

## Cortical Layer V Neurons in the Auditory and Visual Cortices of Normal, *reeler*, and *yotari* Mice

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### ABSTRACT

Both in the Reelin-deficient *reeler* and *Dab1*-deficient *yotari* mice, layer V corticospinal tract neurons in the sensory-motor cortex are radially spread instead of being confined to a single cortical layer. In the present study, we examined distribution pattern of cortical layer V neurons in the visual and auditory cortices of *reeler* and *yotari* mice with the injection of HRP into the superior and inferior colliculi of the adult animals, respectively. After the injection of HRP into the superior colliculus of the normal mouse, retrogradely labeled cells were distributed in layer V of the visual cortex, while the similar injection of HRP in the *reeler* and *yotari* mice produced radial dispersion of retrograde labeling through all of the depths of the visual cortex of these mutant mice. Next, we injected HRP into the inferior colliculus of the normal, *reeler* and *yotari* mice. Retrogradely labeled neurons were distributed in layer V of the normal auditory cortex, whereas they were again radially scattered in the auditory cortex of the *reeler* and *yotari* mice. Taken together with the previous and present findings, layer V cortical efferent neurons are radially scattered in the sensory-motor, visual and auditory cortices of the *reeler* and *yotari* mice.

### INTRODUCTION

*Reeler* mutant mouse, caused by deletion of 3' coding region of *reelin* cDNA, has an autosomal recessive mutation (D'Arcangelo *et al.*, 1995). In this mutant mouse, laminated structures such as cerebral and cerebellar cortices and hippocampus are cytoarchitecturally disrupted (Katsuyama and Terashima, 2009). In addition, non-cortical structures such as branchiogenic motoneurons including trigeminal motor, facial and ambiguus nuclei are cytoarchitecturally abnormal in this mutant mouse (Goffinet, 1984; Terashima *et al.*, 1994). The cellular layers of the cerebral cortex are originally considered to be inverted in the *reeler*. Neuronal components of the layer VI of the normal cortex occupy the most superficial zone, *i.e.*, the polymorphic cell layer (PM) in the *reeler*, while neuronal components of layer II/III occupy the deepest zone, *i.e.*, the medium and small pyramidal cell layer (MP+SP) in this mutant. Thus, the relationship of the corresponding layers of the normal cortex are reversed or upside-down in the *reeler*. However, such a simple inversion of the normal cortex is not correct. Layer V corticospinal tract (CST) neurons are widely distributed in the

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sensory-motor cortex of the *reeler* mouse instead of being confined to a single layer, *i.e.*, the large pyramidal cell layer (LP) which corresponds to layer V of the normal cortex (Terashima *et al.*, 1983; Inoue *et al.*, 1991; Hoffarth *et al.*, 1995; Polleux *et al.*, 1998; Yamamoto *et al.*, 2003). In the *SRK* rat, a Reelin-deficient rat, which is caused by 64 base pair insertion into the rat *reelin* (Kikkawa *et al.*, 2003), CST neurons are ectopically distributed in the sensory-motor cortex (Ikeda and Terashima, 1997). We previously reported the other example of malpositioning of layer V neurons in the visual cortex of the *reeler* mouse (Baba *et al.*, 2007). In this study, HRP was injected into the superior colliculus of the *reeler* mouse, which resulted in malpositioning of layer V visual corticotectal (VCT) neurons. Taken together with these previous studies, it is natural to anticipate that layer V auditory corticotectal neurons (ACT) in the auditory cortex, which project to the inferior colliculus (Huffman and Hensen, 1990), are radially malpositioned in the corresponding cortex of the *reeler*.

