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Altered Sensory Processing in the Somatosensory Cortex of the Mouse Mutant Barrelless

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Abstract

Mice homozygous for the barrelless (brl) mutation, mapped here to chromosome 11, lack barrel-shaped arrays of cell clusters termed ``barrels'' in the primary somatosensory cortex. Deoxyglucose uptake demonstrated that the topology of the cortical whisker representation is nevertheless preserved. Anterograde tracers revealed a lack of spatial segregation of thalamic afferents into individual barrel territories, and single-cell recordings demonstrated a lack of temporal discrimination of center from surround information. Thus, structural segregation of thalamic inputs is not essential to generate topological order in the somatosensory cortex, but it is required for discrete spatiotemporal relay of sensory information to the cortex.

Segregation in the processing of peripheral information is a common principle in the organization of sensory cortical areas. This principle was first demonstrated in the primary visual cortex of cats and monkeys, in which segregation of thalamocortical axons forms the anatomic basis for ocular dominance columns [1]. In rodents, the pattern of mystacial whisker follicles is replicated in layer IV of the primary somatosensory cortex (SI) by an array of cell clusters named ``barrels'' [2]. Each barrel is activated by an individual whisker, the ``center'' whisker, through fast thalamocortical relay, but it also integrates information from neighboring whiskers [3] through slower intracortical circuitry [4]. The one-to-one correspondence between whisker follicles and their cortical representation results from the segregation of thalamocortical axons into barrel domains [5,6]. These axons initiate the parcellation of SI during

development [7], and their geometry is modified after neonatal follicle injury [8]. A spontaneous mutation in our mouse colony generated animals in which the parcellation of SI into barrels does not occur. This mutation has allowed us to investigate the role of barrels in particular, and parcellation of the cerebral cortex in general, in sensory processing.

Barrelless mice were discovered in a line bred for a normal pattern of mystacial vibrissae [9] and now form a true-breeding line. The barrelless phenotype is an autosomal recessive trait. In crosses with C57BL/6J inbred mice, 15 of 32 backcross offspring and 6 of 46 intercross offspring were barrelless. On the basis of simple sequence length polymorphisms [10], the barrelless (brl) locus was mapped to the proximal segment of chromosome 11 because no recombination with the microsatellite D11Mit226 was detected in these offspring. Barrelless mice show no other sign of neurological disorganization.

The cytoarchitectural contours of individual barrels typical of normal mice Figure 1, A and C cannot be detected in layer IV of SI of barrelless mice Figure 1, B and D. However, the distribution of layer IV cells does not always appear uniform, and the faint representation of rows of whisker follicles can sometimes be discerned. The patterning varies among animals, and that shown in Figure 1B is one of the clearest examples observed. In the brainstem trigeminal complex of mutant mice Figure 1, H and J, whisker-related patterns are visible as in normal animals Figure 1, G and I [see [11]]. The whisker-related parcellation of the ventrobasal nucleus of the thalamus into ``barreloids" [12] is less clear in the mutant Figure 1F than in normal Figure 1E mice. In barrelless mice, the patterns in brainstem and thalamus appear at the same times as those in normal mice [13]. Except for the absence of barrels in the mutant mice, the somatosensory cortex of these animals shows no cytoarchitectonic abnormalities at any postnatal age. This aspect of the barrelless phenotype is similar to that in monoamine oxidase A-deficient mice [14].

