Interareal coordination of columnar architectures during visual cortical development

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The formation of cortical columns is often conceptualized as a local process in which synaptic microcircuits confined to the volume of the emerging column are established and selectively refined. Many neurons, however, while wiring up locally are simultaneously building macroscopic circuits spanning widely distributed brain regions, such as different cortical areas or the two brain hemispheres. Thus, it is conceivable that interareal interactions shape the local column layout. Here we show that the columnar architectures of different areas of the cat visual cortex in fact develop in a coordinated manner, not adequately described as a local process. This is revealed by comparing the layouts of orientation columns (*i*) in left/right pairs of brain hemispheres and (*ii*) in areas V1 and V2 of individual brain hemispheres. Whereas the size of columns varied strongly within all areas considered, columns in different areas were typically closely matched in size if they were mutually connected. During development, we find that such mutually connected columns progressively become better matched in size as the late phase of the critical period unfolds. Our results suggest that one function of critical-period plasticity is to progressively coordinate the functional architectures of different cortical areas—even across hemispheres.

cerebral cortex | critical period | postnatal development | visual cortex | orientation columns

A general principle of cerebral cortical organization states that the neocortex is subdivided into numerous functionally and anatomically distinct areas (1, 2). In evolution, the subdivision into distinct areas arose concurrently with the invention of the neocortex in the first mammals (3), and the multiplication of functional areas appears as the central process that increases neocortical functionality in later mammalian evolution (3, 4). In all mammalian brains, multiple functional areas are interconnected within a brain hemisphere, and also across hemispheres, by a dense network of intrahemispheric and callosal interareal connections (2, 5, 6). These connections constitute a large fraction of the cerebral white matter and are likely to physically shape cortical morphology during the growth of the brain (7). Although many cortical areas appear specialized for particular-information processing steps, most functions of cortical processing involve the activation of distributed processing networks that span many anatomically distinct areas. The interactions among these areas are structured such that even the most simple sensory stimuli activate large groups of neurons distributed over multiple areas in a coordinated and temporally overlapping manner (5, 8–10).

Over the past two decades, the important role of distributed nerve-cell networks for sensory perception or the planning and execution of movements utilizing behavioral contextual information has been increasingly taken into account (8, 10–13). In contrast, the role of interareal networks for the developmental specification of the functional processing architecture within an individual area has not yet been analyzed. So far, the predominant view guiding developmental studies is that the functional architecture of a sensory cortical area emerges from the growth, elaboration, and selection of specific thalamic afferents (14–16) and presumably also from the local circuitry within the receiving cortical area (17–20). These processes are thought to be initially guided by systems of molecular clues and later through activity-dependent mechanisms sensitive to correlated neuronal activity (21, 22). Such an account would be perfectly satisfactory if the development of an area's functional architecture was a local, area-autonomous process or was intrinsically determined in each area. Intriguingly, however, in neonates of many species interareal connectivity is more widespread than in the mature brain (6), raising the possibility that interareal interactions across larger regions of the developing brain also contribute to the specification of individual functional areas. In fact, the visual cortex of neonatal kitten receives projections not only from other visual cortical areas (23, 24) but also from auditory, somatosensory, and motor cortex areas (25–27). Even after exuberant interareal connections have been pruned during the first month of life, the density of interareal connections is often similar to that of intraareal connections (28, 29). In line with a relatively large fraction of nonlocal axonal inputs in the neocortical neuropil, Stepanyants et al. (30) recently found that near the center of a local neocortical region of 1 mm-diameter, 74 % of excitatory axons originate from neurons outside the region. In addition, interareal interactions are capable of strongly modulating activity driven by thalamic afferents (31–34), so that one should expect activity-dependent mechanisms of development to be sensitive to interareal interactions. All of these findings raise the possibility that, starting from the earliest stages of cortical circuit development, the processes specifying the local functional architecture of an area might be strongly influenced or even guided by large-scale cortical networks.

Thus, both the developmental time table of interareal connections and the substantial role of activity-dependent mechanisms in cortical development support the possibility that the functional architectures of different cortical areas develop in a coordinated manner. In the present study, we show that columnar architectures of different areas of the cat visual cortex in fact develop in a coordinated manner, not adequately described as a local process. We utilize the pronounced intraareal variability of orientation column layouts in the visual cortex (35, 36) to analyze whether the columnar architectures of different cortical areas are laid out independently or in a coordinated manner. We analyzed orientation columns processing contours in different parts of the visual field in visual cortical areas V1 and V2 (37, 38) of kittens aged between 6 and 15 weeks. The spacing of adjacent orientation columns determines the size of the cortical hypercolumn, which is considered to be the basic processing unit of the visual cortex (2, 36) and exhibits a high degree of intracortical and interindividual variability. Even within an individual area, column spacings often vary

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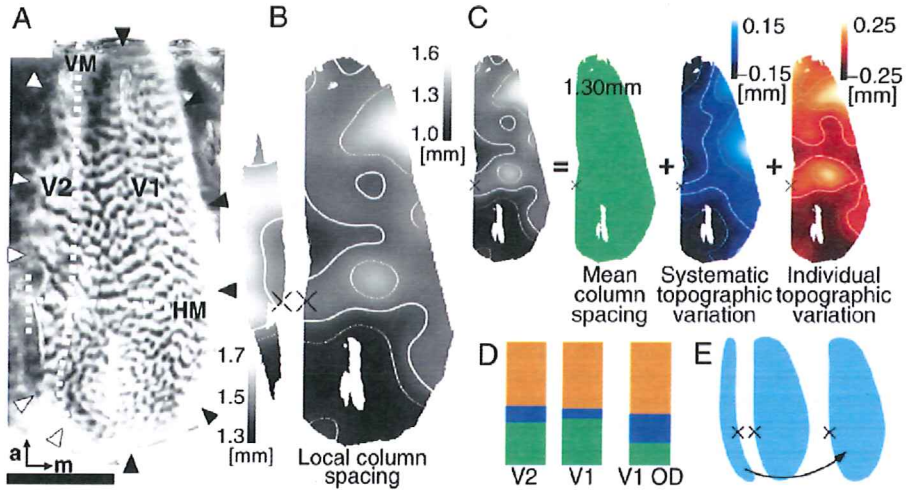

