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Original Article

Somatosensory and Visual Deprivation Each Decrease the Density of Parvalbumin Neurons and Their Synapse Terminals in the Prefrontal Cortex and Hippocampus of Mice

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In the phenomenon known as cross-modal plasticity, the loss of one sensory system is followed by improved functioning of other intact sensory systems. MRI and functional MRI studies suggested a role of the prefrontal cortex and the temporal lobe in cross-modal plasticity. We used a mouse model to examine the effects of sensory deprivation achieved by whisker trimming and visual deprivation achieved by dark rearing in neonatal mice on the appearance of parvalbumin (PV) neurons and the formation of glutamic acid decarboxylase 67 (GAD67)-positive puncta around pyramidal neurons in the prefrontal cortex and hippocampus. Whisker trimming, but not dark rearing, decreased the density of PV neurons in the hippocampus at postnatal day 28 (P28). In the prefrontal cortex, whisker trimming and dark rearing decreased the density of PV neurons in layer 5/6 (L5/6) at P28 and in L2/3 at P56, respectively, whereas dark rearing increased the density of PV neurons in L5/6 at P56. Whisker trimming decreased the density of GAD67-positive puncta in CA1 of the hippocampus at both P28 and P56 and in L5/6 of the prefrontal cortex at P28. Dark rearing decreased the density of GAD67-positive puncta in CA1 of the hippocampus and in both L2/3 and L5/6 of the prefrontal cortex at P28, and in L2/3 of the prefrontal cortex at P56. These results demonstrate that somatosensory or visual deprivation causes changes in the PV-interneuronal network in the mouse prefrontal cortex and hippocampus. The results also suggest that the alteration of the PV-interneuronal network, especially in the prefrontal cortex, may contribute to cross-modal plasticity.

Key words: sensory deprivation, parvalbumin, glutamate decarboxylase (GAD67), prefrontal cortex, hippocampus

Loss of one sensory system often results in the improved functioning of one or more other, intact sensory systems. For example, the lack of visual information experienced by congenitally blind individuals may be compensated for by improved somatosensory or auditory functions. This type of plasticity is known as cross-modal plasticity [1, 2]. A better understanding of the neuronal mechanisms underlying cross-modal plasticity will contribute to the general knowledge regarding brain development and for the applications of neuroscience to the treatment of brain damage. Such information may also shed light on the neural basis of qualia, or subjective sensory experience [3, 4].

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The improvement of intact sensory function following the loss of one sensory system has been explained as being enabled by axonal invasion from intact sensory cortices (*e.g.*, from auditory or somatosensory cortices) into sensory-deprived cortex (*e.g.*, into visual cortex), or by the unmasking of pre-existing projections from intact sensory cortices or thalamus to the visual cortex [1, 2, 4]. Two studies using functional MRI suggest the role of association cortices that integrate multimodal sensory inputs in cross-modal plasticity [5, 6].

The brain's middle temporal (MT)/medial superior temporal (MST) complex (MT/MST) is specialized for visual motion perception. Congenitally blind individuals discriminate the direction and speed of an object's movement by sound, whereas sighted individuals discriminate them by visual information. Consistent with this, the activity of the MT/MST is increased by auditory information in congenitally blind individuals and by visual information in normal individuals. However, the functional connectivity between the primary auditory cortex and the MT/MST is not increased in congenitally blind individuals, instead, the functional connectivity between the MT/MST and the dorsolateral prefrontal cortex is enhanced [5]. These findings suggest that auditory information may be mediated by the prefrontal cortex [6]. It was also reported that the functional connectivity between the visual cortex and the parahippocampal gyrus, which is the principal neocortical input pathway to the hippocampus, is enhanced in congenitally and early-blind individuals [7].

Converging evidence indicates the importance of inhibitory interneurons that contain γ-aminobutyric acid (GABA) as a neurotransmitter in cross-modal plasticity [2]. Among the various GABAergic interneurons, parvalbumin-containing neurons (PV neurons) appear coincident with the onset of a critical period for the formation of the receptive field in the barrel cortex [8] and for ocular dominance plasticity in the primary visual cortex [9, 10]. Sensory deprivation decreases the density of PV neurons and impairs synapse formation by PV neurons in the barrel cortex [11] and the primary visual cortex [12]. PV neurons are more sensitive to sensory deprivation than excitatory neurons [13]. We therefore hypothesized that sensory deprivation would decrease the density of PV neurons and impair synapse formation by PV neurons in the prefrontal cortex and hippocampus if these association cortices contribute to cross-modal plasticity. However, to the best of our knowledge, the influence of sensory deprivation in the early postnatal period on the density of PV neurons and the synapse formation by PV neurons in association cortices has not been examined.

In the present study, we examined the effects of sensory deprivation by whisker trimming and also by dark rearing on the density of PV neurons and glutamic acid decarboxylase 67 (GAD67)-positive perisomatic synapse terminals in the prefrontal cortex and hippocampus of neonatal mice. Both the somatosensory deprivation and the visual deprivation changed the density of PV neurons and decreased the number of GAD67-positive synapse terminals in the prefrontal cortex and hippocampus, suggesting that the alteration of the PV-interneuronal network in the prefrontal cortex may contribute to cross-modal plasticity.

