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Research report

Reduction of early thalamic input alters adult corticocortical connectivity

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Abstract

The functional specificity of mammalian isocortex requires that precise connections be established between cortical areas and their targets. While recent studies of cortical development have focused on intrinsic specification, the role of extrinsic factors has received considerably less attention. In the present study, we examined how early removal of thalamic input affects the development of visual corticocortical connections. Hamster pups received ablations of visual thalamic nuclei on the day of birth. At 30 days of age, an injection of horseradish peroxidase (HRP) was placed into the area of cortex deafferented by the early thalamic ablation to retrogradely label adult corticocortical connections. Ablated animals displayed a significant increase in the number of corticocortical connections compared to control animals. The increased connectivity in ablated animals was primarily due to a significant increase in the number of corticocortical projections arising from non-visual areas. These results demonstrate that an intact thalamocortical projection is necessary for the development of normal cortical connectivity.

Theme: Development and regeneration

Topic: Cerebral cortex and limbic system

Keywords: Thalamic ablation; Thalamocortical projection; Cortical development

1. Introduction

The adult mammalian cortex can be divided into a number of anatomically and functionally distinct areas. A central question in developmental neurobiology is how these unique areas arise during development. While it is presumed that both intrinsic and extrinsic factors contribute to the specification of cortical phenotypes, there has been a current focus on intrinsic cortical specification [41]. The present experiment addresses the importance of an extrinsic cue, the thalamus, in the determination of cortical phenotype.

Recent studies show that the cortical plate is regionalized early in development by intrinsic factors, such as the expression of molecular markers [3,5,13,14,16,20,25,30,32,42]. In mutant mice which lack thalamocortical input because of a deficiency in the *Gbx-2* or *Mash-1* gene, emergence of the expression of molecules is strikingly normal, demonstrating that early isocortical regionalization is not dependent on extrinsic cues from the thalamus [29,32]. However, because the mutants die at birth, these studies were unable to examine the importance of thalamocortical input in late cortical specialization.

Evidence that the thalamus is important in maintaining the regional differences set up early in development is demonstrated in experiments using thalamic ablations. In mice, the fate of cortical cells to postnatally express H-2Z1, a transgene that delineates layer IV of somatosensory cortex, is determined in the ventricular zone [18], yet neonatal ablations of the somatosensory thalamus prevent H-2Z1 expression [19]. Likewise, the unique transient patterns of γ-aminobutyric acid A ($GABA_A$) receptor subtypes that are evident before thalamocortical innervation and that distinguish primary sensory cortices

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from secondary areas are abolished if primary sensory thalamic nuclei are ablated at birth [35].

Similar to the unique expression of particular genes and receptors, it is likely that the development of area-specific patterns of connectivity is dependent on an interaction between intrinsic and extrinsic factors. Deletion of Otx-1, a gene that characterizes a subset of cortical layer V cells during development, alters the normal pattern of subcortical connections of layer V cells in visual cortex [46]. However, reduction of visual thalamic input to cortex during development also disrupts the organization of subcortical projections from visual cortex [23]. In terms of corticocortical connections, the fate of a subset of layer VI cells to postnatally express the protein latexin is determined early in the ventricular zone [1]. Nevertheless, the probability that cells in lateral cortex will express latexin is later regulated by extrinsic cues [2].

In the present study, we examined the importance of thalamic input, an extrinsic cue, in the development of normal corticocortical connectivity. Neonatal visual thalamic ablations were employed to reduce visual thalamic input to cortex and HRP injections in visual cortex were used to retrogradely label cells projecting into the deafferented cortex. Following visual thalamic ablations, we observed a significant increase in corticocortical connections, particularly those between visual cortex and non-visual areas.

2. Materials and methods

Offspring of timed pregnant Syrian hamsters (*Mesocricetus auratus*) from our breeding colony were used for the present experiment. Animals were maintained on a 12L:12D photoperiod and fed food and water ad libitum. Throughout all experiments, animals were maintained in strict accordance to the policies and procedures set forth in The National Institutes of Health Guide for the Care and Use of Laboratory Animals and to the approved regulations of Cornell University (Institutional Animal Use Committee).

2.1. Neonatal thalamic ablations

Day of birth (postnatal day 0; P0) hamster pups were anesthetized by hypothermia and given unilateral electrolytic ablations targeting the visual thalamic nuclei: lateral thalamic nucleus (L), dorsal lateral geniculate nucleus (LGd) and lateral posterior nucleus (LP). Performing this procedure on P0 causes thalamic afferents from the targeted nuclei to degenerate before the majority of these fibers have grown into the cortical plate [28,31]. Specific thalamic nuclei may be ablated at P0 without *directly* injuring the isocortex since posterior cortex has not yet grown over the posterior thalamus. A small hole was made in the skull on the dorsal surface behind the developing cortex. An insulated electrode with a 0.5 mm exposed straight tip or 1 mm exposed bent tip was lowered at a 45° rostral to caudal angle to a depth of 2 mm and current (~5.5 μA) was delivered for 7 s using a Grass SD9 Stimulator. Pups were then rewarmed and returned to their mother.

2.2. Tracer injections in adults

On P30, lesioned animals were reanesthetized with sodium pentobarbital (0.16 cc/100 mg of 50 mg/ml). From 0.1 to 2.0 mg of horseradish peroxidase (HRP; Sigma) was placed into visual cortex presumed to be deafferented by the early ipsilateral thalamic ablation. The HRP was administered either by injection using a 1 μl Hamilton syringe, by implanting a piece of Gelfoam soaked in a 30% solution or by implanting a piece of solid HRP created from the 30% solution that had dried on a glass slide. Following a 3-day survival period, animals were perfused transcardially with 0.9% saline followed by 1.25% gluteraldehyde and 1% paraformaldehyde in 0.1 M phosphate buffer (pH 7.4). Brain tissue was recovered and cyroprotected in a phosphate buffer solution containing 10% sucrose. Each brain was then embedded in gelatin and cut frozen at 40 μm in the coronal plane. All sections were saved and reacted with tetramethylbenzidine. Alternate tissue sections were stained with neutral red for clear visualization of HRP reaction product while the remaining series was stained with cresyl violet or thionin for delineation of cortical and thalamic cytoarchitecture. Unlesioned (control) hamsters (P30) also received HRP injections into visual cortex. Control brains were processed in a manner identical to experimental brains.

