Sensory Activity-Dependent and Sensory Activity-Independent Properties of the Developing Rodent Trigeminal Principal Nucleus

Fu-Sun Lo Reha S. Erzurumlu

Department of Anatomy and Neurobiology, University of Maryland School of Medicine, Baltimore, Md., USA

Key Words

Sensorimotor activity · Patterning · Synaptogenesis · Plasticity

Abstract

The whisker-sensory trigeminal central pathway of rodents is an established model for studies of activity-dependent neural plasticity. The first relay station of the pathway is the trigeminal principal nucleus (PrV), the ventral part of which receives sensory inputs mainly from the infraorbital branch of the maxillary trigeminal nerve (ION). Whisker-sensory afferents play an important role in the development of the morphological and physiological properties of PrV neurons. In neonates, deafferentation by ION transection leads to the disruption of whisker-related neural patterns (barrelettes) and cell death within a specific time window (critical period), as revealed by morphological studies. Whisker-sensory inputs control synaptic elimination, postsynaptic AMPA receptor trafficking, astrocyte-mediated synaptogenesis, and receptive-field characteristics of PrV cells, without a postnatal critical period. Sensory activity-dependent synaptic plasticity requires the activation of NMDA receptors and involves the participation of glia. However, the basic physiological properties of PrV neurons, such as cell type-specific ion chan-

nels, presynaptic terminal function, postsynaptic NMDA receptor subunit composition, and formation of the inhibitory circuitry, are independent of sensory inputs. Therefore, the first relay station of the whisker sensation is largely mature-like and functional at birth. Delineation of activity-dependent and activity-independent features of the postnatal PrV is important for understanding the development and functional characteristics of downstream trigeminal stations in the thalamus and neocortex. This mini review focuses on such features of the developing rodent PrV.

© 2016 S. Karger AG, Basel

Introduction

Development of the brain and the topographic organization and patterning of neural connections depend on both the genetic program and neuronal activities. Overall, genes are responsible for the basic wiring plan of different brain regions [1]. Neuronal activities are responsible for fine-tuning for the formation of precise connections (refinement) via regulation of axonal terminal arborization, dendritic branching, synaptogenesis, synaptic strengthening and elimination, and neurogenesis [2]. Neuronal activities include spontaneous and sensory activities that

play different roles in synaptic refinement. Studies on the development of retinogeniculate connections have yielded perhaps the most prominent examples. The establishment of eye-specific layers, retinotopic maps, and the majority of synaptic refinements depend on patterned spontaneous activity in the form of retinal waves [for reviews, see 3–5]. The visual experience induced by patterned retinal activity further refines and stabilizes the synaptic circuits by changing the synaptic input strength and number [6–8].

The whisker-sensory trigeminal central pathway of nocturnal rodents is another established model for studying activity-dependent synaptic plasticity. In this pathway, the first relay station is the ventral part of the trigeminal principal nucleus (PrV), which receives whisker-sensory information brought by the infraorbital nerve (ION), a thick branch arising from the maxillary nerve. Trigeminal ganglion (TG) cells that contribute axons to the ION show low-frequency spontaneous and high-frequency sensory activities [9, 10]. The spontaneous activity in the TG cells cannot be blocked with conventional sodium channel blockers such as tetrodotoxin, perhaps due to tetrodotoxin-resistant sodium channels and/or voltage-gated calcium channels. Nevertheless, the sensory activity in the TG cells can be blocked by ION transection or crush that leads to synaptic plasticity in the PrV [for a review, see 11]. In the present review, we summarize the activity dependence of various morphological and physiological properties of the developing PrV.

Sensory Activity-Dependent Properties within a Time Window

Barrelette Formation and Consolidation

Barrelettes are built by focalized presynaptic afferent arbors and trigeminothalamic projection neurons, their main partners around birth. The spatial arrangement of these neural modules replicates the punctate distribution of whisker follicles in 5 rows on the snout and the perioral sinus [12–16]. Damage to the sensory periphery (ION) before postnatal day 3 (P3) results in disruption of their central neural correlates [for reviews, see 17–20]. Peripheral nerve injury also leads to aberrant orientation of the dendritic trees of barrelette cells [21, 22]. After this time window (critical period), ION transection fails to alter the neural patterning and dendritic orientation bias. Thus, barrelette formation and consolidation are dependent on an intact sensory periphery and ION during the critical period (P0 to P3).