Materials and Methods

Animals. C57BL/6N mice (Charles River, Kanagawa, Japan) of both sexes were used. Animals were housed under standard conditions with a 12/12-h dark/light cycle and *ad libitum* access to commercial chow and tap water. All experimental protocols were performed in accordance with the U.S. National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals (NIH Publication No. 80–23, revised in 1996) and approved by the Committee for Animal Experiments at the Okayama University Advanced Research Center. All efforts were made to minimize the number of animals used.

Sensory deprivation. For somatosensory deprivation, all whiskers were trimmed every day to within 1 mm from the skin surface using surgical scissors from the mouse's birth date (P0) to postnatal day (P)28 or P56. Control mice were also handled every day without whisker trimming. For visual deprivation, mice were reared in complete darkness (dark rearing) from P2 to P28 or P56.

Cryostat sections. Mice were deeply anesthetized with pentobarbital (80 mg/kg, i.p.) and perfused transcardially with 4% paraformaldehyde in 0.1 M phosphate buffer (PB), pH 7.4. The brains were removed and postfixed in perfusion solution overnight at 4℃. The tissues were cryoprotected by incubation

in 15% sucrose for 7 h followed by 30% sucrose for 20 h at 4℃. The brains were then frozen in O.C.T. Compound (Tissue-Tek, Sakura Finetek, Tokyo, Japan) by freezing in dry ice-cold normal hexane. They were cut into 25 μm-thick coronal sections on a cryostat (CM-1900, Leica, Wetzlar, Germany) at −20℃ and collected in ice-cold phosphate-buffered saline (PBS).

Immunohistochemistry. Free-floating sections were treated with 3% H_2O_2 in PBS to remove endogenous peroxidase activity for 15 min, washed in PBS, and treated with 0.1% Triton X-100 in PBS at room temperature for 15 min. Non-specific binding was blocked during 1-h incubation in PBS containing 1.5% normal goat serum (Funakoshi Corp., Tokyo, Japan) at room temperature. Sections were then incubated with primary antibody directed against PV (1 : 20,000; clone PARV-19, P3088, Sigma-Aldrich Japan, Tokyo, Japan) in PBS overnight at 4℃. The next day, PBS-rinsed sections were incubated in biotinylated rabbit anti-mouse IgG (1 : 1,000; MA01742-3049, Fitzgerald Industries International, Concord, MA, USA) in PBS for 1 h at room temperature. After 3 washes in PBS, the sections were incubated with avidin-biotin-peroxidase complex (VECTASTAIN® ABC kit, Vector Laboratories, Funakoshi Co., Tokyo, Japan) for 1 h at room temperature and visualized with 0.03% 2,3-diaminobenzidine (DAB, Sigma, St Louis, MO, USA), H_2O_2 and ammonium nickel sulfate hexahydrate. The sections were then mounted on glass slides, dehydrated, cleared, and coverslipped.

Assessment of PV neuron density. Light microscopic images were captured using LuminaVision software (version 2.4.0, Mitani Corp., Fukui, Japan), and adjustments of contrast and brightness were made. NIH imageJ software (NIH, Bethesda, MD; http://rsb.info.nih.gov/nih-image/) was used to quantify the number of PV neurons. The density of PV neurons was shown as the number of PV neurons per mm^2. In all cases, the experimenter was blinded to the experimental conditions.

GAD67 staining. For GAD67 staining, sections were permeabilized and blocked as described above and then incubated in PBS containing mouse anti-GAD67 (MAB5406, Millipore, Tokyo, Japan, 1 : 2,000) overnight at 4℃. The sections were washed in PBS and incubated in biotinylated rabbit anti-mouse IgG in PBS for 1 h at room temperature. After 3 washes in PBS, the sections were incubated for 1 h with rhodamine-conjugated streptavidin (1 : 1,000, S6366, Invitrogen, Tokyo, Japan). After 3 washes in PBS, the sections were mounted on glass slides with a ProLong® Antifade Kit (P7481, Molecular Probes, Eugene, OR, USA) and covered with coverslips.

Quantification of GAD67-positive perisomatic puncta. GAD67-stained sections were observed using a confocal laser microscope (Zeiss 510, Carl Zeiss, Oberkochen, Germany) with Argon (488 nm) and HeNe (543 nm) lasers. Images were captured using the standard system operating software provided with the Zeiss 510 microscope (LSM Image Browser version 3.2). To count the number of GAD67-positive perisomatic puncta, we acquired non-overlapping images from a single confocal plane using a 63x water immersion objective lens. Images were saved as TIFF files and analyzed with NIH imageJ software. To estimate the number of GAD67-positive perisomatic puncta around a pyramidal neuron, an area was traced by a line that enclosed the soma but was 2 μm away from the GAD67-negative cell body. GAD67-positive puncta with 0.5−2.5-μm^2 area sizes within the enclosed area were counted as the number of synapse terminals per 100 μm. All quantification was done blind to the sensory deprivation/control conditions.

Statistics. Data were analyzed using paired *t*-test or the Mann-Whitney U-test, and ANOVA for comparisons between groups. Difference were considered significant when $p < 0.05$.