2.3. Subjects

Out of a total of ~40 experimental animals, four lesioned hamsters met the criteria for the subsequent analysis of corticocortical connectivity. These criteria were: (1) the location of the HRP injection in isocortex had to match the location of the thalamic lesion. For instance, only animals with both HRP injections centered on visual cortex and lesions of the visual thalamus were included in the analysis. (2) Remaining thalamic nuclei had to be recognizable for reconstruction. (3) The HRP injection had to match the approximate size and placement of an injection in a control animal. Using these criteria, we were able to examine visual corticocortical connections in four visually thalamic ablated animals and four non-lesioned controls.

2.4. Reconstruction of thalamic ablations

Using a projection microscope, visual thalamic nuclei on the intact side and ablated side (if nucleus was not completely ablated) were outlined in 40 μm coronal

Table 1
Percent of visual thalamic nuclei remaining in lesioned animals[a]

Animal	L	LGd	LP
824.2	100%	56%	73%
755B	100%	25%	56%
755A	57%	0%	19%
806.4	15%	0%	28%

[a] Volume of lesioned nucleus/volume of intact nucleus. L, lateral thalamic nucleus; LGd, dorsal lateral geniculate nucleus; LP, lateral posterior nucleus.

sections of the cresyl violet stained series. Surface area measurements were obtained using NIH Image 1.60 (W. Rasband, US National Institutes of Health, Bethesda, MD) and nuclear volumes were computed. The unablated volume of each remaining nucleus (L, LGd, LP) on the lesioned side was then expressed as a percentage of the volume of the nucleus on the intact side (Table 1). Given that the nuclei targeted lie on the dorsolateral surface of the thalamus, the ablations were readily recognized by gliosis and neuronal absence/reduction immediately dorsal to the external medullary lamina and superior thalamic radiation. Ablations distorted the general shape of the thalamus in some subjects. However, remaining thalamic nuclei retained many of their original characteristics and could be identified on the basis of staining intensity, cell size and density, and relative position. In cases where remaining thalamic nuclei were unrecognizable, brains were excluded from the analysis.

2.5. Cell plots

In tissue stained with neutral red, every 10th coronal section from the hemisphere ipsilateral to the injection site was drawn and the distribution of corticocortical cells retrogradely labeled with HRP was charted. The laminar position of each cell (infragranular versus supragranular) in the different cortical areas was recorded using descriptions from Caviness [6] and Caviness and Frost [7]. In sections containing the HRP injection, we delineated the perimeter of the injection site that included the injection site core and a halo of dark HRP reaction product. Retrogradely labeled

