



The Integrative Function of Silent Synapses on Subplate Neurons in Cortical Development and Dysfunction

Patrick O. Kanold*, Rongkang Deng and Xiangying Meng

Department of Biology, University of Maryland, College Park, MD, United States

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*Correspondence:

Patrick O. Kanold
pkanold@umd.edu

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The thalamocortical circuit is of central importance in relaying information to the cortex. In development, subplate neurons (SPNs) form an integral part of the thalamocortical pathway. These early born cortical neurons are the first neurons to receive thalamic inputs and excite neurons in the cortical plate. This feed-forward circuit topology of SPNs supports the role of SPNs in shaping the formation and plasticity of thalamocortical connections. Recently it has been shown that SPNs also receive inputs from the developing cortical plate and project to the thalamus. The cortical inputs to SPNs in early ages are mediated by N-methyl-D-aspartate (NMDA)-receptor only containing synapses while at later ages α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-receptors are present. Thus, SPNs perform a changing integrative function over development. NMDA-receptor only synapses are crucially influenced by the resting potential and thus insults to the developing brain that causes depolarizations, e.g., hypoxia, can influence the integrative function of SPNs. Since such insults in humans cause symptoms of neurodevelopmental disorders, NMDA-receptor only synapses on SPNs might provide a crucial link between early injuries and later circuit dysfunction. We thus here review subplate associated circuits, their changing functions, and discuss possible roles in development and disease.

Keywords: cortex, development, circuit, NMDA-receptor, silent synapse, subplate neuron

INTRODUCTION

The mammalian cerebral cortex is unique in that it is a laminated structure which is thought to support hierarchical information processing. The transmission of information from the thalamus to the cortex *via* thalamocortical circuits is of central importance for information processing in the mammalian brain. In the adult, thalamic input to the cerebral cortex mainly arrives in layer 4 but inputs to other layers can exist (Meyer et al., 2010; Bruno, 2011; Sherman, 2012, 2017; Constantinople and Bruno, 2013; Ji et al., 2016; Sun et al., 2016).

Given the laminar nature of the cerebral cortex, the development of the cortical layers is a protracted process. Curiously, the development of the cortical layers occurs in an inside-out

fashion such that deeper layers are generated before superficial layers. The first postmitotic neurons from the ventricular zone and the germinative zone of the rostromedial telencephalic wall migrate radially and form the so-called preplate. Subsequent rounds of cell division give rise to the excitatory neurons of the cortical plate. Since these neurons migrate towards the pia, they divide the preplate into the superficial marginal zone and the deep subplate zone (Supèr et al., 1998; Kanold and Luhmann, 2010; Pedraza et al., 2014). Even though the subplate zone is only present in the brain transiently, it plays an important role in cortical development.

Studies both in cats and rodents have shown that subplate neurons (SPNs) are responsible for the functional maturation and segregation of the thalamocortical connections (Ghosh et al., 1990; Ghosh and Shatz, 1992; McConnell et al., 1994; Kanold et al., 2003; Tolner et al., 2012), as well as for the maturation of cortical GABAergic inhibition (Kanold and Shatz, 2006), and critical period plasticity (Kanold and Shatz, 2006). This key role of SPNs is thought to stem from the fact that SPNs are the first neurons to receive thalamic inputs (Friauf and Shatz, 1991; Hanganu et al., 2002; Higashi et al., 2002, 2005; Molnár et al., 2003; Zhao et al., 2009), respond to sensory stimuli (Wess et al., 2017) and relay this information to the developing layer 4 (L4) (Kanold, 2009; Zhao et al., 2009; Butts and Kanold, 2010; Kanold and Luhmann, 2010; Deng et al., 2017; **Figure 1A**). Thus, the subplate might form a functional protomap of the future cortical organization (O’Leary and Borngasser, 2006; O’Leary et al., 2007; Wess et al., 2017).

Given the key position of SPNs in the thalamocortical pathway and their demonstrated role in cortical development, we here aim to review the changing circuits associated with SPNs and their possible functional relevance.

THE SUBPLATE ZONE CONTAINS A DIVERSE POPULATION OF NEURONS

Both glutamatergic and GABAergic neurons are found in the subplate zone. The majority of the cortex projecting SPNs are glutamatergic in ferret, while some of them are positive for GABAergic interneuron markers (Finney et al., 1998). GABAergic SPNs are also found in mouse, cat, and primate (Chun and Shatz, 1989; Antonini and Shatz, 1990; Meinecke and Rakic, 1992; Higo et al., 2007; Kanold and Luhmann, 2010). SPNs have diverse dendritic and axonal morphology. Several distinct morphological types such as bitufted and monoftufted horizontal, multipolar, inverted pyramidal, polymorphous, and fusiform SPNs have been identified (Mrzljak et al., 1988; Hanganu et al., 2002; Marx et al., 2017). Some SPNs have extensive dendritic trees in the cortical plate (Friauf et al., 1990; Finney et al., 1998; Clancy and Cauller, 1999; Piñon et al., 2009; Viswanathan et al., 2012), suggesting that they are integrating synaptic information from other sources. Such sources could originate locally within the cortical plate close to the SPN soma or from distant sources, e.g., other cortical or subcortical regions. Molecular analysis has shown that SPNs express a variety of molecular markers such as CTGF, Nurr1, Cplx3, as well as others (Hoerder-Suabedissen et al., 2009, 2013; Viswanathan et al., 2012). Molecularly defined

