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CHAPTER 2

Commissurotomy studies in animals

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Introduction

Studies of the effects of sectioning the cerebral commissures in animals are important for neuropsychology on two counts. First, they can afford fundamental clues for understanding the functional significance of a major class of connections of the brain for psychological and behavioral activities in animals as well as in man. Second, animal models of experimental epilepsy based on commissurotomy can aid in the analysis of the pathophysiological mechanisms of the interhemispheric spread and generalization of abnormal neuronal discharges. As a consequence, such models have provided a rationale for employing commissurotomy in the treatment of select clinical cases of epilepsy, a category of neurological disorders which have a considerable effect on psychic functioning in man. Besides being therapeutically effective in most cases, this surgical approach has allowed the comparison and contrasting of the findings from commissurotomized animals with corresponding neuropsychological evidence from similarly commissurotomized people. Such comparative analyses have far-reaching implications not only for the clarification of several specific aspects of commissural function and hemispheric interaction, but also for a more complete view of the overall neural organization underlying complex behavior and consciousness.

Since this chapter deals chiefly with the behavioral and gross physiological effects of commissural sections in animals, a detailed description of the anatomy and specific functional properties of the commissures is beyond its scope. Commissurotomy has of course been very useful in anatomy for tracing the origin and termination of commissural fibers based on retrograde and anterograde degeneration, but neuronal labeling techniques have now made this approach largely dispensable. Extensive information about the neuronal organization of interhemispheric pathways can be found in several recent reviews (e.g. Berlucchi, 1981; Elberger, 1982; Innocenti, 1986; Manzoni et al., 1989), as well as in the books written or edited by Harnad et al. (1977), Gazzaniga and Ledoux (1978), Steele Russell et al. (1979), Reeves (1985), Lepore et al. (1986b) and Trevarthen (1989). The following section has the limited aims of defining the basic anatomic terms and stating some neurophysiological concepts which can help understand behavioral and physiological commissurotomy experiments.

Further anatomo-physiological notions will be presented in subsequent sections whenever they are relevant for the interpretation of specific clinical deficits of commissurotomized animals.

Anatomy and basic organization of commissural pathways

At all levels of the central nervous system, from forebrain to spinal cord, there are compact systems of fibers which cross the midline for connecting corresponding or functionally matched structures of the two sides. These bundles of fibers are called commissures. For present purposes consideration will be limited to the encephalic commissures, and especially to the forebrain commissures, which include the corpus callosum, the anterior commissure and the hippocampal commissure. The most massive and physiologically important of these commissures, the corpus callosum, is the commissure of the neocortex. It contains millions of myelinated and unmyelinated fibers of different sizes (Swadlow, 1985) which originate from a relatively tiny population of cortical neurons. Various facets of its main anatomical features will be dealt with in this and following sections.

The much smaller anterior commissure is the commissure of the paleocortex, the amygdalae and the olfactory bulbs, but it also contains fibers of neocortical origin. The neocortical component of the anterior commissure varies considerably from one mammalian species to another (Van Alphen, 1969; Doty and Negrao, 1973; Jouandet and Gazzaniga, 1979; Jouandet, 1982; Jouandet and Hartenstein, 1983; Jouandet et al., 1984, 1986). In mammals devoid of a corpus callosum, such as the monotremes and the marsupials, all interhemispheric connections of the neocortex run in the anterior commissure (Ebner, 1967; Heath and Jones, 1971; Granger et al., 1986). In monkeys, neocortical fibers of the anterior commissure originate from and terminate in relatively ample portions of the frontal and temporal lobes (Gazzaniga and Jouandet, 1979; Jouandet et al., 1984), and their terminals are adjacent to, but probably do not overlap with, those of callosal afferents to the same territories. In carnivores and rodents the neocortical contribution to the anterior commissure is comparatively more limited (Van Alphen, 1969; Jouandet, 1982; Jouandet and Hartenstein, 1983; Jouandet et al., 1984, 1986).

The hippocampal commissure is a predominantly archicortical commissure linking the hippocampal formations and related peri- and parahippocampal structures of the two sides (Voneida et al., 1981; Demeter et al., 1985). Other commissural connections are constituted by a relatively small number of fibers which are neither corticofugal nor corticopetal and serve to link subcortical centers on the two sides of the telencephalon (basal ganglia), diencephalon (thalamic, subthalamic and hypothalamic nuclei) and mesencephalon (pretectum and tectum). These subcortical commissures, called interthalamic commissure, supraoptic commissures, habenular commissure, posterior commissure and intertectal commissure, have not been studied in commissurotomy experiments as intensely as the forebrain commissures.

The forebrain commissures are connection systems endowed with a remarkable anatomical precision and highly differentiated functional actions. Genetic and experiential factors act together in ensuring the maturation of the commissural systems and in establishing their definitive pattern of organization (Innocenti, 1986), and the commissural connections can in turn play a role in the developmental course of non-commissural systems (Elberger, 1982, 1986). In each commissural system the constituent fibers are arranged in an orderly topographic manner which is just one aspect of their overall connection specificity (Pandya and Seltzer, 1986; Jouandet et al., 1986; Nakamura and Kanaseki, 1989). Histological, neurochemical and physiological criteria suggest that all neurons projecting to the corpus callosum have a direct synaptic facilitatory action on their immediate neuronal targets in the opposite hemisphere (Naito et al., 1970; Toyama et al., 1974; Innocenti, 1986; Voigt et al., 1988; Barbaresi et al., 1987; Conti et al., 1988), but powerful indirect inhibitions of cortical neurons by a commissural input can be effected by local interneurons directly activated by this input (Naito et al., 1970; Toyama et al., 1974; Innocenti, 1986). Highly organized spatial patterns of combined and concurrent excitatory and inhibitory effects on discrete target zones, rather than massive inhibitions or facilitations of entire cortical areas, are most probably the systematic physiological consequence of selective activations of commissural inputs (Asanuma and Okuda, 1962). The possibility that the commissural systems are involved in

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widespread or wholesale facilitatory or inhibitory actions, similar to those of the diffuse ascending brainstem pathways, does not seem realistic (Berlucchi et al., 1986), but if such a generic modulatory role is indeed a component of commissural function it must be minor compared to the precisely differentiated cross-midline transmission of sensory, motor and higher-order information.