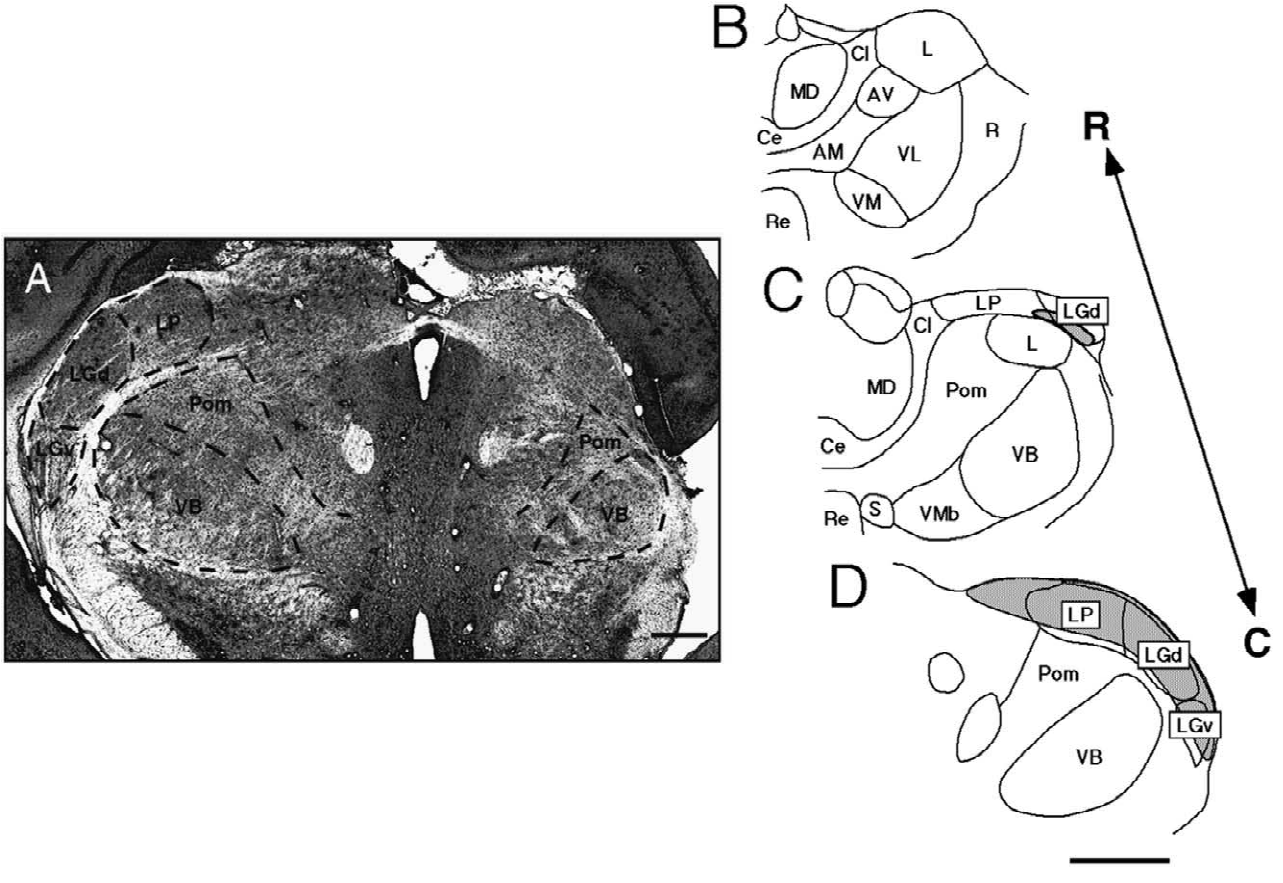

Fig. 1. Thalamic damage produced by a unilateral electrolytic ablation at birth. (A) Bright-field photomicrograph of a Nissl-stained coronal section through the adult thalamus of animal 775B. Note the absence of LGd and LP on the ablated side (right) compared to the unablated side (left). (B)–(D) Schematics of coronal sections at rostral, medial and caudal levels of the thalamus illustrating the extent of damage for animal 775B. AM, anteromedial nucleus; AV, anteroventral nucleus; Ce, central nucleus; CL, central lateral nucleus; L, lateral thalamic nucleus; LGd, dorsal lateral geniculate nucleus; LGv, ventral lateral geniculate nucleus; LP, lateral posterior nucleus; MD, mediodorsal nucleus; Pom, posterior complex, medial nucleus; R, thalamic reticular complex; Re, reuniens nucleus; S, submedial nucleus; VB, ventrobasal nucleus; VL, ventrolateral nucleus; VM, ventromedial nucleus; VMb, ventromedial, basal nucleus; R, rostral; C, caudal. Scale bars=0.5 mm.

cells were not charted in the 200 μm adjacent to the borders of the injection site to ensure that the cells we plotted were labeled by active transport rather than by diffusion of HRP. Cell counts were corrected for injection site size (see below).

2.6. Reconstruction of injection sites

Each lesioned animal was paired with a control animal characterized by a HRP injection of similar size and placement, yet small differences in injection site size between animals can influence the total number of cells labeled by HRP. Thus, injection site volumes were calculated in order to standardize cell counts between animals. Injection sites were outlined in neutral red stained tissue using a Leitz Diaplan Microscope connected to Neurolucida 3.0 (Microbrightfield, Colchester, VT). Surface area measurements were obtained using Morph (Microbrightfield) and injection site volumes were computed. Cell counts for each brain were then multiplied by a correction factor generated by the standardization of each injection site volume to the volume of the largest injection. Comparisons in the number of labeled cells for the two experimental groups were made using paired *t*-tests.

2.7. Reconstruction of injected hemispheres

A dorsal view reconstruction of the entire injected hemisphere was made using measurements from the coronal sections. The reconstructed hemisphere was then fitted to a standard dorsal view map of hamster cortex (Fig. 3A; [27,47]) to facilitate visualization of injection site placement and the distribution of labeled cells. When fitting the map to the reconstructed hemisphere, adjustments were made to account for the cytoarchitecture of the reconstructed brain.

The distinction between visual cortical areas and adjacent cortices was readily made in both control and lesioned animals based on the following characteristics: (1) the presence of a distinct cortical layer IV in parietal cortex but not in immediately adjacent visual cortex (corresponding to V2 in control tissue), (2) a reduction in cortical width between parietal and adjacent visual cortex (i.e. parietal cortex is wider), (3) the presence of large Betz cells in layer V of hindlimb cortex but not in adjacent medial visual cortex, (4) the specific condensation of layer II cells and the presence of small, homogeneously globular cells in retrosplenial cortex but not in medial visual cortex and (5) the presence of a well-defined layer IV and hypocellular layer Vc (but not layer Vb) in temporal cortex but not in lateral visual cortex.

In contrast, the location of the border between primary (V1) and secondary visual cortex (V2) was not readily identified in lesioned animals. Whereas a well-defined cortical layer IV and hypocellular layer V distinguished V1 from V2 in controls, this distinction was not possible in lesioned animals due to the significant loss of layer IV cells [47]. Thus, comparisons in the distribution of cells were made between total visual cortex (V1 and V2 combined) and non-visual areas.

Outside of the visual cortices, the cytoarchitecture of other cortical areas appeared normal in the animals with smaller visual thalamic ablations (animals 775B and 824.4). In the animals with large visual thalamic ablations (animals 775A and 806.4), thalamic damage encroached