PrV Cell Death

Neonatal ION transection leads to cell death in the TG [23–26] and PrV [27–29] due to the loss of sensory activity in TG cells. Neural activity, particularly through N-methyl-D-aspartate receptors (NMDAR), can protect neurons against programmed cell death [30]. Most likely, deafferentation-induced cell death in the PrV is limited to a critical period, as in other brain regions. For example, cell death in the spinal cord dorsal horn by dorsal root injury occurs on P1 to P2 but not on P14 [31]; cell death in the anteroventral cochlear nucleus of mice results from cochlea removal on P5, not on P14 [32]. In addition, ION transection in rats before P7 also leads to transneuronal degeneration (cell death) in the thalamic ventroposteromedial nucleus (VPM). ION transection after P7 does not lead to cell death in the VPM [33]. The existence of a critical period for cell death in the PrV is supported by an early study in rats. Neonatal ION transection led to a 21% reduction of the cross-sectional area of PrV, and ION damage on P60 did not result in a significant change in the area [27].

Sensory Activity-Dependent Properties without a Time Window

Synaptic Refinement

Synaptic connections between the TG and the PrV are subject to postnatal refinement that can be revealed by multiple input index (MII) analysis. This is an electrophysiological estimation approach used to assess developmental changes in synaptic connections in various brain structures [see discussion in 34]. In response to an increasing intensity of trigeminal tract (TrV) stimulation, the amplitude of the excitatory postsynaptic currents (EPSC) in barrelette neurons increases in steps. The number of steps (MII) acts as an index of the minimal number of TrV fibers converging onto each recorded neuron. MII analysis in the PrV has shown that afferent connections decrease by ~30% within 2 postnatal weeks [34]. The synaptic elimination (decrease in MII) does not occur after ION transection on both P0 and P4 (after the critical period); instead, the MII is increased by synaptogenesis (see Suppression of Synaptogenesis), suggesting that synaptic elimination depends on sensory activity without a critical period.

Postsynaptic AMPA Receptor Trafficking

Within the first postnatal week, about 80% of the synapses in the PrV are functional, with both α -amino-3-

hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA)- and NMDAR-mediated postsynaptic responses. About 20% are silent synapses, in which there are almost no AMPAR-mediated response, just like those shown in hippocampal and cortical slices [35–37]. After neonatal ION transection, most functional synapses turn into silent synapses lacking functional AMPAR. Increased AMPAR surface expression (exocytosis) by glycine immediately causes the AMPAR-mediated response to resume. Besides, silent synapses convert to functional synapses by NMDAR-mediated 50-Hz activity, but not by 1-Hz activity, suggesting that NMDAR-mediated high-frequency input activities promote AMPAR exocytosis. Maintenance of AMPAR function also depends on whisker-sensory inputs, because after neonatal ION transection silent synapses persist through the second postnatal week [38]. Neonatal ION crush blocks the conducting function of about two thirds of the ION fibers. ION function recovers partially at 5 days postinjury and the recovery is complete by postinjury day 7. During blockade of ION function, the incidence of silent synapses increases ~3.5-fold in relation to the control value. The incidence of silent synapses drops to the control value on postinjury days 5–7, when the ION function has mostly recovered. Thus, AMPAR trafficking depends on sensory afferents even after the critical period of PrV pattern plasticity [39].

Suppression of Synaptogenesis

After neonatal ION transection, MII analysis demonstrates an increase in excitatory connections from TG cells to single barrelette neurons in the rat PrV. The estimated number of converging ganglion cells (i.e. MII) gradually increases from postinjury day 2 to day 5 and remains unchanged in the second postnatal week. This suggests that at an early stage of postnatal development, after disruption of the sensory input flow, quite a few new synapses form between surviving TG and barrelette cells. In other brain structures of adult animals, deafferentation-induced new synapse formation has been identified as reactive synaptogenesis [40–46]. Reactive synaptogenesis in the deafferented PrV can also be induced by ION transection on P4 (after the critical period) with a similar time course [34], suggesting that reactive synaptogenesis is not limited to a time window.

Reaction of Astrocytes to Deafferentation

Neonatal ION transection leads to significant gliosis in the PrV, with a dramatic increase in astrocyte number and the length and thickness of their processes under

light microscopic observation. Pharmacological and morphological studies suggest that this reaction of astrocytes promotes synaptogenesis [34]. The extracellular ATP concentration increases after ION transection, so that quiescent astrocytes convert to reactive ones with an upregulated glial fibrillary acidic protein (GFAP; astrocyte marker) expression via the activation of purinergic receptors on astrocytes. Subsequently, reactive astrocytes release some molecules such as thrombospondins that promote synaptogenesis [for reviews, see 47–49]. A similar reaction of astrocytes is also observed in the PrV during blockade of ION conduction after ION crush. However, after functional recovery of ION on P10 (after the critical period), this particular reaction is no longer visible with GFAP immunocytochemistry [39]. Therefore, the astrocyte reaction is controlled by sensory afferents without a critical time window.

Reaction of Microglia to Deafferentation

Deafferentation induces an increase in the number, cell body size, and processes of microglia in the PrV. This reaction is no longer present after the recovery of ION function [39]. Although the effects of microglia reaction on synaptic plasticity in the PrV are still unknown, sensory afferents from whiskers do modify microglia function without a critical period.