Another neurological mutant mouse, *yotari*, spontaneously arose from mutation in *Dab1*, a mouse homologue of *Drosophila* gene *disabled (dab)* (Sheldon *et al.*, 1997). The phenotypes of the *yotari* are very similar to those of *reeler* (Yoneshima *et al.*, 1997), although some subtle morphological differences are identified between these two mutant mice (Aoki *et al.*, 2001). We previously demonstrated that layer V CST neurons are radially scattered within the sensory-motor cortex of the *yotari* (Yamamoto *et al.*, 2003, 2009). In the *yotari* mouse, intracortical distribution pattern of layer V cortical efferent neurons other than CST neurons has not been reported elsewhere.

In the present study, a small volume of HRP was injected into the superior and inferior colliculi of the *reeler* and *yotari* mice to elucidate the distribution patterns of VCT and ACT neurons, respectively, to examine whether layer V cortical efferent neurons are malpositioned through the neocortex of the *reeler* and *yotari*.

## MATERIALS AND METHODS

### 1. Animals

The classical *reeler* heterozygous (*Reln*<sup>fl/+</sup>) mice were originally purchased from the Jackson laboratory (Bar Harbor, Me) and raised in our animal facility. Homozygous *yotari* mouse (*Dab1*<sup>yot/yot</sup>) were produced by crosses of heterozygous mice carrying the disrupted *Dab1* gene which were kindly gifted by Drs. Katsuhiko Mikoshiba and Kazunori Nakajima (the Institute of Medical Sciences, the University of Tokyo). Homozygotes of the *reeler* or *yotari* were identified phenotypically by the presence of ataxia. All animals were housed in a temperature-controlled (22 ± 0.5°C) colony room with a 12h/12h L/D cycle in groups in acrylic cages with woodchip bedding and unlimited access to normal laboratory chow and water. All experiments were carried out with the approval of the Committee on Animal Care and Welfare, Kobe University Graduate School of Medicine.

### 2. Retrograde labeling

Fourteen mice of age of 19 postnatal day (5 normal, 4 *yotari* and 5 *reeler*) were used in the present study. The animals were anesthetized with 3.5% chloral hydrate by intraperitoneal injection (0.9 ml per 100 g body weight) and clamped in a stereotactic apparatus (Narishige, Tokyo). For retrograde labeling of VCT neurons, following an incision of skin of the occipital region, a small burr hole was made at right occipital bone over the superior colliculus using a dental drill, and a single injection of 0.1 µl of 10% horseradish peroxidase (HRP; type VI, Sigma Chemical Co., St. Louis, MO) dissolved into distilled water was made into the right superior colliculus through a glass micropipette attached to the barrel of 1 µl Hamilton syringe under an operating microscope. For retrograde labeling of

ACT neurons, following an incision of skin of the temporal region, a small burr hole was made at right occipital bone over the inferior colliculus using a dental drill, and a single injection of 0.1  $\mu$ l of 10% HRP solution was made into the right inferior colliculus through a glass micropipette attached to the barrel of 1  $\mu$ l Hamilton syringe under an operating microscope. Forty-eight hours after injection, the animals were deeply anesthetized with Nembutal (pentobarbital sodium, 0.2 ml per 100 g body weight), and sacrificed by transcardial perfusion of phosphate-buffered saline (PBS) for 5 minutes at room temperature, followed by a mixed solution of 1% paraformaldehyde and 1.25% glutaraldehyde in 0.1M phosphate buffer (PB; pH 7.4) for 25 minutes at 4°C, and were washed by buffered 10% sucrose in PB for 15 minutes at 4°C. After perfusion, the brain and spinal cord were immediately removed from the skull and vertebral canal, respectively, and immersed in 30% sucrose in PB overnight at 4°C. The brains were then sectioned coronally or sagittally at 40  $\mu$ m thickness on a freezing microtome. The sections were reacted for the presence of HRP by using the chromagen tetramethylbenzidine (TMB; Mesulam, 1978), mounted on glass slides pretreated with gelatin, and counterstained with 1% neutral red or 1% methyl green. Brain stems including the injection site were coronally or sagittally cut at 40  $\mu$ m thickness on a freezing microtome and reacted in diaminobenzidine (DAB) according to the method of LaVail *et al.* (1973) to demonstrate the injection site. The atlas of Zilles (1985) was used for definition of cortical areas.