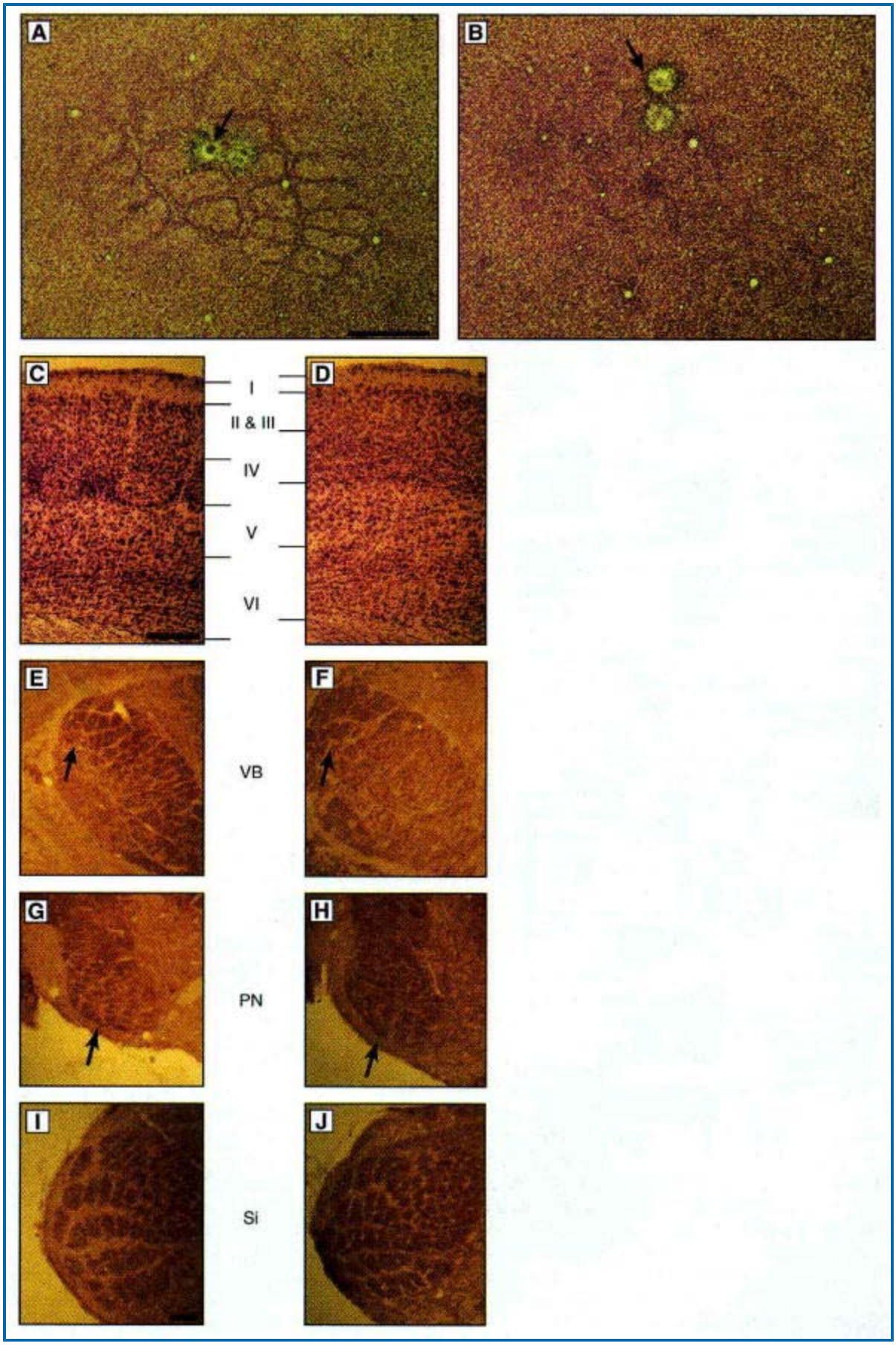

Figure 1. Photomicrographs of central stations of the whisker-to-barrel pathway of normal (A, C, E, G, and I) and barrelless (B, D, F, H, and J) mice. (A and B) Nisslstained sections through layer IV of SI of adult mice revealing individual barrels in normal mice and their absence in mutants. The hemispheres were cut parallel to the pial surface overlying SI. Lesions (arrowheads) indicate sites of

recording of neuronal responses to whisker stimulation. (C and D) Nissl-stained coronal sections through SI of adult mice. The layering (indicated by roman numerals) is similar in normal and mutant mice, but barrelless animals lack the cytoarchitectonic differentiation of relatively cell-poor areas in layer IV that represent whiskers in normal mice. (E to J) Coronal sections of brains from 5-day-old mice stained for cytochrome oxidase [21]. In (E) and (F) the barreloids (arrow) in the ventrobasal nucleus of the thalamus (VB) of barrelless mice are poorly defined. In (G) and (H) whisker representations (arrow) are present in the brainstem of normal and barrelless mice. PN, principal nucleus; Si, subnucleus interpolaris. Scale bars: 500 micro meter (A, also pertains to B), 200 micro meter (C, also pertains to D), and 100 micro meter (I, also pertains to E, F, G, H, and J).