Fig. 1. Decomposition of orientation column spacing in cat visual cortex. (*A*) Overall layout of orientation columns in areas V1 (*Right*) and V2 (*Left*). Black and white arrowheads indicate the external borders of V1 and V2, respectively. Cortical representations of the vertical meridian (VM) (i.e., the V1/V2 border) and the horizontal meridian (HM) of the visual field are represented by the white dashed lines (a = anterior, m = medial; scale bar, 10 mm). (*B*) 2D-maps of LCS in areas V2 and V1 (grayscale coded). Contour lines are drawn at the mean spacing (thick white line) and mean ± SD (thin white lines). Black crosses mark the central visual field representation. (*C*) Each map of LCS is composed of (*i*) the MCS (green) (*ii*) the systematic part of the topographic component of local column spacing (population averaged, blue), and (*iii*) the individual part of topographic component (orange) (here illustrated for the V1 map in *B*). (*D*) According to *C*, the variance of all column spacings in the population is the sum of (*i*) the variance of the mean column spacings of the different areas (green), (*ii*) the variance of the systematic topographic component (blue), and (*iii*) the average variance of the individual topographic component (orange). The percentages of these variance components are represented by colored bars for V2 (*i*, 38%; *ii*, 8%; *iii*, 54%) and V1 (*i*, 34%; *ii*, 14%; *iii*, 52%), and for ocular dominance columns in cat V1 (*i*, 18%; *ii*, 24%; *iii*, 58%). (*E*) For comparing layouts in V1 and V2, V2 spacing maps were mirror-inverted and morphed (shown schematically), aligning regions representing similar parts of the visual field in areas V1 and V2.

by a factor of two (36, 39). The spacing of these columns was quantified locally by using a previously developed wavelet method (36). Because this method provides highly precise estimates of local column spacing (LCS) with an error much smaller than the large intrinsic variability (35, 36) of column spacings (SEM, 15–50 μm), differences and similarities of column spacings in the sample can be identified reliably. Both V1 and V2 contain a complete topographic representation of the contralateral visual field (40, 41). Columns at topographically corresponding locations in the two areas represent similar visual field positions and are selectively and mutually connected by cortico–cortical connections in adults (42). This topography of the two areas enabled us to conveniently compare the layout of distant columns that are mutually connected and represent related aspects of the sensory input. We find that during the critical period, orientation columns in areas V1 and V2 become matched in size in regions that are mutually connected. The same age trend is found for such regions in the left and right brain hemispheres. Our results suggest that a function of critical-period plasticity is to progressively coordinate the functional architectures of different cortical areas.

Results

Mean Column Spacing (MCS) Is Correlated in V1 and V2. We first analyzed the mean spacing of orientation columns in areas V1 and V2 and assessed their statistical and age dependence. We found that MCSs, Λ, varied considerably in different individuals (Fig. S1*C* in the *SI Appendix*). In V1, values ranged from 1.1 mm to 1.4 mm, in V2 from 1.2 mm to 1.8 mm. The distributions for the two areas were partially overlapping with the smallest column spacings from V2 at about the average value of V1. Nevertheless, in all hemispheres, the MCS, Λ, in V2 was substantially larger than in V1, consistent with previous reports (43). MCSs, Λ, did not vary independently across different animals in V1 and V2, but were substantially correlated in both areas (Fig. S1*D* in the *SI Appendix*); $r = 0.62, p < 10^{-5}$, permutation test). A dependence on the age of animals, however, was not observed, neither for MCSs, Λ (see also Fig. 4*F*), nor for their differences between V1 and V2.

Components of Column Spacing Variability. A coordination of column spacings became apparent when we decomposed the spatial variation and covariation of column spacings in areas V1 and V2 into different components. In both areas V1 and V2, orientation columns generally exhibited a substantial intraareal variation in spacing around the MCS (Fig. 1 *A–C*, green map in 2*C* indicates the mean spacing). One part of this variation is common to all

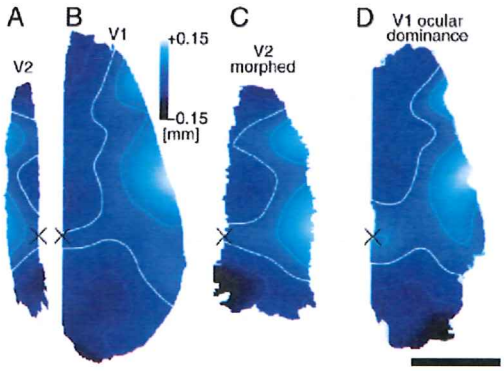

Fig. 2. The STC of column spacing is similar in subregions encoding the same visual field position in areas V1 and V2. (*A* and *B*) STC of orientation column spacing in V2 (*A*) and V1 (*B*) (color scale codes systematic deviation from the mean value; arrangement and symbols as in Fig. S1 in the *SI Appendix*). (*C*) The morphed map from V2 in *A*. (*D*) Population-averaged spacing of ocular dominance columns in cat V1 (modified from ref. 64. SD for V2, 0.052 mm; V1, 0.047 mm; V1 ocular dominance columns, 0.049 mm. Scale bar, 10 mm. Note that for both orientation and ocular dominance maps, columns representing the HM and, in particular, the horizontal periphery were on average wider than columns representing the peripheral parts of the VM. Hence, the systematic variations of orientation columns in V1 and V2 were correlated at topographically corresponding locations (correlation between *B* and *C*, $r = 0.69$), as were those of orientation and ocular dominance columns in V1 (correlation between *B* and *D*, $r = 0.82$).