Results

Developmental changes of the density of PV neurons in the hippocampus and prefrontal cortex in intact control mice. At P10, PV neurons were already present in CA1 and CA3 of the hippocampus (Fig. 1A). They appeared by P12 in the dentate gyrus. Density of PV neurons dramatically increased in the third postnatal week and slightly decreased thereafter in all areas of the hippocampus (Fig. 1A). PV neurons appeared by P14 in layer 5/6 (L5/6) and by P21 in L2/3 of the prefrontal cortex (Fig. 1B). The density of PV neurons was markedly increased in the fourth postnatal week in both L2/3 and L5/6.

Effects of sensory deprivation on the density of PV neurons in the primary sensory cortices.

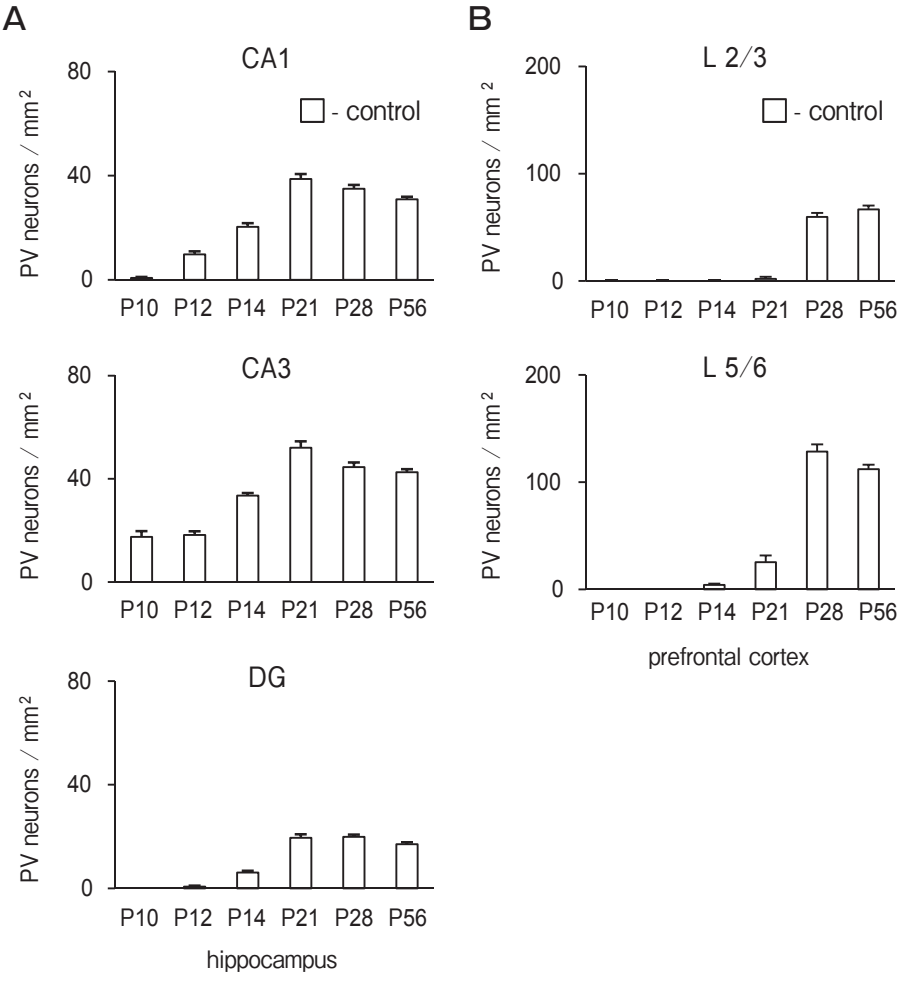

Fig. 1 Developmental changes in the density of PV neurons (per mm^2) in intact mice. **A**, hippocampus. The means ± SEM of 13–43 sections from 5–10 animals are shown. PV neurons appeared by P10 in CA1 and CA3 and by P12 in the dentate gyrus (DG), and gradually increased by P21; **B**, prefrontal cortex. The means ± SEM of 6–38 sections from 3–7 animals are shown. PV neurons appeared by P14 in L5/6 and by P21 in L2/3, and increased by P28.

Whisker trimming from P0 to P28 decreased the density of PV neurons in L4 of the barrel cortex (Fig. 2A, B). The density of PV neurons in L2/3 and L5/6 was not changed. Dark rearing increased the density of PV neurons in L2/3 and L4 of the primary visual cortex (Fig. 2D). A possible reason for the increase in PV neuron density is atrophy of the visual cortex, as shown in Fig. 2C. A comparison of the thickness of the visual cortex revealed a significant decrease ($p < 0.05$, by Mann-Whitney U-test) of the thickness in the dark-reared mice ($731.3 \pm 4.7\,\mu m$) compared to the control mice ($747.0 \pm 5.8\,\mu m$).

A previous study demonstrated that monocular deprivation decreased the density of GAD67-positive perisomatic puncta in L5, but not in other layers, of the visual cortex [12]. To test this finding, we quantified GAD67-positive perisomatic puncta in L5 of the visual cortex. Dark rearing from P2 to P28 decreased the density of GAD67-positive perisomatic puncta around putative pyramidal neurons in L5 (Fig. 2E, F).