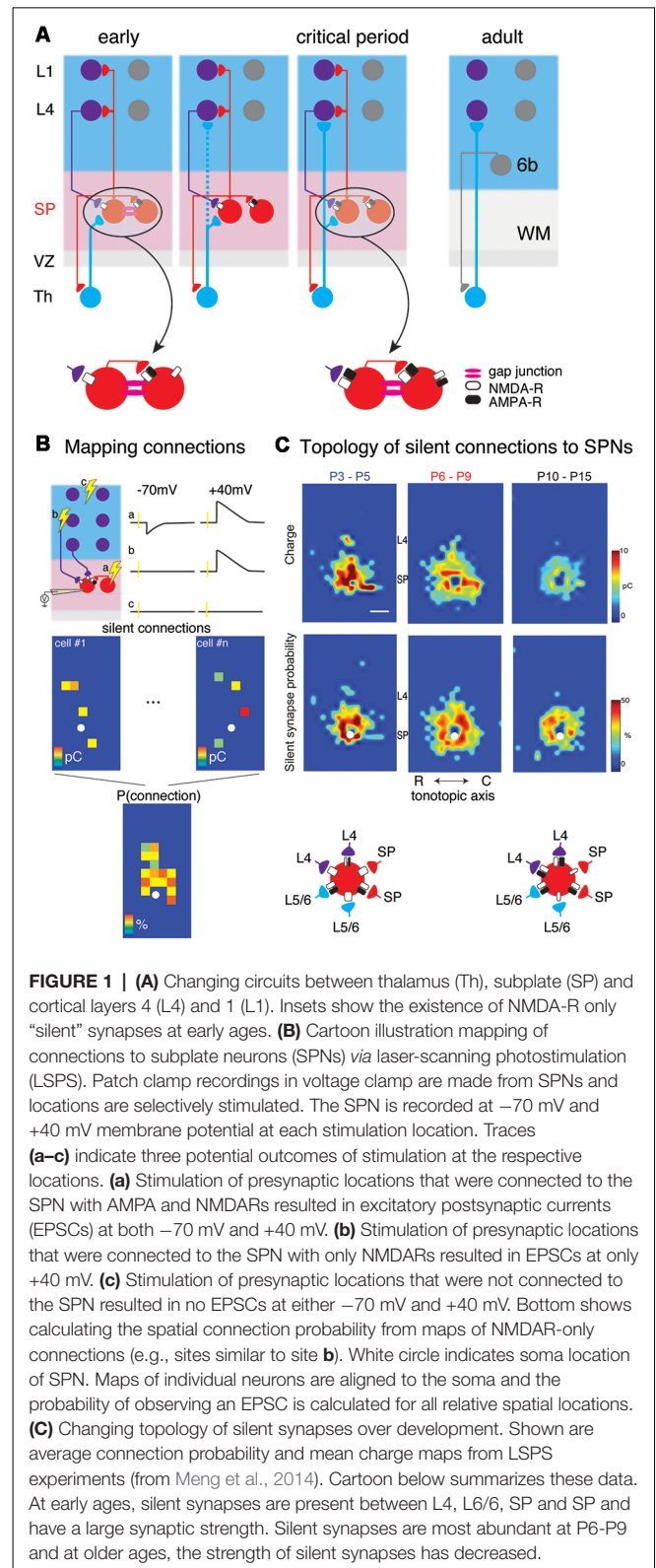


FIGURE 1 | (A) Changing circuits between thalamus (Th), subplate (SP) and cortical layers 4 (L4) and 1 (L1). Insets show the existence of NMDA-R only “silent” synapses at early ages. **(B)** Cartoon illustration mapping of connections to subplate neurons (SPNs) via laser-scanning photostimulation (LSPS). Patch clamp recordings in voltage clamp are made from SPNs and locations are selectively stimulated. The SPN is recorded at -70 mV and $+40$ mV membrane potential at each stimulation location. Traces **(a–c)** indicate three potential outcomes of stimulation at the respective locations. **(a)** Stimulation of presynaptic locations that were connected to the SPN with AMPA and NMDARs resulted in excitatory postsynaptic currents (EPSCs) at both -70 mV and $+40$ mV. **(b)** Stimulation of presynaptic locations that were connected to the SPN with only NMDARs resulted in EPSCs at only $+40$ mV. **(c)** Stimulation of presynaptic locations that were not connected to the SPN resulted in no EPSCs at either -70 mV and $+40$ mV. Bottom shows calculating the spatial connection probability from maps of NMDAR-only connections (e.g., sites similar to site **b**). White circle indicates soma location of SPN. Maps of individual neurons are aligned to the soma and the probability of observing an EPSC is calculated for all relative spatial locations. **(C)** Changing topology of silent synapses over development. Shown are average connection probability and mean charge maps from LSPS experiments (from Meng et al., 2014). Cartoon below summarizes these data. At early ages, silent synapses are present between L4, L5/6, SP and SP and have a large synaptic strength. Silent synapses are most abundant at P6–P9 and at older ages, the strength of silent synapses has decreased.

classes of SPNs have been shown to have dendritic trees in the cortical plate (Viswanathan et al., 2012) suggesting that molecular cellular identity might co-vary with morphology (reviewed in Luhmann et al., 2018).

OUTPUTS: SYNAPTIC TARGETS OF SPNs

While the subplate zone contains both glutamatergic and GABAergic neurons, ventricular zone derived SPNs are glutamatergic. SPNs send excitatory projections into the developing cortical plate and axons from SPNs target excitatory and GABAergic cells in L4 (Zhao et al., 2009; Deng et al., 2017; **Figure 1A**). Besides L4, SP axons are found in sub- as well as supragranular layers including layer 1 (L1) where they can potentially activate L1 neurons as well as apical dendrites of many other cortical cells (Clancy and Cauller, 1999; Viswanathan et al., 2017). Moreover, Cajal Retzius cells in L1 have been shown to receive GABAergic inputs from subplate (Myakhar et al., 2011), thus SPNs potentially target cells across the cortical column.

At young ages, SPNs are also coupled to each other as well as to some cortical plate neurons *via* gap junctions (**Figure 1A**; Dupont et al., 2006). In the adult cerebral cortex gap junction coupling is mostly present between GABAergic neurons (Galarreta and Hestrin, 1999, 2001, 2002; Gibson et al., 1999; Venance et al., 2000; Deans et al., 2001; Connors and Long, 2004; Butovas et al., 2006; Fukuda et al., 2006; Ma et al., 2011) while in development gap junction coupling more widespread (Niculescu and Lohmann, 2014). Gap junction coupling could synchronize neuronal activity, cause network oscillations, and contribute to circuit formation and plasticity (Peinado et al., 1993a,b; Roerig and Feller, 2000; Connors and Long, 2004; Cruikshank et al., 2005; Kotak et al., 2007; Postma et al., 2011; Niculescu and Lohmann, 2014; Yao et al., 2016). Thus, gap junctions between SPNs could synchronize local groups of SPNs and thereby amplify their effects on synaptic targets.