hemispheres. In this article, we will call this variation the systematic topographic component (STC) of column spacings (the blue map in Fig. 1*C*). The STC is the intraareal variation (in V1 or V2) averaged over the entire population of hemispheres; thus it is a 2D spacing map with zero mean. For averaging, the V1/V2 borders of different hemispheres were aligned, and maps from right hemispheres were mirror-inverted. The remaining component of variation characterizes an individual hemisphere and is called individual topographic component (ITC) of column spacings in the following (the orange map in Fig. 1*C*). The ITC is also a 2D spacing map with zero mean calculated by subtracting from the map of LCS its (i.e., the map's) own mean and the STC. The variances of the STC, of the ITC, and of the MCS add up to the total variance of LCSs in the sample. The ITC accounted for the largest part of the variance of column spacings in both areas V1 and V2 (Fig. 1*D*).

Mirror Symmetry of MCS Maps. Next, we examine the STC, which demonstrates that on average, orientation columns in the two areas are coordinated. In V1, the STC exhibited virtually the same overall 2D organization as the one in V2, appearing as a horizontally stretched mirror image of the V2 map when displayed side by side (Fig. 2 *A* and *B*). The systematic variation in areas V1 and V2 ranged between −0.15 mm and +0.15 mm. In both areas, columns were systematically wider than average along the representation of the horizontal meridian (HM) with this tendency increasing toward the periphery. In contrast, columns smaller than average prevailed along the peripheral representations of the vertical meridian (VM). In order to conveniently compare topographically corresponding parts in areas V1 and V2, the V2 map was mirror-inverted and morphed by superimposing major landmarks, such as the representations of the VM (located along the V1/V2 border), the central visual field, and the HM. The morphed V2 map strongly resembled the V1 map (compare Fig. 2 *B* and *C*), and the cross-correlation between the maps was high ($r = 0.66$). Furthermore, the STC observed in a comparable dataset of ocular dominance column spacings in cat V1 (Fig. 2*D*) also exhibited a very similar intraareal organization with a strong cross-correlation of $r = 0.82$ to the STC for orientation columns in V1 (compare Fig. 2 *B* and *D*). No significant age dependence was found for the STC of column spacings when calculated separately for groups of younger and older animals.

Individual Column Spacing Maps Are Coordinated in V1 and V2. Next, we analyzed the ITC of LCSs. Like the STC, the ITC was often similar in V1 and V2 in regions analyzing the same part of the visual field and being mutually connected. The examples shown in Fig. 3 *A–C*, display the same general pattern in both areas V1 and V2, with maxima (white) and minima (dark orange) at approximately corresponding retinotopic locations. More examples are shown in the *SI Appendix*. Among different brains, the patterns of individual components differed considerably. To quantify the similarity of the ITC in V1 and V2, we calculated, for each hemisphere, the absolute value of the difference between both maps averaged over all analyzed locations, called their mismatch Δ_{V1V2} (see Fig. 4*C*). The mismatches Δ_{V1V2} were significantly smaller than values obtained for randomly assigned pseudo-V1/V2 pairs ($p = 0.03$, permutation test). Thus, in an individual hemisphere the ITC is coordinated at topographically corresponding locations of both areas.

