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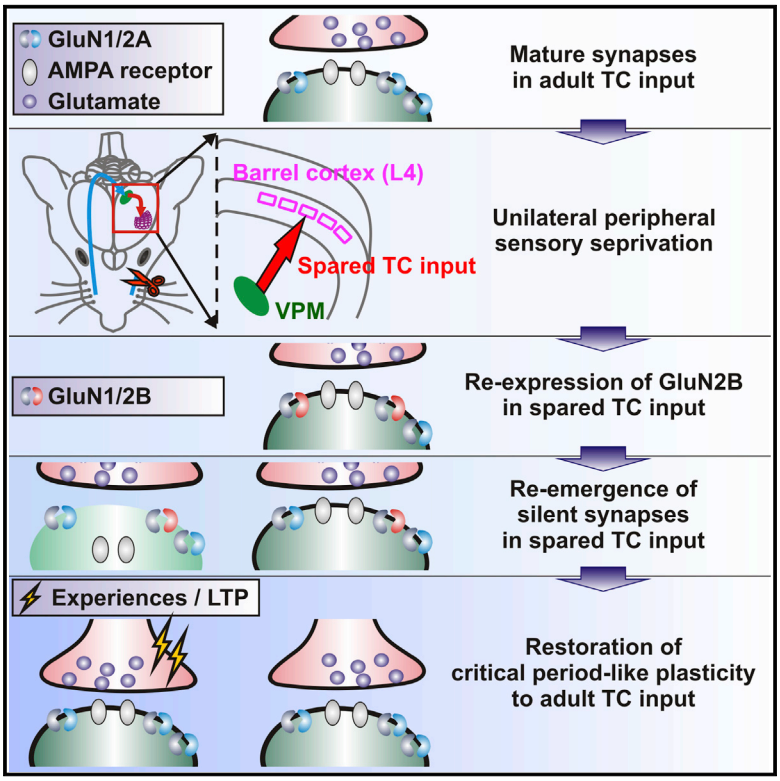
Peripheral Sensory Deprivation Restores Critical-Period-like Plasticity to Adult Somatosensory Thalamocortical Inputs

Graphical Abstract



Highlights

- Unilateral sensory deprivation leads to GluN2B re-expression in spared adult TC input
- Re-expression of GluN2B contributes to reappearance of silent synapses and LTP ability
- Anatomical map plasticity is also reactivated by unilateral sensory deprivation
- Peripheral sensory deprivation restores critical period-like plasticity in adult TC input

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In Brief

Chung et al. find that unilateral sensory deprivation restores LTP in the adult thalamocortical input. Restoration of LTP is accompanied by reappearance of silent synapses, which requires re-expression of synaptic GluN2B receptors. These results demonstrate that critical period-like plasticity can be restored by peripheral sensory modulation in the adult TC input.

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Peripheral Sensory Deprivation Restores Critical-Period-like Plasticity to Adult Somatosensory Thalamocortical Inputs

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SUMMARY

Recent work has shown that thalamocortical (TC) inputs can be plastic after the developmental critical period has closed, but the mechanism that enables re-establishment of plasticity is unclear. Here, we find that long-term potentiation (LTP) at TC inputs is transiently restored in spared barrel cortex following either a unilateral infra-orbital nerve (ION) lesion, unilateral whisker trimming, or unilateral ablation of the rodent barrel cortex. Restoration of LTP is associated with increased potency at TC input and reactivates anatomical map plasticity induced by whisker follicle ablation. The reactivation of TC LTP is accompanied by reappearance of silent synapses. Both LTP and silent synapse formation are preceded by transient re-expression of synaptic GluN2B-containing N-methyl-D-aspartate (NMDA) receptors, which are required for the reappearance of TC plasticity. These results clearly demonstrate that peripheral sensory deprivation reactivates synaptic plasticity in the mature layer 4 barrel cortex with features similar to the developmental critical period.

INTRODUCTION

Thalamocortical (TC) inputs to the primary sensory cortex exhibit robust synaptic plasticity during early postnatal development that correlates with the critical period for experience-dependent plasticity. After the end of the critical period, plasticity is greatly reduced so that sensory maps in the thalamorecipient layer 4 primary sensory cortex become resistant to experience-driven plasticity (Barth and Malenka, 2001; Crair and Malenka, 1995; Hubel and Wiesel, 1970). However, after the end of the critical period, plasticity of sensory maps still occurs in the superficial cortex, driven largely by intracortical synaptic plasticity (Diamond et al., 1993, 1994; Fox, 1992, 2002; Hickmott and Merzenich, 2002; Kaas and Catania, 2002; Nudo et al., 1990; Qi et al., 2014; Snow et al., 1988; Wallace and Fox, 1999).

Recent work has challenged the view that plasticity does not occur at TC inputs to layer 4 in the adult whisker barrel cortex. For example, studies on the rodent somatosensory barrel cortex show that the number of TC synapses is reduced by whisker trimming during adulthood (Oberlaender et al., 2012; Wimmer et al., 2010). A unilateral lesion of the infra-orbital nerve (ION), which contains sensory afferents from the whisker pad, induces robust plasticity of TC inputs in the spared layer 4 barrel cortex a month after the end of the critical period (Yu et al., 2012). These results and others from the visual cortex and auditory cortex (Alvarez et al., 2007; Dringenberg et al., 2007; Gagolewicz and Dringenberg, 2011; Heynen and Bear, 2001; Kuo and Dringenberg, 2008; Mainardi et al., 2010; Montey and Quinlan, 2011; Petrus et al., 2014) indicate that TC inputs in layer 4 can express plasticity after the end of the critical period. In none of these cases have the detailed synaptic mechanisms underlying this plasticity been described.

A useful paradigm for studying the mechanisms for post-critical period reactivation of TC synaptic plasticity has recently been described (Yu et al., 2012). A unilateral lesion of the ION in 4- to 6-week-old rats produced an increase in activation of the spared barrel cortex evoked by electrical stimulation in vivo, assayed using either blood oxygenation level dependent (BOLD) fMRI or in vivo electrophysiology. This increased activation was associated with increased synaptic strength of TC synaptic input to glutamatergic stellate cells in layer 4 of the barrel cortex, as measured in vitro in slice. During development, long-term potentiation (LTP) at TC inputs produces synaptic strengthening in a mechanism requiring N-methyl-D-aspartate (NMDA) receptor