## RESULTS

### 1. Retrograde labeling of VCT neurons

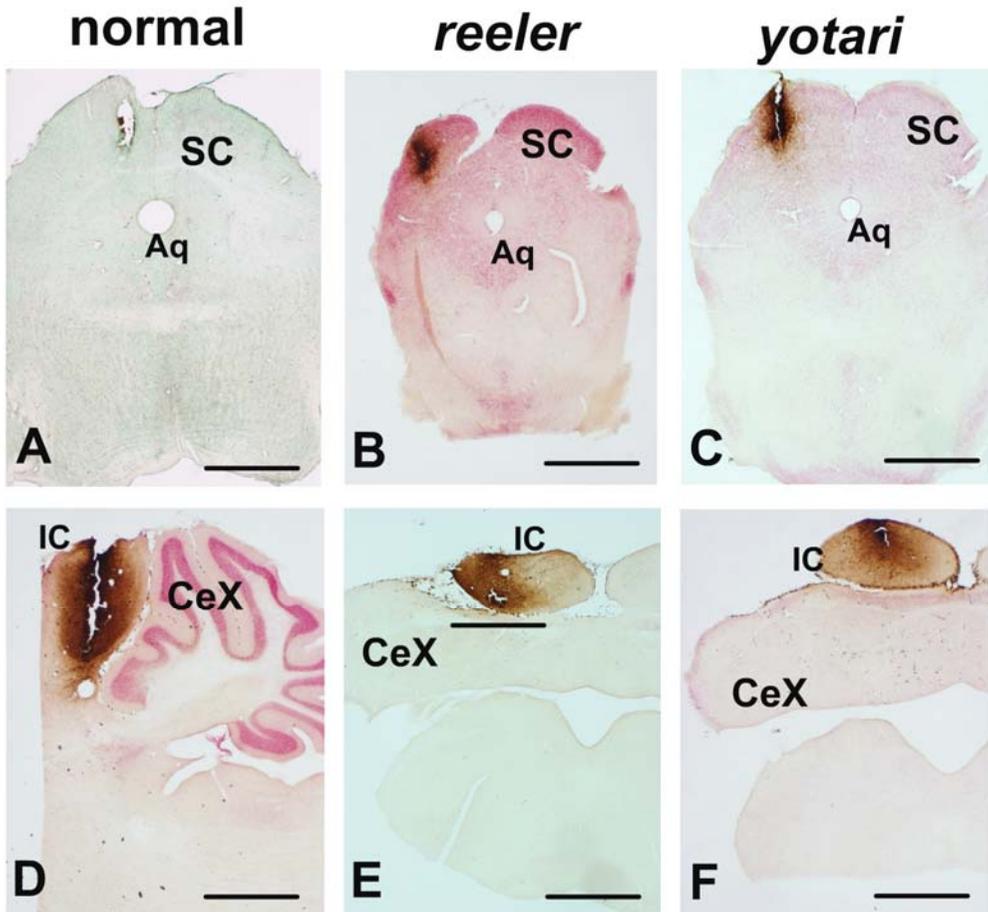
Typical injection sites of HRP into the superior colliculus of the normal, *reeler* and *yotari* mice are shown in Figure 1 (A, normal; B, *reeler*, C, *yotari*). No spread of HRP solution into areas adjoining to the superior colliculus were observed. Retrogradely labeled VCT neurons were confined to layer V of the primary visual cortex of the normal cortex (Fig. 2A, D). They were typical pyramidal neurons with an upright apical dendrite (Fig. 2G, arrows). Both in the *reeler* and *yotari*, labeled VCT neurons were radially scattered from the white mater to the pia mater in the primary visual cortex (Fig. 2B, E, *reeler*; C, F, *yotari*). Both in the *reeler* and *yotari*, labeled cells deeply situated in the visual cortex were typical pyramidal cells with an upright apical dendrite, whereas those in the superficial layer of the visual cortex were atypical pyramidal neurons with an inverted or horizontally-directed apical dendrite (Fig. 2H, I), as previously reported for CST neurons in the *reeler* mouse (Terashima *et al.*, 1983; Yamamoto *et al.*, 2003). It should be noted that many labeled cells just beneath the pia mater had very simple morphology: only cell bodies were labeled, and neither apical dendrites nor basal dendrites were recognized.