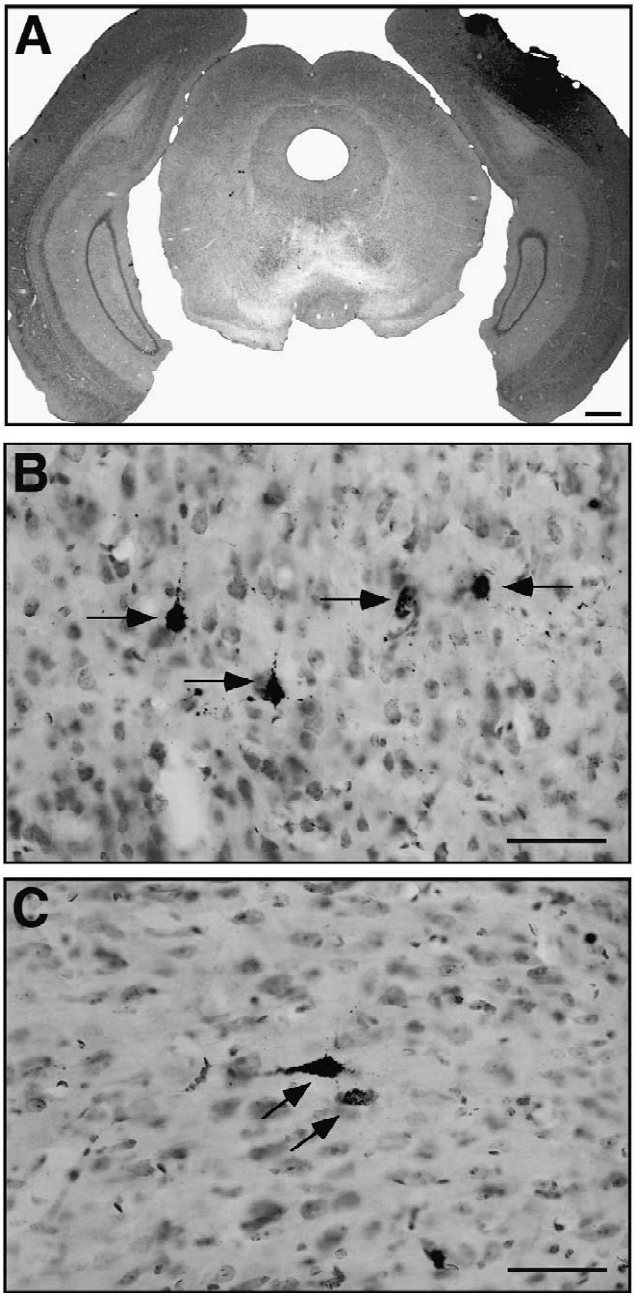

Fig. 2. HRP label in the adult cortex of a control animal. (A) Bright-field photomicrograph of a Nissl-stained coronal section illustrating a representative HRP injection in visual cortex. (B, C) Corticocortical cells retrogradely labeled with HRP in layer V of secondary visual (B) and retrosplenial (C) cortices. Scale bars=500 μm (A) and 50 μm (B, C).

into non-visual thalamic nuclei located ventral to the visual nuclei, thereby affecting the cytoarchitecture of some non-visual cortices. Specifically, we observed a decrease in the thickness of layer IV and VI in the parietal and temporal cortices ipsilateral to the ablation, compared to these cortices in the contralateral hemisphere. The thickness of layer IV in forelimb and hindlimb cortex was also reduced in the ablated hemisphere. No noticeable differences were detected in the retrosplenial or frontal cortices of the deafferented hemisphere, compared to the control hemisphere.