SPNs are also thought to pioneer the corticothalamic pathway (McConnell et al., 1994) and as such SPNs have been shown to send projections to the thalamus (Viswanathan et al., 2017; Hoerder-Suabedissen et al., 2018). The described thalamic projecting SPNs have targeted higher-order thalamic nuclei (Viswanathan et al., 2017; Hoerder-Suabedissen et al., 2018), which develop early and also support multisensory processing in early development (Henschke et al., 2018). Thus, SPNs might play a role in early multisensory integration or synchronization.

INPUTS: SUBPLATE NEURONS INTEGRATE CORTICAL INFORMATION VIA A VARYING SET OF SYNAPSES

Functional sources of cortical inputs to SPNs have been identified by studies in brain slices of the developing mouse auditory cortex (Viswanathan et al., 2012; Meng et al., 2014). These studies have shown that SPNs receive excitatory AMPA receptor-mediated and GABAergic inputs from the cortical plate (Viswanathan et al., 2012). In particular, these inputs originated in deep cortical layers, but subpopulations of SPNs also received inputs from L4. SPNs receiving L4 input were more prominent after thalamocortical connections to L4 were established roughly around ear opening at \sim P11 in the mouse (**Figure 1C**).

Besides glutamatergic and GABAergic inputs, SPNs also receive neuromodulatory inputs from a variety of sources. For example, SPNs have both acetylcholine (ACh; Hanganu et al., 2002, 2009; Hanganu and Luhmann, 2004) and serotonin receptors (Kanold and Luhmann, 2010; Liao and Lee, 2011, 2014), and cholinergic as well as serotonergic fibers are present in the developing subplate (Krpmotić-Nemanić et al., 1983; Voigt and de Lima, 1991; Nakazawa et al., 1992; Mechawar and Descarries, 2001) suggesting that they form functional circuits with SPNs.

SUBPLATE NEURONS RECEIVE CORTICAL INFORMATION VIA SILENT SYNAPSES

Ionotropic glutamatergic neural transmission is the major form of excitatory neural transmission in the central nervous system. Presynaptic release of glutamate is sensed by AMPA receptors (AMPA receptors) and also by NMDA receptors (NMDARs) on the postsynaptic sites. Binding of glutamate alone is not enough to make NMDARs active. Membrane depolarization is also required due to Mg^{2+} block of NMDARs (Nowak et al., 1984). Thus, when glutamatergic synapses conducting currents only at depolarized membrane potential were identified, they were named as “silent synapses” (Isaac et al., 1995, 1997; Liao et al., 1995; Durand et al., 1996; Isaac, 2003). This silent synapse phenomenon is most likely due to lacking AMPARs on the postsynaptic site, but other mechanisms could exist (Kullmann and Asztely, 1998; Kullmann, 2003).

Due to the blockage by Mg^{2+} and lack of AMPARs in early development many glutamatergic synapses in several brain regions are mediated by silent synapses and the abundance of silent synapses in cells decreases over development (Isaac et al., 1997; Rumpel et al., 1998, 2004; Deng et al., 2017). Silent synapses can be turned into AMPAR-containing synapses through long-term potentiation protocols. Together, they support the hypothesis that neural activity unsilencing silent synapses is a mechanism for building mature neural circuits (Kerchner and Nicoll, 2008; Hanse et al., 2013). Indeed, the glutamatergic connections from layer 2/3 (L2/3) to L5 pyramidal neurons in the cortex are mediated by silent synapses during the first postnatal week. These NMDAR-only connections can be turned into AMPAR-containing connections by elevated network activity (Anastasiades and Butt, 2012).

In vitro studies in slices of neonatal mouse auditory cortex using Laser Scanning Photostimulation (LSPS; **Figure 1B**) showed that cortical input to SPNs were mediated by silent synapses for most of SPNs from postnatal day 3 (P3) to P15 (Meng et al., 2014), which encompasses the period from before the formation of thalamocortical synapses past the critical period. In these experiments, presynaptic neurons were activated by uncaging glutamate sequentially in a grid over the A1, while GABAergic transmission was blocked. By holding SPNs either at -70 mV or $+40$ mV the nature of the connection between the activated presynaptic neuron at each stimulus location and the recorded SPN could be probed. Presence of

AMPA results in excitatory postsynaptic currents (EPSCs) at both -70 mV and $+40$ mV (e.g., from within SP at stimulation site a in **Figure 1B**). In contrast, when only NMDARs are present, the connection is “silent” at -70 mV and EPSCs are only observed at $+40$ mV (stimulation site b in **Figure 1B**). By sequentially stimulating many locations to cover the extent of the slice, maps of NMDAR-only (“silent”) connections can be obtained. For each stimulation site, the size of the evoked EPSCs is quantified. By mapping multiple neurons, the probability of having NMDAR-only connections from each spatial location can be calculated (**Figure 1B** bottom). Mapping inputs to SPNs across age and calculating the spatial connection probability as well as the average strength of such a connection shows that circuits to SPNs change over development (**Figure 1C**). SPNs had connections that could either be NMDAR-only or AMPAR-containing. Overall, SPNs at young ages have silent connections mediating inputs from cortical cells located at larger distances from the SPN soma (**Figure 1C**). Many of these silent connections at early ages originated in L4. Comparing the abundance of silent connections, a transient increase in silent connections from the cortical plate occurred from P6 to P9 suggesting the formation of glutamatergic connections during this time period. A population analysis revealed that SPNs could be categorized into four different groups based on their functional connectivity patterns and in particular, their inputs from L4 (Meng et al., 2014; **Figures 2A,B**). Moreover, groups of SPNs varied in their amount and extent of intralaminar integration along the rostro-caudal direction, which in A1 is the dominant tonotopic axis. For example, SPNs in both groups 2 and 4 receive “silent” L4 input but vary in the amount of rostro-caudal integration and thus presumably in their functional integration across the frequency axis. These studies indicate that SPNs form a diverse integrative neural circuit and that the nature of integration varies with age. In particular, feedback inputs from L4 are mediated by NMDARs at early ages but contain AMPARs at older ages.

SPNs are not the only cerebral cortical neurons sporting silent synapses. GABAergic neurons have also been shown to have silent synapses and some of these silent synapses originate from connections from SPNs (Deng et al., 2017). Thus, the presence of silent synapses on cortical neurons seems to be a ubiquitous feature of the developing cerebral cortex.