Several principles have been proposed to account for the general plan of organization of the commissural connections. The homotopic principle, stating that commissural fibers interconnect homologous corresponding regions of the two sides in a reciprocal fashion, is supported by much histological and electrophysiological evidence. Yet it cannot be accepted in its most restrictive formulation, first because in all or most commissural systems there also exist numerous fibers linking definitely heterotopic sites, and second because even within a very precise homotopic arrangement the connections are not really reciprocal at the cellular level. This is due to the fact that commissural fibers often terminate in cortical layers different from those containing commissural projecting neurons, and even when they do they do not as a rule contact commissural neurons (Berlucchi, 1981; Innocenti, 1986).

According to the heterolateral principle, originally proposed by Mettler (1935), a cortical area is commissurally connected not only with its symmetrical opposite counterpart, but also with as many contralateral cortical areas as it is connected with in the ipsilateral hemisphere. Although the patterns of intra- and interhemispheric connections do indeed share many hodological features, the homolateral principle is only partially supported by the evidence insofar as intrahemispheric cortico-cortical connections are directed to more numerous and diffuse targets compared to interhemispheric connections (Innocenti, 1986).

Flechsig's general theory of the cortex (1989) has been used to account for the very uneven cortical distribution of commissural neurons and terminals, suggesting that commissural connections are restricted to association areas (Geschwind, 1965). However, while it is true that commissural connections seem to avoid extensive portions of primary sensory and motor cortex, all cytoarchitectural divisions of the cortex are now known to give rise to and receive interhemispheric projections in at least some of their subareas.

Sperry's principle of supplemental complementarity (1962) envisages the pattern of organization of the commissural connections as a means by which the activity of each cerebral hemisphere is supplemented in an orderly manner with different and complementary information about concurrent activities in the other hemisphere. The organization of the afferent and efferent neural projections is such that each cerebral hemisphere is in receipt of information from the opposite half of the sensory spaces and in control of the contralateral half of the musculature. The commissures provide the anatomical and functional continuity between the sensory and motor half maps on the two sides of the midline by establishing discrete connections between appropriate neuronal populations of the two hemispheres. For example, the representation of each hand in the contralateral hemisphere via specific afferent pathways can be supplemented and complemented at some stage of cortical processing by a callosally transmitted representation of the other hand. This arrangement is both supplementary, because the representations of the two hands add to one another in each hemisphere, and complementary, because this addition can provide a unitary substrate for the control of bimanual movements and active touch.

At the single-neuron level the principle of supplemental complementarity is best illustrated by the presence of neurons with homogeneous bilateral receptive fields in the visual system of cats (Berlucchi and Rizzolatti, 1968; Berlucchi et al., 1986, 1987; Berlucchi and Antonini, 1989) and monkeys (Gross and Mishkin, 1977). Such bilateral receptive fields extend continuously across the vertical midline of the general visual field, and are built up by a precise combination between an intrahemispheric input from the contralateral half field and an interhemispheric input from the ipsilateral half field. After severing the corpus callosum these receptive fields lose their portion lying in the ipsilateral visual field and become purely contralateral. As first proposed by Whitteridge (1965), the callosal connections which contribute to building up bilateral receptive fields in visual cortical areas must be limited to neurons 'looking at' visual field regions abutting or including the central vertical meridian. Such limitation is needed both for the continuity of the bilateral receptive fields and for the unification of the maps of the right and left visual hemifields which belong in different hemispheres (Berlucchi et al., 1986, 1987; Berlucchi and Antonini, 1989).

It has been argued that the commissural connections of the visual cortex obey the vertical midline rule because of developmental constraints which control the convergence of intra- and interhemispheric visual inputs on single neurons (Berlucchi, 1981). The developing brain is characterized by an excess of callosal fibers which is eliminated during a critical postnatal period (Innocenti, 1986). The elimination is assumed to be based on the acceptance by cortical neurons of callosal afferents transmitting visual information which is congruous and synchronous with that conveyed by the intrahemispheric afferents to the same neurons, and on the rejection of callosal afferents which do not undergo such coactivation. In a normal visual environment coactivation is highly probable for intra- and interhemispheric inputs from continuous visual field regions matched at the vertical meridian, and highly unlikely for intra- and interhemispheric inputs from totally disparate visual field regions. Visual information from visual field regions away from the vertical meridian can, however, be transmitted interhemispherically by callosal neurons with wide receptive fields extending from the meridian to the far visual periphery (Berlucchi et al., 1986, 1987; Berlucchi and Antonini, 1989).

The principle of supplemental complementarity and the vertical meridian rule can be shown to apply to the somatosensory system as well (Shanks et al., 1985; Lepore et al., 1986a; Ledoux et al., 1987; Manzoni et al., 1989), but there are some important differences with the visual system. For example, while in many somesthesic areas callosal connections conform to the vertical midline rule by being much more prominent in the representations of the axial parts of the body, in the second somatosensory area SII a region clearly unrelated to the midline such as the hand representation is also provided with dense callosal connections. This, however, in no way contradicts the supplemental complementarity principle and the postulated coactivation mechanism, insofar as the two hands are often submitted to synchronous and congruous somesthetic stimulation as they cooperate in bimanual stereognosis (Manzoni et al., 1984).

The supplemental complementarity principle, the vertical midline rule and the coactivation mechanism can probably also account for the pattern of callosal connections between cortical regions subserving other sensory modalities as well as between motor areas, but the available relevant evidence is very scanty. It is important to emphasize that supplemental complementarity is fully compatible with the proven existence of both homotopic and heterotopic commissural connections, inasmuch as the coactivation mechanism can link up both symmetric and non-symmetric homofunctional cortical sites of the two hemispheres.

It is perhaps naive, though not unreasonable, to state that the anatomical and physiological features of the forebrain commissures must be such as to allow the monitoring of information across the midline at all stages of coftical processing (Berlucchi, 1981; Hamilton, 1982; Innocenti, 1986). But after granting that learning processess, memory engrams, ideas, thoughts, emotions and motivations can be communicated between the hemispheres via the commissures along with elementary sensory signals and motor commands, it must be admitted that the analysis of the neuronal codes used in such interhemispheric exchanges of highly digested information is fraught with enormous conceptual and technical dif-

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ficulties. Perhaps breaking the 'callosal code' (Gazzaniga, 1970) will help in breaking the complete 'brain code' (Cook, 1986), yet advances in the understanding of the mechanisms of commissural transmission of information are more likely to follow than precede advances in the knowledge of the general cerebral bases of psychological functions. At present, behavioral commissurotomy studies are still a tool of choice for inferring the functional significance of interhemispheric interaction and transfer and for guiding anatomical and physiological analyses of the underlying mechanisms.