Effects of sensory deprivation on the density of PV neurons in the hippocampus. There was a significant reduction of PV neurons in CA1 and CA3 of the hippocampus in the whisker-trimmed mice compared to the intact control mice (Fig. 3B). In addition, the PV immunoreactivity of neuronal processes was

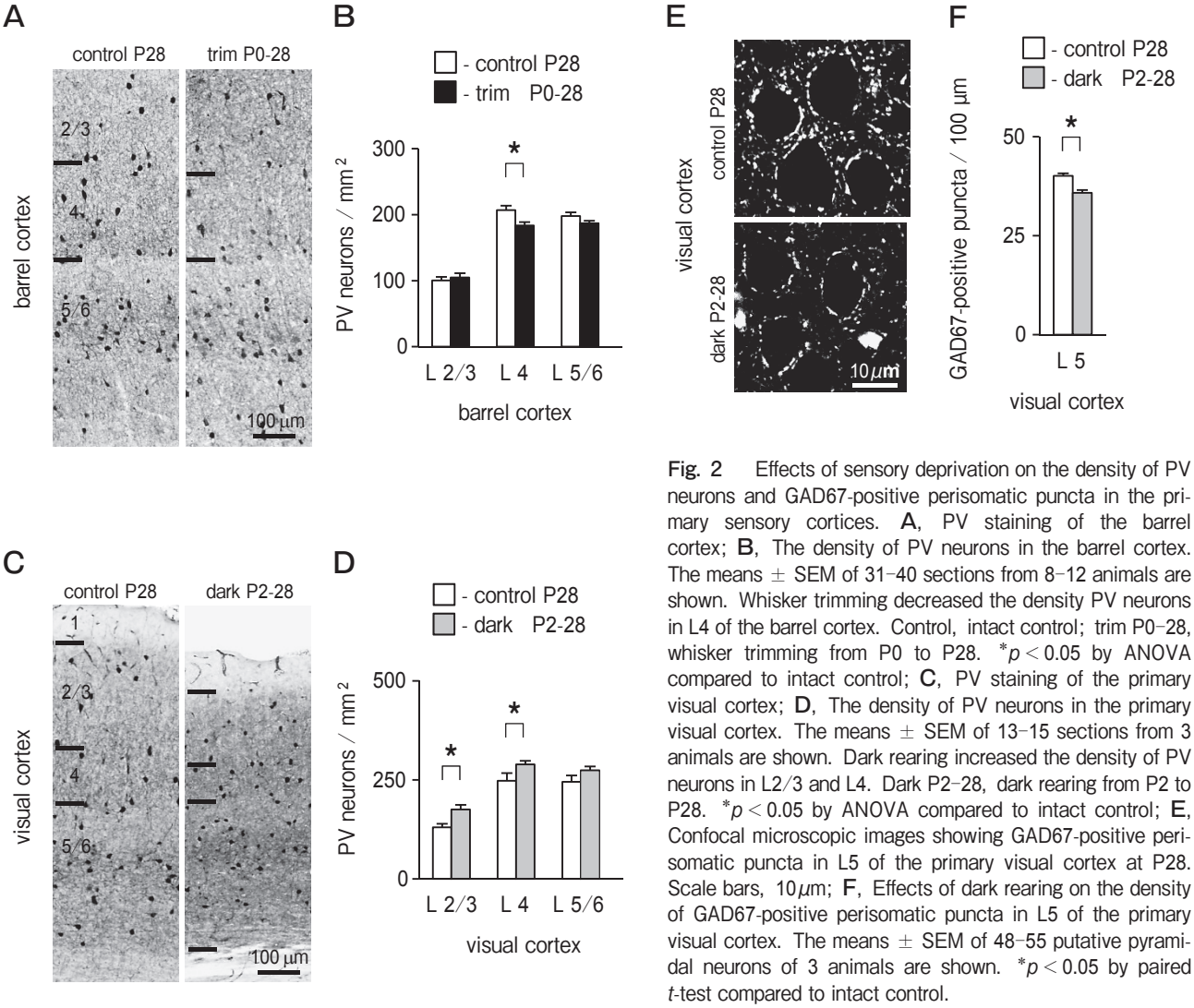

Fig. 2 Effects of sensory deprivation on the density of PV neurons and GAD67-positive perisomatic puncta in the primary sensory cortices. **A**, PV staining of the barrel cortex; **B**, The density of PV neurons in the barrel cortex. The means ± SEM of 31–40 sections from 8–12 animals are shown. Whisker trimming decreased the density PV neurons in L4 of the barrel cortex. Control, intact control; trim P0–28, whisker trimming from P0 to P28. $^{*}p < 0.05$ by ANOVA compared to intact control; **C**, PV staining of the primary visual cortex; **D**, The density of PV neurons in the primary visual cortex. The means ± SEM of 13–15 sections from 3 animals are shown. Dark rearing increased the density of PV neurons in L2/3 and L4. Dark P2–28, dark rearing from P2 to P28. $^{*}p < 0.05$ by ANOVA compared to intact control; **E**, Confocal microscopic images showing GAD67-positive perisomatic puncta in L5 of the primary visual cortex at P28. Scale bars, 10 μm; **F**, Effects of dark rearing on the density of GAD67-positive perisomatic puncta in L5 of the primary visual cortex. The means ± SEM of 48–55 putative pyramidal neurons of 3 animals are shown. $^{*}p < 0.05$ by paired *t*-test compared to intact control.