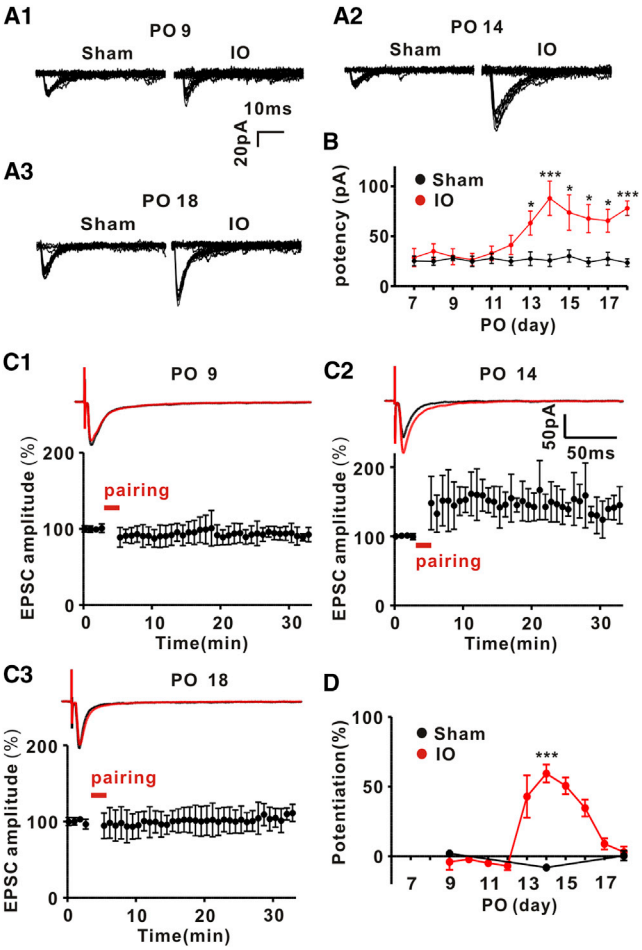

Figure 1. Unilateral ION Lesioning Restores LTP Capability to Adult TC Inputs Transiently

(A1–A3) Representative TC EPSC traces evoked by minimal stimulation on PO9 (A1), PO14 (A2), and PO18 (A3) in the sham and ION lesion (IO) groups.

(B) Time courses for potencies of single fiber-activated TC EPSCs in both groups (IO group: n = 6, 6, 5, 6, 7, 6, 10, 8, 7, 7, 9, and 8 on each PO from PO7 to PO18, respectively; sham group: n = 9, 9, 7, 7, 7, 8, 7, 7, 7, 7, 7, and 7 on each PO from PO7 to PO18, respectively; mean and SEM). Two-way ANOVA with post hoc Bonferroni test: sham versus IO; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

(C1–C3) LTP induction at TC inputs induced by pairing in slices from PO9 (C1), PO14 (C2), and PO18 (C3).Top: representative traces showing EPSCs before (average of 20 traces, black line) and after (average of 180 sweeps, red line) LTP pairing stimuli. Bottom: averaged time courses for EPSC amplitude during LTP induction on PO9, PO14, and PO18 following ION lesioning in the IO group. Data are shown as mean and SEM.

(D) Summarized time course of TC LTP in ION lesion or sham groups (IO group: n = 6, 6, 6, 6, 8, 6, 6, 6, 6, and 6 on each PO from PO9 to PO18, respectively; sham group: n = 6, 6, and 7 on PO9, PO14, and PO18, respectively; mean and SEM). The amount of LTP induced in the ION on PO14 was compared with the equivalent PO14 time point for sham (two-way ANOVA with post hoc Bonferroni test: sham versus IO, ***$p < 0.001$).

activation and the activation of silent synapses (Crair and Malenka, 1995; Isaac et al., 1997; Kirkwood and Bear, 1995). After the critical period, TC inputs lose their ability to express LTP, and this loss of plasticity correlates with the disappearance of silent synapses and a switch from GluN2B- to GluN2A-containing NMDA receptors at TC synapses (Barth and Malenka, 2001; Crair and Malenka, 1995; Daw et al., 2007a; Isaac et al., 1997; Kirkwood and Bear, 1995; Lu et al., 2001).

Here, the mechanisms for the strengthening of the TC input in the spared layer 4 barrel cortex following a unilateral ION lesion in post-critical-period rats was studied. 11 days following the ION lesion, GluN2B is re-expressed at TC synapses. 13 days after the ION lesion, LTP reappears, and this is associated with formation of silent synapses, both of these coincide with strengthening of the TC input. TC input strength remains increased for up to at least 18 days after the ION lesion, but the ability to induce LTP and the existence of silent synapses is lost, indicating a transient window of reactivation of plasticity mechanisms. In addition, we found that a unilateral ION lesion restores structural map plasticity in the spared barrel cortex induced by lesioning of the whisker follicles. Furthermore, the transient restoration of TC synaptic plasticity is also produced by unilateral peripheral sensory deprivation or ablation of the S1 barrel cortex (in the absence of an ION lesion). The earliest functional change detected was re-expression of GluN2B, suggesting that GluN2B is required for reactivation of the plasticity. Consistent with this idea, chronic in vivo blockade of GluN2B, by infusing ifenprodil into the layer 4 barrel cortex, prevented ION lesion-induced TC plasticity. Therefore, peripheral nerve injury leads to a TC synaptic plasticity program being reactivated in the post-critical-period somatosensory cortex that is similar to that observed during the critical period.

RESULTS

Transient Reappearance of LTP at TC Inputs in Layer 4 of the Spared Barrel Cortex following a Unilateral ION Lesion

Previous work showed that a unilateral ION lesion in 4-week-old rats leads to a potentiation of TC inputs in layer 4 in the spared barrel cortex 2 weeks after the lesion (Yu et al., 2012). During normal development, TC inputs in the layer 4 barrel cortex exhibit a well-defined critical period in which they are plastic only during the first postnatal week (Barth and Malenka, 2001; Crair and Malenka, 1995). Therefore, the hypothesis that, following a unilateral ION lesion, developmental TC plasticity may be reactivated in the spared cortex was tested. To investigate this idea, the timing of the increase in TC synaptic strength relative to onset of the ION lesion was defined. Using TC brain slices prepared from rats on various days following the ION lesion, the potency (the amplitude of excitatory postsynaptic currents [EPSCs], excluding failures) of TC EPSCs in stellate cells (SCs) using whole-cell patch-clamp recordings and single TC axon stimulation was measured as previously described (Yu et al., 2012). The potency of the TC input begins to increase 12 days post-ION lesion (PO), and this increase in synaptic strength was maintained until at least PO18 (Figures 1A and 1B). The potency in slices from rats that underwent sham surgery was unchanged throughout this time period.

LTP is well established as an important mechanism for experience-dependent plasticity in the layer 4 primary sensory cortex during the critical period, including in the whisker barrel cortex (Crair and Malenka, 1995; Daw et al., 2007a; Dudek and