Arborizations of thalamocortical axons (TCAs) were mostly confined to barrels in layer IV of SI in normal mice Figure 2A, with a less dense projection to upper layer VI Figure 2C [15]. In barrelless mice, TCAs also terminated in layers IV and VI but were continuously distributed in layer IV, rather than being confined to barrel-like structures Figure 2, B and D. The labeling did not show a row-like pattern in any of the barrelless mouse brains examined in a tangential plane. In normal animals, individual TCA arbors were restricted to one barrel Figure 2E, confirming earlier studies [5]. In barrelless mice, these arbors extended within layer IV over distances that would incorporate a tangential area of up to 10 normal barrels Figure 2F. Thus, substantial overlap of TCA arbors appropriate to adjacent whiskers must occur in barrelless animals.

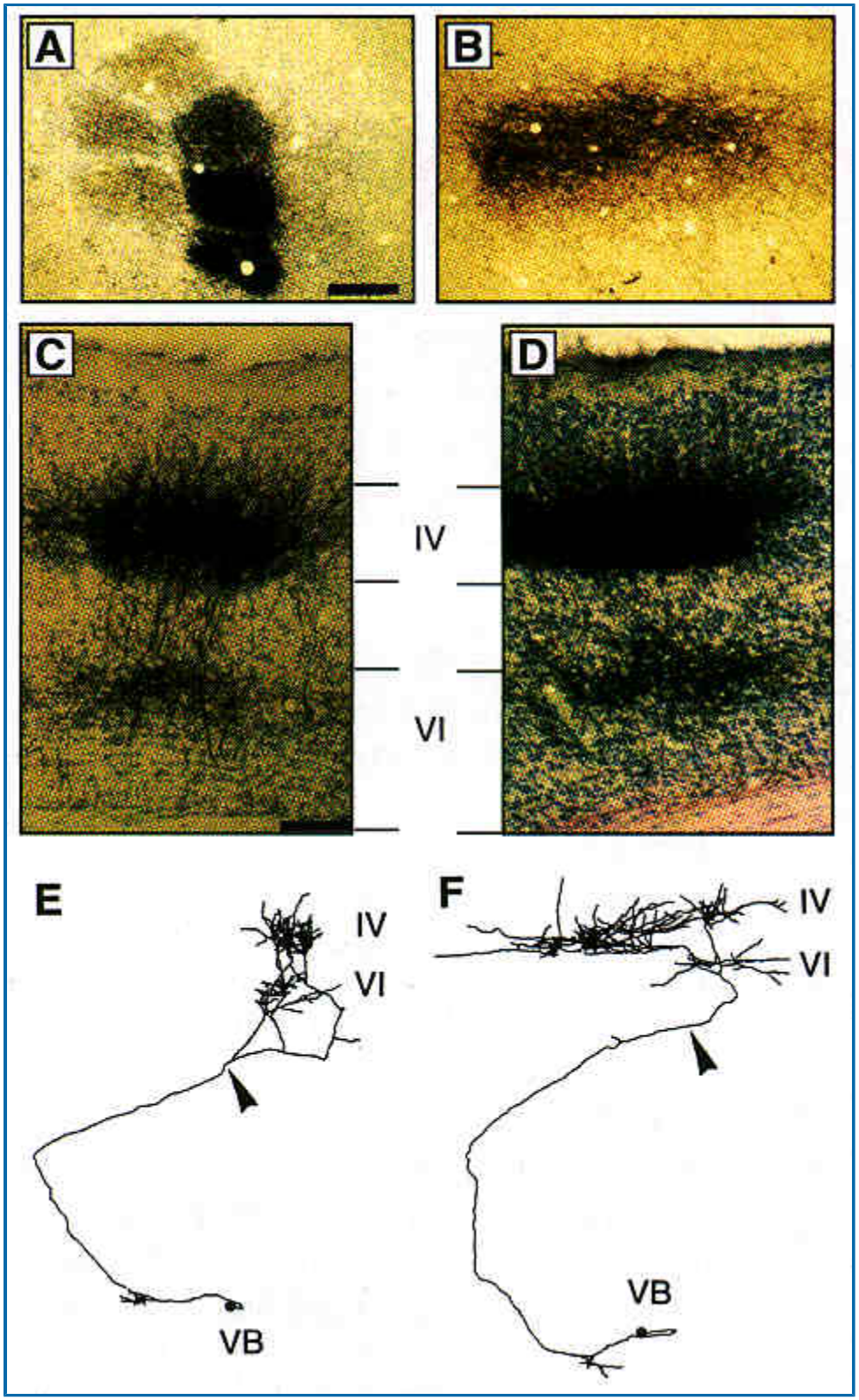

Figure 2. Thalamocortical projections from the ventrobasal nucleus of the thalamus (VB) in normal (A, C, and E) and barrelless (B, D, and F) mice. (A and B) Tangential sections through layer IV of SI of normal mice reveal labeling (dextran) that is confined to the inside of barrels, leaving septa between barrels (relatively) free of label. In barrelless mice, labeling forms a continuous zone. Although intracortical collaterals of retrogradely labeled neurons may have contributed to the labeling, the photomicrographs illustrate the lack of tangential