### 2. Retrograde labeling of ACT neurons

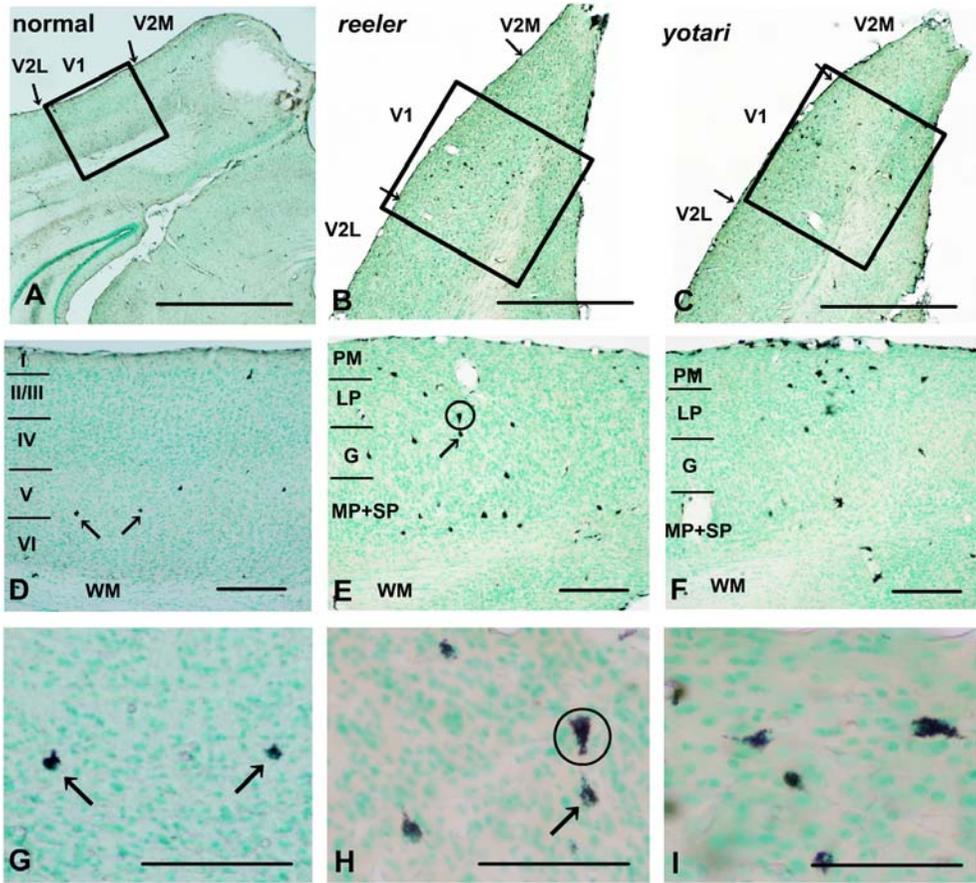
Typical injection sites of HRP into the inferior colliculus of the normal, *reeler* and *yotari* mice are shown in Figure 1 (D, normal; E, *reeler*, F, *yotari*). HRP solution into areas adjoining to the inferior colliculus were not observed. Retrogradely labeled cells were confined to layer V of the primary auditory cortex of the normal cortex (Fig. 3A, D). Retrogradely labeled ACT neurons were typical pyramids with an upright apical dendrite (Fig. 3D, G). Both in the *reeler* and *yotari*, labeled VCT neurons were radially scattered from the white mater to the pia mater in the primary auditory cortex (Fig. 3B, E, *reeler*; C, F, *yotari*). Labeled ACT neurons in the deep tier of the primary auditory cortex were typical pyramidal cells with an upright apical dendrite (Fig. 3H), whereas those in the superficial tier of the primary auditory cortex tended to be atypical pyramidal neurons with an inverted or horizontally-directed apical dendrite, as previously reported for CST neurons in the *reeler*