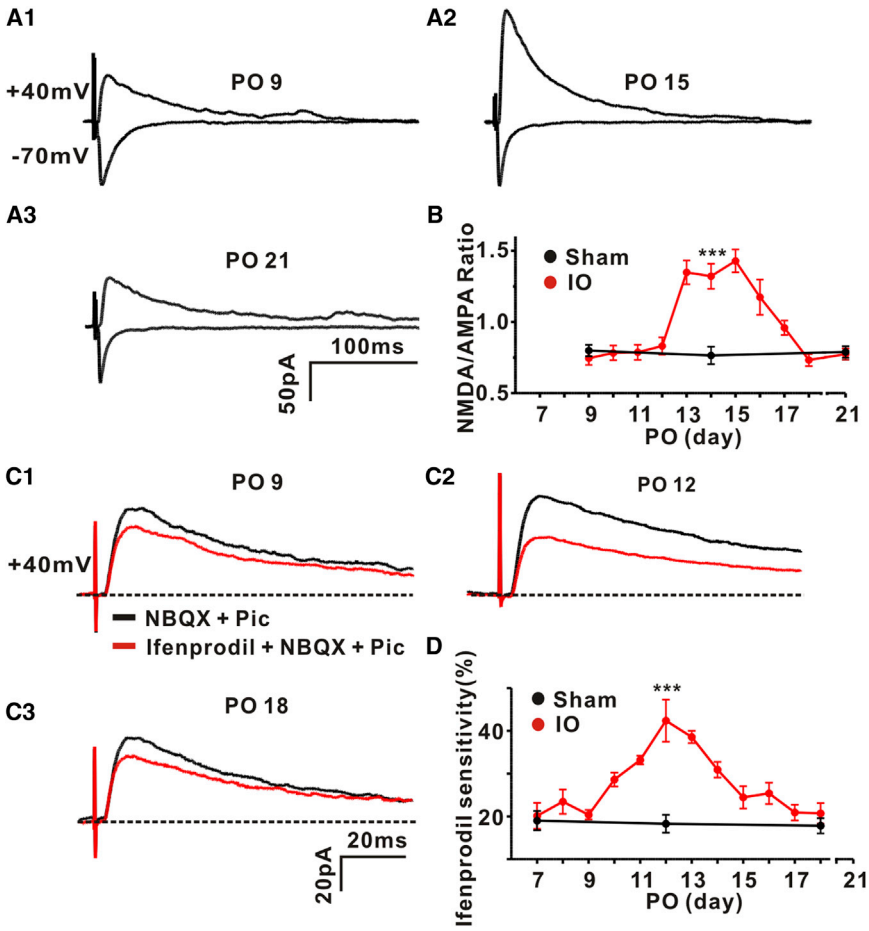

Figure 2. Re-expression of GluN2B at TC Synapses following Unilateral ION Lesioning

(A1–A3) Representative traces showing NMDA and AMPA TC EPSCs on PO9 (A1), PO15 (A2), and PO21 (A3), respectively, following ION lesioning.

(B) Time course for NMDA:AMPA ratios in both groups (IO group: n = 8, 10,12, 6, 15, 10, 12, 6, 12, 6, and 12 on each PO from PO9 to PO18 and PO21; sham group: n = 6, 6, and 6 on PO9, PO14, and PO21; mean and SEM). Two-way ANOVA with post hoc Bonferroni test: sham versus IO, ***$p < 0.001$.

(C1–C3) Representative traces of NMDA EPSCs recorded in slices from animals on PO9 (C1), PO12 (C2), and PO18 (C3) before (black lines) and after application (red lines) of 5 μM ifenprodil.

(D) Time course for ifenprodil sensitivity of TC NMDA EPSCs following ION lesioning or for sham (IO group: n = 6, 6, 6, 6, 6, 8, 6, 6, 6, 6, 6, and 6 on each PO from PO7 to PO18, respectively; sham group: n = 6, 6, and 6 on PO7, PO12, and PO18, respectively; mean and SEM). Two-way ANOVA with post hoc Bonferroni test: sham versus IO, ***$p < 0.001$.

Friedlander, 1996; Feldman et al., 1998; Kirkwood and Bear, 1995). In the developing layer 4 barrel cortex, LTP at TC inputs exhibits a critical period, disappearing by post-natal day 7 (Crair and Malenka, 1995). Thus, it was determined whether LTP could be induced at TC inputs following a unilateral ION lesion as a candidate mechanism for the strengthening of TC inputs. LTP could be induced in SCs using a pairing protocol in slices prepared from rats following an ION lesion on PO13–PO17 but not in slices from sham-operated rats (Figures 1C and 1D). Notably, this reappearance of LTP was transient, lasting for about 5 days and disappearing by PO18.

Re-expression of GluN2B at TC Synapses following a Unilateral ION Lesion

Similar to other cortical areas, GluN2B-containing NMDA receptors are prominent at TC synapses early postnatally in the barrel cortex and are required for LTP but lost during development (Crair and Malenka, 1995; Harlow et al., 2010; Lu et al., 2001; Philpot et al., 2001; Quinlan et al., 1999a). To determine whether TC inputs exhibit changes in NMDA receptor subtype following an ION lesion, the relative contribution of NMDA receptors to TC EPSCs was determined by measuring the amplitude of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor-mediated EPSC (AMPA EPSC), measured at a holding potential of −70 mV, and that of the pharmacologically isolated NMDA receptor-mediated EPSC (NMDA EPSC) at +40 mV in the same cells. This NMDA:AMPA ratio increased transiently on PO13, returning to baseline levels by PO18, but was unaffected in slices from sham-operated rats (Figures 2A and 2B). To determine the contribution of GluN2B-containing NMDA receptors, the sensitivity of the NMDA EPSC to 5 μM ifenprodil was measured. The NMDA EPSC showed a transient increase in ifenprodil sensitivity from PO10–PO15 that was not detected in controls (Figures 2C and 2D). Associated with the electrophysiological evidence for increases in GluN2B, increases in GluN2B protein were also detected transiently in layer 4 barrel cortex synaptosomes during this same time period (Figure S1). Thus, a unilateral ION lesion elicits an increase in GluN2B expression and an increase in GluN2B-containing NMDA receptor function at TC synapses in the spared barrel cortex.

Reappearance of Silent Synapses following a Unilateral ION Lesion

The enhancement in the NMDA:AMPA ratio of the TC EPSC following the unilateral ION lesion may reflect the re-emergence of silent synapses that contain NMDA receptors but no AMPA receptors (Isaac et al., 1995; Kullmann, 1994; Liao et al., 1995). Notably, silent synapses are evident at TC inputs onto SCs in the layer 4 barrel cortex early in postnatal development, are converted to AMPA receptor-containing synapses during developmental LTP, and are developmentally downregulated and lost by the end of the first postnatal week (Ashby and Isaac, 2011; Isaac et al., 1997). To test whether silent synapses re-emerge