segregation of TCAs in barrelless mice. (C and D) Coronal sections through SI reveal labeling (dextran) in layer IV and in the upper part of layer VI in both strains. (E and F) Individual TCAs (biocytinlabeled) were reconstructed with a computer-microscope and the Neurolucida program (Microbrightfield, Colchester, Vermont, USA). Arrowheads indicate the site where the axon enters SI. The axon of the normal mouse terminates in a confined area of SI, whereas in barrelless animals it terminates in a large area. Scale bars: 200 micro meter (A, also pertains to B), 100 micro meter (C, also pertains to D), and 500 micro meter (E, also

pertains to F).

Deoxyglucose (DG) uptake measurements showed that the normal topology of the whisker representation was preserved in barrelless mice Figure 3. Behavioral activation of whiskers of rows B and D produced two separated uptake zones in layer IV, leaving a relatively DG-free area representing the intermediate C row, in both barrelless and normal animals [16]. The distance between the centers of the two DG spots was similar in the two lines of mice: 677 plus minus 28 micro meter (mean plus minus SD, n equals 6) in normal mice and 685 plus minus 55 micro meter (n equals 6) in barrelless animals. Moreover, no significant difference was apparent between the two lines in the areal extent of the zones of stimulus-dependent DG uptake, as determined at levels of 25 and 50% above background.