HOW THEN ARE SILENT CONNECTIONS TO SPNs UNSILENCED?

The neural activity necessary to depolarize SPNs in order to displace the Mg^{2+} could come from depolarizing network activity during development. There are multiple non-exclusive sources of depolarizing inputs: (i) ascending sensory inputs; (ii) depolarizing GABAergic inputs; and (iii) depolarizing neuromodulatory inputs.

Ascending sensory activity mediated by AMPARs at thalamocortical terminals could provide depolarizing neural activity to SPNs and regulate the unsilencing of silent synapses on SPNs. Perturbing sensory activity resulted in

the prolonged existence of silent synapses in the visual and somatosensory cortices (Ashby and Isaac, 2011; Funahashi et al., 2013; Han et al., 2017). Similarly, removing auditory inputs by cochlear ablation in early life altered the spatial distribution of AMPAR- and NMDAR-mediated connections on GABAergic neurons in the auditory cortex (Deng et al., 2017). In deaf mice, AMPAR-mediated connections were present for more distal connections from L2/3 neurons while L5/6 connections originated from more proximal locations. The spatial pattern of NMDAR-only connections was also altered in deaf animals. This suggests that glutamatergic synapse maturation is regulated with input specificity but that both extrinsic and intrinsic cortical activity such as sensory-evoked activity as well as endogenous cortical activity might play a role.

A second source of depolarizing activity might be provided by GABAergic inputs. When silent synapses are gradually replaced by AMPAR-containing synapses, the dominant form of cortical network activity is driven by depolarizing GABA (Ben-Ari et al., 1997; Ben-Ari, 2002; Allène et al., 2008). This suggests that depolarizing GABA may provide the neural activity for the unsilencing of silent synapses (Ben-Ari et al., 1997; Ben-Ari, 2002). Indeed GABA receptor-mediated depolarization is required for the unsilencing of silent synapses in the developing neocortex (Wang and Kriegstein, 2008) and during the development of adult-generated dentate granule cells (Chancey et al., 2013), but silent synapses can also be unsilenced by seizure activity (Zhou et al., 2011; Sun et al., 2018).

Besides the depolarizing action of GABA, neuromodulators which depolarize SPNs could also play a role in unsilencing silent connections. SPNs have both ACh (Hanganu et al., 2002; Hanganu and Luhmann, 2004) as well as serotonin receptors (Kanold and Luhmann, 2010; Liao and Lee, 2011, 2014) which can act depolarizing. Thus, the actions of these neuromodulators could contribute to the functional unsilencing of silent connections to SPNs.

Thus, in summary, there are multiple non-exclusive sources of depolarizing inputs that might individually or jointly act in unsilencing silent connections to SPNs.

WHAT ARE SILENT SYNAPSES GOOD FOR? WHAT DO THEY TELL US?

NMDAR-mediated connections are not only present in the developing mammalian cerebral cortex but also in other structures. Thus, the computational roles of such connections might be similar. First, it is well-established that NMDAR-only mediated synaptic connections can function as a coincidence detector. The activation of NMDAR not only requires glutamate binding but also membrane depolarization to remove the Mg^{2+} from the channel pore. One role of a coincidence detector is to enable the refinement of topographic connections as illustrated in the retinogeniculate system. During early development, structured spontaneous activity is present in the retina (Galli and Maffei, 1988; Meister et al., 1991;