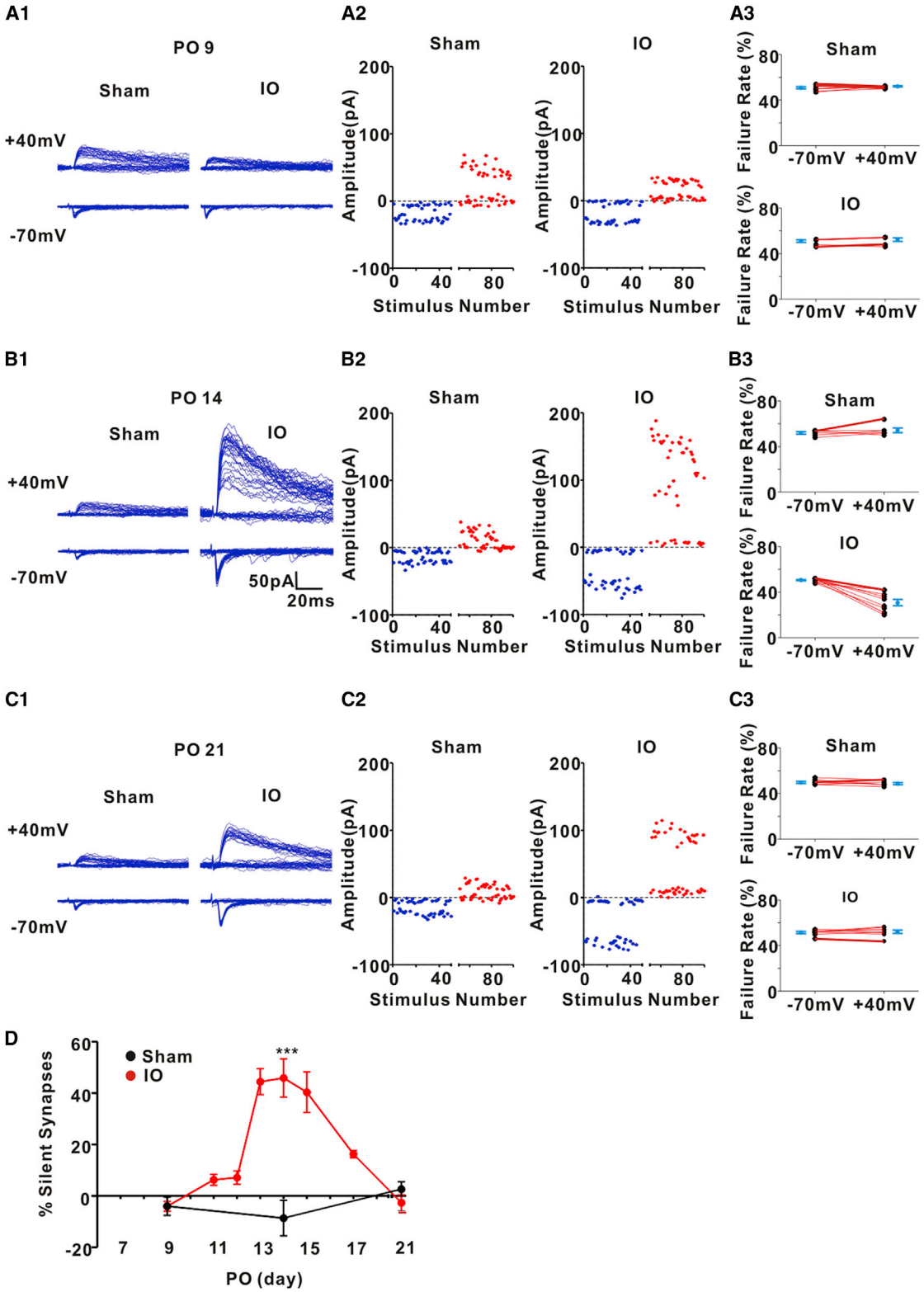

Figure 3. Reappearance of Silent Synapses following Unilateral ION Lesioning

(A1, B1, and C1) Representative traces for EPSCs evoked by minimal stimulation for 50 trials at holding potentials of −70 mV or +40 mV in slices from animals on PO9 (A1), PO14 (B1), and PO21 (C1) for the IO and sham groups.

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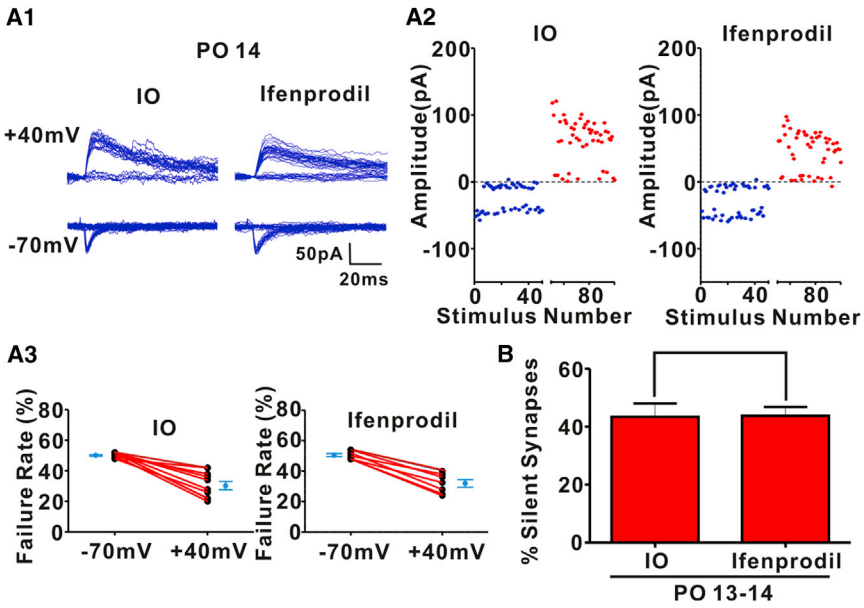

Figure 4. NMDA EPSCs at Silent Synapses Are Not Primarily Mediated by GluN2B-Containing NMDARs

(A1) Representative traces for EPSCs evoked by minimal stimulation at holding potentials of −70 mV or +40 mV in slices from animals on PO14 following ION lesioning, recorded in the absence (left) or presence of 5 μM ifenprodil (right) (these example experiments are from different cells).

(A2) Time course of EPSC amplitudes for the examples of cells shown in (A1).

(A3) Failure rates for the responses at −70 mV and +40 mV on PO14 in the absence or presence of 5 μM ifenprodil. Data are shown as mean and SEM.

(B) Summary of the ifenprodil effect on percent silent synapses (IO group: n = 10; IO + ifenprodil group: n = 10; mean and SEM).

following a unilateral ION lesion, the proportion of silent synapses was measured using minimal stimulation, comparing failure rates at holding potentials of −70 mV and +40 mV (Liao et al., 1995). There was no evidence for silent synapses at TC inputs in slices from sham-operated controls, but silent synapses could be readily detected by PO13 following the ION lesion and persisted until PO17 (Figure 3).

One explanation for the re-appearance of GluN2B-containing NMDA receptors and silent synapses is that GluN2B-containing NMDA receptor re-expression occurs preferentially at silent synapses following an ION lesion. This was tested by comparing the failure rates at −70 mV and +40 mV in slices from ION-lesioned animals (on PO14) in the presence or absence of ifenprodil (5 μM). Ifenprodil did not affect the number of silent synapses detected, indicating that GluN2B-containing NMDA receptors are not selectively expressed at silent synapses (Figure 4). We also confirmed this finding by measuring silent synapses directly using a minimal stimulation intensity at which no AMPA EPSCs were detected (at −70 mV) and then depolarizing the neuron to +40 mV to detect NMDA-only EPSCs (Isaac et al., 1995, 1997; Figures S2A and S2B). NMDA-only EPSCs were detected in all TC inputs recorded on PO14 following the ION lesion (n = 12); however, NMDA-only TC EPSCs were never detected in slices of sham-operated controls (n = 7). To directly test whether there is any contribution from GluN2B-containing NMDA receptors to the NMDA EPSC at silent synapses, ifenprodil was applied to the isolated silent synapses. Ifenprodil caused a small but significant reduction in the amplitude of the NMDA EPSC at isolated silent synapses but no change in failure rate, indicating that the majority of the NMDA EPSC is mediated by GluN2A-containing NMDA receptors (NMDARs) (Figures S2C and S2D). Taken together, these findings show that there is a transient re-expression of silent synapses at TC inputs following unilateral ION lesioning; however, these synapses do not preferentially contain GluN2B-containing NMDARs. This suggests that the majority of the NMDA current at silent synapses is mediated by GluN2A-containing NMDARs.

