Commentary

Factors Shaping the Corpus Callosum

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Perhaps because of its prominence in midline sections of the human brain, the corpus callosum, one of the few brain structures identifiable by even the slowest student, has attracted wide interest throughout history. Cajal described how the visual field representation was first inverted by the lens of the eye and split into two halves, represented in the two hemispheres, and then knit together by the corpus callosum into a single representation of the visual world. This general idea has fared well since that time (Sperry, 1962; Berlucchi, 1981).

In many species, including the cat and lower primates, the representation of the visual field is not cleanly split between the two hemispheres but includes a region of overlap, represented in both (Illing and Wässle, 1981). The callosum was envisioned as providing corticocortical connections to this region of overlap. As the nature of corticocortical connections within each hemisphere was elucidated, it became possible to entertain the hypothesis that the corpus callosum consisted merely of particularly long fibers that played the same role between the hemispheres as was played by the local connections within each hemisphere (Innocenti, 1986). Insofar as local connections within a hemisphere exhibit various types of specificity according to functional cortical modules, such as orientation and ocular dominance columns, it was not surprising that investigations of the callosum suggested similar specificity. In this view, it did not matter that the visual field was split vertically and that the representations of the primary and secondary visual areas (areas 17 and 18) were joined at the representation of the vertical meridian, the precise point at which the visual field representations were divided between the two cortical hemispheres. Symmetrical corticocortical connections could have joined any split in the representation of the visual field.

Recent work has shown that the real connection between the hemispheres is different from this simple model in at least three ways. First, although the cells that project through the corpus callosum are fairly widespread, their terminals are strongly focused on a narrow transition zone (TZ) between areas 17 and 18 that is part of neither area (Payne, 1990, 1991; Payne and Siwek, 1991). This transition zone represents the ipsilateral visual field principally through the contralateral eye, owing to the fact that a region of temporal retina near the area centralis projects both contralaterally and ipsilaterally. Second, connections between the two hemispheres are not bilaterally symmetrical. Instead, these connections link topographically corresponding positions, that is, positions in the two hemispheres that are concerned with the same area of the visual field (Olavarria, 1996). For example, callosal cells located laterally in the callosal zone, i.e., in the TZ where the ipsilateral visual field is represented, project to a medial region of the callosal zone of the other hemisphere, containing a representation of the same area of the visual field. Third, on page 441–457 of the present issue, Olavarria shows that callosal connections are not just specific for the same part of the visual world; they also specifically connect ocular dominance (OD) columns serving the same eye. This stands in contrast to intrahemispheric connections that are predominantly orientation-selective. Strikingly, the eye specificity of the callosal pathway results in cells in the TZ occupying contralateral eye ocular dominance columns, whereas those in immediately adjacent portions of areas 17 and 18 proper are found primarily in the ipsilateral eye columns. Without the careful distinction made between the TZ and areas 17 and 18 proper, it would have appeared that callosal connections were not specifically related to ocular dominance columns, and their fine topography would have been overlooked. Figure 1 summarizes Olavarria's findings; it illustrates the anatomical organization of callosal connections at the area 17–18 border in relation to topography and ocular dominance.