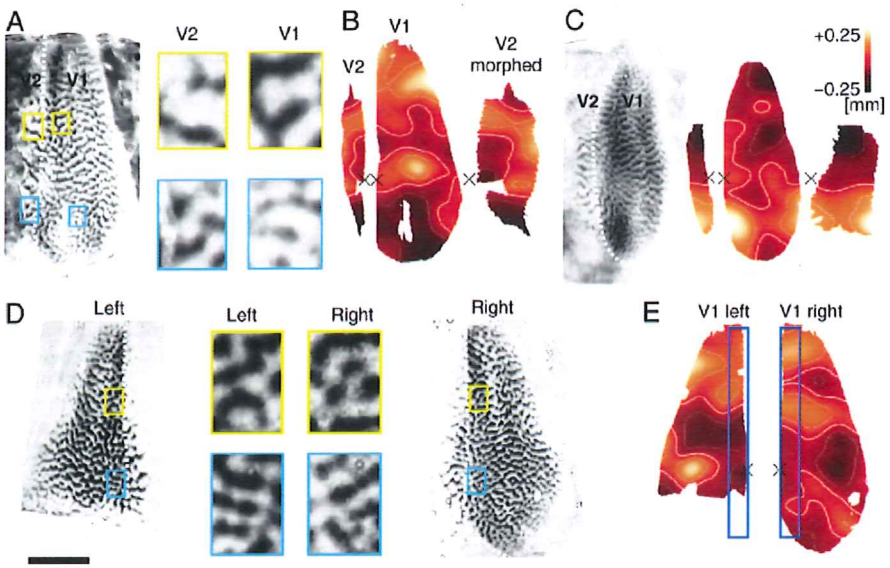

Fig. 3. Columns in different areas are closely matched in size at topographically corresponding subregions. (*A-C*) Similarity of the ITC of column spacings in V1 and V2. (*A*) The overall layout of orientation columns for the hemisphere shown in Fig. S1 of the *SI Appendix*. A pair of topographically corresponding subregions from the more anterior part of V1 and V2 (yellow boxes) and a pair from the more posterior part (blue boxes) are displayed, magnified such that all differences but the individual variation were equalized. The relative difference of MCSs in V1 and V2 was $\Lambda_{V2}/\Lambda_{V1} = 1.3$. To equalize this difference, the subregions from V1 were magnified relative to those from V2 by this factor. To equalize the differences due to the STC the two posterior subregions were magnified by an additional factor of 1.05. Note that the spacing of columns is similar within each pair. (*B*) Patterns of individual variation of column spacing for V2, V1, and the morphed version of V2 for the hemisphere in *A* (color scale, black cross and contour lines as in Fig. S1 of the *SI Appendix*). (*C*) Similarity of the individual variation in V1 and V2 at topographically matched locations in another example. (*D* and *E*) Similarity of the ITC of column spacings in the left-and right-brain hemispheres. (*D*) The overall layout of orientation columns in the left and right hemisphere of an individual animal. A pair of topographically corresponding regions from the anterior part of the VM representation in V1 of both hemispheres (yellow boxes) and a pair from a more posterior part in V1 (blue boxes) was magnified such that all differences except the ITC were equalized. MCSs Λ^r_{V1} and Λ^l_{V1} were equal in both hemispheres, and the STSs were equalized by magnifying the two posterior subregions by a factor 0.98. Note that the spacing of columns is similar within each pair. (*E*) Patterns of the individual variation of LCS in V1 for the hemispheres in *D* displayed with the representation of the VM side by side (crosses and contour lines as in Fig. S1 of the *SI Appendix*). In both residual maps, the blue rectangles (width, 3 mm) are positioned at the representation of the VM. Note that the residual maps tend to be similar only along the VM representations. Scale bar, 10 mm.

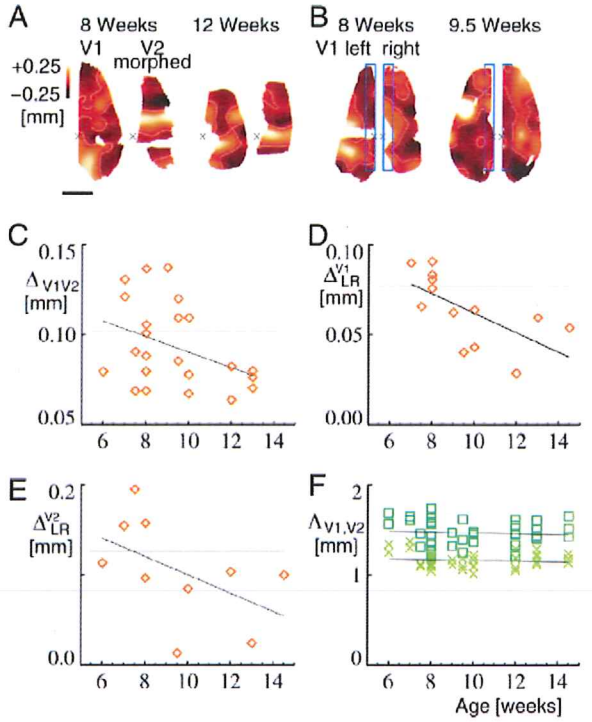

Fig. 4. Emergence of column-size matching with age. (*A* and *B*) Illustration of ITC of column spacing in V1/V2 pairs (*A*) and in left/right pairs from V1 (*B*) at earlier and later ages. Maps for different ages were obtained from diferent animals. (*C*) Distances Δ_{V1V2} between the ITCs in V1 and V2 versus age. (*D*) Distances Δ_{LR} between the V1 ITCs in the left and right brain hemispheres versus age (calculated within the blue rectangles in *B*). (*E*) Distances Δ_{LR} for V2 (calculated in the blue rectangles in *B* from the morphed maps of V2). In *C-E*, a gray horizontal line marks the average mismatch calculated for randomly assigned pairs. In *F* MCSs Λ in V1 (crosses) and V2 (boxes) (from Fig. S1*C* in the *SI Appendix*) versus age. Correlations with age are significant in *C* ($r = -0.64$, $p = 0.007$), *D* ($r = -0.5$, $p = 0.02$) and *E* ($r = -0.39$, $p = 0.01$), but were not significant in *F* ($p = 0.05$).

Callosally Connected Columns Are Matched in Spacing. Intriguingly, this column-size matching also applied to columns at corresponding locations in left/right pairs of areas from both hemispheres. Whereas maps of the ITC in pairs of both hemispheres differed at mirror-symmetric locations, they were often very similar along the V1/V2 border, i.e. in the region containing the cortical representations of the VM (Fig. 3*E*). Orientation columns at the representations of the VM in both hemispheres receive similar afferent input and also mutual input mediated by callosal connections concentrated in the vicinity of the VM representation (44, 45). By the mismatch Δ_{LR}, we quantified the absolute value of differences between left and right maps averaged over a strip of 3 mm width adjacent to the V1/V2 border. Values of Δ_{LR} were significantly smaller than those obtained for randomly assigned pairs of hemispheres ($p = 0.01$, permutation test). Mismatches calculated for parts of V1 distant more than 5 mm from the V1/V2 border were not significantly different from values for randomly assigned pairs of hemispheres ($p = 0.93$, permutation test). A similar behavior was found for V2, but the ITC near the V1/V2 border was only significantly similar in animals aged older than 9 weeks ($p = 0.02$, permutation test).