Behavioral and physiological effects of commissurotomy in animals

Early assessments of the consequences of cutting the cerebral commissures in animals (reviews in Mingazzini, 1922; Bremer et al., 1956) failed in general to demonstrate specific behavioral deficits from hemisphere disconnection because the testing methods were usually inadequate and/or the symptomatology was contaminated by the effects of unintended extracommissural brain damage. It was only when the effects of commissurotomy began to be examined in relation to the capacity for bilateral sensory-sensory or sensory-motor integration, perceptual equivalence and transfer of training that selective impairments in interhemispheric integration and communication became evident.

Bilateral sensory-sensory integration, perceptual equivalence and transfer of training are special instances of stimulus generalization and sensory equipotentiality. These general terms allude to the fact that objects and images maintain their identity over space and time even when they are perceived through entirely different sensory channels, both within and across sensory modalities. As a special case of this integration, sensory inputs issuing from the two halves of the visual field or from receptors on opposite sides of the body can normally be compared, combined and fused into single percepts. Physiologically the extrapolation of the singleness and identity of an object from an array of heterogeneous and varying sensory signals is likely to be based on the convergence of all possible inputs generated by the object onto a functionally unitary brain mechanism which can integrate such inputs and ascribe them to a common external source. Inputs originating from opposite sides of the body or of the external space are usually conveyed by the largely lateralized sensory pathways to different hemispheres, so that as a rule their cross-midline integration occurs by an interhemispheric cooperation. In other words, the unitary cerebral substrate for representing an object projected in part to one hemisphere and in part to the other hemisphere must include a commissural component (Gross and Mishkin, 1977; Hamilton, 1982; Berlucchi and Marzi, 1982; Berlucchi and Antonini, 1989). A similar interhemispheric cooperation is bound to be required in bilateral sensory-motor integration, when a motor activity controlled by one hemisphere must be emitted to a sensory stimulus projected to the other hemisphere, and in bilateral motor coordination. Studies of the effects of commissurotomy on bilateral sensory-sensory, sensory-motor integration or motor coordination, perceptual equivalence and transfer of training attempt to demonstrate that the unity of the transhemispheric perceptual/representational mechanism or the cross-midline link between sensory input and motor output is indeed disrupted by sectioning the critical commissural component.

The experimental questions asked in these studies are rather direct. After an animal has acquired specific reactions or formed specific memories based on sensory inputs restricted to a single cerebral hemisphere, can those reactions or memories be retrieved when the same inputs are directed to the other hemisphere? Can an animal compare and contrast identical or different sensory signals simultaneously or successively delivered to different hemispheres, or cross-integrate motor reactions of the two sides, or couple motion on one side with sensory inputs from the other side? Can interhemispheric sensory-sensory, sensory-motor and motor integration, transfer and equivalence, if present, be selectively interfered with by sectioning appropriate components of the commissural systems? Bykov and Speranski's report (1924; see also Bykoff, 1924) that callosotomy rendered dogs incapable of transferring between flanks a conditioned alimentary response to a tactile stimulus made a good start toward providing affirmative answers to at least some of these questions. However, systematic studies on commissurotomy and interhemispheric communication were spawned only much later by the seminal experiments of Myers and Sperry (1953) and Myers (1955, 1956) on interocular transfer in the cat. These studies profitted from the superior opportunity offered by the visual modality compared to the other modalities for an absolute restriction of the relevant afferent inputs to a single hemisphere. The following account will therefore focus on experiments on interhemispheric interaction in vision.

Interhemispheric interactions in vision

The prototypic experiment is based on two facts: (1) in mammals with partially crossed optic pathways each retina projects to both cerebral hemispheres, and (2) visual pattern discriminations learned with one eye transfer successfully to the other eye. A midline section of the optic chiasm which interrupts all crossed fibers, thus leaving each retina connected solely to the ipsilateral hemisphere via the intact uncrossed fibers, does not interfere with interocular transfer (Myers, 1955). Since in these 'split-chiasm' animals inputs from different eyes go to different hemispheres, the convergence of the two monocular inputs onto a common substrate for interocular transfer must, as argued above, be ensured by interhemispheric connections. The above hypothesis was first proven, and the crucial interhemispheric connection indentified, by demonstrating that in split-chiasm cats with an additional sectioning of the corpus callosum ('split-brain' cats) interocular transfer failed (Myers, 1956), and discriminations acquired through one eye had to be completely relearned through the other eye (Sperry et al., 1956). Sectioning the corpus callosum in cats with an intact optic chiasm does not interfere with interocular transfer because the two monocular inputs can amply converge in each hemisphere owing to the existence of both crossed and uncrossed projections from each retina.

The callosal fibers mediating interocular transfer in the split-chiasm cat appear to be rather specific because a transection of the anterior two-thirds of the callosum leaves transfer unaffected whereas a selective section of the posterior third, including the splenium, causes the same effect as a complete callosal section, that is abolition of transfer (Myers, 1959). The posterior portions of the cat corpus callosum contain the interhemispheric connections of most if not all visual cortical areas (Jouandet et al., 1986; Nakamura and Kanaseki, 1989).

Since interocular transfer of learned responses can be observed in virtually all classes of vertebrates (Sperry, 1961; Cuénod, 1972; Doty and Negrao, 1973), experiments similar to those first performed in the cat were repeated in several other species, generally with comparable results. The presence of interocular transfer of visual pattern dicriminations in split-chiasm non-human primates, as well as its abolition by appropriate commissurotomy, were first demonstrated by Downer (1959, 1962) and Sperry (1961) using macaques, and by Black and Myers (1964) using chimpanzees. In contrast to the cat, both splenium and anterior commissure must be transected in these primates to obtain a complete suppression of interocular transfer (Black and Myers, 1964; Noble, 1968; Sullivan and Hamilton, 1973a,b; Doty and Negrao, 1973; Butler, 1979). The reason for this is that the commissural connections of all visual cortical areas run in the posterior corpus callosum in the cat, whereas in non-human primates visual areas in the inferior temporal lobes of the two sides are connected across the midline by fibers of both splenium and anterior commissure (Doty and Negrao, 1973; Zeki, 1973; Gross and Mishkin, 1977; Jouandet and Gazzaniga, 1979; Hamilton, 1982). Areas in the inferior temporal cortex are thought to be critical for object vision in primates (Gross and Mishkin, 1977; Mishkin, 1979), and it is not suprising that their commissural connections can have an important role in perceptual constancy across visual hemifields (Seacord et al., 1977; see below). Section of the splenium and anterior commissure has also been shown to interfere with the ability of monkeys with intact optic pathways to transfer learned visually guided responses from one visual hemifield to the other (Eacott and Gaffan, 1989).