significantly attenuated in the hippocampus of the whisker-trimmed mice (Fig. 3A). There was no difference in the density of PV neurons in the hippocampus of the dark-reared mice compared with the intact control mice (Fig. 3B). When whisker trimming or dark rearing was continued to P56, there was no difference in the density of PV neurons between the sensory-deprived mice and intact mice (Fig. 3C).

Effects of sensory deprivation on the density of PV neurons in the prefrontal cortex. PV immunoreactivity was attenuated in the prefrontal cortex by whisker trimming (Fig. 4A, B). Whisker trimming and dark rearing significantly decreased the density of PV neurons in L5/6, but not in L2/3, of the prefrontal cortex (Fig. 4C). When whisker trimming or dark rearing was continued to P56, it significantly decreased the density of PV neurons in L2/3, whereas visual deprivation significantly increased the density of PV neurons in L5/6 (Fig. 4D).

Effects of sensory deprivation on the density of GAD67-positive perisomatic puncta in the hippocampus and prefrontal cortex. To examine the effects of sensory deprivation on the synaptic innervation by PV neurons, we quantified GAD67-positive puncta around putative pyramidal neurons. GAD67 is abundant in synapse terminals of PV neurons, but not in those of cholecystokinin-containing basket cells [14]. Therefore, GAD67-positive puncta

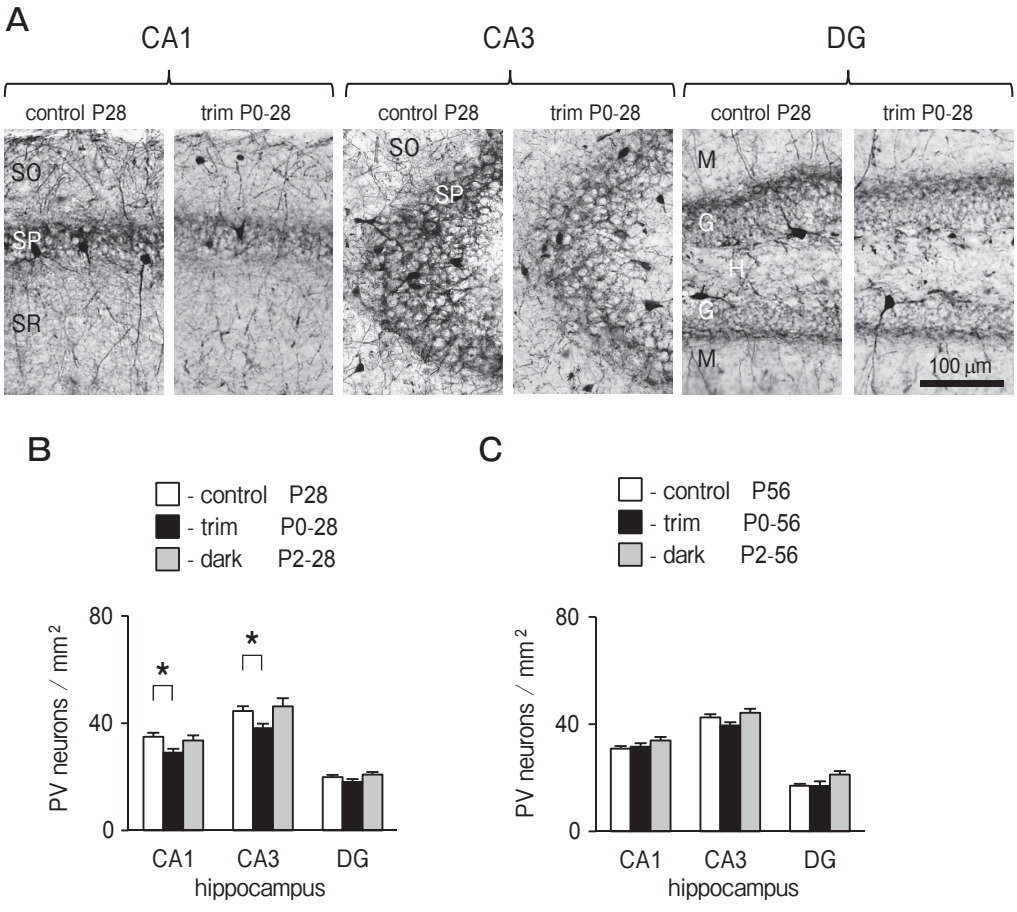

Fig. 3 Effects of sensory deprivation on the density of PV neurons in the hippocampus. **A**, PV staining at P28. Coronal sections of the dorsal hippocampus are shown. In the whisker-trimmed mice, the PV immunoreactivity in cell bodies and neuronal processes was weak compared to that of the intact controls. G, granule cell layer; H, hilus; M, molecular layer; SO, stratum oriens; SP, stratum pyramidale; SR, stratum radiatum. Other abbreviations are the same as in Fig. 2. Scale bars, 100 μm; **B**, The density of PV neurons at P28. The means ± SEM of 17–34 sections from 3–7 animals are shown. Whisker trimming significantly decreased the PV neuron density in CA1 and CA3. Dark rearing did not change the PV neuron density. Abbreviations are the same as in Fig. 2. $^{*}p < 0.05$ by ANOVA compared to intact control; **C**, The density of PV neurons at P56. The means ± SEM of 17–43 sections from 3–8 animals are shown.