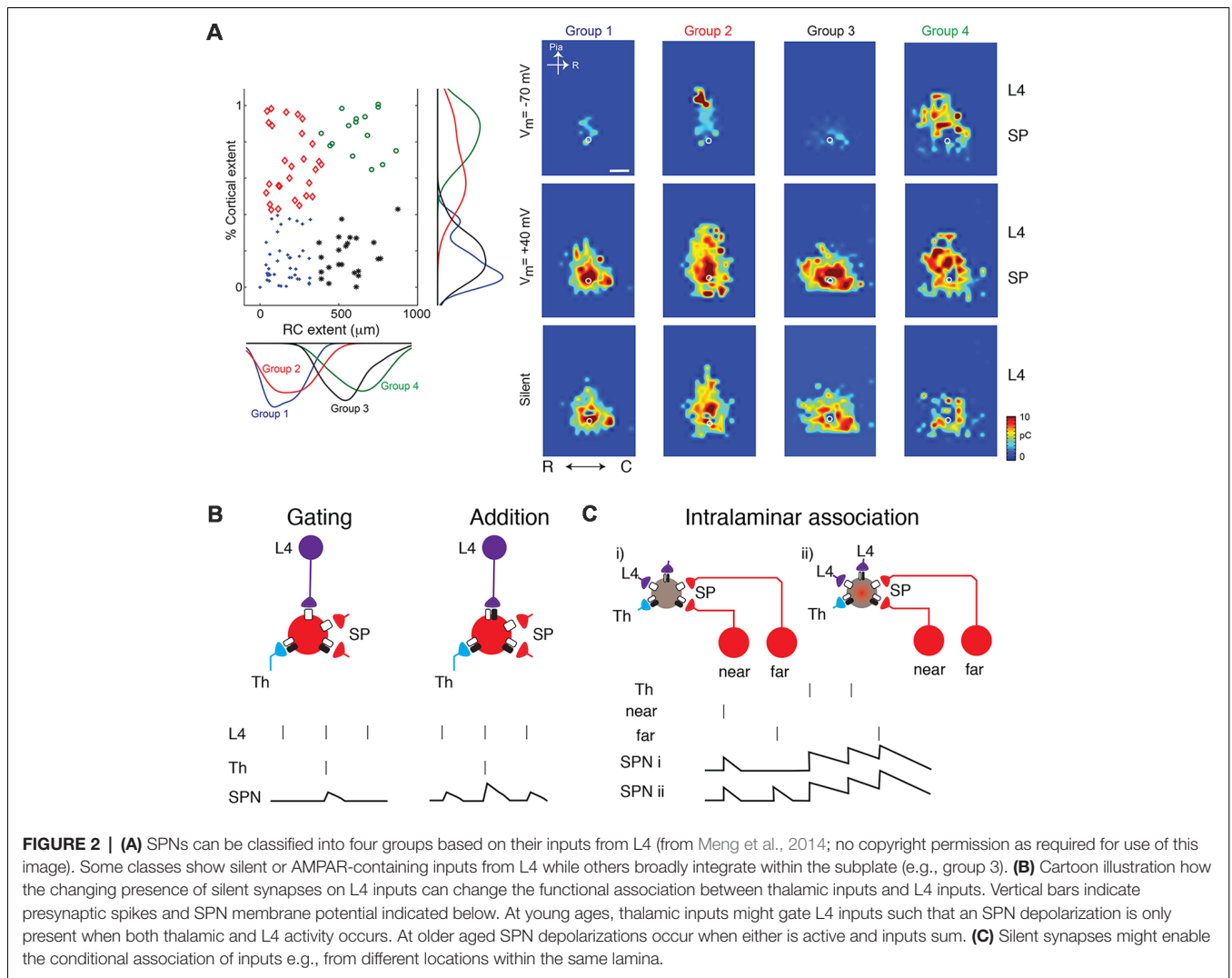


FIGURE 2 | (A) SPNs can be classified into four groups based on their inputs from L4 (from Meng et al., 2014; no copyright permission as required for use of this image). Some classes show silent or AMPAR-containing inputs from L4 while others broadly integrate within the subplate (e.g., group 3). **(B)** Cartoon illustration how the changing presence of silent synapses on L4 inputs can change the functional association between thalamic inputs and L4 inputs. Vertical bars indicate presynaptic spikes and SPN membrane potential indicated below. At young ages, thalamic inputs might gate L4 inputs such that an SPN depolarization is only present when both thalamic and L4 activity occurs. At older aged SPN depolarizations occur when either is active and inputs sum. **(C)** Silent synapses might enable the conditional association of inputs e.g., from different locations within the same lamina.

Feller et al., 1996; Firth et al., 2005) and competition between the two eyes drives retino-geniculate (Penn et al., 1998) and retino-collicular (Shah and Crair, 2008) segregation. Blockade of NMDA signaling alters the segregation of retinal ganglion afferents in both the lateral geniculate nucleus as well as the optic tectum (Hahm et al., 1991; Ruthazer et al., 2003; Ben Fredj et al., 2010).

However, the functional contribution of silent synapses to these processes remains unclear possibly because few retino-geniculate connections are truly “silent” (Hohnke et al., 2000). Moreover, it seems that at least in the retino-geniculate system, silent synapses peak after the increase in sensory-driven activity, thus might play a role at slightly later stages in development (Lu and Constantine-Paton, 2004).

A second potential role of NMDAR-only mediated synaptic connections is to integrate multiple subthreshold EPSCs over time and improve the synchrony between different cells due to a longer activation time scale. This is consistent with the role of NMDARs in supporting synchronized oscillations in the rodent somatosensory cortex (Dupont et al., 2006; Yang et al., 2009).

A third role of silent synapses has been shown recently in the mammalian retina to enhance motion processing by enabling differential processing of a single source of glutamate by two cells (Sethuramanujam et al., 2017).

Given the fact that activity in developing networks is slow and adapting, it seems likely that silent synapses on SPNs are involved in associating activity over longer time scales but do not enhance processing of stimuli, activity, or coincidence on fast time scales.

Moreover, since silent synapses can be unsilenced by correlated activity thus, by extension, the pattern of unsilenced, AMPAR- and NMDAR-containing, connections are in effect a readout of the past amount of correlated activity of inputs to a particular neuron. However, since unsilencing requires coincidence, the pattern of unsilenced neurons might not necessarily reflect the amount of activity *per se*. Thus, the presence of AMPAR-containing synapses on connections from deep layers indicates that those layers were likely correlated with SPNs. The emergence of AMPAR-containing synapses from L4 to SPNs after ear opening in the auditory cortex (Meng et al., 2014) indicates that L4 activity likely was correlated

with SPN activity just before ear opening (**Figure 1B**). Such an interpretation would be consistent with the increased evoked correlated activity between SPNs and L4 at similar stages of development in ferret (Wess et al., 2017). Interestingly, just before ear opening, correlated activity is largest in the beta band, possibly indicating that such activity might be effective in unsilencing of synapses. Moreover, the spatial pattern of unsilenced synapses from the cortical plate shows a columnar pattern indicating synchronous activity across a cortical column consistent with microelectrode studies (Yang et al., 2009, 2013; Colonnese and Khazipov, 2010; Minlebaev et al., 2011).

SPN MIGHT ENABLE THE GENERATION OF NORMAL ACTIVITY PATTERNS IN THE DEVELOPING CORTEX

The existence of abundant NMDAR-only silent synapses in SPNs and other cortical neurons suggests that most excitatory activity during early development is mediated by NMDARs. Accordingly, cortical network activity *in vitro* during the first postnatal week can be almost completely blocked by application of the NMDAR antagonist AP5 (Allène et al., 2008). These results suggest that NMDAR-only “silent” synapses are in fact not “silent” but conduct current and regulate cortical network activity. Thus, NMDAR-only synapses are not truly “silent” but represent a unique early developmental mode of activity generation and propagation.

The electrical activity in the developing brain and especially the cortex is dominated by oscillations. These oscillations can be present spontaneously, that is without any overt external trigger, or they can be evoked by sensory stimuli such as light flashes, motor twitches, or sounds (Khazipov et al., 2004; Hanganu et al., 2006; Marcano-Reik and Blumberg, 2008; Yang et al., 2009; Colonnese and Khazipov, 2010; Chipaux et al., 2013; Blumberg et al., 2015). Moreover, spontaneous activity can be generated endogenously in the cortex (Garaschuk et al., 2000; Adelsberger et al., 2005; Siegel et al., 2012) or even in cortical slice culture (Stewart and Plenz, 2008) as well as be reflective of spontaneously generated activity in the sensory periphery e.g., the retina or cochlea (Galli and Maffei, 1988; Meister et al., 1991; Feller et al., 1996; Firth et al., 2005; Tritsch et al., 2007; Siegel et al., 2012; Wang and Bergles, 2015).