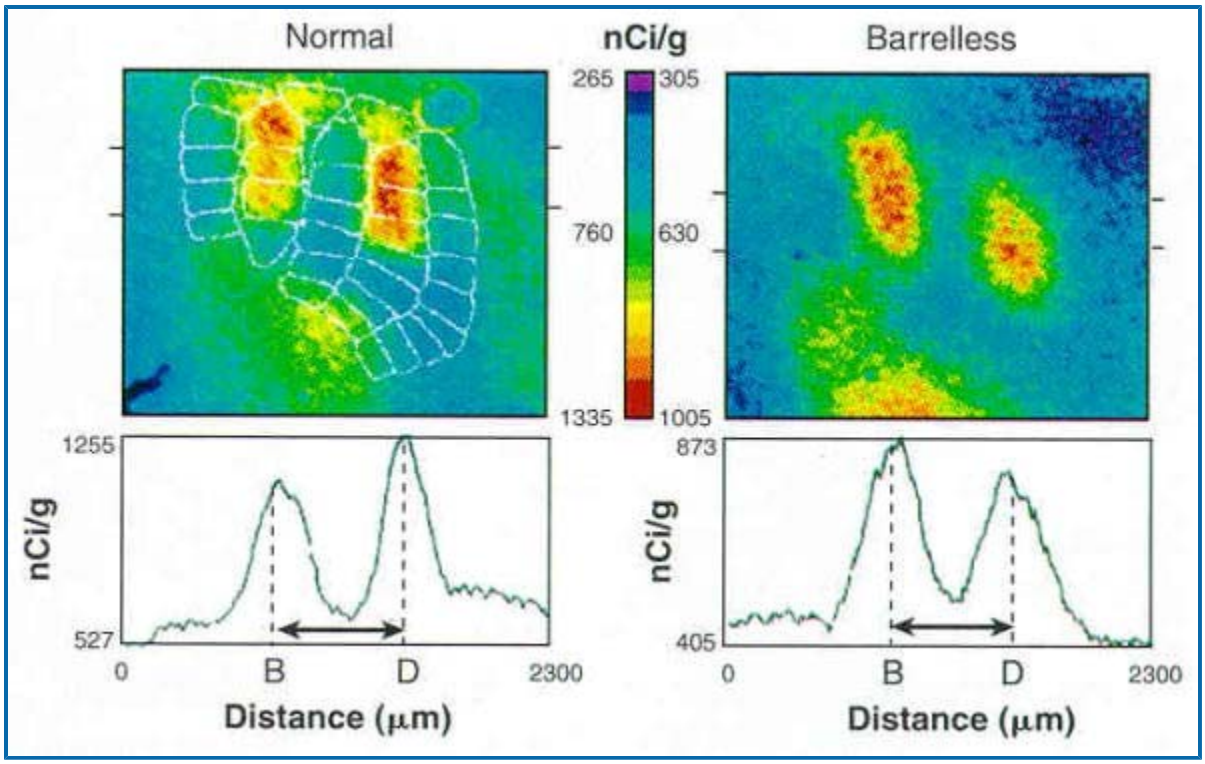

Figure 3. Cortical representations of the three caudalmost whiskers of rows B and D in normal and barrelless mice as revealed by DG uptake. The extent of DG uptake is represented by color (according to the indicated scales). In normal mice, stimulus-dependent DG uptake was confined to barrels (reconstructed from the counterstained sections) corresponding to the stimulated whiskers. A similar pattern was apparent in barrelless mice. The plots represent the mean density of DG label (in nanocuries per gram of brain tissue) measured in the zone delineated by the small line segments placed near the border of the pseudocolor images. The distance between centers of representation of rows B and D was measured (horizontal arrows).

Exploratory penetrations of SI during physiological recording sessions also indicated the same topological order for whisker representation in barrelless and normal mice. We analyzed the magnitude and latency of single-unit responses to activation of center and surround whiskers Figure 4 [17]. In normal animals (n equals 7; 33 units), the response to the fastest surround whisker was one-third the magnitude of that to the center whisker, with a latency that was 5 to 25 ms greater than that for the center whisker. In barrelless mice (n equals 10; 44 units), response magnitudes to surround whiskers were larger than those in normal mice, about one-half those to the center whisker, and notably, these responses did not differ significantly in latency from those to the center whisker. This lack of temporal separation and the greater surround response in barrelless mice correlate well with the extensive spatial overlap of TCA arbors: A layer IV neuron in mutant animals receives converging thalamic input from several whisker follicles. These profound functional differences in receptive field organization between the two lines are not reflected in DG uptake, which appears to represent the response to the center whiskers only.