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mouse (Fig. 3I). (Terashima *et al.*, 1983; Yamamoto *et al.*, 2003). In addition, many labeled cells of which apical dendrite was not filled with HRP were distributed in the superficial tier of the auditory cortex (Fig. 3J).

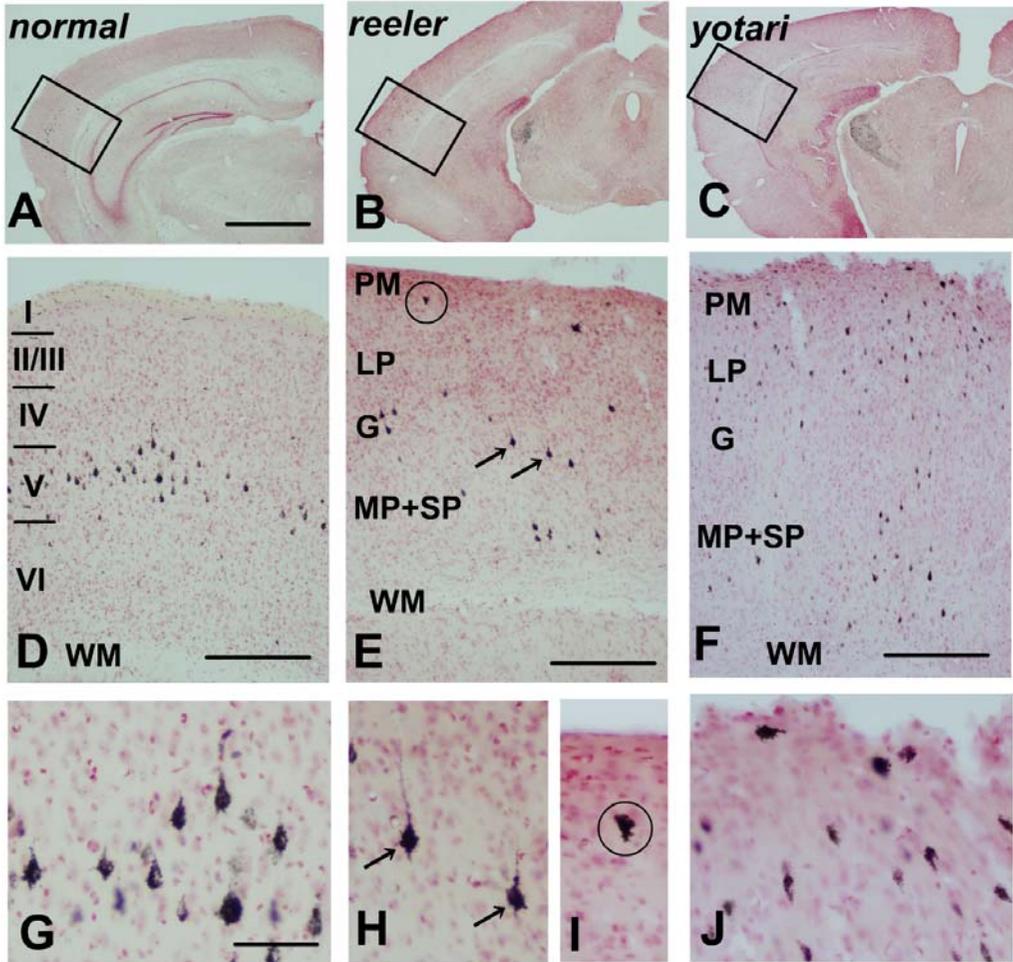


**Figure 1.** Typical injection site of HRP solution. **A-C:** Injection site is confined to the superior colliculus (SC) of the normal (**A**), *reeler* (**B**) and *yotari* (**C**) mice. **D-F:** Injection site is confined to the inferior colliculus (IC) of the normal (**A**), *reeler* (**B**) and *yotari* (**C**) mice. Other abbreviations: Aq, cerebral aqueduct; CeX, cerebellar cortex. Coronal (**A-C**, **E**, **F**) and sagittal (**D**) sections counterstained with methyl green (**A**) or neutral red (**B-F**). DAB method. Scale bars: 1 mm (**A-F**).



**Figure 2.** Retrogradely labeled visual corticotectal (VCT) neurons after the injection of HRP solution into the superior colliculus (SC) of the normal, *yotari* and *reeler* mice. A-C: These low-power photographs show the coronal sections of the occipital cortex of the normal (A), *reeler* (B) and *yotari* (C) mice. Arrows in A-C show borders between V1 and the secondary visual cortex (V2M, medial area; V2L, lateral area). D-F: D, E, and F are enlarged from the rectangle in A, B, and C, respectively. Retrogradely labeled VCT neurons are distributed in layer V of the V1 of the normal mouse (D), but radially scattered in the corresponding cortical area both in *yotari* (E) and *reeler* (F). G-I: These high-power photographs are enlarged from D-F, respectively. In the normal mouse, labeled VCT neurons are typical pyramids with an upright apical dendrite and distributed in layer V of the V1 (arrows in D and G). The arrow in E and H shows a typical pyramidal neuron with an upright apical dendrite in the V1 of the *reeler*. The circle in E and H shows an inverted pyramidal neuron with an upside-down apical dendrite. In the *yotari*, atypical pyramidal-form neurons occupy the superficial zone of the V1. Other abbreviations: I-VI, cortical layers I-VI; G, granular cell layer; LP, large pyramidal cell layer; MP+SP, medium and small pyramidal cell layer; PM, polymorphic cell layer; WM, white matter. Coronal sections counterstained with methyl green. TMB method. Scale bars: 1mm (A), 0.5 mm (B-F), 100  $\mu$ m (G-I).