These activity patterns are complex and are comprised of fast nested oscillatory patterns, the so-called “spindles,” and slower transients, “SATs” (Vanhatalo et al., 2002; Tolonen et al., 2007; Benders et al., 2015). Centrally and peripherally generated spontaneous activity show different amounts of synchronizing, wave progression, and developmental profile (Siegel et al., 2012). These early activity patterns are thought to be crucially required for the functional maturation of cortical circuits as they enable high local synchrony of activity (Vanhatalo and Kaila, 2006; Tolonen et al., 2007; Kilb et al., 2011; Siegel et al., 2012; Khazipov et al., 2013; Winnubst et al., 2015; Yang et al., 2016; Luhmann and Khazipov, 2018). Many activity patterns can be replicated using *in vitro* preparations indicating that at minimum cortical circuits and thalamocortical inputs

are required (Sun and Luhmann, 2007; Sun et al., 2010). The origin of early cortical oscillations is not known but likely involve the complex interplay of ascending thalamocortical and descending corticothalamic circuits (Yang et al., 2013, 2016; Murata and Colonnese, 2016). Due to their location at the center of thalamocortical and corticothalamic circuits, SPNs can influence cortical activity patterns. Indeed, electrical stimulation of SPNs in an *in vitro* preparation could cause oscillations (Sun and Luhmann, 2007) and removal of SPNs *in vitro* abolishes oscillations (Dupont et al., 2006). Further evidence for the crucial role of SPNs in the development of cortical oscillations came from selective ablation studies (Tolner et al., 2012). These *in vivo* ablation studies showed that SPNs are required for both spontaneous and sensory-evoked oscillations (Tolner et al., 2012). Together, these observations point to a key role of SPNs in the generation or transmission of cortical oscillations. Since, during the time when spontaneous activity is present, many connections to SPNs are NMDAR-only, this suggests that NMDAR-only synapses on SPNs might play a key role in controlling cortical oscillations. Indeed, the synchronized oscillations in developing somatosensory cortex are mediated through NMDARs (Dupont et al., 2006; Minlebaev et al., 2009; Yang et al., 2009).

SPNs MIGHT CONDITIONALLY INTEGRATE ASCENDING AND INTRACORTICAL ACTIVITY VIA SILENT SYNAPSES

The above reflections and the emerging connectivity diagram suggest that the presence of abundant silent and non-silent synapses on SPNs enables SPNs to play important associative roles during development. As mentioned above, SPNs are heterogenous and can functionally be classified into two main groups based on their amount of L4 input but which can further be subdivided based on the amount of intralaminar connectivity which in auditory cortex likely reflects integration across the frequency axis (Meng et al., 2014). One group of SPNs (**Figure 2A** groups 1 and 3) does not receive L4 inputs and thus primarily depends on feed-forward inputs. The second group (**Figure 2A** groups 2 and 4) does not only integrate feed-forward thalamocortical inputs from MGB but also receives significant feedback inputs from L4. Thus, both feed-forward and feed-back inputs are affected by the resting potential. Both groups of SPNs can be further subdivided based on the amount of lateral intralaminar integration. Given the heterogeneity, the role of silent connections likely differs between these subgroups of SPNs.

On one hand, SPNs receive early spontaneous and sensory-evoked inputs *via* the thalamus and on the other hand, they receive early cortical inputs. While sensory stimulation can lead to activity in the matching cortical area (e.g., sounds in auditory cortex or touch in somatosensory cortex), other sources of intracortical activity can also be present such as activity, e.g., multisensory, originating in other cortical areas or intrinsically generated non-sensory evoked activity (Garaschuk et al., 2000; Adelsberger et al., 2005; Khazipov and Luhmann, 2006; Siegel et al., 2012). Thus, by virtue of their position between ascending

thalamic circuits and cortical circuits, SPNs can potentially associate ascending and intracortical activity. Moreover, the presence of NMDARs, and not AMPARs, allows SPNs to directly gate and associate cortical activity with ascending thalamic information (**Figure 2B**). This is due to the fact that NMDARs will not signal unless SPNs are depolarized. Ascending thalamic input can depolarize SPNs and thus remove the Mg^{2+} block from NMDARs. If sufficient cortical activity is present at the same time then cortico-SP synapses will signal, enhancing the SPN response. Since SPNs innervate L4 and beyond, a temporal coincidence of cortical activity with the ascending activity will boost the ascending thalamic signal. Moreover, because SPNs also project to the thalamus (Viswanathan et al., 2017; Hoerder-Suabedissen et al., 2018), which is involved in generating oscillatory activity, boosted SPN activity has the potential to influence the generation of thalamocortical oscillations. Thus, over time this scenario likely leads to an association or synchronization of both sources of activity.

The changing presence of silent synapses changes the association between thalamic and cortical inputs. The addition of AMPARs at intracortical inputs at later ages transforms the initial conditional or gating association of thalamic and cortical inputs into an additive association (**Figure 2B**).

Besides ascending thalamic inputs other sources of activity can activate silent synapses and change the associative properties of SPNs. Because developing SPNs might have a slightly depolarized resting potential (Zhao et al., 2009), NMDAR-mediated synapses can potentially be activated by slight depolarizations from the resting potentials. In particular, the GABAR-mediated inputs to SPNs can be depolarizing due to high intracellular Cl^- level at early ages (Luhmann et al., 2016). Thus, depolarizing GABA might be able to activate the silent synapses on SPNs. Besides, since developing SPNs tend to have higher membrane resistances (Zhao et al., 2009), which leads to longer time constants, weak depolarizing inputs could be integrated in SPNs and potentially activate the NMDAR-only mediated inputs.

Thus, the existence of silent synapses from spatially specific presynaptic cells suggests a very interesting hypothesis on the functional topology of the developing cortical circuit: the inter- and intra-columnar connections involving SPNs could be dynamic (**Figure 2C**). In other words, silent synapses can enable SPNs to integrate inputs from either close by or farther away in a state-dependent manner.