GluN2B-Containing NMDAR Activation Is Not Required for LTP Induction but Is Required In Vivo for Reactivation of TC Plasticity

In the neocortex, including the layer 4 barrel cortex, loss of synaptic GluN2B-containing NMDARs correlates with the end of the critical period and loss of the ability of TC synapses to express LTP. However, the precise role of GluN2B in this developmental downregulation of plasticity is unclear (Carmignoto and Vicini, 1992; Crair and Malenka, 1995; Harlow et al., 2010; Lu et al., 2001; Philpot et al., 2001; Quinlan et al., 1999a, 1999b). To determine the role of the re-expressed GluN2B in the plasticity following a unilateral ION lesion, the effect of ifenprodil on LTP induction was measured. In slices prepared from animals on PO14, ifenprodil (5 μM) had no effect on LTP induction; however, LTP was prevented by the broad-spectrum NMDAR antagonist D-AP5 (10 μM; Figures 5A and 5B). Thus, NMDAR activation is necessary for LTP induction, but GluN2B is not required. Considering that the earliest change detected was an increase in GluN2B, the role of GluN2B-containing NMDARs during the

(A2, B2, and C3) Time course of EPSC amplitudes for examples cells shown in (A1) (A2), (B1) (B2), and (C1) (C2) collected at −70 mV (blue symbols) and +40 mV (red symbols).

(A3, B3, and C3) Failure rates for EPSCs at −70 mV or +40 mV in slices from animals on PO9 (A3), PO14 (B3), and PO21 (C3) for the IO and sham groups (mean and SEM).

(D) Time course for percentage silent synapse proportions for the IO and sham groups (IO group: n = 8, 10, 12, 6, 15, 10, 12, 6, 12, 6, and 12 on PO9, PO11, PO13, PO14, PO15, PO17, and PO21; sham group: n = 6, 6, and 6 on PO9, PO14, and PO21; mean and SEM). Two-way ANOVA with post hoc Bonferroni test: sham versus IO, ***$p < 0.001$.

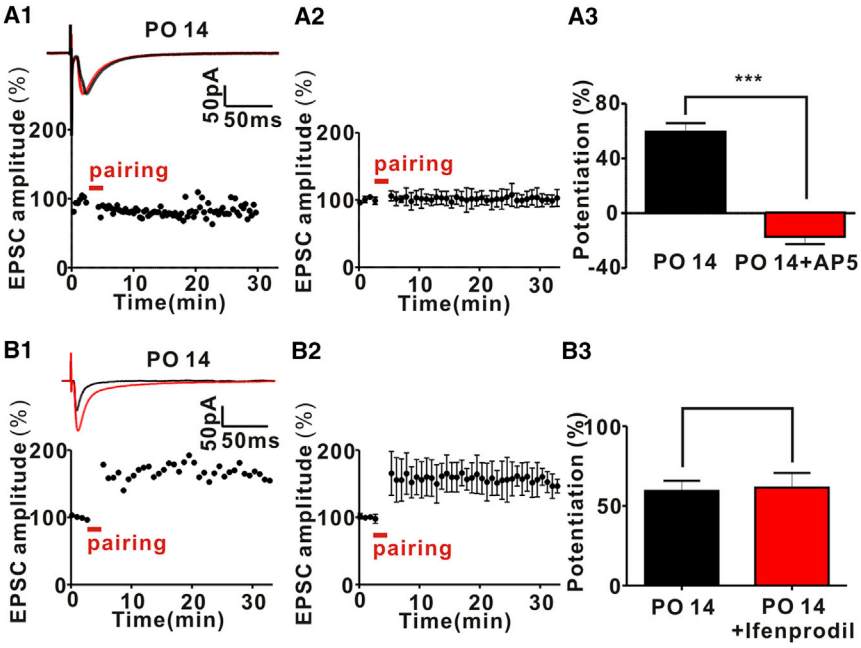

Figure 5. TC LTP following ION Lesioning Is NMDAR-Dependent but GluN2B-Independent

(A1) Top: representative traces for the effect of 10 μM D-AP5 on LTP induction on PO14 following ION lesioning. Bottom: time course of EPSC amplitude for the same experiment.

(A2) Averaged time course of EPSC amplitude for LTP experiments in the presence of AP-5 on PO14 following ION lesioning. Data are shown as mean and SEM.

(A3) Summary of AP5 effects on LTP induction on PO14 following ION lesioning (ION group: n = 6; ION + AP5 group: n = 5; mean and SEM; unpaired t test; ***$p < 0.001$).

(B1) Top: representative traces for the effect of 5 μM ifenprodil on LTP induction on PO14 following ION lesioning. Bottom: time course for EPSC amplitude for the same experiment.

(B2) Averaged time course for EPSC amplitude for LTP experiments in the presence of ifenprodil on PO14 following ION lesioning. Data are shown as mean and SEM.

(B3) Summary of ifenprodil effects on LTP induction on PO14 following ION lesioning (ION group: n = 6; ION + ifenprodil group: n = 7; mean and SEM).

2 weeks after the ION lesion was investigated. Ifenprodil, or saline as a control, was infused continuously into layer 4 of the barrel cortex for 2 weeks after the ION lesion using osmotic minipumps implanted on the day of the ION lesion surgery. In vivo infusion of ifenprodil prevented the re-emergence of both TC LTP and silent synapses, as assessed in subsequent brain slice experiments (Figure 6). In the saline-infused animals, the re-expression of LTP and silent synapses was the same as in animals that had no infusion. Thus, even though the re-activated TC LTP following the unilateral ION lesion is NMDAR-dependent, it does not require acute activation of GluN2B-containing NMDARs. Rather, GluN2B re-expression is required to reactivate plasticity at TC synapses, possibly by triggering the re-expression of silent synapses.

The Role of Whisker-Evoked Activity in the Reactivation of Plasticity at TC Inputs

To determine whether other manipulations besides a unilateral ION lesion can reactivate plasticity in the spared barrel cortex, the effect of unilateral whisker trimming (UWT) every other day for 13 days, starting at 4 weeks of age, on TC synaptic plasticity in the spared barrel cortex was investigated. Similar to a unilateral ION lesion, the potency of minimal stimulation-evoked AMPA EPSCs at TC inputs in layer 4 SCs was increased in the spared barrel cortex when measured at PO14 (the day after the last UWT; Figures 7A and 7C). Furthermore, the ability to induce LTP was also restored (Figures 7C1 and 7D).

To further understand the contribution of whisker-evoked sensory activity in gating the reactivation of TC synaptic plasticity, we investigated whether whisker-evoked sensory input is required for the reactivation of plasticity following unilateral ION lesioning. We found that the increase in AMPA EPSC potency observed on PO14 was prevented by daily trimming of the whiskers on the contralateral (spared) whisker pad starting on PO12 (Figures 7A and 7B), indicating that sensory experience is necessary for the ION lesion-induced reactivation of TC plasticity.

We also tested whether a unilateral reduction of barrel cortex activity alone induces TC plasticity in the spared barrel cortex by unilaterally ablating the barrel field cortex (BFC) in 4-week-old rats (Figure S3) and measuring TC synaptic strength and LTP in layer 4 of the spared barrel cortex 2 weeks later. A unilateral ablation lesion of the BFC led to synaptic potentiation of TC inputs in the spared barrel cortex and restoration of LTP to a similar extent as observed for a unilateral ION lesion (Figure 7). Thus, three different manipulations that produce a unilateral decrease in activity of the barrel cortex (unilateral ION lesioning, UWT, and unilateral BFC ablation) produce reactivation of plasticity of TC inputs in the spared barrel cortex.