Receptive Fields of PrV Cells

Receptive-field properties of the PrV cells are investigated with in vivo recording techniques. In the first in vivo recordings of the rat PrV [50], the recorded cell types were not identified. Later studies [51] identified barrelette (trigeminothalamic relay) cells of the PrV by antidromic activation from thalamic stimulation, and further investigations [9, 52–57] revealed that rat barrelette cells respond to whisker deflection by tonic (slowly adapting, a train of spikes) or phasic (rapidly adapting, a few spikes) discharges. Sanchez-Jimenez et al. [57] demonstrated that the two responses are caused by differential action of the somatosensory cortex on a unique type of PrV cell. Aspiration of the contralateral somatosensory cortex results in almost complete disappearance of phasic responses in the PrV by loss of corticofugal projection-induced inhibition (membrane hyperpolarization). Electrophysiological and numerical simulative results [57] show that the somatosensory cortex exerts strong modulation on the responses of PrV cells by direct projection or indirectly via intranuclear connections arising from the spinal trigeminal nucleus [56, 58, 59]. PrV barrelette cells also have 2 types of receptive fields, responding to a single

whisker (majority) and multiple whiskers (minority). A polysynaptic pathway in the brainstem might mediate the response to multiple whiskers [54].

Neonatal ION transection induces expansion of the receptive fields of the PrV cells to other areas such as the lower jaw and intraoral fields, the skin of the nose, and the whiskers by the eye and the ear [27]. This suggests that PrV cells receive new synaptic connections from other afferent fibers. Because reactive synaptogenesis occurs also in adult animals, the expansion of receptive fields should take place even after ION injury in adults despite the negative results from an earlier study [27].

Sensory Activity-Independent Properties

Cell Type-Specific Ion Channels in the PrV

The PrV contains 3 types of cells: barrelette (relay to VPM), interbarrelette (interconnections among the brainstem trigeminal nuclei), and GABAergic interneuron (form inhibitory circuits). Barrelette and interbarrelette cells can be identified by their specific ion channels with combined biocytin intracellular staining and whole-cell patch recording from in vitro PrV brainstem slice preparations [60]. Barrelette cells possess A-type potassium conductance. Interbarrelette cells show a low-threshold spike mediated by T-type Ca^{2+} channels. In addition, some presumable GABAergic interneurons show fast-spiking properties with a narrow action potential and a high-frequency firing pattern upon membrane depolarization. Thus, each type of PrV cell can be identified electrophysiologically. Cell type-specific channels are not dependent on the sensory afferents, because after ION transection surviving PrV cells show the same specific ion channels.

Development of the Membrane Properties of PrV Cells

As early as P1, both barrelette and interbarrelette cells display mature-like morphological and electrophysiological characteristics. During postnatal development (P1 to P13), there are no further changes in resting potential, the composition of active conductances, or Na^+ spikes. The only notable change is a decline in the input resistance of both cell types because of cell growth. For interbarrelette cells, the amplitude of low-threshold spikes is slightly increased [22]. Thus, there are no significant changes in the membrane properties of PrV cells during postnatal development. After ION transection, the basic membrane properties of the surviving barrelette cells and the interbarrelette cells are similar to those of normal PrV cells, despite the disruption of barrelettes and the symmetrical

orientation of the dendritic trees of the surviving barrelette cells [22]. Therefore, the development of membrane properties in the PrV does not depend on sensory synaptic inputs.

Presynaptic Transmitter Release Probability of Trigeminal Afferent Terminals

PrV cells receive whisker-sensory afferents via the trigeminal tract (TrV), formed by the central axonal branches of the TG cells. A paired-pulse protocol was used to reveal the transmitter release probability of the TG central terminals. The Pr varied from low to high in a Gaussian distribution of paired pulse ratios with a peak at 100% [61]. This presynaptic property may facilitate the transmission of continuous TG responses [62] to the PrV neurons. Thus, the PrV differs from the thalamic VPM nucleus and the barrel cortex, which receive exclusively high Pr presynaptic afferent terminals downstream from the PrV [63–72]. Neonatal ION transection induces the death of 9–10% of TG cells [25, 26]. The central terminals of the surviving TG cells are still functional, although their peripheral branches are transected. The distribution of paired pulse ratios also fits to similar Gaussian functions in the deafferented PrV [61], and thus the broad spectrum of presynaptic transmitter release probabilities is not sensory activity dependent.