3. Results

3.1. Extent of neonatal thalamic ablations

Thalamic ablations successfully targeted the visual

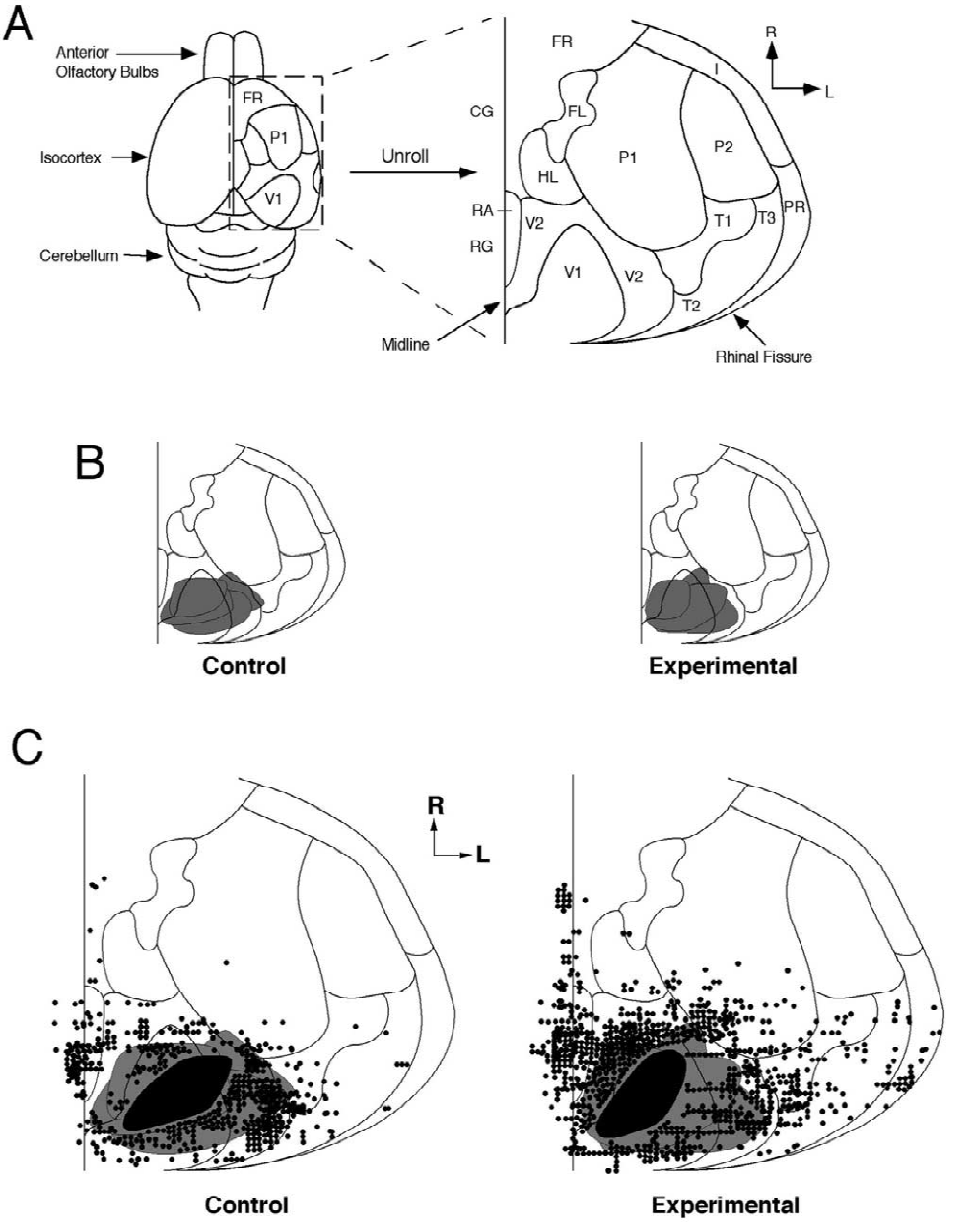

Fig. 3. The location of HRP injection sites and retrogradely labeled corticocortical cells in control and thalamic ablated hamsters. (A) A dorsal view representation of normal (left) and unrolled (right) adult hamster isocortex illustrating the cortical parcellation scheme for the present study. (B) Dorsal view representations showing the combined location of injection sites in visual cortex for control (left) and thalamic ablated (right) animals. (C) Superimposed composites of HRP-labeled corticocortical cells in control (left) and thalamic ablated (right) hamsters illustrating the relative number and distribution of cells for each experimental group. Composites were generated from cell plots of coronal sections. The light-gray region represents the composite of the injection sites for animals within that experimental group. The black region illustrates the area of overlap for the four injection sites. CG, cingulate cortex; FL, forelimb of somatic-motor cortex; FR, frontal cortex; HL, hindlimb of somatic-motor cortex; I, insular cortex; P1, parietal cortex 1; P2, parietal cortex 2; PR, perirhinal cortex; RA, retrosplenial agranular cortex; RG, retrosplenial granular cortex; T1, temporal cortex 1; T2, temporal cortex 2; T3, temporal cortex 3; V1, primary visual cortex; V2, secondary visual cortex.

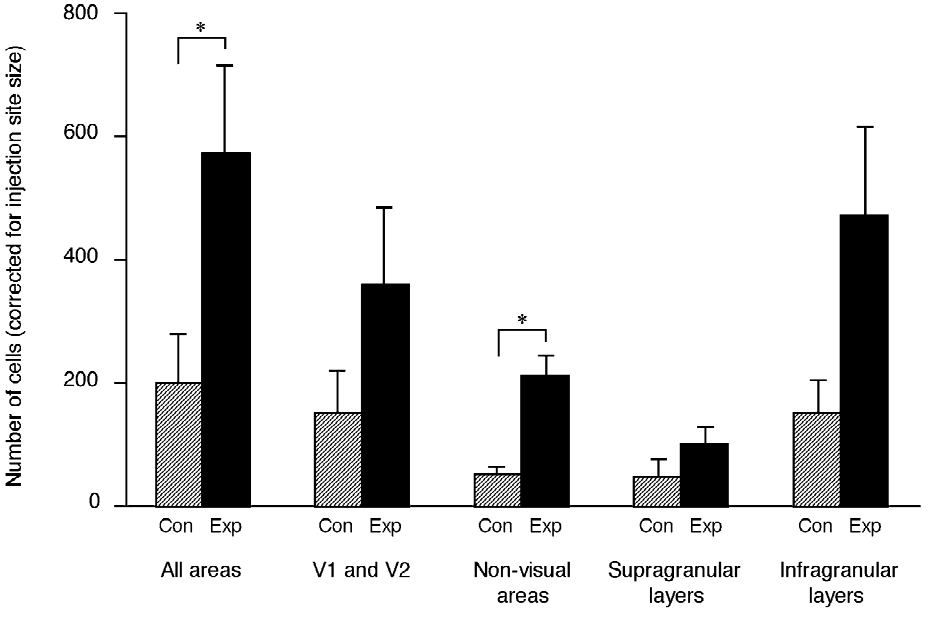

Fig. 4. Comparison of the number of HRP labeled corticocortical cells in control ($n=4$) and experimental animals ($n=4$). Values represent means±S.E.M. that have been corrected for injection site size. Graph shows comparisons between groups for total number of cells in all areas ($P=0.026$; paired t-test), number of cells in visual areas (V1 and V2; $P=0.078$; paired t-test), number of cells in non-visual areas (CG, FL, FR, HL, I, P1, P2, PR, RA, RG, T1, T2 and T3; $P=0.013$; paired t-test), number of cells in supragranular layers ($P=0.278$; paired t-test) and number of cells in infragranular layers ($P=0.062$; paired t-test).

thalamus, yet the amount of damage to visual thalamic nuclei varied among experimental animals (Table 1). Two hamsters with unilateral visual thalamic ablations had complete removal of LGd and substantial damage to L and LP while the remaining two animals had ~50–75% removal of LGd and varying damage to LP but not L. An example of a unilateral visual thalamic ablation is presented for animal 775B in Fig. 1A–D in which LGd and LP were reduced to 25% and 56% of their normal size, respectively.

3.2. Injection site placements

Matched HRP injection sites in experimental and control animals included V1 and V2. A representative HRP injection in the visual cortex of a control animal is shown in Fig. 2A while Fig. 2B and C show corticocortical neurons retrogradely labeled from the injection. A composite of the reconstructed injection sites for control versus experimental brains is presented in the dorsal view maps in Fig. 3B (see Fig. 3A for parcellation of the cortical map). The combined injection sites for the two groups are similar. Injections were tangentially confined to V1 and V2 for all but one control animal (animal 898.4) where the halo of HRP had diffused slightly into posterior parietal and temporal cortex.