around cell bodies are, for the most part, synapse terminals of PV neurons. Here, the intensity of GAD67 staining was attenuated in the prefrontal cortex of the sensory-deprived mice at P28 (Fig. 5A). The density of GAD67-positive puncta was significantly decreased in CA1 of the hippocampus of both the whisker-trimmed and dark-reared mice compared to the intact mice (Fig. 5B). Whisker trimming significantly decreased GAD67-positive puncta in L5/6, but not in L2/3 of the prefrontal cortex (Fig. 5D). Dark rearing significantly decreased GAD67-positive puncta in both L2/3 and L5/6 of the prefrontal cortex (Fig. 5D).

When the whisker trimming and the dark rearing were continued to P56, each significantly decreased the density of GAD67-positive puncta in CA1 of the hippocampus (Fig. 5C). Dark rearing decreased the density of GAD67-positive puncta in L2/3 of the prefrontal cortex (Fig. 5E).

Discussion

We first examined the critical period for the appearance of PV neurons in the hippocampus and the prefrontal cortex of the intact mouse. The density of PV neurons increased in the third and fourth postnatal

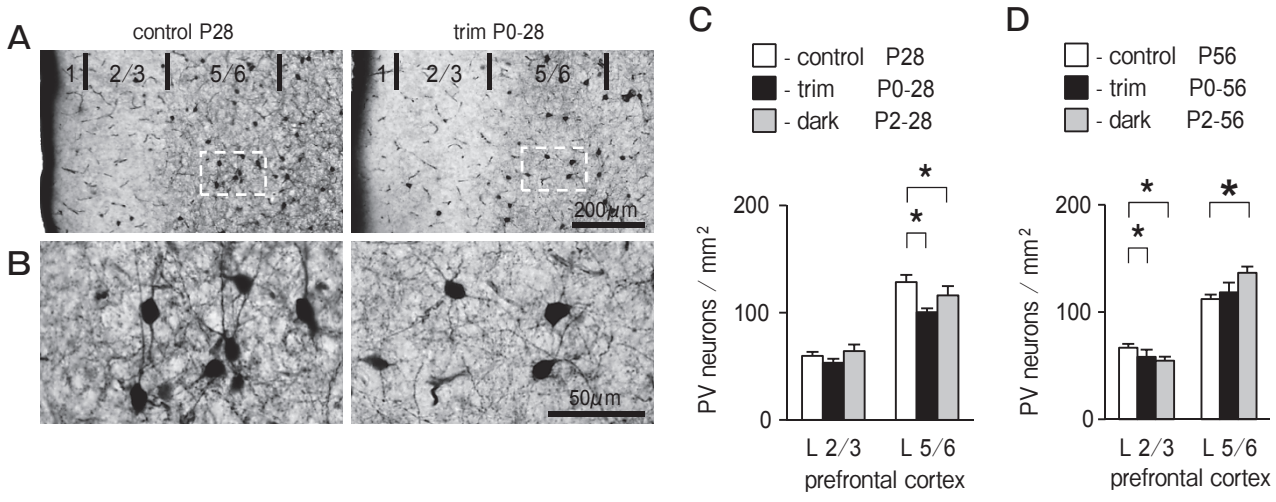

Fig. 4 Effects of sensory deprivation on the density of PV neurons in the prefrontal cortex. **A**, PV staining of coronal sections of the prefrontal cortex at P28. Abbreviations are the same as in Fig. 2. The left side is the pial surface. Scale bars, 200 μm; **B**, Expanded images of L5/6 (the areas indicated by dotted squares in **A**). The left side is the pial surface. Note that PV immunoreactivity in neuronal processes is weaker in this sensory-deprived mouse than in the intact control mouse. Scale bars, 50 μm; **C**, The density of PV neurons at P28. The means ± SEM of 13–38 sections from 3–7 animals are shown. Whisker trimming and dark rearing decreased the PV neuron density in L5/6. Abbreviations are the same as in Fig. 2. $^*p < 0.05$ by ANOVA compared to intact control; **D**, The density of PV neurons at P56. The means ± SEM of 13–32 sections from 3–6 animals are shown. Both whisker trimming and dark rearing significantly decreased the density of PV neurons in L2/3, whereas only dark rearing significantly increased it in L5/6. $^*p < 0.05$ by ANOVA compared to intact control.

week in the hippocampus and the prefrontal cortex, respectively. The third postnatal week is coincident with the beginning of whisking behavior, and the fourth postnatal week is coincident with eye opening. The results of the present experiment indicate that the appearance of PV neurons in the mouse hippocampus and the prefrontal cortex is coincident with the increase of sensory inputs to the primary sensory cortices.