NMDAR Subunit Composition of PrV Cells

NMDAR are made of an essential NR1 subunit and NR2 and/or NR3 subunits. NR2A and NR2B are the predominant subunits. The kinetic properties of NMDA channels, such as the decay speed of EPSC, depend on the NMDAR subunit composition that can be determined by the weighted decay time constant (τ_w) of NMDAR-mediated EPSC and Western blot analysis [for reviews, see 73, 74]. The τ_w measurement reveals that NMDAR contain both NR2A and NR2B subunits in barrelette and interbarrelette cells. The NR2A/NR2B ratio does not change during postnatal development (P0 to P14) [75], so that NMDAR-mediated EPSC always has a slow decay, i.e. a longer duration. Because tonic firing is the common response to whisker deflection for the majority of the TG cells [76], a longer EPSP in the PrV may facilitate the synaptic transmission of tonic signals. The unchanged NR2A/NR2B ratio is also confirmed by Western blot analysis [74]. This is another unique property in the first relay station of the trigeminal central pathway. In the barrel cortex and thalamic VPM, there is a switch from NR2B to NR2A subunits during postnatal development [77–79]. Additionally, the subunit composition of postsynap-

tic NMDAR is independent of the sensory afferent activity because, after neonatal deafferentation, the NR2A/NR2B ratio of the surviving PrV cells remains unchanged [75].

Inhibitory Circuits

In neonatal PrV-brainstem slices, stimulation of the trigeminal afferent fibers induces both postsynaptic excitatory and inhibitory responses in barrelette cells, suggesting that postsynaptic circuits have formed by birth. Latency analyses have shown that a monosynaptic circuit mediates the excitatory response, while a disynaptic circuit mediates the inhibitory response [59]. Neonatal ION transection results in cell death in both TG [23–26] and PrV [27–29] and strengthening of excitatory synaptic connections as described above. The inhibitory response is still present in the surviving barrelette cells, suggesting that both the formation and the stabilization of inhibitory circuits in the PrV do not depend on sensory inputs.

Discussion and Conclusion

The Sensory Pathway from the Whiskers to the PrV Is Functionally Mature at Birth

Whisker and circumoral sensation is critical for development of newborn rodent pups. The lack of a passive whisker touch at an early neonatal stage diminishes postnatal weight gain and impairs whisker sensorimotor coordination behaviors [80]. At birth, the whisker-related neural pattern (barrelettes) is formed already, and specific morphological and physiological characteristics differentiate 3 types of PrV cells. The excitatory and inhibitory circuits are mostly functional. The presynaptic release probability of TG axon terminals, the membrane properties of PrV cells, and the NMDAR subunit composition in the PrV are adult-like, without remarkable postnatal development. The only important postnatal development is synaptic pruning that refines synaptic connections. Compared to the thalamic VPM and the barrel cortex, the PrV has unique properties, such as a broad spectrum of presynaptic release probability, and further lacks NMDAR subunit composition shifts. The physiological mechanisms underlying the prenatal development of the PrV need elucidation.

Activation of NMDAR Plays a Pivotal Role in Synaptic Plasticity in the PrV

NMDAR-mediated high-frequency activity (as similarly induced by sensory inputs) is required for AMPAR exocytosis. This suggests that high-frequency activation

of NMDAR may induce long-term potentiation and strengthen the synaptic connections. Synaptic elimination (refinement) in the PrV also depends on high-frequency sensory activity rather than low-frequency spontaneous activity. This seems to contradict the general conception that a lower Ca^{2+} influx by low-frequency NMDAR-mediated activity triggers long-term depression (LTD) that results in synaptic elimination. However, this view has been revised and expanded by recent studies [81–83] showing that LTD induction does not require a Ca^{2+} influx. LTD is induced by nonionotropic (metabotropic) NMDAR signaling, so that high-frequency synaptic activation can induce LTD if the Ca^{2+} flux through the NMDAR is blocked. This may normally occur when a synapse is hyperactive while surrounding synapses onto the same cell are inactive, or when excitatory synapses are active during inhibitory tone [81].

It is noteworthy that the effects of ION transection and loss of NMDAR function are similar to each other. In the PrV, ION transection results in a lack of orientation of the dendritic trees of barrelette cells [22], while the same change in the dendritic trees of barrelette cells is present in the PrV of NR1 subunit knockdown mice [84]. In addition, ION transection leads to an increase in MII in the PrV of rats [33], while cortex-specific knockout of the NR1 subunit in mice results in a similar increase in MII in layer 4 of the barrel cortex [85]. These findings suggest that NMDAR-mediated activity is involved in dendrite branching and synaptogenesis.

Reaction of Glia in Activity-Dependent Plasticity

Deafferentation leads to the reaction of astrocytes and microglia in the PrV of rats without a time window. Morphological and pharmacological studies have shown that reactive astrocytes mediate synaptogenesis in deafferented PrV [33]. However, more studies are needed to detail the effects of reactive astrocytes and microglia on PrV development more comprehensively.