Progressive Interareal Coordination During the Critical Period. Analyzing the dependency of column-size matching on age, we found that matching improves between different areas during the late phase of the critical period. Examples are shown in Fig. 4 *A* and *B*. Whereas in younger animals the patterns of ITCs differed in V1 and V2 (Fig. 4*A*) and along the V1/V2 border (Fig. 4*B*), they were relatively similar in older animals. Fig. 4 *C–E*, shows the column spacing mismatches Δ for topographically corresponding columns in V1/V2 pairs and in left/right pairs of V1 and of V2 as a function of age. For animals older than nine weeks, almost all mismatches were smaller than the average mismatch of randomly assigned pairs. For all three pairs of areas, mismatches in this age group were significantly smaller than for randomly assigned hemisphere pairs (V1/V2, $p = 0.05$; LR V1, $p = 0.01$; LR V2, $p = 0.02$, permutation test). Regions remote from the V1/V2 border did not show significantly reduced mismatches in this age group (LR V1, $p = 0.86$; LR V2, $p = 0.10$, permutation test). Substantial mismatches were only observed in animals younger than 10 weeks. In older animals, mismatches of column spacings were, in general, <0.1mm. Consequentially, all three measures were significantly anticorrelated with animal age (Δ_{V1V2}, $r = -0.39$, $p = 0.01$; Δ_{LR} for V1, $r = -0.64$, $p = 0.007$; for V2, $r = -0.50$, $p = 0.02$). In contrast, the average column spacing in areas V1 and V2 was independent of age (Fig. 4*F*). Thus, whereas the average column spacing in areas V1 and V2 remained constant, locally the column spacing increased or decreased such that mutually connected columns in different areas became coordinated in size. In contrast, left/right pairs of columns that were not connected by callosal fibers did not develop significant column-size matching.

Discussion

Intraareal Variability of Orientation Columns. Our study is based on a quantitative dissection of the large interindividual and intraareal variability of column layouts. It is therefore important to assess the potential influence of artifactual sources for apparent column-size heterogeneity. Even if orientation columns were of perfectly equal size throughout the visual cortex, apparent column-size heterogeneity may in principle result from unfolding of cortical sulci during the flat-mounting procedure or from varying sectioning angles in the preparation of flat-mount sections. In all likelihood, the influence of such artifactual sources of column-size heterogeneity is minute in our dataset. Quantitatively, we estimate that an undulating sectioning angle can at most result in an apparent column-size heterogeneity on the order of a few percent and thus is much smaller than the actual heterogeneity. With respect to potential tissue distortions, it is important to note that in cats, the cortex region containing V1 and V2 is a relatively planar sheet that is folded mainly along sulci running in the anterior–posterior direction (46). Only at the caudal pole of the brain is the cortical sheet actually curved in more than one dimension. Cortical areas V1 and V2 can therefore be flattened relatively easily without application of major forces (47). In addition, the pattern of sulci in V1 and V2 is relatively stereotyped so that sulcus-induced systematic errors should be apparent in the STC of column spacing. The structures in this map, however, appeared unrelated to the organization of the anterior–posterior sulci. Finally, it appears to us virtually impossible to conceive of a plausible pattern of sulcus- or sectioning-generated artifacts that would induce column-spacing similarity between areas V1 and V2 or even between opposite brain hemispheres.

Our analysis decomposes the variability of local orientation column spacings into three distinct components: the MCS, the STC and the ITC. If all orientation columns of an area were of essentially equal size, then the MCS would be dominant among these components and major differences in observed column spacings would only arise from interindividual variation. We found, however, that columns in different subregions of areas V1 and V2 differed systematically in their size and spacing. Orientation columns representing the horizontal meridian were systematically wider than average and columns smaller than average prevailed along the peripheral representations of the vertical meridian. This systematic intraareal variability is represented by the STC of LCSs and appears as a relatively small fraction of the total variability.

Intriguingly, our results show that knowledge of these two components together would not permit to successfully reconstruct the topographic organization of column spacings in areas V1 or V2. The variances of both MCSs and the STC are substantially smaller than the variance accounted for by the ITC of LCS. This behavior is reminiscent of the variability reported previously for the system of ocular dominance columns in monkey and human visual cortices (48–51). Interestingly, Horton and Hocking in their original report on ocular dominance variability in macaque V1 mentioned in passing an impression of similarity between left–right pairs of ocular dominance maps (48). The ITC at first sight appears as an entirely idiosyncratic and haphazard feature of functional architecture. It is thus a most surprising result of our study that this seemingly haphazard feature of the landscape of column spacings is matched among widely separated areas of an individual brain. This phenomenon reveals that the cortical functional architecture is organized across spatial scales much larger than previously assumed.

Column-Size Matching and the Critical Period. Analyzing the covariation of orientation column spacings in cat visual cortex, we observed the emergence of column-size matching in three pairs of visual areas. Our evidence indicates coordinated changes in the left and right area V1, in the left and right area V2, and in areas V1 and V2 from the same hemisphere. The changes involve large parts of each of these areas and result in a refined coordination of column sizes among mutually connected regions. As assessed by monocular deprivation, the critical period peaks at postnatal-week 6 and slowly decreases afterward (52, 53). The progressive matching of functional architectures that we observe takes place during the late phase of the critical period between postnatal-weeks 8 and 14. During the critical period, cortical circuits are in a state of flux characterized by high turnover rates of synaptic connections (54). This turnover is likely to involve in particular the connections that appear implicated in the progressive matching of mutually connected columns. Both the connections from V1 to V2 and the callosal connections undergo a process of refinement over the late phase of the critical period. The densities of these connections are maximal between week 4 and week 10 and then gradually decline over the following months (28, 29). Our results thus suggest that a slowly progressing reorganization of cortical representations is occurring concomitant with the extensive synaptic turnover characteristic of neuronal circuits during the critical period and that this process is coordinated among different cortical areas.