Much less evidence is available for assessing the participation of discrete commissural pathways in the interhemispheric transfer of specific visual information in mammals lower than carnivores. Although surgical splitting of the chiasm has been performed successfully in rats (Cowey and Franzini, 1979) and rabbits (Steele-Russell et al., 1987), interocular transfer of visual discriminations has not been tested in these split-chiasm preparations, and therefore there are no data to be directly compared with the above findings in split-chiasm cats and monkeys. Contrasting results have been obtained in studies of the effect of callosotomy on interocular transfer of visual discriminations in rats with intact optic pathways, insofar as transfer has been found to be significantly impaired in some experiments (Sheridan, 1965; Levinson and Sheridan, 1969; Steele Russell and Safferstone, 1973) but not in others (Buresova and Bures, 1971; Cowey and Parkinson, 1973; Mohn and Russell, 1981). The discrepancy between results can be accounted for by variations in the number and functional significance of uncrossed optic fibers between albino and pigmented animals, the nearly complete absence of overlap between the two monocular visual fields in animals with laterally implanted eyes, and other contextual conditions which may affect performance on tests of interocular transfer (Cowey and Parkinson, 1973; Sheridan et al., 1980; Mohn and Russell, 1981; Mohn, 1984). All these factors have no direct bearing on the interpretation of commissurotomy effects for the understanding of commissural function, and a reasonable inference from the complex of the results is that, similar to the case in higher mammals, the posterior corpus callosum is the exclusive or predominant path for transferring highly specific visual information between the hemispheres of rodents (Mohn and Russell, 1981). The successful interocular transfer of brightness and pattern discriminations found in split-chiasm brush-tailed opossums is most likely to depend on the anterior commissure, which ensures the interhemispheric connectivity of the neocortex in the acallosal marsupials (Robinson, 1982). However, this hypothesis has not been crucially tested by cutting both optic chiasm and anterior commissure.

Experiments on interhemispheric transfer in fish and birds, reviewed by Cuénod (1972), Doty and Negrao (1973), Savage (1979) and Yeo (1979), take advantage of the fact that the optic pathways of these animals are completely crossed, so that the limitation of the visual input to a single hemisphere is a natural consequence of monocular stimulation. Interocular transfer of monocularly learned visual discriminations may not be present in fish and birds under all testing conditions (e.g. McCleary, 1960; Goodale and Graves, 1982; Gaston, 1983); when present, it must depend on an interhemispheric transfer via commissures that are functionally equivalent to the mammalian corpus callosum. The dorsal supraoptic decussation has been implied as the crucial pathway for visual interhemispheric transfer in birds (see e.g. Cuénod, 1972; Goodale, 1985), whereas the hypothalamic minor and horizontal commissures and the posterior commissure may constitute separate routes for interhemispheric transfer of, respectively, color and brightness, orientation, and shape information in fish (Hemsley and Savage, 1987). The tectal commissure has generally been regarded as uninvolved in interhemispheric visual transfer in fish (Ingle and Campbell, 1977), but other work suggests that it may be important for certain aspects of visual transfer in fish (Mark, 1966; Mark et al., 1973) as well as birds (Hamassaki and Britto, 1987).

With respect to the neuronal mechanisms, the supraoptic commissure may subserve interocular transfer in the pigeon because it generates binocular units in the visual Wulst, an avian counterpart of the mammalian visual cortex, just as the corpus callosum can sustain binocular interactions in visual cortical areas of split-chiasm mammals (Goodale, 1985). However, a bilateral lesion of the visual Wulst is not equivalent to a section of the supraoptic commissure, since it is compatible with a successful interocular transfer of visual discriminations (Francesconi et al., 1982). Perhaps the supraoptic commissure mediates binocular interactions not only in the visual Wulst, but also in other visual centers such as the superior colliculus.

Do subcortical commissures contribute to interhemispheric transfer of visual discriminations in mammals? The old idea that the recognition of patterned stimuli requires the cortex whereas the simple perception of the intensity of a sensory stimulus relies on subcortical substrates has been tested by examining interhemispheric transfer of different classes of visual discriminations. Earlier reports that the interocular transfer of brightness discriminations (Meikle and Sechzer, 1960) as well as the interocular comparison of brightnesses (Robinson and Voneida, 1964) persist in split-chiasm cats after transection of the corpus callosum, and their abolition requires an additional section of non-callosal commissures (Meikle, 1964; Robinson and Voneida, 1964), must be reconsidered on the basis of more recent experiments by Peck et al. (1979). These experiments point to the splenium of the corpus callosum as the essential pathway for interhemispheric transfer of not only pattern discriminations but also brightness and movement discriminations, and suggest that the previously reported persistence of the capacity for interhemispheric integration of brightness information in split-chiasm callosotomized cats might have been artefactual. Conversely, the relative unimportance of the posterior and intertectal commissures for interhemispheric transfer of pattern discriminations in split-chiasm cats is indicated by the high degree of transfer found after sectioning these commissures in the midbrain while leaving the corpus callosum intact (Berlucchi et al., 1987b).

In keeping with the above experiments on cats, many studies in macaques have implicated the corpus callosum as the main, and perhaps the only, route for interhemispheric transfer of brightness, color and movement discriminations (Downer, 1962; Hamilton and Gazzaniga, 1964; Hamilton et. al., 1968; Hamilton and Lund, 1970). The apparent survival of interocular transfer of brightness discriminations described by Trevarthen (1962) in split-brain monkeys was probably not due to a subcortical interhemispheric transmission of specific information, and is now attributed by Trevarthen himself (1987) to a relatively unspecific orientational and motivational modulation of bilateral cortical activities by undivided brainstem systems. The observation of a successful interocular transfer of brightness and color discriminations in split-chiasm, callosotomized chimpanzees (Black and Myers, 1968) still stands as the only evidence for an extracallosal interhemispheric transfer of non-spatial visual information in learning tasks in subhuman primates.

