride reversal potential, multi-spike bursting) and circuit configurations (eg., reciprocal connections between both nuclei) roughly coincides with the developmental transition to mature thalamocortical network activity. Thus, the maturation of these relationships is likely an important contributor to the maturation of cortical activity patterns.

However, until *in vivo* studies of the role of TRN and thalamic relay nuclei are completed, the exact roles of developing TRN and thalamic inhibitory circuits in early oscillation and maturation will remain ambiguous. One important area for study will be to determine the roles of each neuronal subtype in TRN. TRN is heterogeneous in its makeup (Pinault, 2004). A recent study shows TRN neurons expressing parvalbumin and somatostatin have different connectivity and functions (Clemente-Perez et al., 2017). The detailed characterization and classification of anatomical, physiological and circuit properties of each TRN interneuron type will yield useful information for future studies. An interesting question is whether early activity controls development of GABAergic neurons in TRN, as in iso-cortex (Wamsley and Fishell, 2017). This is particularly relevant clinically, as development of GABAergic neurons are more likely to be affected by genetic and environmental risk factors for neurodevelopmental and psychiatric disorders. Future studies on normal and pathological development of TRN and thalamic GABAergic circuits will help understand the circuit-level etiology of core symptoms in mental disorders.

Funding

This work was supported by NIH Grant R01 EY022730 (MTC).

Abbreviations

TRN	thalamic reticular nucleus
dLGN	dorsal lateral geniculate nucleus
VPM	ventral posterior medial nucleus
VPN	ventral posterior nucleus
MGv	ventro medial geniculate nucleus
VBN	ventrobasal nucleus
EEG	electroencephalogram

PV	parvalbumin
SOM	somatostatin
IPSC	inhibitory postsynaptic current
REM	rapid eye movement
EGO	early gamma oscillation
I_h	hyperpolarization-activated sodium currents
P	postnatal day
E	embryonic day
GW	gestational week

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Highlights

- Functional development of thalamic inhibition *in vivo* is poorly understood
- Weak interaction between TRN and relay thalamus allows for amplification of activity during development.
- TRN is a potential mediator of early thalamocortical oscillations and maturation.
- Thalamic Inhibition matures simultaneously with elimination of immature oscillations.
- TRN bursting paces emergence of mature EEG grapho-elements such as sleep-spindles.

Figure 1. Developmental timelines of thalamocortical activity and inhibitory circuits in humans and rodents.

Developmental timelines of thalamocortical activity, global brain state, intrinsic cellular property, and connectivity, derived from both *in vivo* and *in vitro* studies, are shown for human (top), rodent visual system (middle) and rodent somatosensory system (bottom). Colors indicate the locus: cortex (blue), thalamus (green) and TRN (red). These timelines are based on literature cited in the main text.

Figure 2. Development of thalamic inhibitory circuits and thalamocortical activity.

Circuit diagrams of developmental changes in intrinsic firing, bursting properties, and synaptic (black lines for excitatory; red for inhibitory) and electrical (zigzag lines) connectivity in relation to thalamocortical network activity and state modulation. (Left) Immature thalamocortical oscillations prevail until the late trimester in pregnancy in humans and until the second postnatal week in rodent visual system. A lack of reliable inhibition in thalamus and cortex allows for recurrent feedback amplification of early thalamocortical oscillations such as spindle-bursts and EGOs. (Middle) Initial emergence of mature thalamocortical activity around term in humans and in the second postnatal week in rodents. Incorporation of inhibitory circuits in thalamocortex, particularly TRN, terminates early oscillations and provides continuous desynchronized activity modulated by behavioral states (e.g. slow/delta oscillations). (Right) Emergence of sleep-spindles around 2–3 months of age in humans and third and fourth postnatal weeks in rodents. Further maturation of thalamic inhibitory circuits, especially emergence of multi-spike bursts in TRN and relay nuclei, is likely the circuit basis of acquiring sleep-spindles. (Bottom) Timelines of developmental transitions in thalamocortical activity in humans and rodents (visual system). GW: gestational week. P: postnatal day.