We next examined the effect of sensory deprivation on the appearance of PV neurons in the primary sensory cortices to test whether whisker trimming or dark rearing decreases sensory inputs to the primary sensory cortices. Whisker trimming from P0 to P28 decreased the density of PV neurons in L4 of the barrel cortex, as described previously [11]. In contrast, dark rearing from P0 to P28 increased the density of PV neurons in L2/3 and L4 of the visual cortex. A possible reason for this unexpected result is atrophy of the visual cortex caused by visual deprivation, as described in the Results section. Dark rearing decreased the density of GAD67-positive puncta in L5 of the visual cortex as described in the monocular deprivation of the mouse [12].

Whisker trimming from P0 to P28 decreased the density of PV neurons in CA1 and CA3 of the hippocampus (Fig. 3B). The reduction of PV neurons is likely due to a decreased expression of PV protein, because the density of PV neurons recovered to the control level when whisker trimming was continued to P56 (Fig. 3C). In the prefrontal cortex, both whisker trimming and dark rearing decreased the density of PV neurons in L5/6 at P28 (Fig. 4C) and in L2/3 at P56 (Fig. 4D). However, dark rearing increased the density of PV neurons in L5/6 of the prefrontal cortex at P56 (Fig. 4D). These results suggest that the decrease in the density of PV neurons in the prefrontal cortex may be due, at least in part, to delayed migration or apoptosis of PV neurons, and that long-term visual deprivation may prevent the apoptosis of PV neurons.

Both whisker trimming and dark rearing decreased the density of GAD67-positive puncta in both the hippocampus and the prefrontal cortex. The reduction of the density of GAD67-positive puncta likely reflects the reduction of synapse terminals of PV neurons, because it has been shown that overexpression of