The hypothesis that under special training conditions some non-callosal, especially subcortical, commissures may be recruited for the interhemispheric transfer of at least some types of visual discrimination has been tested repeatedly. Sechzer (1964) found that interhemispheric transfer of the discrimination of line orientation, which is typically absent in split-chiasm cats trained with food reward, became successful if the reinforcement for learning and transfer ,was changed to shock-avoidance. An instrumentally conditioned limb flexion for avoiding a shock signaled by an intermittent light stimulus was similarly reported to transfer between the hemispheres of split-brain cats; this interhemispheric transfer was diminished but not abolished by an additional section of the commissure of the superior colliculi (Voneida, 1963). In contrast, no interhemispheric transfer was possible in split-brain cats when the emission of the shock-avoiding limb flexion required the discrimination between two different frequencies of intermittent light stimulation (Majkowski, 1967). Recent attempts to assess the role of subcortical commissures in the interhemispheric transfer of visuomotor responses for shock avoidance have met with failure mainly because of the erratic performance of cats trained with this procedure (Lepore et al., 1985). Some retention of learning with the second eye has been observed on tests of interocular transfer of pattern discriminations in split-brain cats with forebrain and thalamic commissurotomies which had to jump on, rather than walk toward, the discriminanda (Lepore et al., 1985). This low-degree capacity for interhemispheric transfer has been attributed to task-dependent motivational factors which encourage the use of secondary cues helping in the discrimination. Minor residual capacities for interhemispheric transfer that probably rely on subcortical commissures have also been reported in macaques (Tieman and Hamilton, 1973) and cats (Berlucchi et al., 1978a) submitted to an extensive practice with similar transfer tests before sectioning the cortical commissures. Extensive practice with transfer tests (Berlucchi et al., 1978a) and special training procedures employed during initial acquisition (e.g. Mascetti and Mancilla, 1984) have proved apt to facilitate subsequent transfers. It seems possible that practice may also induce a reorganization of the mechanisms for transfer in the presence of intact neocortical commissures, thereby allowing the maintenance of some capacity for transfer after severing the latter commissures.

The overwhelming majority of experiments on visual interhemispheric transfer have tested whether the forebrain commissures allow a cerebral hemisphere to perform a visual discrimination learned through an optic input restricted to the other hemisphere. A few other experiments have examined whether and which of the forebrain commissures are involved in the interhemispheric transfer of responses that depend on forms of learning other than the simple acquisition of visual discriminations. In split-chiasm monkeys which had 'learned to learn' several types of visual discrimination with the optic input restricted to one hemisphere, such a learning set appeared to be available to the other hemisphere only if the anterior portion of the corpus callosum was intact (Noble, 1973). Interhemispheric transfer was thus based on callosal information different from that transmitted by the posterior callosum in the interhemispheric transfer of simple visual discriminations. Mascetti et al. (1981) and Mascetti and Arriagada (1988) found that split-chiasm, but not split-brain, cats were capable of transferring between the eyes a set for reversal learning and an extinction response on visual discriminations, showing that the corpus callosum was essential for these types of transfer, as much as for the transfer of discrimination acquisition. Using a delayed matching-to-sample task and a running recognition task Doty et al. (1988) checked whether split-chiasm monkeys could recognize with one eye photographic slides after a single exposure to their other eye. These tasks differ from the usual discrimination tasks, which require the repeated presentation of the discriminanda, because they are intended to test for memory for 'events' rather than for memory for habits, a distinction now deemed very important for differentiating neural systems subserving memory in both man (Squire, 1987) and animals (Mishkin and Appenzeller, 1987). Nonetheless the essential commissural pathways for interhemispheric transfer on delayed recognition tasks proved to be the same as those involved in the interhemispheric transfer of discrimination habits, i.e. the anterior commissure and the splenium of the corpus callosum (Doty et al., 1988).

The above findings raise the problem of what and how many types of information are communicated by the commissures in experiments on interhemispheric transfer. Consider the successful interocular transfer of monocularly learned discriminations in the split-chiasm cats of the prototypic experiments of Myers (1955), or the successful monocular recognition of complex stimuli seen only once with the other eye in the split-chiasm monkeys of the experiment by Doty et al. (1988). The outstanding question is: During the acquisition period does the hemisphere connected to the exposed eye send an immediate duplicate of the visual input to the other hemisphere via the appropriate commissural connections, so that learning based on such information proceeds in parallel on both sides of the brain and each hemisphere forms its own memory trace or engram? Or is the engram laid down solely in the directly stimulated hemisphere, and made available through the commissures to the other hemisphere upon testing for interocular transfer, when the visual input is shifted to the other eye? In spite of more than three decades of ingenious theorizing and experimentation, there is no single definite answer to this question. Successful interocular transfer was found in some experiments in which commissurotomy was performed upon completion of the initial acquisition but before the test for interocular transfer, a finding compatible with the hypothesis of bilateral engrams and incompatible with the assumption of a transcommissural utilization of a unilateral engram (Myers, 1962, 1965; Gazzaniga, 1966; Butler, 1968; Sullivan and Hamilton, 1973b; Hamilton, 1977; Lepore et al., 1982). On the other hand there are also available several commissurotomy results which suggest a lateralization of memory to the hemisphere receiving the input and a subsequent commissural 'read-out' and/or 'write-in' of such unilateral engrams to the other hemisphere (Myers and Sperry, 1958; Myers, 1962; Gazzaniga, 1966; Doty and Negrao, 1973; Bures et al., 1988).

Evidence for a transcommissural utilization of unilateral engrams has been sought in elegant experiments by Doty et al. (1973, 1977). They cut the anterior commissure and the corpus callosum except the splenium in monkeys, and put a ligature around the intact splenium. The monkeys were then trained to press a lever in response to electrical stimulation of the striate visual cortex in one hemisphere. After completion of learning it was shown that a comparable stimulation of the opposite striate cortex elicited the same conditioned response. If, however, the ligature around the splenium was pulled, thus completing the callosal section, stimulation of the original cortical site could still produce the response, while contralateral stimulation could not, suggesting that the engram was confined to the originally stimulated hemisphere and was made continuously available to the other hemisphere through the splenium. The existence of bilateral engrams was instead indicated by similar experiments on completely callosotomized monkeys with an intact anterior commissure, in which pulling the ligature around the latter commissure did not prevent the contralateral generalization of the conditioned response after conditioning with unilateral electrical stimulation of the striate cortex. The conclusion that hemispheric interactions are associated with unilateral engrams when mediated by the splenium and with bilateral engrams when mediated by the anterior commissure (Doty et al., 1973, 1977) has been questioned by Hamilton (1977) and Bures et al. (1988) on account of the possible contaminating effects of an acute traumatic commissurotomy and the artificial nature of the learning situation.