3.3. Effects of early thalamic ablation on corticocortical connections to visual cortex

Corticocortical neurons projecting to visual cortex originated from the same cortical areas in lesioned and control animals, however, lesioned animals showed a significant increase in the number of labeled corticocortical neurons compared to controls (Fig. 3C and 4). In control animals, the majority of HRP cells were located in the visual cortices (V1, V2) surrounding the injection site (Fig. 3C). A much smaller number of labeled cells were found in temporal (T1, T2, T3) and retrosplenial (RA, RG) cortices and in the caudal parts of parietal (P1), frontal (FR) and perirhinal (PR) cortices. Lesioned animals, like controls, had a greater number of labeled cells in visual areas compared to non-visual areas (Fig. 4). However, lesioned animals showed a significant increase in the number of labeled cells in non-visual areas compared to controls (Fig. 4). The differences in labeled cells between the two groups were most notable in the cingulate (CG), retrosplenial (RG), parietal (P1), temporal (T1, T2, T3) and perirhinal (PR) cortices (Fig. 3C).

The laminar distribution of corticocortical cells did not change significantly after thalamic ablation (Fig. 4). Like control animals, those with ablations had a greater proportion of labeled cells in the infragranular layers compared to the supragranular layers (Fig. 4). Most cells contributing to corticocortical connections were identified as pyramidal cells of layers 2/3 and 5 (see Fig. 2B and C). Few labeled cells were detected in layers IV and VI.

In terms of ablation size, the magnitude of increase of labeled corticocortical cells in experimental animals was associated with the severity of visual thalamic damage (Fig. 5A). Specifically, animals with large thalamic ablations (775A and 806.4) had a greater increase in con-

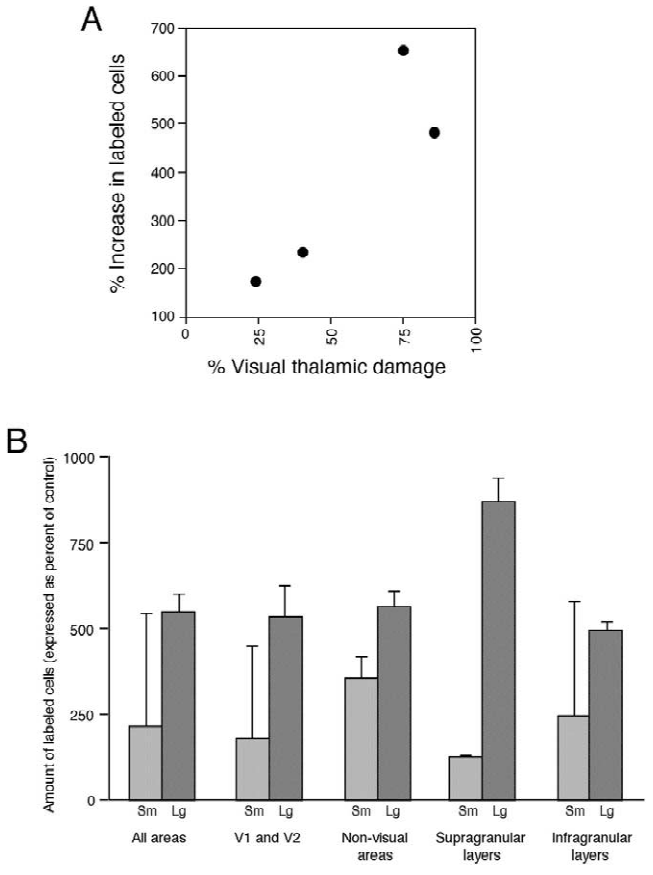

Fig. 5. Size of thalamic ablation is related to the increase in corticocortical projections. (A) Graph shows an association between the percent of total visual thalamic damage (damage to L, LGd and LP combined) and the percent increase (above values in matched controls) of labeled corticocortical cells in lesioned animals. (B) Graph shows the amount of labeled corticocortical cells for animals with small (Sm) versus large (Lg) thalamic ablations for the various projection categories. Values represent means±S.E.M. that have been corrected for injection site size and are expressed as a percentage of control values.

nections (expressed as a percentage of controls) for all projection categories (Fig. 5B) compared to those with small ablations (824.2 and 775B). Interestingly, the two animals with small ablations had more variable projections than the two animals with large ablations.

4. Discussion

Using neonatal visual thalamic ablations, we show that thalamic input is an important extrinsic factor in the development of cortical connectivity. Corticocortical cells labeled by a HRP injection in the visual cortex of normal animals were located primarily within the primary and secondary visual cortices, in agreement with previous studies in the hamster [15], rat [26,33] and mouse [43]. In contrast, labeled corticocortical cells in ablated animals were significantly increased in non-visual cortices, such as parietal, temporal, retrosplenial and perirhinal cortices.

The increase in corticocortical projections after early thalamic ablation seems unlikely to be due to the stabilization of a diffuse projection pattern that is refined during development. While early experiments have shown that developing corticocortical pathways are characterized by transient connections [10,21,24,36], more recent studies indicate that cortical projections are less exuberant than previously believed [4,22], and that exuberance is primarily localized to the white matter rather than cortex [37]. Furthermore, we find little evidence of transient innervation, overextension or retraction of projections following a detailed analysis of the development of corticocortical connectivity in the hamster [8].

A reduction of ‘instructive’ sensory input following thalamic ablation may be responsible for the alteration in corticocortical connectivity. Perhaps one of the best demonstrations that sensory input is ‘instructive’ is illustrated by cross-modal rewiring experiments in ferrets [44]. In these studies, patterned visual input rerouted to auditory cortex via auditory thalamic afferents results in a well-refined, yet altered, organization of callosal and horizontal connections in auditory cortex [17,34]. In addition to the visual topography and visual response properties that develop in the auditory cortex of rewired ferrets [39,40], these rewired animals appear to perceive visual stimuli through the cross-modal pathway [45], suggesting that the auditory cortex has become ‘visual’ in many regards.