What causes the gradual emergence of column-size matching between different visual cortical areas? A priori, it is conceivable that intrinsic factors, such as a heterogeneous pattern of receptor or ligand expression or a heterogeneous density of particular cell types, determine the organization of column-size heterogeneity in different visual cortical areas. In order to explain our observation that column-size matching dynamically emerges during the late phase of the critical period, such factors would have to be laid down in an idiosyncratic but coordinated fashion in the different areas and would have to become effective in shaping cortical circuitry only after the peak of the critical period. Currently, however, intrinsic factors and chemical clues are considered to be most effective during the initial stages of development preceding the later activity-dependent refinement of circuits (21). It thus seems much more natural to hypothesize that the emergence of column-size matching is brought about by activity-dependent interactions mediated by interareal connections. In fact, it has been shown that pharmacologically shifting the balance of inhibition and excitation during development modifies column spacing in cat V1 (17). It is thus parsimonious to assume that during normal development column spacings are also determined by the local inhibitory–excitatory balance. In this case, the balance may be set by regulatory mechanisms such as synaptic scaling (55) that are sensitive to neuronal activity. Similarly, the emergence of size-matched columns in distant cortical regions might also be caused by a particular balance of inhibition and excitation in these regions that emerges from their mutual synaptic coupling. Such a dynamical interaction scenario is in fact suggested by our observation that column-size matching between the two brain hemispheres emerged only for regions of V1 and V2 that are mutually connected by callosal fibers.

This interpretation of our results is consistent with previous studies that emphasized the apparent stability of the columnar architecture when assessed over periods on the order of one or two weeks during the early phase of visual development (56, 57). Unlike these studies, we observed changes of the columnar architecture that progress over several weeks and happen during later developmental stages. Our observations thus suggest that the time scales involved in the normal developmental reorganization of cortical representations are substantially larger than the brief periods, on the order of few days that are required for the initial emergence of stimulus selectivity (56, 58–60) or its reorganization in response to sensory deprivation (52, 53, 61, 62).

Why Does the Critical Period Take so Long? Our results also shed light on a longstanding enigma concerning the role of the critical-period plasticity in normal cortical development. As exemplified by the critical period for the effects of monocular deprivation (52, 53, 61), in the visual cortex of mammals, the period when circuits are particularly susceptible to changes of visual input typically lasts many weeks. The onset of this period is delayed relative to the onset of visual experience (16, 65, 66), and key response properties of neurons are already present in almost adult form well before critical-period onset (59, 67). What then is the function of a period of relatively strong plasticity at such a late stage of development? Evidently, it enables the cortex to adapt to deprivations from visual input (52, 53, 68) that may be caused by injuries or disease or, under normal conditions, by the shadows of retinal blood vessels (69). By the same token, however, short periods of abnormal vision can cause permanent deficits. Pettigrew called it "the paradox of the critical period" that it seems to provide only little benefit compared with its great potential for handicap (70). Alternatively, it has often been suggested that a period of plasticity plays an important role for the development of normal vision by refining neural circuits through structured patterns of cortical activity. In fact, under normal experience, vision improves during this period (71), but no evidence for a reorganization of visual cortical representations has been observed so far (56, 57). Our study suggest that one function of critical-period plasticity is to progressively coordinate the functional architectures of different cortical areas—even across hemispheres. It appears very plausible that such interareal coordination requires a much longer period of plasticity than the formation of basic response selectivities within an individual cortical area.

The trend to minimize the mismatch of column sizes between different areas described here suggests a process of optimization of columnar architectures that is not confined to individual areas, but potentially spans the entire visual system. Known mechanisms may underlie the emergence of coordinated column layouts in widely distributed cortical regions. Because cortical processing in general takes place in networks distributed across many areas, it is conceivable that a progressive matching of local circuits serving different submodalities is a general characteristic of cortical network formation.

Materials and Methods

We analyzed 2-deoxyglucose-labeled patterns of orientation columns in the visual cortex (V1 and V2) of 27 normally reared cats (41 hemispheres) (43, 72, 73). Column spacing maps were calculated for multiple flatmount sections as described before (36, 64). Column spacing maps from V2 were morphed on those from V1 by thin-plate spline interpolation. Permutation tests were used to test for statistical significance. In these tests, the value of a statistic (e.g. for cross-correlation or for an average differences) was

compared with values obtained for randomized data. Usually, 10^4 random realizations were sampled. Detailed *Materials and Methods* can be found in the *SI Appendix*.