On balance, it appears that the ability of the commissures to establish concurrent bilateral memories during learning has been proven beyond question, whereas the possibility of a commissural access by one hemisphere to memories fully lateralized to the other hemisphere has not been so well established in animals with surgical commissurotomies (see discussion in Hamilton, 1982). The delayed commissural transfer of fully lateralized engrams can perhaps be studied best in the reversible split-brain experimental system, which is obtained by temporarily inactivating one hemisphere with a chemical spreading depression. Although this system is a potentially viable alternative to the surgically split-brain animal for investigating various aspects of hemispheric interaction (Buresova and Bures, 1969; Bures et al., 1988), several problems of interpretation still exist, and the results are not easily amenable to direct neurophysiological analysis of the commissures involved in transfer.

Perhaps the commissural mechanisms of interhemispheric transfer of visual discrimination can be better understood within the framework of a general model of visual perception and memory. A currently popular model proposes that visual information is processed sequentially by hierarchies of cortical areas before being eventually relayed to limbic and motor structures which mediate learning and behavioral output (e.g. Mishkin, 1972, 1982; Mishkin and Appenzeller, 1987). In some experimental conditions callosal connections are shown to be essential for enabling visual information to progress from early stages in the cortical hierarchy to successive stages. For example, by isolating visual cortical areas in one hemisphere of the cat by sectioning all cortico-cortical intrahemispheric connections, Sperry et al. (1960) showed that this cortical island could still contribute to visual perception and memory provided its callosal connections with the other hemisphere were left intact. Successful visual control of behavior by the cortical island evidently required communication with the intact subsequent processing stages on the other side. A similar callosal participation in a sequential analysis of visual information has been described by Mishkin (1972, 1979) in the monkey. A removal of the first stage of the cortical hierarchy, the striate visual cortex, in one hemisphere and of the last stage of the hierarchy, the inferotemporal cortex in the other hemisphere, did not interfere with visual perception and memory so long as the corpus callosum was intact. Transection of the corpus callosum disrupted visually guided behavior presumably because visual information from the intact striate cortex could no longer be relayed to the remaining contralateral inferotemporal cortex, and perhaps also to other non-visual cortical areas (Nakamura and Mishkin, 1986).

Gross and Mishkin (1977) have argued that the interhemispheric transfer of visual discriminations in monkeys with intact cortices also requires a cross-midline transmission of visual information to the inferotemporal cortex. Their argument is based on the strong (though incomplete) reduction of interocular transfer in split-chiasm monkeys with bilateral inferotemporal lesions (Seacord et al., 1979) and on the already mentioned presence (pp. 11, 12) in the inferotemporal cortex of neurons that receive visual information from large portions of both halves of the visual field (Gross et al., 1977). The input which these neurons receive from the ipsilateral half field is removed by section of the splenium of the corpus callosum and of the anterior commissure, i.e. by the same commissural disconnection that disrupts behavioral interhemispheric transfer (Gross et al., 1977). Callosal connections between visual cortical areas earlier in the hierarchy, such as for example those between the prestriate cortices (Zeki, 1967, 1977; Hamilton and Vermeire, 1986), can, however, participate in interhemispheric transfer, as indicated by the above-mentioned experiments (Mishkin, 1972) with contralateral striate and inferotemporal lesions, in which visual information conveyed across the midline to the remaining inferotemporal cortex obviously could not originate from the contralateral inferotemporal cortex.

The participation of different cortical areas and neuronal populations in interhemispheric transfer in the cat has been investigated with electrophysiological recordings in intact, split-chiasm and split-brain animals as well as in behavioral studies using circumscribed cortical lesions. Following the initial experiment of Berlucchi and Rizzolatti (1968), it has been repeatedly demonstrated that after the splitting of the chiasm and the consequent elimination of the crossed optic fibers, neurons in all known visual cortical areas (Lepore and Guillemot, 1982; Lepore et al., 1986a; Antonini et al., 1983, 1985; Cynader et al., 1981, 1986; Maffei et al., 1986; Ptito et al., 1986; Milleret and Buser, 1987; Berardi et al., 1987) and even in a subcortical center such as the superior colliculus (Antonini et al., 1978, 1979) can still receive visual information from the contralateral eye via specific callosal connections, and combine it with direct information from the ipsilateral eye in accord with the principle of supplemental complementarity (Berlucchi et al., 1986, 1987; see page 12). Responses of neurons in cortical areas 17 and 18 of split-chiasm cats to stimulation of the contralateral eye may be potentiated by a prolonged occlusion of the other eye at an early age (Cynader et al., 1981, 1986) or even in adulthood (Milleret and Buser, 1987), suggesting some kind of competition between the intrahemispheric and interhemispheric visual inputs.

The crucial proof of the callosal mediation of the input from the contralateral eye in split-chiasm cats is provided by the disappearance of that input, but not the input from the ipsilateral eye, after a posterior callosal transection. In addition, a callosal section in cats with intact optic pathways has been shown to abolish response to stimuli from the ipsilateral visual field, but not from the contralateral visual field, in several visual cortical areas (Dow and Dubner, 1971; Marzi et al., 1980, 1982; Lepore and Guillemot, 1982; Berlucchi et al., 1987) as well as in the superior colliculus (Antonini et al., 1979). Although the existence of callosal connections in the early stages of visual cortical processing such as areas 17, 18 and 19 has been proved beyond question (Berlucchi, 1972, 1981; Innocenti, 1986), the region of the visual field from which these connections transmit information is limited to a narrow strip running along the vertical meridian of the visual field (Berlucchi et al., 1967; Hubel and Wiesel, 1967; Shatz, 1977; Lepore and Guillemot, 1982; Antonini et al., 1985; Berlucchi et al., 1987), while behavioral visual interhemispheric transfer is liable to occur over the entire visual field.