Unilateral ION Lesioning Reactivates Anatomical Map Plasticity in the L4 Barrel Cortex

Peripheral sensory manipulations can produce an anatomical reorganization of the barrel cortex as well as functional plasticity during the critical period (Belford and Killackey, 1980; Crair and Malenka, 1995; Durham and Woolsey, 1984; Schlaggar et al., 1993; Van der Loos and Woolsey, 1973). To determine whether a unilateral ION lesion in 4-week-old rats also reactivates anatomical barrel map plasticity, we first measured whether the unilateral ION lesion changed the total size of the barrels in layer 4 in the posterior medial barrel subfield (PMBSF), measured using cytochrome oxidase (CO) staining. On PO18, the total area occupied by the barrels (barrel field area [BFA], measured for rows B–D, arcs 1–4) was increased compared with sham, and the individual barrels, C1 and C2, were significantly increased (Figures S4A–S4C). To determine whether anatomical map plasticity in the spared barrel cortex is reactivated by a unilateral ION lesion, follicles of the C row whiskers of the spared barrel cortex were electrocauterized on PO11 or

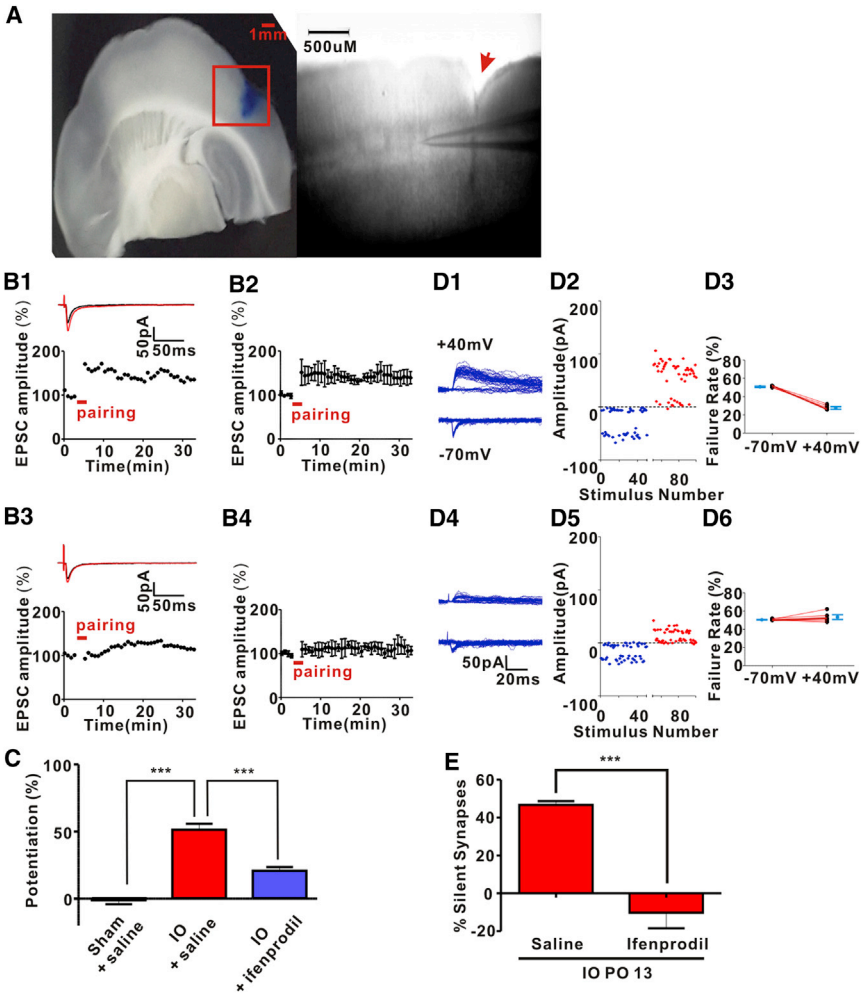

Figure 6. Activation of GluN2B-Containing NMDARs Is Required In Vivo for Reappearance of Silent Synapses and TC LTP

(A) Left: bright-field image of a TC slice showing the injection site (red box) in a methylene blue-injected rat. Right: bright-field image of a TC slice showing the recording electrode and injection site (red arrow head).

(B1) Top: representative traces for the effect of in vivo saline injection on LTP induction on PO14 following ION lesioning. Bottom: time course of EPSC amplitude for the same experiment.

(B2) Averaged time course of EPSC amplitude for LTP experiments in slices from PO14 ION lesion rats in the saline-injected group (n = 6; mean and SEM).

(B3) Top: representative traces for the effect of in vivo ifenprodil injection on LTP induction on PO 14. Bottom: time course of EPSC amplitude for the same experiment.

(B4) Averaged time course of EPSC amplitude for LTP experiments in slices from PO14 ION lesion rats in the ifenprodil-injected group (n = 6; mean and SEM).

(C) Summary of the effect of saline or ifenprodil injection on LTP induction on PO14 in the sham and ION lesion groups (sham + saline: n = 7; IO + saline: n = 6; IO + ifenprodil: n = 6; mean and SEM; one-way ANOVA with post hoc Tukey test; *$p < 0.05$; ***$p < 0.001$).

(D1) Representative traces for EPSCs at −70 mV and +40 mV evoked by minimal stimulation on PO14 in ION lesion rats in the saline-injected group.

(D2) Time course of EPSC amplitude for the experiment shown in (D1).

(D3) Failure rates for the responses at −70 mV and +40 mV on PO14 in ION lesion rats in the saline-injected group. Data are shown as mean and SEM.

(D4) Representative traces for EPSCs at −70 mV and +40 mV evoked by minimal stimulation on PO14 in ION lesion rats in the ifenprodil-injected group.

(D5) Time course of EPSC amplitude for the experiment shown in (D4).

(D6) Failure rates for the responses at −70 mV and +40 mV on PO14 in ION lesion rats in the ifenprodil-injected group. Data are shown as mean and SEM.

(E) Summary data for the effect of saline or ifenprodil injection on percent silent synapses on PO14 following ION lesioning (saline: n = 5; ifenprodil: n = 5; mean and SEM; unpaired t test; ***$p < 0.001$).

after the sham operation. Using a map plasticity index (MPI; Experimental Procedures) to quantify any plasticity, we found that this electrocauterization of the C row whiskers caused a significant reduction in the C row BFA compared with the adjacent B and D rows in the ION-lesioned but not the sham control animals (Figures S4D and S4E). Thus, a unilateral ION lesion induces a change in the size of the anatomical map and also restores anatomical map plasticity in 4- to 6-week-old rats.

DISCUSSION

Here we have shown that a unilateral ION lesion in 4-week-old rats causes a re-emergence of silent synapses and reactivates synaptic plasticity of the TC input to layer 4 in the spared barrel cortex. This occurs at an age that is 3 weeks after the end of the developmental critical period for TC synaptic plasticity. TC plasticity required transient re-expression of GluN2B-containing NMDARs starting at 10 days post-lesion. This was followed by the transient re-appearance of silent synapses and LTP 2 days later, resulting in a stable increase in the strength of the TC input in layer 4. Notably, activation of GluN2B-containing NMDARs was required in vivo for the plasticity mechanism to occur; however, the GluN2B-containing NMDAR subtype is not necessary for acute LTP induction. These findings are summarized in Figure S5, which illustrates a working model for the sequence of synaptic changes that occur at TC inputs following unilateral ION lesioning.