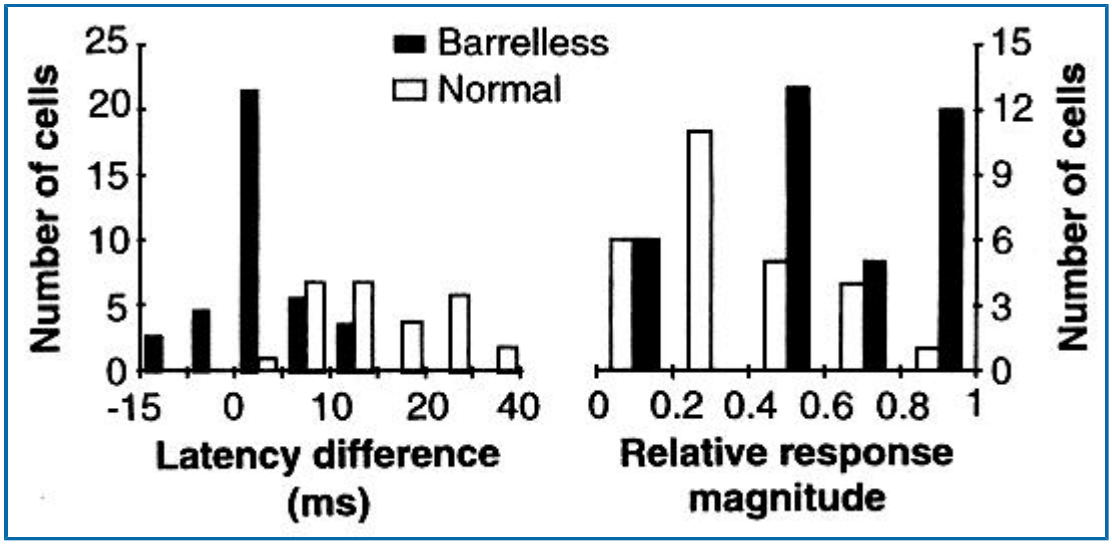

Figure 4. Response characteristics of layer IV neurons in normal barrelless mice. (Left) Distribution of differences in response latencies to the center and surround whiskers. In normal mice, the median latency difference was 13.5 ms [interquartile range (IQR), 9.0 to 21.0 ms)], whereas in barrelless mice it was 2.5 ms (IQR, 0.9 to 4.6 ms; P less than 0.0001, Mann-Whitney test). (Right) Distributions of relative response magnitudes of surround whiskers to center whiskers. In normal mice, the response ratio (surround/center) was 0.33 (IQR, 0.21 to 0.57), whereas in barrelless mice it was 0.56 (IQR, 0.43 to 0.83; P less than 0.003, Mann-Whitney test).

Homozygosity for barrelless is associated with a partial failure of patterning of the whisker-to-barrel pathway. The normal formation of whisker representations in the brainstem of barrelless mice suggests that the mutation may affect segregation of axonal arbors at the level of VB (afferents from the trigeminal brainstem) and somatosensory cortex (TCAs), or that it might disturb maturation of VB, resulting in incomplete formation of barreloids and aberrant TCA arborization. The row-like organization apparent in the distribution of cortical neurons of some mice may reflect an early step in the development of barrel cortex but occurs to a variable extent in barrelless mice. Cortical lamination as well as overall size and topological organization of the cortical whisker representation remains unaffected in barrelless mice, providing evidence that different aspects of the patterning of the cerebral cortex are at least partially independent [18].

We conclude that the failure of TCA arbors to segregate in barrelless mice does not affect the topological organization of the somatosensory cortex. The overlap of TCAs in this mutant is greater than suggested by the topology demonstrated by DG uptake. A comparable situation was observed in SI of monkeys, in which TCA arbors also span a greater cortical area than the functionally determined topological map [19]. We also conclude that the functional operation of the cerebral cortex depends on the pattern of thalamocortical connectivity. Segregation of TCAs in sensory cortex promotes independence of processing inputs that characterize neighboring, but nonadjacent, groups of sensory receptors such as whisker follicles. Overlap of TCAs in barrelless mice generates receptive fields of cortical neurons that are more appropriate to a continuous and less discriminate representation of the tactile periphery. This overlap excludes the possibility that single-whisker information can be processed separately within a discrete group of cortical neurons before further intracortical relay. Most theories on sensory discrimination and map modification by sensory experience depend on precise spatiotemporal ordering of sensory inputs [20]. The defective temporal differentiation and impaired spatial separation of sensory inputs uncovered here within the somatosensory cortex of barrelless mice provide a model for testing such hypotheses.

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16. ``Mystacial whiskers are distributed in five horizontal rows (named A through E). For the DG uptake experiments, the caudalmost whiskers of rows A, C, and E were clipped on the left side. Animals were injected intraperitoneally with 2-[1-(^{14}) C]deoxy-D-glucose (16. 5 mu Ci per 100 g of body mass) and placed in an objectfilled cage for 45 min, after which they were anesthetized and their brains processed for autoradiography [E. Welker, S. B. Rao, J. Dorfl, P. Melzer, H. Van der Loos, J. Neurosci. 12, 153 (1992)]." [Context Link]

17. ``Recordings were made from mice under urethane anesthesia (2 mg per gram of body mass, administered by intraperitoneal injections of a 10% solution in distilled water). Units were situated 350 to 480 micro meter below the pial surface. The center whisker was defined as that giving the largest response magnitude. Data for the surround whisker refer to the one with the shortest latency. Response magnitudes were measured by the mean number of spikes generated per 50 deflections [E. Welker, M. Armstrong-James, H. Van der Loos, R. Kraftsik, Eur. J. Neurosci. 5, 691 (1993) **Bibliographic Links**]." [Context Link]

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22. ``Our dear collaborator Hendrik Van der Loos died in October 1993.We thank N. Trapp and G. Skabardonis for technical assistance and S. Catsicas, P. G. H. Clarke, A. Fine, J.-P. Hornung, G. M. Innocenti, and J. H. Kaas for comments on the manuscript. Supported by the Swiss National Science Foundation (grant 31-39184), the Wellcome Trust (M.A.-J.), and the Medical Research Council of Canada (grant MT-12941)."