In contrast to the rewiring experiments that alter the nature of thalamic input to a cortical area, it is unclear how a reduction in thalamic input alters a cortical area. One possibility is that primary sensory cortex deafferented of its sensory thalamic input defaults to surrounding secondary sensory cortex. In terms of our results, the increase in corticocortical projections from non-visual areas following thalamic ablation may be due to an areal reduction in primary visual cortex coupled with a simultaneous expansion of secondary visual cortex, the latter of which is normally characterized by substantial connections to parietal and temporal cortices, compared with the former [26]. In agreement with this hypothesis, enucleation in fetal monkeys causes a border shift such that cortex normally destined to become primary visual cortex appears to become normal secondary visual cortex following deafferentation, as defined cytoarchitectonically [12]. Furthermore, rat primary sensory cortices deafferented of early sensory thalamic input display γ-aminobutyric acid A ($GABA_A$) receptor expression very similar to that of secondary sensory areas [35]. However, other enucleation studies in monkeys examining cytoarchitecture [38] or cortical enzymatic expression [11] suggest that primary sensory cortex does not necessarily default to secondary sensory cortex. The discrepancy between these studies highlights the importance of examining multiple properties when analyzing a deafferented cortical area.

Interestingly, corticocortical connectivity is not the only characteristic to be altered following early thalamic ablation. Related studies have shown that, following visual thalamic ablations, deafferented visual cortex also displays

altered callosal connectivity [9,27], subcortical connectivity [23], cytoarchitecture [47] and neurotransmitter receptor expression [35]. Together, these experiments demonstrate that numerous properties of visual cortex can change after visual thalamic ablation. Perhaps future studies which examine the behavioral and electrophysiological consequences of early thalamic ablations will provide the best insight as to the functional capabilities of the deafferented visual sensory cortex that accommodates an increased number of corticocortical inputs from non-visual cortical areas.

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References

[1] Y. Arimatsu, M. Ishida, M. Sato, M. Kojima, Corticocortical associative neurons expressing latexin: specific cortical connectivity formed in vivo and in vitro, Cereb. Cortex 9 (1999) 569–576.
[2] Y. Arimatsu, M. Ishida, K. Takiguchi-Hayashi, Y. Uratani, Cerebral cortical specification by early potential restriction of progenitor cells and later phenotype control of postmitotic neurons, Development 126 (1999) 629–638.
[3] Y. Arimatsu, M. Miyamoto, I. Nihonmatsu, K. Hirata, Y. Uratani, Y. Hatanaka, K. Takiguchi-Hayashi, Early regional specification for a molecular neuronal phenotype in the rat neocortex, Proc. Natl. Acad. Sci. USA 89 (1992) 8879–8883.
[4] P. Barone, C. Dehay, M. Berland, H. Kennedy, Role of directed growth and target selection in the formation of cortical pathways: prenatal development of the projection of area V2 to area V4 in the monkey, J. Comp. Neurol. 374 (1996) 1–20.
[5] A. Bulfone, S.M. Smiga, K. Shimamura, A. Peterson, L. Puelles, J.L. Rubenstein, T-brain-1: a homolog of Brachyury whose expression defines molecularly distinct domains within the cerebral cortex, Neuron 15 (1995) 63–78.
[6] V.S. Caviness, Architectonic map of neocortex of the normal mouse, J. Comp. Neurol. 164 (1975) 247–264.
[7] V.S. Caviness, D.O. Frost, Tangential organization of thalamic projections to the neocortex in the mouse, J. Comp. Neurol. 194 (1980) 335–367.
[8] B. Clancy, M.A. Kingsbury, M.J. Lipon, E. Graf, J. Yost, A. Sung, M. Parsons, B.L. Finlay, Development of axonal projections from different areas of neonatal hamster isocortex, Soc. Neurosci. Abs. (2001) 315.
[9] C.G. Cusick, R.D. Lund, Modification of visual callosal projections in rats, J. Comp. Neurol. 212 (1982) 385–398.
[10] C. Dehay, J. Bullier, H. Kennedy, Transient projections from the fronto-parietal and temporal cortex to areas 17, 18 and 19 in the kitten, Exp. Brain Res. 57 (1984) 208–212.
[11] C. Dehay, P. Giroud, M. Berland, H.P. Killackey, H. Kennedy, Phenotypic characterisation of respecified visual cortex subsequent to prenatal enucleation in the monkey: development of acetylcholinesterase and cytochrome oxidase patterns, J. Comp. Neurol. 376 (1996) 386–402.
[12] C. Dehay, P. Giroud, M. Berland, H. Killackey, H. Kennedy, Contribution of thalamic input to the specification of cytoarchitectonic cortical fields in the primate: effects of bilateral enucleation in the fetal monkey on the boundaries, dimensions, and gyrification of striate and extrastriate cortex, J. Comp. Neurol. 367 (1996) 70–89.
[13] M.J. Donoghue, P. Rakic, Molecular gradients and compartments in the embryonic primate cerebral cortex, Cereb. Cortex 9 (1999) 586–600.
[14] M.J. Donoghue, P. Rakic, Molecular evidence for the early specification of presumptive functional domains in the embryonic primate cerebral cortex, J. Neurosci. 19 (1999) 5967–5979.
[15] M.R. Dursteler, C. Blakemore, L.J. Garey, Projections to the visual cortex in the golden hamster, J. Comp. Neurol. 183 (1979) 185–204.
[16] G.D. Frantz, J.M. Weimann, M.E. Levin, S.K. Mcconnell, Otx1 and Otx2 define layers and regions in developing cerebral cortex and cerebellum, J. Neurosci. 14 (1994) 5725–5740.
[17] W. Gao, S.L. Pallas, Cross-modal reorganization of horizontal connectivity in auditory cortex without altering thalamocortical projections, J. Neurosci. 19 (1999) 7940–7950.
[18] Y. Gitton, M. Cohen-Tannoudji, M. Wassef, Specification of somatosensory area identity in cortical explants, J. Neurosci. 19 (1999) 4889–4898.
[19] Y. Gitton, M. Cohen-Tannoudji, M. Wassef, Role of thalamic axons in the expression of H-2Z1, a mouse somatosensory cortex specific marker, Cereb. Cortex 9 (1999) 611–620.
[20] H.L. Horton, P. Levitt, A unique membrane protein is expressed on early developing limbic system axons and cortical targets, J. Neurosci. 8 (1988) 4653–4661.
[21] H. Kennedy, J. Bullier, C. Dehay, Transient projection from the superior temporal sulcus to area 17 in the newborn macaque monkey, Proc. Natl. Acad. Sci. USA 86 (1989) 8093–8097.
[22] H. Kennedy, P. Salin, J. Bullier, G. Horsburgh, Topography of developing thalamic and cortical pathways in the visual system of the cat, J. Comp. Neurol. 348 (1994) 298–319.
[23] M.A. Kingsbury, E.R. Graf, B.L. Finlay, Altered development of visual subcortical projections following neonatal thalamic ablation in the hamster, J. Comp. Neurol. 424 (2000) 165–178.
[24] R. Lent, C. Hedin-Pereira, J.R. Menezes, S. Jhaveri, Neurogenesis and development of callosal and intracortical connections in the hamster, Neuroscience 38 (1990) 21–37.
[25] K. Mackarehtschian, C.K. Lau, I. Caras, S.K. McConnell, Regional differences in the developing cerebral cortex revealed by ephrin-A5 expression, Cereb. Cortex 9 (1999) 601–610.
[26] M.W. Miller, B.A. Vogt, Direct connections of rat visual cortex with sensory motor and association cortices, J. Comp. Neurol. 226 (1984) 184–202.
[27] B. Miller, M.S. Windrem, B.L. Finlay, Thalamic ablations and neocortical development: alterations in thalamic and callosal connectivity, Cereb. Cortex 1 (1991) 241–261.
[28] B. Miller, L. Chou, B.L. Finlay, The early development of thalamocortical and corticothalamic projections, J. Comp. Neurol. 335 (1993) 16–41.
[29] E.M. Miyashita-Lin, R. Hevner, K.M. Wassarman, S. Martinez, J.L. Rubenstein, Early neocortical regionalization in the absence of thalamic innervation, Science 285 (1999) 906–909.
[30] T. Mori, A. Wanaka, A. Taguchi, M. Kazumasa, M. Tohyama, Localization of novel receptor tyrosine kinase genes of the eph family MDK1 and its splicing variant, in the developing mouse nervous system, Mol. Brain Res. 34 (1995) 154–160.
[31] J.R. Naegele, S. Jhaveri, G.E. Schneider, Sharpening of topographical projections and maturation of geniculocortical axon arbors in the hamster, J. Comp. Neurol. 277 (1988) 593–607.
[32] Y. Nakagawa, J.E. Johnson, D.D. O'Leary, Graded and areal expression patterns of regulatory genes and cadherins in embryonic neocortex independent of thalamocortical input, J. Neurosci. 19 (1999) 10877–10885.
[33] J. Olavarria, V.M. Montero, Reciprocal connections between the