On the whole, whisker-related sensory activities play a crucial role in the postnatal development of the first relay station of the central trigeminal pathway. Additionally, other factors contribute to pre- and postnatal development. For example, the formation of a barrelette map in the PrV depends on molecular signals from the whisker follicles that retrogradely regulate the expression of positional identity genes in the TG through the ION, so that TG axons project to the PrV topographically [86, 87]. Such signaling seems to be missing at postnatal stages, indicating that postnatal consolidation of barrelettes relies exclusively on sensory activities.

The studies discussed here clearly show that central sensory relay areas of the mammalian brain do not share common features solely based on the first, second, etc., relay zones but rather most likely based on their specific location along the neuraxis. In this context, the first relay station of the visual pathway from the optic nerve, i.e. the lateral geniculate nucleus of the thalamus, differs significantly from the PrV but most likely shares commonalities with the second relay station of the trigeminal somato-

sensory pathway, i.e. the thalamic VPM nucleus. Perhaps there are more common features between the brainstem sensory nuclei, such as the dorsal column nuclei and the nucleus of the solitary tract and the PrV.

Acknowledgement

This study was supported by NIH grant NS037070.

References

- Goodman CS, Shatz CJ: Developmental mechanisms that generate precise patterns of neuronal connectivity. *Cell* 1993;72:77–98.
- Bruel-Jungerman E, Davis S, Laroche S: Brain plasticity mechanisms and memory: a part of four. *Neuroscientist* 2007;13:492–505.
- Torborg CL, Feller MB: Spontaneous patterned retinal activity and the refinement of retinal projections. *Prog Neurobiol* 2005;76:213–235.
- Huberman AD, Feller MB, Chapman B: Mechanisms underlying development of visual maps and receptive fields. *Annu Rev Neurosci* 2008;31:479–509.
- Assali A, Gaspar P, Rebsam A: Activity dependent mechanisms of visual map formation – from retinal waves to molecular regulators. *Semin Cell Dev Biol* 2014;35:136–146.
- Hong YK, Chen C: Wiring and rewiring of the retinogeniculate synapse. *Curr Opin Neurobiol* 2011;21:228–237.
- Hong YK, Park S, Litvina EY, Morales J, Sanes JR, Chen C: Refinement of the retinogeniculate synapse by bouton clustering. *Neuron* 2014;84:332–339.
- Lin DJ, Kang E, Chen C: Changes in input strength and number are driven by distinct mechanisms at the retinogeniculate synapse. *J Neurophysiol* 2014;112:942–950.
- Minnery BS, Simons DJ: Response properties of whisker-associated trigeminothalamic neurons in rat nucleus principalis. *J Neurophysiol* 2003;89:40–56.
- Shoykhet M, Shetty P, Minnery BS, Simons D: Protracted development of responses to whisker deflection in rat trigeminal ganglion neurons. *J Neurophysiol* 2003;90:1432–1437.
- Lo FS, Erzurumlu RS: Neonatal sensory nerve injury-induced synaptic plasticity in the trigeminal principal sensory nucleus. *Exp Neurol* 2016;275:245–252.
- Bates CA, Killackey HP: The organization of the neonatal rat's brainstem trigeminal complex and its role in the formation of central trigeminal patterns. *J Comp Neurol* 1985;240:265–287.
- Belford GR, Killackey HP: Vibrissae representation in subcortical trigeminal centers of the neonatal rat. *J Comp Neurol* 1979;183:305–322.
- Erzurumlu RS, Bates CA, Killackey HP: Differential organization of the thalamic projection cells in the brainstem trigeminal complex of the rat. *Brain Res* 1980;193:427–433.
- Ma PM: Barrellettes: architectonic vibrissal representations in the brainstem trigeminal complex of the mouse. 2. Normal postnatal development. *J Comp Neurol* 1993;327:376–397.
- Ma PM, Woolsey TA: Cytoarchitectonic correlates of the vibrissae in the medullary trigeminal complex of the mouse. *Brain Res* 1984;306:374–379.
- Erzurumlu RS, Killackey HP: Defining critical and sensitive periods in neurobiology; in Hunt RK (ed): *Current Topics in Developmental Biology – Neural Development: Part III*. New York, Academic Press, 1982, vol 17, pp 207–240.
- Jhaveri S, Erzurumlu RS: Two phases of pattern formation in the developing rat trigeminal system; in Sharma SC, Goffinet AM (eds): *Development of the Central Nervous System in Vertebrates*. New York, Plenum Press, 1992, pp 167–178.
- O'Leary DDM, Ruff NL, Dyck RH: Development, critical period plasticity, and adult reorganizations of mammalian somatosensory systems. *Curr Opin Neurobiol* 1994;4:535–544.
- Woolsey TA: Peripheral alteration and somatosensory development; in Coleman EJ (ed): *Development of Sensory Systems in Mammals*. New York, Wiley, 1990, pp 461–516.
- Arends JA, Jacquin MF: Lucifer yellow staining in fixed brain slices: optimal methods and compatibility with somatotopic markers in neonatal brain. *J Neurosci Methods* 1993;50:321–339.
- Lo FS, Erzurumlu RS: Neonatal deafferentation does not alter membrane properties of trigeminal nucleus principalis neurons. *J Neurophysiol* 2001;85:1088–1096.
- Aldskogius H, Arvidsson J: Nerve cell degeneration and death in the trigeminal ganglion of the adult rat following peripheral nerve transection. *J Neurocytol* 1978;7:229–250.
- Aldskogius H, Arvidsson J, Grant G: The reaction of primary sensory neurons to peripheral nerve injury with particular emphasis on transganglionic changes. *Brain Res* 1985;357:27–46.
- Sugimoto T, Xiao C, Ichikawa H: Neonatal primary neuronal death induced by capsaicin and axotomy involves an apoptotic mechanism. *Brain Res* 1998;807:147–154.
- Sugimoto T, Jin H, Fijita M, Fukunaga T, Nagaoka N, Yamaai T, Ichikawa H: Induction of activated caspase-3-immunoreactivity and apoptosis in the trigeminal ganglion neurons by neonatal peripheral nerve injury. *Brain Res* 2004;1017:238–243.
- Waite PM: Rearrangement of neuronal responses in the trigeminal system of the rat following peripheral nerve section. *J Physiol* 1984;352:425–445.
- Miller MW, Kuhn PE: Neonatal transection of the infraorbital nerve increases the expression of proteins related to neuronal death in the principal sensory nucleus of the trigeminal nerve. *Brain Res* 1997;769:233–244.
- Miller MW: A longitudinal study of the effects of prenatal ethanol exposure on neuronal acquisition and death in the principal sensory nucleus of the trigeminal nerve: interaction with changes induced by transection of the infraorbital nerve. *J Neurocytol* 1999;28:999–1015.
- de Rivero Vaccari JC, Casey GP, Aleem S, Park WM, Corriveau RA: NMDA receptors promote survival in somatosensory relay nuclei by inhibiting Bax-dependent developmental cell death. *Proc Natl Acad Sci USA* 2006;103:16971–16976.
- Chew DJ, Leinster VH, Sakthithasan M, Robson LG, Carlstedt T, Shortland PJ: Cell death after dorsal root injury. *Neurosci Lett* 2008;433:231–234.
- Mostafapour SP, Cochran SL, Del Puerto NM, Rubel EW: Patterns of cell death in mouse anteroventral cochlear nucleus neurons after unilateral cochlea removal. *J Comp Neurol* 2000;426:561–571.