Interhemispheric transfer of visual pattern discriminations has been studied in split-chiasm cats with lesions of areas 17 and 18, since such lesions do not abolish learning (Berlucchi, 1972; Berlucchi et al., 1978c; Berlucchi and Sprague, 1981; Berlucchi and Marzi, 1982). No deficits in interhemispheric transfer were found in these animals, and the capacity for transfer was subsequently eliminated by a callosal section; hence it was concluded that such ability depended on callosal connections of areas beyond 17 and 18. Comparable lesion studies attributed an essential role in interhemispheric transfer to a complex of visual cortical areas in the suprasylvian gyri (Berlucchi et al., 1979; Berlucchi and Sprague, 1981; Berlucchi and Marzi, 1982) and perhaps also to the superior colliculus (Berlucchi, 1982). The large bilateral receptive fields of neurons in these regions, whose ipsilateral component is mediated by the corpus callosum, are appropriate for collecting information from large portions of the visual field, in spite of their organization being in accord with the vertical meridian rule, and can thus provide a suitable substrate for behavioral interhemispheric transfer of visual dicriminations (Antonini et al ., 1983; Berlucchi et al., 1986). The callosum-dependent input from each visual hemifield to the ipsilateral superior colliculus (Antonini et al., 1979) can be accounted for by a serial connection between the cortico-cortical callosal pathway and the cortico-tectal pathway, in keeping with theories of cortico-subcortical interactions in visually guided behavior (Thompson, 1965; Sprague et al., 1971) and with a similar serial arrangement between interhemispheric cortico-cortical and intrahemispheric cortico-thalamic fibers in the somatosensory system (Landry et al., 1984).

If the callosal connections of the primary visual cortical areas are not involved in the interhemispheric transfer of visual discriminations, are they perhaps used for more basic visual functions (Pasik and Pasik, 1964; Berlucchi, 1975)? Commissurotomy studies have tested the possible role of these connections in interhemispheric interactions presumably necessary for some aspects of binocular stereopsis, binocular convergence and optokinetic nystagmus.

It is believed that the fundamental mechanism for the binocular perception of depth and appreciation of distance is provided by neurons that code for the horizontal disparity of the right and left monocular images of an object (Bishop, 1981). Object points lying directly behind or in front of the fixation point pose a special problem for binocular stereopsis to the extent that their monocular images are formed on heteronymous halves of the two retinae, i.e. either on both temporal or both nasal hemiretinae. Since the organization of the optic pathways is such that projections from heteronymous hemiretinae are largely directed to different cerebral hemispheres, neurons in each hemisphere that compare images falling on heteronymous hemiretinae must in principle receive both intra- and interhemispheric visual inputs (Blakemore, 1969). The evidence reviewed above proves that there exists an abundance of cortical visual neurons which receive intra- and interhemispheric (callosal) inputs from regions of both visual hemifields matched at the vertical meridian. In principle, binocular stereopsis in the central visual field should be expected to be deficient after a section of the corpus callosum which eliminates the input from the ipsilateral visual field to these neurons. This expectation has been at least partly confirmed by the finding of deficient binocular stereopsis in the vertical meridian region in patients with surgical callosal sections (Mitchell and Blakemore, 1970; Hamilton and Vermeire, 1986; Hamilton et al., 1987; Jeeves, 1989), as well as in patients with callosal agenesis (Jeeves, 1989). However, deficits in the tachistoscopic judgement of distance-in-depth were found over the whole visual field in split-brain and callosum-agenetic patients by Lassonde (1986). On the basis of these results Lassonde (1986) has argued in favor of a general unspecific facilitatory influence of the corpus callosum on stereopsis.

The effects of callosotomy in animals do not generally provide strong support for the hypothesis of a crucial role of the corpus callosum in binocular stereopsis. The threshold for binocular stereoacuity is not affected by a posterior callosal section in monkeys (Cowey, 1982) and cats (Timney et al., 1985), and no significant impairment in the binocular discrimination of random-dot stereograms follows callosotomy in either cat (Lepore et al., 1986c) or monkey (Hamilton and Vermeire, 1986). In contrast, massive deficits in stereoacuity and discrimination of random-dot stereograms are induced by a section of the optic chiasm in both monkey (Hamilton and Vermeire, 1986) and cat (Timney et al., 1985, 1989; Lepore et al., 1986c). It is possible that split-chiasm cats may have some extremely limited residual capacity for binocular stereopsis (Lepore et al., 1986c; Timney et al., 1989) and that this capacity is lost after callosotomy (Lepore et al., 1986c). No residual binocular stereopsis has been found after splitting of the chiasm in monkeys (Hamilton and Vermeire, 1986). The application to the same animals of tests of global and local and of fine and coarse stereopsis (Bishop, 1981), as well as due consideration of the enormous variability in binocular stereopsis in normal humans (Hamilton et al., 1987), will perhaps provide more satisfactory answers to the question of the commissural contribution to binocular stereoperception.

Controversial reports of the effects of a callosal disconnection on electrophysiological binocular interactions in areas 17 and 18 of cats with intact visual pathways have been published. The percentage of binocular neurons at the border between areas 17 and 18 was reported to fall significantly after an ablation of the contralateral corresponding cortical regions in some experiments (Dreher and Cottee, 1975; Blakemore et al., 1983) but not in others (Cynader et al., 1986). On the basis of the effects of unilateral visual cortical removals Gardner and Cynader (1987) have recently reaffirmed the participation of the corpus callosum in the generation of disparity-sensitive neurons in visual cortical areas 17 and 18 of the cat, but not in the generation of binocular interactions as such when the visual pathways are intact. However, the effects on the visual cortex of a removal of the contralateral corresponding areas may not be fully equivalent to section of the corpus callosum. Studies reviewed by Payne (1986) indicate that a callosal section caused a permanent reduction – from about 80% to about 40% – in the percentage of binocular neurons in those portions of areas 17 and 18 which represent the visual field near the vertical meridian. In contrast, Minciacchi and Antonini (1984) and Elberger and Smith (1985) found no effect of a callosal section on binocular interaction in areas 17 and 18 of cats callosotomized as adults, although the latter authors produced a significant reduction in the percentage of binocular neurons by performing the callosotomy early in life. Recently Berlucchi et al. (1987) confirmed that callosotomy does not disrupt binocular interaction in visual cortical areas 17 and 18 of adult cats with normal visual pathways, although it causes a significant reduction of receptive fields crossing the vertical meridian. Further experimentation in the cat as well as in other mammals is clearly needed for understanding the reasons for the discrepancies in these results.