The ocular preference of callosal cells has prompted the author to suggest a mechanism for the selection and stabilization of callosal connectivity during development. According to Olavarria's "uniocular" hypothesis, the key players are the bilateral projections originating from the temporal retina. Coherent activity between ganglion cells in the same eye is conveyed through the geniculocortical pathway to different points in the cortex in the two hemispheres, and callosal fibers connecting these points are stabilized.
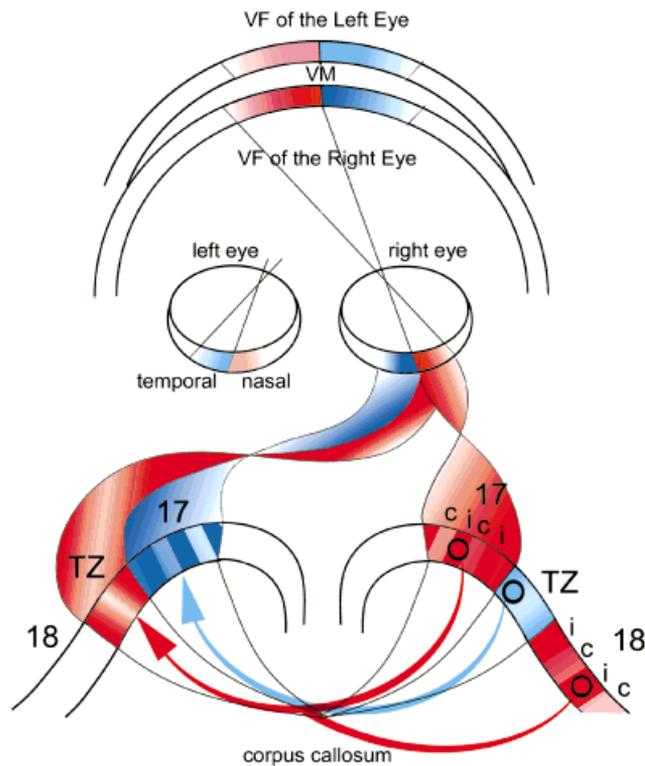
Fig. 1. Diagram relating retinal projections, the visual field representation in the callosal zone of areas 17 and 18 (the portions of these areas receiving from and sending to the corpus callosum), and the topography and ocular dominance of callosal connections. The diagram was adapted from Figure 8 of Olavarria (1996). For simplicity, the visual thalamus and the topographic and callosal organization in area 18 in the left hemisphere are not represented. The most central portion of the right visual field (VF) is represented in blue (light blue, right VF seen by the left eye; dark blue, right VF seen by the right eye). The most central portion of the left VF is represented in red (light red, left VF seen by the left eye; dark red, left VF seen by the right eye). The nasal and temporal retinae of both eyes receiving visual information from the central portion of the VF are color coded in the same manner. *The gradient of color saturation indicates topography*: from dark (vertical meridian; VM) to light (more peripheral). The representation of the VF in the callosal zone of areas 17 and 18 through direct thalamocortical projections: The callosal zone in each hemisphere contains the representation of portion of the contralateral VF via projections serving the nasal retina of the contralateral eye and the temporal retina of the ipsilateral eye. These two sets of projections give rise to alternating ocular dominance columns serving the ipsilateral (i) and contralateral (c) eyes. The transition zone (TZ) between areas 17 and 18 contains the representation of a central portion of the ipsilateral VF, via direct projections serving the temporal retina of the contralateral eye. *Organization of callosal connections in relation to VF topography and ocular dominance*: Olavarria (1996) has demonstrated that callosal connections linking areas 17 and 18 in the two hemispheres are topographic and not mirror-symmetric. Olavarria also shows (this issue) that the cells of origin of callosal connections are in register with ocular dominance columns serving the bilateral projections of the temporal retina of the same eye. The diagram illustrates that, in the right visual cortex, callosal cells are located in the ocular dominance columns of the ipsilateral (right) eye in areas 17 and 18 proper, which represent the contralateral VF and receive uncrossed input from the temporal retina. In the TZ, where the ipsilateral VF is represented using crossed input from the temporal retina, callosal cells are located in the ocular dominance of the contralateral (left) eye.

Over the past few years, detailed anatomical and physiological studies in several species have greatly improved our understanding of the complex organization of the callosal pathway linking the primary visual areas 17 and 18 of the two hemispheres (see Houzel and Milleret, 1999). However, the specific mechanisms by which sets of callosal connections are maintained or eliminated during development and the origin of the puzzling patchy organization of callosal connections in the visual areas of the adult animal are still not fully understood.

There is general agreement that factors promoting coherence between the information carried by thalamocortical and interhemispheric pathways would ensure the stabilization of the appropriate callosal connections during development. Electrophysiological studies generally confirm the notion that fusion of the two visual hemifields along the vertical meridian might be one of the principal functions of the corpus callosum. In mammals with frontal eyes, the regions of area 17 sending projections to and receiving from the corpus callosum contain a *binocular* representation of the central portion of the visual field, comprising the vertical meridian (VM) and portions of the visual field on either side of the VM. Callosal connections within this representation would be maintained during development because visual stimuli presented along the VM would be activated in a synchronous and congruous manner for both the callosal and the thalamocortical pathways (Hubel and Wiesel, 1967; Berlucchi and Rizzolatti, 1968; Berlucchi, 1981; Lepore and Guillemot, 1982; Payne, 1990, 1991; Payne and Siwek, 1991; for reviews see Innocenti, 1986; Houzel and Milleret, 1999). A generalization of this hypothesis, supported by anatomical evidence, suggests that matched retinotopy between callosal and intrahemispheric projections, not necessarily linked to the VM representation, could be the driving force for the stabilization of callosal connections during development (Olavarria, 1996; Bosking et al., 2000).