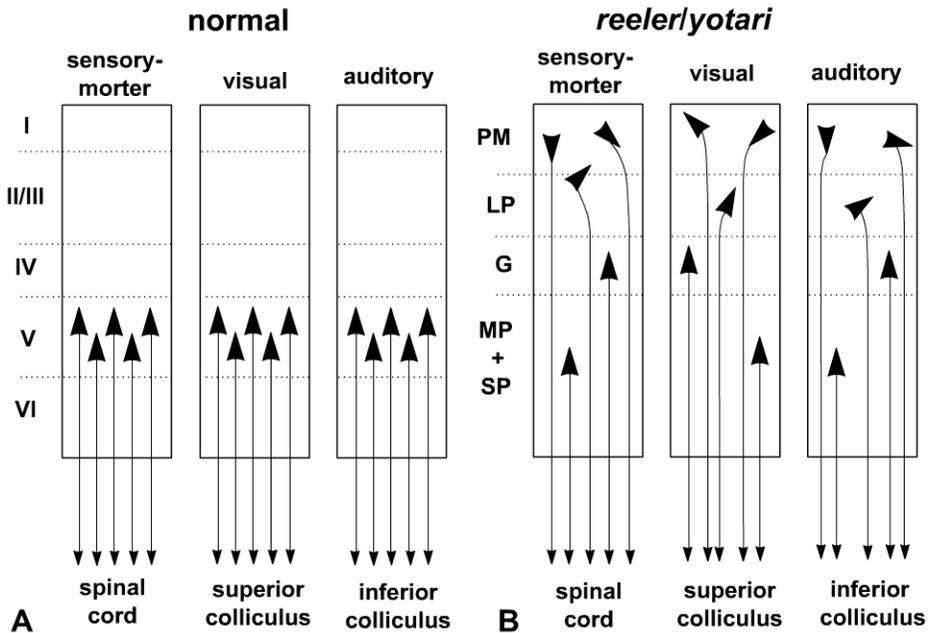
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**Figure 3.** Retrogradely labeled auditory corticotectal (ACT) neurons after the injection of HRP solution into the inferior colliculus of the normal, *yotari* and *reeler* mice. A-C: These low-power photographs show the coronal sections of the temporal cortex of the normal (A), *reeler* (B) and *yotari* (C) mice. D-F: D, E, and F are enlargements from the rectangle in A, B, and C, respectively. Retrogradely labeled ACT neurons are distributed in layer V of the normal auditory cortex (D), but radially scattered in the corresponding cortical area of the *reeler* (E) and *yotari* (F). G: This high-power photograph, enlarged from D shows that labeled ACT neurons in the normal cortex are large pyramidal cells with an upright apical dendrite. H, I: These high-power photographs are enlarged from E. Arrows in E and H show that typical pyramidal neurons with an upright apical dendrite are distributed in the deep tier of the *reeler* cortex. The circle in E and H shows an inverted pyramidal neuron with an upside-down apical dendrite. J: This high-power photograph, enlarged from F, shows atypical pyramidal-form neurons in the superficial zone of the visual cortex of the *yotari*. See other abbreviations in Figure 2. Coronal sections stained with neutral red. TMB method. Scale bars: 1 mm (A-C), 0.5 mm (D-F), 100  $\mu$ m (G-J).

**DISCUSSION**

The present study has shown that VCT neurons and ACT neurons, which are confined to layer V of the visual and auditory cortices of the normal mouse, respectively, are radially scattered from the deepest depth of the neocortex to the most superficial layer just beneath pia mater, both in the *reeler* and *yotari* (Fig. 4). We previously demonstrated that CST neurons are radially malpositioned in the sensory-motor cortex of these two neurological mutants, *reeler* and *yotari* (Yamamoto *et al.*, 2003, 2009). Taken together with the present and previous findings, layer V cortical efferent neurons are radially malpositioned in the cerebral neocortex of *reeler* and *yotari* mice instead of being confined to a single layer, LP, which corresponds to layer V of the normal neocortex.



**Figure 4.** Cortical output neurons in layer V of the normal cerebral neocortex are malpositioned both in the *reeler* and *yotari* mice. **A:** In the normal neocortex, corticospinal tract (CST) neurons, visual corticotectal (VCT) neurons, and auditory corticotectal (ACT) neurons are confined to layer V of the sensory-motor, visual and auditory cortices without exception. **B:** In the *reeler* and *yotari* mice, CST, VCT and ACT neurons are radially scattered from the deepest depth of the neocortex to the most superficial layer just beneath pia mater.

Previous autoradiographic studies demonstrated that cell types normally found deep in the cerebral cortex are located superficially, and conversely those that are normally superficial tend to be located in the deeper layers (Caviness and Sidman, 1973; Caviness, 1982), supporting the reversed or upside-down model of the *reeler* cortex. However, the cellular architectonics of the *reeler* cortex differs from what would be expected by assumption of a simple inversion of the normal cortex (Caviness and Frost, 1983). For example, studies based on Golgi impregnation methods revealed that large pyramidal cells in layer V are not only distributed in the LP corresponding to the layer V of the normal cortex but scattered radially through the whole thickness of the cerebral neocortex of the *reeler*