- 33 Baldi A, Calia E, Ciampini A, Riccio M, Vetuschi A, Persico AM, Keller F: Deafferentation-induced apoptosis of neurons in thalamic somatosensory nuclei of the newborn rat: critical period and rescue from cell death by peripherally applied neurotrophins. *Eur J Neurosci* 2000;12:2281–2290.
- 34 Lo FS, Zhao S, Erzurumlu RS: Astrocytes promote peripheral nerve injury-induced reactive synaptogenesis in the neonatal CNS. *J Neurophysiol* 2011;106:2876–2887.
- 35 Isaac JT, Nicoll RA, Malenka RC: Evidence for silent synapses: implications for the expression of LTP. *Neuron* 1995;15:427–434.
- 36 Isaac JT, Crair MC, Nicoll RA, Malenka RC: Silent synapses during development of thalamocortical inputs. *Neuron* 1997;18:269–280.
- 37 Liao D, Hessler NA, Malinow R: Activation of postsynaptically silent synapses during pairing-induced LTP in CA1 region of hippocampal slice. *Nature* 1995;375:400–404.
- 38 Lo FS, Erzurumlu RS: Conversion of functional synapses into silent synapses in the trigeminal brainstem after neonatal peripheral nerve transection. *J Neurosci* 2007;27:4929–4934.
- 39 Lo FS, Zhao S, Erzurumlu RS: Neonatal infraorbital nerve crush-induced CNS synaptic plasticity and functional recovery. *J Neurophysiol* 2014;111:1590–1600.
- 40 Matthews DA, Cotman C, Lynch G: An electron microscopic study of lesion induced synaptogenesis in the dentate gyms of the adult rat. 2. Reappearance of morphologically normal synaptic contacts. *Brain Res* 1976;115:23–41.
- 41 Cotman CW, Anderson KJ: Synaptic plasticity and functional stabilization in the hippocampal formation: possible role in Alzheimer's disease. *Adv Neurol* 1988;47:313–335.
- 42 Hamori J: Morphological plasticity of post-synaptic neurones in reactive synaptogenesis. *J Exp Biol* 1990;153:251–260.
- 43 Dieringer N: 'Vestibular compensation': neural plasticity and its relations to functional recovery after labyrinthine lesions in frog and other vertebrates. *Prog Neurobiol* 1995;46:97–125.
- 44 Deller T, Frotscher M: Lesion-induced plasticity of central neurons: sprouting of single fibres in the rat hippocampus after unilateral entorhinal cortex lesion. *Prog Neurobiol* 1997;53:687–727.
- 45 Collazos-Castro JE, Nieto-Sampedro M: Developmental and reactive growth of dentate gyrus afferents: cellular and molecular interactions. *Restor Neurol Neurosci* 2001;19:169–187.
- 46 Marrone DF, Petit TL: The role of synaptic morphology in neural plasticity: structural interactions underlying synaptic power. *Brain Res Rev* 2002;38:291–308.
- 47 Ullian EM, Christopherson KS, Barres BA: Role for glia in synaptogenesis. *Glia* 2004;47:209–216.
- 48 Risher WC, Eroglu C: Thrombospondins as key regulators of synaptogenesis in the central nervous system. *Matrix Biol* 2012;31:170–177.
- 49 Allen NJ: Role of glia in developmental synapse formation. *Curr Opin Neurobiol* 2013;23:1027–1033.
- 50 Shipley MT: Response characteristics of single units in the rat's trigeminal nuclei to vibrissa displacements. *J Neurophysiol* 1974;37:73–90.
- 51 Jacquin MF, Golden J, Panneton WM: Structure and function of barrel 'precursor' cells in trigeminal nucleus principalis. *Brain Res* 1988;471:309–314.
- 52 Veinante P, Deschênes M: Single- and multi-whisker channels in the ascending projections from the principal trigeminal nucleus in the rat. *J Neurosci* 1999;19:5085–5095.
- 53 Sosnik R, Haidarliu S, Ahissar E: Temporal frequency of whisker movement. 1. Representations in brainstem and thalamus. *J Neurophysiol* 2001;86:339–353.
- 54 Minnery BS, Bruno RM, Simons DJ: Response transformation and receptive-field synthesis in the lemniscal trigeminothalamic circuit. *J Neurophysiol* 2003;90:1556–1570.
- 55 Moreno A, Garcia-Gonzalez V, Sanchez-Jimenez A, Panetsos F: Principalis, oralis and interopolaris responses to whisker movements provoked by air jets in rats. *Neuroreport* 2005;16:1569–1573.