Since a crucial variable in acutely un silencing silent synapses is the resting membrane potential, relatively slow acting neuromodulatory inputs could play a major role in determining the amount of integration taking place in SPNs. As mentioned above, SPNs have ACh as well as serotonin receptors (Hanganu et al., 2002, 2009; Hanganu and Luhmann, 2004; Kanold and Luhmann, 2010; Liao and Lee, 2011, 2014). Moreover, layer 6b neurons in adult, a subset of which represents surviving SPNs (Marx et al., 2017), are modulated by neurotensin controlling wakefulness (Case and Broberger, 2018). It is possible that SPNs are modulated by neuropeptides even at early ages and that their function varies thru the sleep-wake cycle due to differential

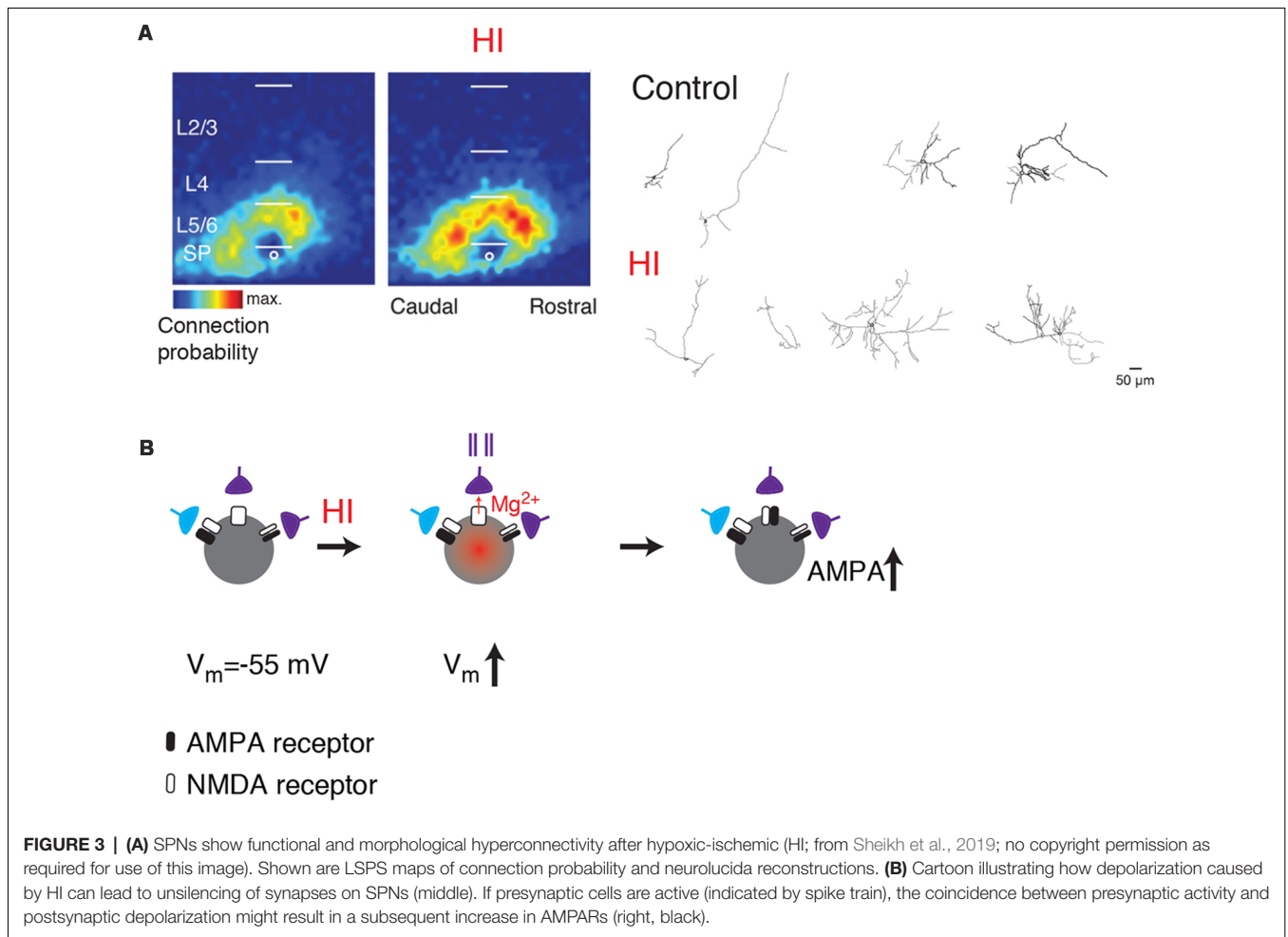
recruitment of local AMPAR-mediated vs. distal NMDAR-only mediated inputs.

DISRUPTION OF SPN IN CLINICAL CONDITIONS AND POTENTIAL ROLE OF SILENT SYNAPSES

Given the central position of SPNs, disruption of SPNs can alter many aspects of cortical development (Ghosh et al., 1990; Ghosh and Shatz, 1992; McConnell et al., 1994; Kanold et al., 2003; Kanold and Shatz, 2006; Tolner et al., 2012). Because of their early maturation and connectivity, SPNs are also susceptible to injury and resulting malfunction. For example, neonatal hypoxic-ischemic (HI) injuries in animals can lesion SPNs or in milder forms cause hyperconnectivity of SPNs (McQuillen et al., 2003; Mikhailova et al., 2017; Sheikh et al., 2019; **Figure 3A**). Such injuries are associated with altered cortical function and plasticity (Failor et al., 2010; Ranasinghe et al., 2015) similar to those observed after SPN lesion (Kanold et al., 2003; Kanold and Shatz, 2006; Tolner et al., 2012) suggesting that SPN damage after the HI injury might be leading to the downstream effects in the cortical plate.

In humans, SPN generation begins around the fifth postconceptional week and fully formed between the 20–26th week (Kanold and Luhmann, 2010). Environmental insults that occur during the first trimester can increase the risk of autism. For instance, valproate (VPA) exposure during the first trimester correlates negatively with language outcome in children (Nadebaum et al., 2011). In mice, subplate birth occurs between E11–13, and full formation of subplate by E14 (Kanold and Luhmann, 2010). Although this is outside of the first “trimester,” maternal VPA exposure during this narrow time window results in autistic phenotypes in the offspring (Mabunga et al., 2015; Nicolini and Fahnstock, 2018). Recent *in vitro* studies in rodents have shown that such prenatal VPA exposure causes miswiring of circuits to SPNs (Nagode et al., 2017). While these circuit changes were detected shortly after birth (Nagode et al., 2017), earlier ages were not studied, thus it is possible that even earlier effects of VPA on SPNs are present. Together, these studies in animal models suggest that SPNs might form a key element in the progression from prenatal insult to disease phenotype in multiple neurodevelopmental disorders.