striate cortex and extrastriate cortical visual areas in the rat, Brain Res. 217 (1981) 358–363.
[34] S.L. Pallas, T. Littman, D.R. Moore, Cross-modal reorganization of callosal connectivity without altering thalamocortical projections, Proc. Natl. Acad. Sci. USA 96 (1999) 8751–8756.
[35] J. Paysan, A. Kossel, J. Bolz, J.M. Fritschy, Area-specific regulation of gamma-aminobutyric acid type A receptor subtypes by thalamic afferents in developing rat neocortex, Proc. Natl. Acad. Sci. USA 94 (1997) 6995–7000.
[36] D.J. Price, C. Blakemore, Regressive events in the postnatal development of association projections in the visual cortex, Nature 316 (1985) 721–724.
[37] D.J. Price, T.J. Zumbroich, Postnatal development of corticocortical efferents from area 17 in the cat's visual cortex, J. Neurosci. 9 (1989) 600–613.
[38] P. Rakic, I. Suner, R.W. Williams, A novel cytoarchitectonic area induced experimentally within the primate visual cortex, Proc. Natl. Acad. Sci. USA 88 (1991) 2083–2087.
[39] A.W. Roe, S.L. Pallas, J.-O. Hahm, M. Sur, A map of visual space induced in primary auditory cortex, Science 250 (1990) 818–820.
[40] A.W. Roe, S.L. Pallas, Y. Kwon, M. Sur, Visual projections routed to the auditory pathway in ferrets: receptive fields of visual neurons in primary auditory cortex, J. Neurosci. 12 (1992) 3651–3664.
[41] J.L. Rubenstein, P. Rakic, Genetic control of cortical development, Cereb. Cortex 9 (1999) 521–523.
[42] J.L. Rubenstein, S. Anderson, L. Shi, E. Miyashita-Lin, A. Bulfone, R. Hevner, Genetic control of cortical regionalization and connectivity, Cereb. Cortex 9 (1999) 524–532.
[43] P.A. Simmons, V. Lemmon, A.L. Pearlman, Afferent and efferent connections of the striate and extrastriate visual cortex of the normal and reeler mouse, J. Comp. Neurol. 211 (1982) 295–308.
[44] M. Sur, P.E. Garraghty, A.W. Roe, Experimentally induced visual projections into auditory thalamus and cortex, Science 242 (1988) 1437–1441.
[45] L. von Melchner, S.L. Pallas, M. Sur, Visual behaviour mediated by retinal projections directed to the auditory pathway, Nature 404 (2000) 871–876.
[46] J.M. Weimann, Y.A. Zhang, M.E. Levin, W.P. Devine, P. Brulet, S.K. McConnell, Cortical neurons require Otx1 for the refinement of exuberant axonal projections to subcortical targets, Neuron 24 (1999) 819–831.
[47] M.S. Windrem, B.L. Finlay, Thalamic ablations and neocortical development: alterations of cortical cytoarchitecture and cell number, Cereb. Cortex 1 (1991) 230–240.