- 56 Sanchez-Jimenez A, Panetsos F, Murciano A: Early frequency-dependent information processing and cortical control in the whisker pathway of the rat electrophysiological study of brainstem nuclei principalis and interopolaris. *Neuroscience* 2009;160:212–226.
- 57 Sanchez-Jimenez A, Torets C, Panetsos C: Complementary processing of haptic information by slowly and rapidly adapting neurons in the trigeminothalamic pathway: electrophysiology, mathematical modeling and simulations of vibrissae-related neurons. *Front Cell Neurosci* 2013;7:79.
- 58 Malmierca E, Chaves-Coira I, Rodrigo-Angulo M, Nuñez A: Corticofugal projections induce long-lasting effects on somatosensory responses in the trigeminal complex of the rat. *Front Syst Neurosci* 2014;8:100.
- 59 Furuta T, Timofeeva E, Nakamura K, Okamoto-Furuta K, Togo M, Kaneko T, Deschênes M: Inhibitory gating of vibrissal inputs in the brainstem. *J Neurosci* 2008;28:1789–1797.
- 60 Lo FS, Guido W, Erzurumlu RS: Electrophysiological properties and synaptic responses of cells in the trigeminal principal sensory nucleus of postnatal rats. *J Neurophysiol* 1999;82:2765–2775.
- 61 Lo FS, Erzurumlu RS: Peripheral nerve damage does not alter release properties of developing central trigeminal afferents. *J Neurophysiol* 2011;105:1681–1688.
- 62 Jones LM, Lee SH, Trageser JC, Simons DJ, Keller A: Precise temporal responses in whisker trigeminal neurons. *J Neurophysiol* 2004;92:665–668.
- 63 Castro-Alamancos MA: Properties of primary sensory (lemniscal) synapses in the ventrobasal thalamus and the relay of high-frequency sensory inputs. *J Neurophysiol* 2002;87:946–953.
- 64 Laurent A, Goillard JM, Cases O, Lebrand C, Gaspar P, Ropert N: Activity-dependent pre-synaptic effect of serotonin 1B receptors on the somatosensory thalamocortical transmission in neonatal mice. *J Neurosci* 2002;22:886–900.
- 65 Deschênes M, Timofeeva E, Lavallee P: The relay of high-frequency sensory signals in the whisker-to-barrel pathway. *J Neurosci* 2003;23:6778–6787.
- 66 Yanagisawa T, Tsumoto T, Kimura F: Transiently higher release probability during critical period at thalamocortical synapses in the mouse barrel cortex: relevance to differential short-term plasticity of AMPA and NMDA EPSCs and possible involvement of silent synapses. *Eur J Neurosci* 2004;20:3006–3018.
- 67 Fontanez DE, Porter JT: Adenosine A1 receptors decrease thalamic excitation of inhibitory and excitatory neurons in the barrel cortex. *Neuroscience* 2006;137:1177–1184.
- 68 Lu HC, Butts DA, Kaeser PS, She WC, Janz R, Crair MC: Role of efficient neurotransmitter release in barrel map development. *J Neurosci* 2006;26:2692–2703.
- 69 Iwasato T, Imam M, Kanki H, Erzurumlu RS, Itohara S, Crair MC: Cortical adenylyl cyclase 1 is required for thalamocortical synapse maturation and aspects of layer IV barrel development. *J Neurosci* 2008;28:5931–5943.
- 70 Lee CC, Sherman SM: Synaptic properties of off-thalamic and intracortical inputs to layer 4 of the first- and higher-order cortical areas in the auditory and somatosensory systems. *J Neurophysiol* 2008;100:317–326.
- 71 Wang H, Zhang ZW: A critical window for experience-dependent plasticity at whisker sensory relay synapse in the thalamus. *J Neurosci* 2008;28:13621–13628.
- 72 Zhu JJ: Activity level-dependent synapse-specific AMPA receptor trafficking regulates transmission kinetics. *J Neurosci* 2009;29:6320–6335.
- 73 Paoletti P, Bellone C, Zhou Q: NMDA receptor subunit diversity: impact on receptor properties, synaptic plasticity and disease. *Nat Rev Neurosci* 2013;14:383–400.
- 74 Sanz-Clemente A, Nicoll RA, Roche KW: Diversity in NMDA receptor composition: many regulators, many consequences. *Neuroscientist* 2013;19:62–75.
- 75 Lo FS, Zhao S: N-methyl-D-aspartate receptor subunit composition in the rat trigeminal principal nucleus remains constant during postnatal development and following neonatal denervation. *Neuroscience* 2011;178:240–249.
- 76 Lichtenstein SH, Carvell GE, Simons DJ: Responses of at trigeminal ganglion neurons to movements of vibrissae in different directions. *Somatosens Mot Res* 1990;17:47–65.