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1. Brodmann, K (1909) *Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues* (Joh Ambr Barth, Leipzig).
2. Creutzfeldt O (1995) *Cortex Cerebri: Performance, Structural and Functional Organization of the Cortex* (Oxford Univ Press, Oxford).
3. Kaas J (2006) *Evolution of Nervous Systems: A Comprehensive Reference*, ed Kaas J (Elsevier, Amsterdam).
4. Krubitzer L, Huffman K (2000) Arealization of the neocortex in mammals: Genetic and epigenetic contributions to the phenotype. *Brain Behav Evol* 55:322–335.
5. Felleman D, Van Essen D (1991) Distributed hierarchical processing in the primate cerebral cortex. *Cereb Cortex* 1:1–47.
6. Innocenti G, Price D (2005) Exuberance in the development of cortical networks. *Nat Rev Neurosci* 6:955–965.
7. Van Essen D (1997) A tension-based theory of morphogenesis and compact wiring in the central nervous system. *Nature* 385:313–318.
8. Andersen R (1997) Multimodal integration for the representation of space in the posterior parietal cortex. *Philos Trans R Soc Lond Ser B* 352:1421–1428.
9. Freiwald W, Kreiter A, Singer W (2001) Synchronization and assembly formation in the visual cortex. *Prog Brain Res* 130:111–140.
10. Diamond M, von Heimendahl M, Knutsen P, Kleinfeld D, Ahissar E (2008) 'where' and 'what' in the whisker sensorimotor system. *Nat Rev Neurosci* 9:601–612.
11. Engel A, Fries P, Singer W (2001) Dynamic predictions: Oscillations and synchrony in top-down processing. *Nat Rev Neurosci* 2:704–716.
12. Duhamel J (2002) Multisensory integration in cortex: Shedding light on prickly issues. *Neuron* 34:493–495.
13. Kayser C, LN (2007) Do early sensory cortices integrate cross-modal information? *Brain Struct Funct* 212:121–132.
14. Goodman CS, Shatz CJ (1993) Developmental mechanisms that generate precise patterns of neuronal connectivity. *Neuron* 10:77–98.
15. Crair M (1999) Neuronal activity during development: permissive or instructive? *Curr Opin Neurobiol* 9:88–93.
16. Katz L, Crowley J (2002) Development of cortical circuits: lessons from ocular dominance columns. *Nat Rev Neurosci* 3:34–42.
17. Hensch T, Stryker M (2004) Columnar architecture sculpted by GABA circuits in developing cat visual cortex. *Science* 303:1678–1681.
18. Mooser F, Bosking W, Fitzpatrick D (2004) A morphological basis for orientation tuning in primary visual cortex. *Nat Neurosci* 7:872–879.
19. Shouval H, Goldberg D, Jones J, Beckerman M, Cooper L (2000) Structured long-range connections can provide a scaffold for orientation maps. *J Neurosci* 20:1119–1128.
20. Wolf F (2006) Symmetry, multistability, and long-range interactions in brain development. *Phys Rev Lett* 95:208701.
21. Cline H (2003) Sperry and hebb: Oil and vinegar? *Trends Neurosci* 26:655–661.
22. Price D, et al. (2006) The development of cortical connections. *Eur J Neurosci* 23:910–920.
23. Innocenti G (1981) Growth and reshaping of axons in the establishment of visual callosal connections. *Science* 212:824–827.
24. Price D, Blakemore C (1985) The postnatal development of the association projection from visual cortical area 17 to area 18 in the cat. *J Neurosci* 5:2443–2452.
25. Innocenti G, Clarke S (1984) Bilateral transitory projection to visual areas from auditory cortex in kittens. *Brain Res* 316:143–148.
26. Dehay C, Bullier J, Kennedy H (1984) Transient projections from the fronto-parietal and temporal cortex to areas 17, 18 and 19 in the kitten. *Exp Brain Res* 57:208–212.
27. Dehay C, Kennedy H, Bullier J (1988) Characterization of transient cortical projections from auditory, somatosensory, and motor cortices to visual areas 17, 18, and 19 in the kitten. *J Comp Neurol* 272:68–89.
28. Price D, Ferrer J, Blakemore C, Kato N (1994) Postnatal development and plasticity of corticocortical projections from area 17 to area 18 in the cat's visual cortex. *J Neurosci* 14:2747–2762.
29. Aggoun-Aouaoui D, Kiper D, Innocenti G (1996) Growth of callosal terminal arbors in primary visual areas of the cat. *Eur J Neurosci* 8:1132–1148.
30. Stepanyants A, Martinez LM, Ferecsko AS, KisvÃ¡rday ZF (2009) Fractions of short- and long-range connections in the visual cortex. *Proc Natl Acad Sci USA* 106:3555–3560.
31. Engel A, König P, Kreiter A, Singer W (1991) Interhemispheric synchronization of oscillatory neuronal responses in cat visual cortex. *Science* 252:1177–1779.
32. Engel A, Kreiter A, König P, W., S (1991) Synchronization of oscillatory neuronal responses between striate and extrastriate visual cortical areas of the cat. *Proc Natl Acad Sci USA* 88:6048–6052.
33. Carmeli C, Lopez-Aguado L, Schmidt K, De Feo O, Innocenti G (2007) A novel interhemispheric interaction: modulation of neuronal cooperativity in the visual areas. *PLoS ONE* 2:e1287.
34. Makarov V, Schmidt K, Castellanos N, Lopez-Aguado L, Innocenti G (2008) Stimulus-dependent interaction between the visual areas 17 and 18 of the 2 hemispheres of the ferret (mustela putorius). *Cereb Cortex* 18:1951–1960.
35. Shmuel A, Grinvald A (2000) Coexistence of linear zones and pinwheels within orientation maps in cat visual cortex. *Proc Natl Acad Sci USA* 97:5568–5573.
36. Kaschube M, Wolf F, Geisel T, Löwel S (2002) Genetic influence on quantitative features of neocortical architecture. *J Neurosci* 22:7206–7217.
37. Hubel D, Wiesel T (1962) Receptive fields, binocular interaction and functional architecture in cat's visual cortex. *J Physiol* 160:215–243.