Retinotopy is generally continuous, so the patchy organization of the callosal pathway poses a puzzle. Several authors have attempted to link such callosal clusters to the modular functional systems of the visual cortex. A match between callosal connections and one or more of the functional domains of the visual cortex would provide the neural basis for a coherent integration of thalamocortical and callosal pathways and their consequent stabilization during development. However, the evidence for such a link remains indirect. Boyd and Matsubara (1994) found an association of callosal cell clusters with cytochrome oxidase blobs both inside and outside the TZ. The correspondence of callosal clusters with the system of cortical columns coding for orientation selectivity is also indirect and derives from single unit recordings in split-chiasm cats showing that the same orientation tuning is conveyed to cortical cells by thalamocortical and callosal inputs (for review see Houzel and Milleret, 1999). This conclusion was confirmed by EEG coherence and interhemispheric synchronization studies (considered to reflect functional connectivity between cortical loci under investigation) demonstrating strong interhemispheric synchronization upon presentation of isooriented gratings but not of gratings of different orientations (Engel et al., 1991; Kiper et al., 1999; Knyazeva et al., 1999). However, Schmidt et al. (1997) found an association of callosal cells with ocular and orientation cortical domains only in strabismic cats. Furthermore, Bosking et al. (2000) have shown in the tree

shrew striate cortex that, unlike tangential projections within the same hemisphere, callosal cells do not project to orientation-specific domains, as defined by optical imaging. Finally, in the cat, during the second and third weeks of age, when orientation selectivity is already well-established in the visual cortex (Crair et al., 1998), the majority of cells activated through the corpus callosum are not orientation-selective (Milleret et al., 1994).

Olavarria's new results on the close association between the cells of origin of the callosal pathway and the OD organization provide an answer for the patchy organization of callosal connections in area 17. Compatible with this finding is the evidence that both the OD system and callosal connectivity appear to mature together early in development. Indeed, the earliest columnar organization of callosal terminals in the cortical plate is observed at about P12–P20 (Aggoun-Zouaoui et al., 1996), when ocular dominance columns are just forming (Crair et al., 2001) and responses of neurons in each hemisphere are strongly dominated by the contralateral eye (Crair et al., 1998). The preference of callosal cells for ipsilateral eye OD columns outside the TZ is consistent with the contralateral eye dominance of responses in the opposite hemisphere. Olavarria's finding of OD specificity does not contradict the physiological evidence in the cat of matched orientation selectivity between thalamocortical and callosal responses; callosal cells within an OD domain may also prefer a specific orientation. Furthermore, the OD preference of callosal cells is not in conflict with the role of the corpus callosum in the binocular integration across the VM, if one considers, as Olavarria does, that callosal cells may be binocular. Indeed, both inside and outside the TZ many are located at the borders between OD columns, where binocular responses are more common (see Olavarria's Figs. 2–4). The preference of callosal cells inside the TZ for contralateral eye OD columns is expected because the TZ predominantly represents the ipsilateral visual field (Payne, 1990), which, in consideration of the direct thalamocortical projections, must be conveyed via the temporal retina of the contralateral eye. We do not know whether the TZ contains ipsilateral eye OD columns.

Olavarria's "uniocular" hypothesis that callosal connections link cortical regions that are driven by each eye rather than being shaped by seeing the same object through both eyes is thought-provoking but difficult to test beyond the findings on strabismus that he has reported. The "uniocular" hypothesis does provide a mechanism for the eye specificity of callosal connections in the absence of vision. Deprivation experiments have shown that vision per se is necessary for some aspects of callosal connection specificity, but these experiments did not determine the relationship to ocular dominance columns (Innocenti et al., 1985; Frost and Moy, 1989; Olavarria and Van Sluyters, 1995; Zufferey et al., 1999). One would therefore predict that, if the "uniocular" hypothesis is valid, the specificity of callosal connections for OD columns would persist after dark rearing or lid suture despite a change in the overall density of connections.

How can Olavarria's "uniocular" hypothesis as the driving rule for callosal development accommodate the wealth of previous work pointing to binocular influence in callosal maturation? Although one report found little evidence that monocularly induced strabismus affected the distribution of callosal neurons in area 17 (Bourdet et al., 1996), other laboratories have found an expansion of the callosal zone (Lund et al., 1978; Innocenti and Frost, 1979; Berman and Payne, 1983), suggesting that a binocular mechanism is involved in the normal development of callosal connectivity. Other experimental paradigms in which binocularity has been altered (monocular enucleation, deprivation or retinal inactivation) also cause an expansion of the callosal zone (Innocenti and Frost, 1979, 1980; Grigonis and Murphy, 1991). Although Olavarria's new work shows us that connections between the two hemispheres can be organized by factors within one eye, the earlier findings taken together suggest that callosal connectivity is also shaped by binocular interactions.

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