- 77 Lu HC, Gonzales E, Crair MC: Barrel cortex critical period plasticity is independent of changes in NMDA receptor subunit composition. *Neuron* 2001;32:619–634.
- 78 Liu XB, Murray KD, Jones EG: Switching of NMDA receptor 2A and 2B subunits at thalamic and cortical synapses during early postnatal development. *J Neurosci* 2004;24:8885–8895.
- 79 Mierau SB, Meredith RM, Upton AL, Paulsen O: Dissociation of experience-dependent and -independent changes in excitatory synaptic transmission during development of barrel cortex. *Proc Natl Acad Sci USA* 2004;101:15518–15523.
- 80 Arakawa H, Erzurumlu RS: Role of whiskers in sensorimotor development of C57BL/6 mice. *Behav Brain Res* 2015;287:146–155.
- 81 Nabavi S, Kessels HW, Alfonso S, Aow J, Fox R, Malinow R: Metabotropic NMDA receptor function is required for NMDA receptor-dependent long-term depression. *Proc Natl Acad Sci USA* 2013;110:4027–4032.
- 82 Kehoe LA, Bellone C, De Roo M, Zanduetta A, Dey PN, Pérez-Otaño I, Muller D: GluN3A promotes dendritic spine pruning and destabilization during postnatal development. *J Neurosci* 2014;34:9213–9221.
- 83 Stein IS, Gray JA, Zito K: Non-ionotropic NMDA receptor signaling drives activity-induced dendritic spine shrinkage. *J Neurosci* 2015;35:12303–12308.
- 84 Lee LJ, Lo FS, Erzurumlu RS: NMDA receptor-dependent regulation of axonal and dendritic branching. *J Neurosci* 2005;25:2304–2311.
- 85 Lo FS, Akkentli F, Tsytarev V, Erzurumlu RS: Functional significance of cortical NMDA receptors in somatosensory information processing. *J Neurophysiol* 2013;110:2627–2636.
- 86 Hodge LK, Klassen MP, Han BX, Yiu G, Hurrell J, Howell A, Rousseau G, Lemaigre F, Tessier-Lavigne M, Wang F: Retrograde BMP signaling regulates trigeminal sensory neuron identities and the formation of precise face maps. *Neuron* 2007;55:572–586.
- 87 da Silva S, Hasegawa H, Scott A, Zhou X, Wagner AK, Han BX, Wang F: Proper formation of whisker barrelettes requires periphery-derived Smad4-dependent TGF-beta signaling. *Proc Natl Acad Sci USA* 2011;108:3395–3400.