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mouse (Caviness, 1976; Pinto-Lord and Caviness, 1979). Although it has been known for some time that various classes of neurons in the neocortex of this mutant are intermixed, the present study provides a convincing evidence that a single neuronal class classified as layer V cortical efferent neurons are radially dispersed throughout the neocortex both in the *reeler* and *yotari*. Almost 30 years ago, Lemmon and Pearlman (1981) identified VCT neurons by antidromic stimulation with electrodes in the superior colliculus of the *reeler* mice and found that VCT neurons are not confined to a single layer corresponding to layer V, but are distributed from the white matter to the pial surface. Recently, Dekimoto *et al.* (2010) revealed that neurons expressing cortical layer-specific markers are intermingled in the neocortex of the *reeler*: ER81-expressing layer V neurons in the visual cortex of the *reeler* mouse are radially scattered as reported in the present study. Further studies based on combination of a neural tracing method and *in situ* hybridization method using layer-specific markers will be awaited to elucidate whether cortical efferent neurons in layer V including CST, VCT and ACT neurons express ER81 mRNA signals or not. No previous studies are available to identify wide dispersion of cortical layer V efferent neurons in the auditory cortex of the *reeler*. However, Hayzoun *et al.* (2007) reported that the pattern of cytochrome oxidase activity, a marker of neuronal activity, is not clearly recognizable in the auditory cortex of the *reeler*, indicating cellular components affiliated with a single cortical layer of the auditory cortex are also intermingled in the *reeler*.

The present study has revealed that VCT neurons in the deeper zone of the primary visual cortex of the *reeler* and *yotari* mice show normal upright pyramids, but those in the superficial layer show atypical pyramids of which apical dendrites direct in the downward or horizontal direction. The similar finding is also obtained for ACT neurons in the auditory cortex (present study) and CST neurons in the sensory-motor cortex (Yamamoto *et al.*, 2003, 2009). The reason why such a relationship between the cellular configuration of cortical efferent neurons and their intracortical position has remained obscure. The original hypothesis to explain relationship between the cellular morphology of cortical efferent neurons and their intracortical position is that apical dendrites grow into the direction of axon-rich strata (Pinto-Lord and Caviness, 1979). Thus, apical dendrites of large pyramidal cells below the axon-rich strata proceed upwards to produce normal pyramids and those over the axon-rich strata develop downwards to produce inverted pyramids. Another hypothesis is as follows. The growth of apical dendrites toward the pial surface is regulated by semaphorin 3A (Sema3A), a diffusible chemoattractant, which is expressed within the cortical plate at late embryonic and early postnatal days (Pollex *et al.*, 2000). Although Sema3A is expressed by all cortical plate neurons, higher density of neurons in the superficial cortical plate may allow the outside-in gradient of Sema3A within the cortical plate. This polarized gradient of Sema3A causes cortical neurons to extend their apical dendrites toward the pial surface. In the *reeler* and *yotari*, cortical plate neurons accumulate under the cortical plate instead of penetrating it (Rouvroit and Goffinet, 1998), which may result in formation of the reversed gradient of Sema3A to generate atypical pyramids in the superficial zone of the mutant cortex.

Our previous studies demonstrated that the superficial 3 layers of the superior colliculus of the Reelin-deficient animals, *reeler* and *SRK*, are disorganized to form a single layer, the fused superficial zone (Sakakibara *et al.*, 2003; Baba *et al.*, 2007). Although Cytoarchitectural abnormality of the inferior colliculus of the *reeler* has not been reported elsewhere, the expression pattern of cytochrome oxidase activity within the inferior colliculus is different between the normal and *reeler* mice (Hayzoun *et al.*, 2007). The *reeler* and *yotari* mice share common phenotypes, and therefore, the similar abnormalities may be

recognized in the superior and inferior colliculi of the *yotari* mice. If this hypothesis is true, our present results suggest that displaced VCT and ACT neurons in the cortex of the *reeler* and *yotari* can find their target within the disrupted mesencephalic tectum, *i.e.*, inferior and superior colliculi.

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