Because subplate disappears before the onset of ASD symptoms, no direct link has been made between subplate and ASD in humans. However, one of the more intriguing indirect links is the relatively consistent finding of a blurred gray-white matter boundary in the brains of ASD individuals (Avinio and Hutsler, 2010; Hutsler and Casanova, 2016), possibly due to an increase in the number of interstitial neurons in the superficial white matter. Interstitial neurons are believed to be remnants of the fetal subplate (Chun and Shatz, 1989; Reep, 2000; Torres-Reveron and Friedlander, 2007; Suárez-Solá et al., 2009; Judaš et al., 2010), and their overabundance could reflect dysfunctional apoptotic mechanisms in ASD (Courchesne and Pierce, 2005; Avinio and Hutsler, 2010; Courchesne et al., 2011; McFadden and Minschew, 2013). Autistic patients also show an altered columnar



structure in frontal cortex (Buxhoeveden et al., 2006) and patches of disorganization are seen in L4 and L5 of the prefrontal cortex in children with autism (Stoner et al., 2014). Given the putative role of subplate in setting up protomaps of cortical organization (O’Leary and Borngasser, 2006; O’Leary et al., 2007; Wess et al., 2017; Kanold, 2019) and given that alterations are present in the target layers of SPNs, these observations are consistent with a potential role of early SPN dysfunction in the emergence of ASDs. However, the ultimate test of this possibility would require to reverse or to prevent the changes in the SPNs, which in turn could lead to treatment and prevention approaches in humans. The consequences of increased “adult subplate” or interstitial cells on circuit function are not known.

Additional indirect evidence points to a role of SPNs in ASDs. Expression profiling has identified an enrichment in subplate genes for association with ASDs (Hoerder-Suabedissen et al., 2013) but there are additional potential links between subplate damage and ASDs. Hypoxia/ischemia preferentially damages SPNs in rodents (McQuillen et al., 2003; Mikhailova et al., 2017; Sheikh et al., 2019). Birth injuries or preterm labor can lead to hypoxic situations, and both of these have been shown to increase the risk of ASD (reviewed in Rennie et al., 2007; Agrawal et al., 2018; Rogers et al., 2018). Perinatal anoxia in rats also causes ASD

phenotypes (Laviola et al., 2004). Importantly, preterm birth is also associated with an increased risk of ASD, and this might be due to an increase in the incidence of pre-eclampsia in mother of preterm infants, among other things (Buchmayer et al., 2009).

Thus, while direct evidence of SPN disruptions in ASDs is currently lacking, multiple lines of evidence suggest that understanding SPN function and susceptibility will be important in understanding the etiology of many neurodevelopmental disorders. One common thread is the vulnerability of SPNs to hypoxia/ischemia. While the acute effects of hypoxic/ischemic injuries on SPNs are unknown, anoxia can induce depolarization in cortical pyramidal cells (Luhmann et al., 1993; Rosen and Morris, 1994; O’Reilly and Haddad, 1996; Pisani et al., 1997). Thus, hypoxia might be able to “unsilence” silent synapses onto SPNs leading to an increased co-activation of presynaptic neurons and postsynaptic SPNs (Figure 3B). Such co-activation would be expected to result in increased connectivity, which is experimentally seen after HI (Sheikh et al., 2019). Indeed, *in vitro* studies showed that combined oxygen and glucose deprivation depolarizes SPNs (Albrecht et al., 2005). Moreover, hypoxia-induced seizures can diminish silent synapses in hippocampus consistent with such a scenario (Zhou et al., 2011). Thus, activation of silent synapses on SPNs by hypoxia or other

insults might be a key step in linking early insults to later circuit dysfunctions.

CONCLUSION AND OPEN QUESTIONS

While SPNs as a population of neurons are coming into clearer view, many unknowns remain. SPNs as a group are both the target of initial thalamic inputs but also receive extensive cortical input. In particular, there is an extensive connectivity of SPNs with the cortical plate mediated by NMDAR-only containing “silent” synapses at the earliest ages. These synapses are very sensitive to the resting potential of the cell, thus subtle modulation of the resting potential can modulate their activity and thus their ability to integrate inputs. Activation of silent synapses on SPNs by hypoxia or other insults might be the initial key step in a cascade of events leading to the manifestation of neurodevelopmental disorders. Therefore, interventions that limit the amount of depolarization or NMDAR signaling might be effective in preventing this chain of events. Indeed, hypothermia has been shown to be effective in reducing the effects of hypoxia on cortical neurons (Hiramatsu et al., 1993; Rosen and Morris, 1994) and improves clinical outcomes (Gunn and Bennet, 2008; Jacobs et al., 2013; Papile et al., 2014).

It is becoming clear that multiple classes of SPNs exist, but the functional roles of the subclasses are unknown. Moreover, given that SPNs are present in all cortical areas, it is likely that there are functional differences between SPNs in different cortical areas. This has not been explored at all. Most importantly, the role of SPNs in development has only been assessed in primary sensory areas, thus important roles of SPNs in other areas, e.g., frontal areas, that might relate to a potential role of SPNs in neurodevelopmental disorders is lacking. SPNs are present in all mammalian species but given that the size of the subplate zone varies between species, it is likely that there are species-dependent differences in SPN organization and

possibly function. Such differences have not been elucidated. In particular, the function of SPNs in primates has not been studied. Thus, future studies need to address the functional diversity of SPN within but also across species. Moreover, there is growing evidence of SPN dysfunction in multiple neurodevelopmental disorders. What is lacking is direct functional evidence of SPN disruption in human patients at the relevant early developmental ages. Moreover, while SPNs have been studied in primary sensory areas the phenotypes of many neurodevelopmental disorders have been most prevalent in frontal areas leaving open the possibility that dysfunctions might be more widespread or that a selective vulnerability exists for circuits in frontal areas. Functional imaging or EEG methods might be able to provide such evidence.

AUTHOR CONTRIBUTIONS

All authors made direct and intellectual contribution to the work and approved it for publication. PK wrote the manuscript with contributions from XM and RD.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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