Although previous work has suggested that LTP can be induced at adult TC synapses in the primary sensory cortex under certain conditions in vivo (Cooke and Bear, 2010; Hogsden and Dringenberg, 2009; Lee and Ebner, 1992), a cellular mechanism for such adult TC plasticity has not been described. The present work demonstrates that a unilateral ION lesion re-activates a plasticity mechanism that appears to be identical to

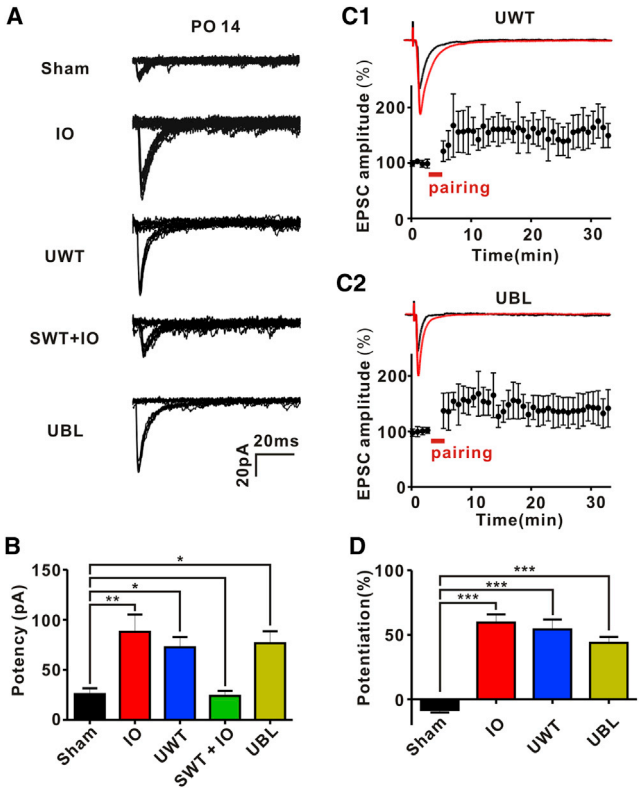

Figure 7. UWT or Ablation of the BFC Restores Long-Term Plasticity to TC Input in the Spared Barrel Cortex, Similar to a Unilateral ION Lesion

(A) Top to bottom: representative TC EPSC traces evoked by minimal stimulation on PO14 in the sham, IO, unilateral whisker-trimmed (UWT), ION lesion with spared whisker-trimmed (SWT + IO), and unilateral BFC-lesioned (UBL) groups. The traces for the sham and IO groups are the same as in Figure 1A2. UWT and BFC lesioning were performed at the age of 4 weeks, similar to the IO and sham operations. Spared whiskers were trimmed daily from PO12 to PO14 in spared whisker-trimmed ION-lesioned rats.

(B) Averaged summary for potencies of single fiber-activated TC EPSCs in each group (sham group: 25.6 ± 6.0 pA, n = 7; IO group: 88.6 ± 17.2 pA, n = 7; UWT group: 72.4 ± 10.4 pA, n = 7; SWT + IO group: 24.0 ± 5.1 pA, n = 7; UBL group: 76.6 ± 12.0 pA, n = 8; mean and SEM). One-way ANOVA with post hoc Tukey test; *p < 0.05, **p < 0.01.

(C1 and C2) LTP induction at TC inputs induced by pairing in slices from PO14 following UWT (C1) or BFC lesioning (C2). Top: representative traces showing EPSCs before (average of 20 traces, black line) and after (average of 180 sweeps, red line) LTP pairing stimuli. Bottom: averaged time courses for EPSC amplitude during LTP induction on PO14 following UWT (C1, n = 7) or BFC lesioning (C2, n = 6). Data are shown as mean and SEM.

(D) Averaged summary for TC LTP on PO14 in the sham, IO, UWT, and UBL groups. Sham group: −8.0% ± 2.2%, n = 6; IO group: 59.4% ± 6.4%, n = 6; UWT group: 54.2% ± 7.7%, n = 7; UBL group: 43.9 ± 4.6 pA, n = 6; mean and SEM. One-way ANOVA with post hoc Tukey test; *p < 0.05, **p < 0.01.

that observed early in development during the critical period. Moreover, the re-appearance of the various features of plasticity—GluN2B expression, silent synapses, and LTP—is transient, with a similar duration (5–6 days) as that observed during development in the layer 4 barrel cortex (Daw et al., 2007b).

Previous studies of plasticity during development in the barrel cortex have noted a co-incident loss of GluN2B-containing NMDAR expression at TC synapses and the end of the critical period for LTP. Moreover, induction of developmental TC LTP is prevented by the GluN2B-selective antagonist ifenprodil (Barth and Malenka, 2001; Lu et al., 2001). Nevertheless, it has also been shown, using GluN2A knockout mice in which GluN2B expression persists at TC synapses beyond the end of the critical period, that the loss of GluN2B-containing NMDARs is not required for the loss of LTP (Lu et al., 2001). Thus, the mechanistic role of GluN2B in regulating the timing of the critical period for TC LTP is unclear. In the present study, GluN2B re-expression at TC synapses in the barrel cortex was a requirement for the re-activation of TC plasticity, arguing for a role of GluN2B in re-opening TC plasticity. The data indicate that the role of GluN2B is not in the acute induction of LTP but rather suggests that GluN2B is required to induce new silent synapses at TC inputs onto L4 SCs. We hypothesize that these silent synapses provide the requisite substrate for LTP. A role for GluN2B in inducing silent synapses is supported by genetic gain- and loss-of-function studies showing that GluN2B expression can drive synaptogenesis and the formation of silent synapses in hippocampal neurons (Gambrill and Barria, 2011; Gray et al., 2011; Hall et al., 2007). Furthermore, GluN2B has been shown to preferentially recruit an intracellular signaling complex via its C terminus that drives new synapse formation and synaptic plasticity (Foster et al., 2010; Kim et al., 2005; Ryan et al., 2013; Wang et al., 2011). The fact that LTP opens and then closes again in this post-critical period model of plasticity should enable future studies of the detailed cellular and molecular mechanisms causing these transitions.

It remains unclear what the neural mechanisms are by which a unilateral ION lesion produces activation of plasticity in the spared barrel cortex. A unilateral ION lesion produces a loss of sensory-evoked activity in the deprived barrel cortex that may lead to a reduction of cross-hemispheric inhibition onto the spared barrel cortex, allowing increased activation of the spared barrel cortex by ascending sensory input (Adam and Güntürkün, 2009; Levy and Trevarthen, 1976; Levy et al., 1972; Urgesi et al., 2005). This is consistent with hypotheses from previous work on unilateral denervation of sensory input (Pelled et al., 2007) and also consistent with visual cortex studies showing that loss of sensory input can lead to reactivation of experience-dependent plasticity in adult animals (Eaton et al., 2016; Montey et al., 2013; Montey and Quinlan, 2011). In the present study, we show that either unilateral ablation of the BFC or UWT produces reactivation of plasticity similar to a unilateral ION lesion. Moreover, trimming the whiskers on the spared side also prevented unilateral ION lesion-induced plasticity, suggesting the possibility that the plasticity may be reactivated in response to increased behavioral use of the whiskers on the spared side and not directly by the damage or deprivation on the other side. Therefore, these findings all point to an important role for the abrupt and sustained change in sensory-evoked activity in the deprived cortex as the initiator of plasticity reactivation.