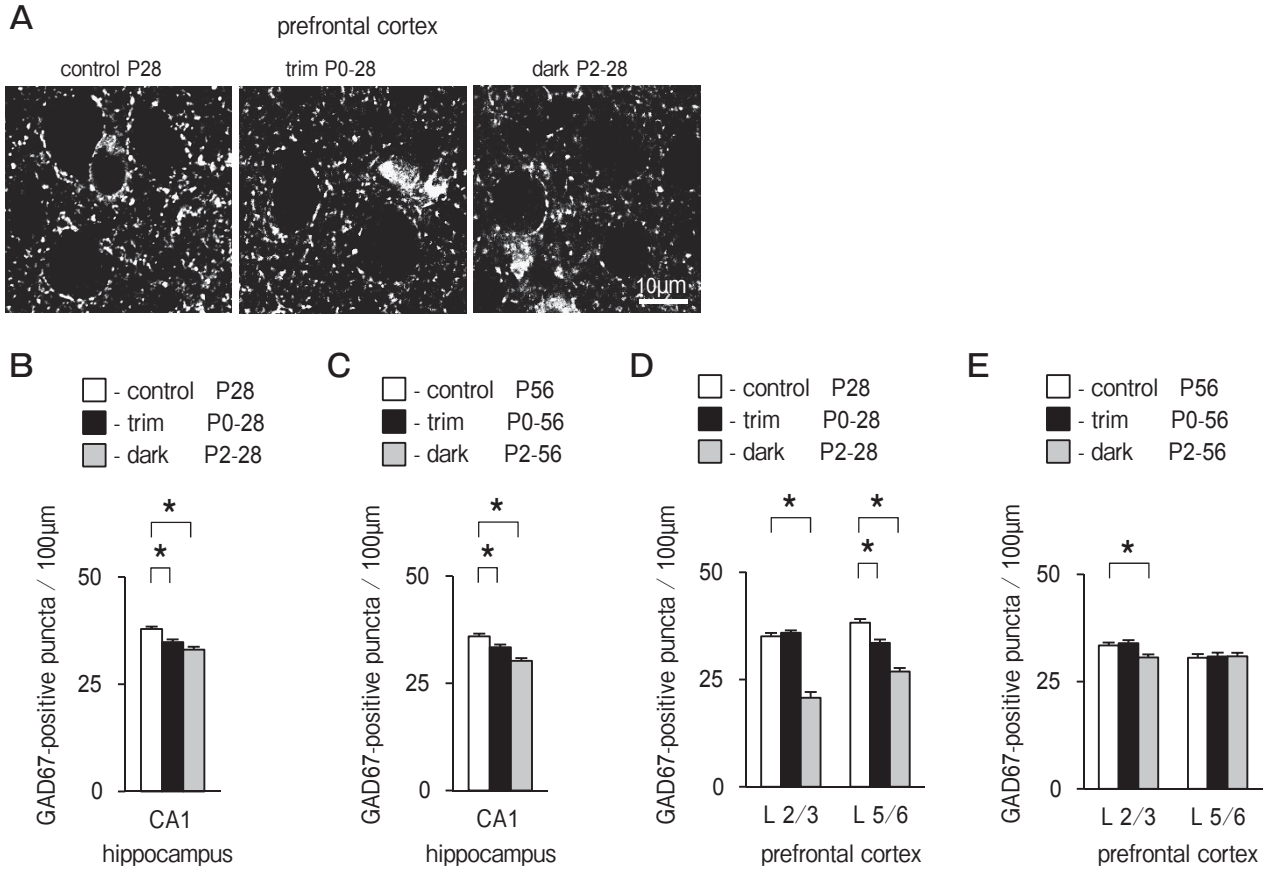

Fig. 5 Effects of sensory deprivation on the density of GAD67-positive perisomatic puncta in the hippocampus and prefrontal cortex. **A**, Confocal microscopic images of GAD67-positive perisomatic puncta in L5/6 of the prefrontal cortex at P28. Scale bars, 10μm. Abbreviations are the same as in Fig. 2; **B** and **C**, The density of GAD67-positive perisomatic puncta in CA1 of the hippocampus at P28 (**B**) and P56 (**C**). The means ± SEM of 48–68 putative pyramidal neurons of 3–7 animals are shown. The density of GAD67-positive perisomatic puncta was decreased by whisker trimming and by dark rearing at both P28 and P56. $^*p < 0.05$ by ANOVA compared to intact control. Abbreviations are the same as in Fig. 2; **D** and **E**, The density of GAD67-positive perisomatic puncta in the prefrontal cortex at P28 (**D**) and P56 (**E**). The means ± SEM of 28–61 putative pyramidal neurons of 3–7 animals are shown. Whisker trimming decreased the density of GAD67-positive perisomatic puncta in L5/6 at P28. Dark rearing decreased the density of GAD67-positive perisomatic puncta in both L2/3 and L5/6 at P28, and in L2/3 at P56. Abbreviations are the same as in Fig. 2. $^*p < 0.05$ by ANOVA compared to intact control.

GAD67 facilitates synapse formation by PV neurons whereas genetic knockout of GAD67 impairs synapse formation [15]. Here, dark rearing did not decrease the density of PV neurons in the hippocampus but it decreased the density of GAD67-positive puncta in CA1 of the hippocampus (Fig. 3B, C and Fig. 5B, C). In the prefrontal cortex, the dark rearing decreased the density of PV neurons in L5/6 at P28, but the decrease was not prominent compared to the decrease by whisker trimming (Fig. 4C).

In contrast, dark rearing caused a prominent reduction in the density of of GAD67-positive puncta in both L2/3 and L5/6 at P28 (Fig. 5D). The dissociation between the PV neuron density and GAD67-positive synapse density suggests that the role of sensory inputs in the appearance of PV neurons is different from that in the synapse formation by PV neurons.

Both whisker trimming and dark rearing decreased the density of synapse terminals of PV neurons in the prefrontal cortex and in CA1 of the hippocampus. The significance of reduced synaptic innervations by PV neurons in the hippocampus is not clear. We cannot exclude the possibility that it may be related to somatosensory or visual memory rather than cross-modal

plasticity. On the other hand, the prefrontal cortex has reciprocal connections between visual, auditory and somatosensory cortices as well as the basal ganglia and the thalamus [16]. A characteristic of cortical activity is the rhythmic and synchronous oscillation of the membrane potential of the population of pyramidal neurons. Cortical inhibition is an essential element of the fast oscillations in the beta and gamma frequency range (20–80 Hz). Gamma oscillations are proposed to contribute to the merging of information processed in distinct cortical regions [17].

PV neurons innervate axon initial segments (chandelier cells) or cell bodies and proximal dendrites (basket cells) of pyramidal neurons in the cerebral cortex [14, 18]. They control the output of pyramidal neurons and play a key role in the generation of gamma oscillations [17]. The prefrontal cortex is agranular cortex that lacks L4. Pyramidal neurons in L5/6 of the prefrontal cortex project to L1 or L2 of the visual, auditory and somatosensory cortices [19]. This circuit architecture is ideal for eliminating distractors, signals that distract the attention, through interaction with calbindin neurons in L2. Pyramidal neurons in L5/6 of the prefrontal cortex also project to reticular and mediodorsal nuclei of the thalamus that innervate sensory relay nuclei of the thalamus.

L2/3 pyramidal neurons of the prefrontal cortex receive projections from the mediodorsal thalamic nucleus [19]. This reciprocal connection between the prefrontal cortex and thalamus is thought to efficiently magnify salient signals and suppress distractors. Reduced innervation by PV neurons in L5/6 is expected to enhance the transmission of salient signals to the sensory cortices. In the present study, the reduction of GAD67-positive puncta in L5/6 was significant at P28, but not at P56. This may be a reason why congenitally and early-blind individuals, but not late-blind individuals, have improved somatosensory or auditory functions. An important question is whether the reduction of synaptic innervation by PV neurons impairs or facilitates the generation of gamma oscillations and causes persistent alterations in reciprocal connections between the prefrontal cortex and sensory cortices or the thalamus. Electrophysiological studies and anatomical studies using tracers are necessary to clarify this issue. Nonetheless, our results suggest that changes of PV-interneuronal networks in the prefrontal cortex may contribute to cross-modal plasticity.

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