38. LeVay S, Nelson S (1991) in *Vision and Visual Dysfunction* (Macmillan, Houndsmill), pp 266–315.
39. Xu X, Anderson TJ, Casagrande V (2007) How do functional maps in primary visual cortex vary with eccentricity? *J Comp Neurol* 501:741–755.
40. Tusa R, Palmer L, Rosenquist A (1978) The retinotopic organization of area 17 (striate cortex) in the cat. *J Comp Neurol* 177:213–235.
41. Tusa R, Rosenquist A, Palmer L (1979) Retinotopic organization of areas 18 and 19 in the cat. *J Comp Neurol* 185:657–678.
42. Salin P, Kennedy H, Bullier J (1995) Spatial reciprocity of connections between areas 17 and 18 in the cat. *Can J Physiol Pharmacol* 73:1339–1347.
43. Löwel S, Freeman B, Singer B (1987) Topographic organization of the orientation column system in large flat-mounts of the cat visual cortex: A 2-deoxyglucose study. *J Comp Neurol* 255:401–415.
44. Olavarria J (2001) Callosal connections correlate preferentially with ipsilateral cortical domains in cat areas 17 and 18, and with contralateral domains in the 17/18 transition zone. *J Comp Neurol* 433:441–457.
45. Olavarria J (2002) in *The Cat Primary Visual Cortex*, eds Payne B, Peters A (Academic, San Diego), pp 259–318.
46. Otsuka R, Hassler R (1962) On the structure and segmentation of the cortical center of vision in the cat. *Arch Psychiatr Nervenkr Z Gesamte Neurol Psychiatr* 203: 212–34.
47. Freeman B, Löwel S, Singer W (1987) Deoxyglucose mapping in the cat visual cortex following carotid artery injection and cortical flat-mounting. *J Neurosci Methods* 20:115–29.
48. Horton JC, Hocking DR (1962) Intrinsic variability of ocular dominance column periodicity in normal macaque monkeys. *J Neurosci* 16:7228–39.
49. Adams DL, Horton JC (2003) Capricious expression of cortical columns in the primate brain. *Nat Neurosci* 6:113–4.
50. Horton JC, Adams DL (2005) The cortical column: a structure without a function. *Philos Trans R Soc Lond Ser B* 360:837–62.
51. Adams DL, Sincich LC, Horton JC (2007) Complete pattern of ocular dominance columns in human primary visual cortex. *J Neurosci* 27:10391–403.
52. Olson C, Freeman R (1980) Profile of the sensitive period for monocular deprivation in kittens. *Exp Brain Res* 39:17–21.
53. Jones K, Spear P, Tong L (1984) Critical periods for effects of monocular deprivation: Differences between striate and extrastriate cortex. *J Neurosci* 4:2543–2552.
54. Holtmaat A, et al. (2005) Transient and persistent dendritic spines in the neocortex in vivo. *Neuron* 45:279–291.
55. Desai N, Cudmore R, Nelson S, Turrigiano G (2002) Critical periods for experience-dependent synaptic scaling in visual cortex. *Nat Neurosci* 5:783–789.
56. Chapman B, Stryker M, Bonhoeffer T (1996) Development of orientation preference maps in ferret primary visual cortex. *J Neurosci* 16:6443–6453.
57. Sengpiel F, et al. (1998) Intrinsic and environmental factors in the development of functional maps in cat visual cortex. *Neuropharmacol* 37:607–621.
58. Albus K, Wolf W (1984) Early post-natal development of neuronal function in the kitten's visual cortex: A laminar analysis. *J Physiol* 348:153–185.
59. Crair M, Gillespie D, Stryker M (1998) The role of visual experience in the development of columns in cat visual cortex. *Science* 279:566–570.
60. White L, Coppola D, Fitzpatrick D (2001) The contribution of sensory experience to the maturation of orientation selectivity in ferret visual cortex. *Nature* 411:1049–1052.
61. Blakemore C, Sluyters RV (1974) Reversal of the physiological effects of monocular deprivation in kittens: Further evidence for a sensitive periode. *J Physiol* 237:195–216.
62. Antonini A, Stryker M (1993) Rapid remodeling of axonal arbors in the visual cortex. *Science* 260:1819–1821.
63. Schmidt K, Stephan M, Singer W, Löwel S (2002) Spatial analysis of ocular dominance patterns in monocularly deprived cats. *Cerebral Cortex* 12:783–796.
64. Kaschube M, et al. (2003) The pattern of ocular dominance columns in cat primary visual cortex: Intra- and interindividual variability of column spacing and its dependence on genetic background. *Eur J Neurosci* 18:3251–3266.
65. Crair M, Horton J, Antonini A, Stryker M (2001) Emergence of ocular dominance columns in cat visual cortex by 2 weeks of age. *J Comp Neurol* 430:235–249.
66. Sur M, Leamey C (2001) Development and plasticity of cortical areas and networks. *Nat Rev Neurosci* 2:251–262.
67. Crowley J, Katz L (2000) Early development of ocular dominance columns. *Science* 290:1321–1324.
68. Sengpiel F, Stawinski P, Bonhoeffer T (1999) Influence of experience on orientation maps in cat visual cortex. *Nat Neurosci* 2:727–732.
69. Adams D, Horton J (2002) Shadows cast by retinal blood vessels mapped in primary visual cortex. *Science* 298:572–576.
70. Pettigrew J (1978) in *Neuronal Plasticity*, ed Cotman CW (Raven Press, NY), pp 311–330.
71. Giffin F, Mitchell D (1978) The rate of recovery of vision after early monocular deprivation in kittens. *J Physiol* 274:511–537.
72. Löwel S, Bischof HJ, Leutenecker B, Singer W (1988) Topographic relations between ocular dominance and orientation columns in the cat striate cortex. *Exp Brain Res* 71:33–46.
73. Löwel S, Singer W (1990) Tangential intracortical pathways and the development of iso-orientation bands in cat striate cortex. *Dev Brain Res* 56:99–116.