Peripheral sensory manipulations lead to anatomical and/or functional re-organization of the layer 4 barrel cortex during the developmental critical period, with lesions typically producing more profound anatomical map plasticity, whereas whisker trimming/plucking produces functional map plasticity with little anatomical change (Belford and Killackey, 1980; Crair and

Malenka, 1995; Durham and Woolsey, 1984; Fox, 1992, 2002; Li and Crair, 2011; Schlaggar et al., 1993; Van der Loos and Woolsey, 1973). The dissociation between the effects of certain peripheral sensory manipulations of anatomical plasticity and functional plasticity indicates that these two forms of plasticity likely share some, but not all, mechanisms of induction. Notably, in the present study, we show that the anatomical plasticity in layer 4 can be reactivated and that the same manipulation also produces a reactivation of TC synaptic plasticity. Further work will be needed to determine whether the two processes are mechanistically distinct or whether TC plasticity is a necessary requirement for anatomical map plasticity.

It is not clear what the effects of this plasticity are on whisker-related behaviors or whether the plasticity is adaptive or maladaptive. It could be that there is increased acuity in whisker sensation, similar to enhanced hearing in mice that have been made blind, which is a manipulation that also induces TC plasticity in the auditory pathway (Petrus et al., 2014). Although not specifically studied here, there is also increased potentiation from the spared whisker cortex to the deprived whisker cortex via the corpus callosum following ION lesion (Yu et al., 2012). Recently this has been shown to block takeover of the deprived whisker barrel cortex by neighboring somatosensory areas, suggesting that the plasticity in the spared cortex may be important for this protection of the cortex for whisker processing (Yu and Koretsky, 2014). Independent of the behavioral relevance for plasticity, the mechanisms clearly demonstrate that LTP and silent synapses can re-appear at this central synapse in response to peripheral nerve damage.

In summary, a synaptic plasticity program is re-activated at TC synapses in the spared barrel cortex following unilateral lesioning of sensory afferent input, UWT, or unilateral BFC ablation. This reactivated plasticity appears to be identical to what occurs during the critical period of development of this neural pathway. The sequence of events is a transient increase in GluN2B, followed by formation of silent synapses that coincide with the ability to induce LTP in slices, and increased synaptic strength and in vivo potentiation. Increased synaptic strength is maintained even though the appearance of silent synapses and LTP are transient. In addition, unilateral peripheral sensory lesioning also restores whisker lesion-induced anatomical map plasticity in the spared barrel cortex. The re-opening and subsequent closing of synaptic plasticity should enable a detailed analysis of the factors controlling plasticity in the adult brain. Studying such mechanisms holds promise for manipulating plasticity in adults to aid recovery from injury or identifying ways to recover synaptic function in neurodegenerative diseases.

EXPERIMENTAL PROCEDURES

All animal work was performed according to animal protocols approved by the Institutional Animal Care and Use Committee of the National Institutes of Neurological Disorders and Stroke, NIH and the Yonsei University Health System.

ION Denervation

Four-week-old male Sprague-Dawley rats were used for ION denervation. The procedure for unilateral ION lesioning was similar to that employed previously (Dietrich et al., 1985; Yu et al., 2012). For the detailed procedure of ION denervation, refer to the Supplemental Experimental Procedures.

Electrophysiology

TC slices (450 μm thick) were prepared from adult male Sprague-Dawley rats (6–7 weeks-old) as described previously (Agmon and Connors, 1991; Isaac et al., 1997; Yu et al., 2012) with some modifications. Detailed procedures for TC slice preparation and electrophysiological experiments are described in the Supplemental Experimental Procedures.

For whole-cell recording, cells were held at −70 mV during recordings unless otherwise indicated. TC EPSCs were evoked at 0.1 Hz by ventrobasal (VB) stimulation and accepted as monosynaptic when they exhibited a short and constant latency that did not change with increasing stimulus intensity as previously described (Feldman et al., 1998; Isaac et al., 1997). For the minimal stimulation protocol, VB thalamic stimulation intensity was adjusted to find the lowest intensity that elicited a mixture of synaptic responses and failures. Failure rate was calculated as the number of failures/total number of trials. Potency was calculated as the mean EPSC peak amplitude excluding failures (Chittajallu and Isaac, 2010; Isaac et al., 1997; Stevens and Wang, 1995). Percent silent synapses were calculated using the following equation: $1-\mathrm{Ln}(F_{-70})/\mathrm{Ln}(F_{+40})$, in which F_{-70} was the failure rate at −70 mV and F_{+40} was the failure rate at +40 mV (Huang et al., 2009; Liao et al., 1995). The criteria for single-axon stimulation were all or no synaptic events and no change in the mean amplitude of the EPSC evoked by small increases in stimulus intensity, as previously reported (Chittajallu and Isaac, 2010; Gil et al., 1999). For the experiments measuring the NMDA:AMPA ratio and ifenprodil sensitivity of the NMDA EPSC, pharmacologically isolated NMDA EPSCs were recorded in the presence of 100 μM picrotoxin and 5 μM 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo[f]quinoxaline-2,3-dione (NBQX). For the LTP experiments, LTP was induced by pairing stimuli at 2 Hz for 2 min with postsynaptic depolarization to 0 mV.

Whisker Trimming

For the detailed procedure of whisker trimming, refer to the Supplemental Experimental Procedures.

Ablation of the BFC

Lesions of the BFC determined by a rat brain atlas (George Paxinos, 2013) were produced by subpial ablation, as previously reported (Rema and Ebner, 2003). For the detailed procedure of BFC ablation, refer to the Supplemental Experimental Procedures.

Whisker Row Lesioning

Whisker row lesioning was performed as previously reported with some modification (Van der Loos and Woolsey, 1973). For the detailed procedure of lesioning of whisker rows, refer to the Supplemental Experimental Procedures. An MPI for the C row lesion was calculated by measuring the areas of the lesioned barrels and adjacent barrels using the following formula: $\mathrm{MPI} = 2 \times (C1 + C2)/(B1+B2+D1+D2)$ (Lu et al., 2001).

Osmotic Pump Implantation

Osmotic pump implantation was performed as described in the Supplemental Experimental Procedures.

Data Analysis

All data are presented as mean ± SEM, and n represents the number of cells used in each experiment. Typically, one slice was used from each animal; one recording was made from each slice. We used unpaired Student's t test to compare mean values from the two groups and one-way ANOVA from three or more groups. Two-way ANOVA was used to compare mean values during the specific time course between two groups. p values < 0.05 were considered statistically significant. These statistical analyses were performed using Prism 5.0 (GraphPad).

SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Experimental Procedures and five figures and can be found with this article online at http://dx.doi.org/10.1016/j.celrep.2017.06.018.

AUTHOR CONTRIBUTIONS

S.C. performed brain slice patch recordings, infraorbital nerve denervation surgery, and osmotic pump implantation and wrote the manuscript. S.K. performed cytochrome oxidase immunohistochemistry, western blotting, and data analysis J.H.J. performed whisker trimming, BFC ablation, and whisker row lesioning. Y.H.K. assisted with western blotting and whisker trimming. S.C., J.T.R.I., and A.P.K. designed the experiments and contributed to the editing and revision of the manuscript. X.Y. contributed to the revision of the manuscript.

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