The participation of the corpus callosum in cortical binocular interaction is well established only in albino animals with a genetically determined excessive crossing of the visual pathways, such as the Siamese cat. Neurons responding to photic stimulation of both eyes abound in the visual cortical suprasylvian areas of Siamese cats, in spite of the drastically reduced input from each eye to ipsilateral primary visual cortical areas 17 and 18. The corpus callosum is essential for the existence of a visual input from each eye to ipsilateral suprasylvian areas beyond 17 and 18, since this input is virtually lost after a posterior callosal section (Marzi et al., 1980, 1982; Zeki and Fries, 1980). Similar to Siamese cats, in normally pigmented cats submitted to an early surgical strabismus neurons in areas 17 and 18 are dominated by the input from the contralateral eye, in contrast with a balanced converging binocular input to visual suprasylvian neurons (Marzi et al., 1986). However, unlike Siamese cats, following callosotomy these strabismic cats show only a reduction, rather than an abolition, of the ipsilateral eye input to suprasylvian neurons, suggesting the existence of an alternative route for the interhemispheric conveyance of the latter input (Bedard et al., 1988). Binocular interactions found in areas 17 and 18 of albino rats have also been attributed to a callosal mediation, based on the disappearance of the response to stimulation of the ipsilateral eye during cooling of the contralateral cortex (Diao et al., 1983).

In mammals with frontal eyes, such as cat (Montarolo et al., 1981), monkey (Pasik and Pasik, 1964, 1972) and man (van Die and Collewijn, 1982, Ohmi et al., 1986), horizontal optokinetic nystagmus can be elicited in both directions from either eye and via both crossed and uncrossed retinal fibers. Optokinetic following of the stimulus in either direction can indeed be demonstrated when the visual inflow is appropriately channeled into a single hemifield of either eye of man, or restricted to a single hemiretina of monkeys or cats by monocular stimulation following either a midsagittal section of the optic chiasm or a transection of one optic tract. These analyses reveal only slight asymmetries in favor of stimulus movement in the temporonasal direction upon stimulation of either nasal hemiretina (crossed retinal fibers), and in favor of the nasotemporal direction upon stimulation of either temporal hemiretina (uncrossed retinal fibers). By contrast, in afoveate mammals with laterally placed eyes, optokinetic nystagmus upon monocular stimulation shows a strong predominance in favor of the temporonasal direction (Tauber and Atkin, 1986). This largely unidirectional nystagmic response appears to depend solely on the crossed fiber systems from the nasal hemiretinae, since the interruption of these systems by a chiasmatic section abolishes optokinetic nystagmus in both rat (Cowey and Franzini, 1979) and rabbit (Steele-Russell et al., 1987), in spite of the fact that the intact uncrossed fibers from the temporal hemiretinae prove capable of mediating other forms of visually guided behavior.

Bilateral ablations of occipital cortex in both cat (e.g. Montarolo et al., 1981) and monkey (e.g. Zee et al., 1987) cause a marked impairment in optokinetic nystagmus. Postoperative nystagmic responses resemble those of afoveate animals, particularly because of the emergence during monocular viewing of a conspicuous temporonasal preponderance due to a reduction of the response to nasotemporal motion. An essential component for optokinetic nystagmus is the nucleus of the optic tract in the pretectum: a lesion of this nucleus on one side abolishes optokinetic following of stimuli moving toward that side (Kato et al., 1986, 1988). While at least in the cat each nucleus of the optic tract may receive direct visual inputs from both hemiretinae of both eyes (Montarolo et al., 1981), these direct visual inputs, and especially the uncrossed input from ipsilateral temporal hemiretina, are reinforced by indirect inputs from visual cortical areas via cortico-pretectal projections (Montarolo et al., 1981; Hoffmann and Distler, 1986; Zee et al., 1987). One of the normal functions of these pathways is that of ensuring a balanced oculomotor reactivity to horizontal motion in both directions (Zee et al., 1987).

Experiments on monkeys strongly suggest that some of the cortico-pretectal pathways controlling the brainstem substrates for optokinetic nystagmus include an interhemispheric, predominantly callosal component. Horizontal optokinetic nystagmus elicited by stimulating each temporal hemiretina of split-chiasm monkeys occurs normally in either direction. If, however, the corpus callosum is sectioned in addition to the chiasm, optokinetic responses to temporonasal motion are normal in each eye, whereas responses to nasotemporal motion undergo a massive reduction (Pasik and Pasik, 1964, 1971, 1972). Similarly, monkeys submitted to a combined callosotomy and section of one optic tract exhibit a strong asymmetry in favor of optokinetic responses toward the lesioned side (Pasik and Pasik, 1972). Combined splitting of chiasm and corpus callosum also disturbs vertical optokinetic nystagmus from monocular stimulation, with paradoxical oblique downward movement evoked by upward motion and vice versa (Pasik et al., 1971).

These results in split-brain monkeys are not easy to explain on the basis of our present understanding of the pretectal substrates of optokinetic nystagmus. It can only be concluded that a normal optokinetic nystagmus requires that both hemispheres receive visual information. In the split-chiasm, monocularly occluded monkey the corpus callosum must supply at least part of this information to the hemisphere contralateral to the seeing eye. The neuronal mechanisms by which the corpus callosum can influence the brainstem substrates for optokinetic nystagmus are still largely unknown. A recent preliminary report by Hoffmann et al. (1988) indicates that neurons in the nucleus of the optic tract in the monkey receive visual information via the corpus callosum. Bilateral receptive fields, extending into both halves of the visual field, are typically recorded in the nucleus of the optic tract of normal monkeys. In two callosotomized monkeys receptive fields in the same nucleus were consistently restricted to the contralateral half field. This loss of ipsilateral receptive field components following callosotomy is akin to that described in the cat superior colliculus by Antonini et al. (1978, 1979). In conclusion, there is suggestive evidence that the callosal connections of primary visual cortical areas may partake in the mediation of rather elementary sensory functions such as binocular stereopsis, binocular convergence and optokinetic nystagmus, but more work is necessary for proving this functional involvement beyond question, as well as for differentiating such forms of interhemispheric interaction from those related to learning and memory.

Interhemispheric integration of non-visual sensory information

Somesthetic information from each side of the body is conveyed by crossed specific afferent pathways mainly but not exclusively to the contralateral hemisphere. Somatosensory cortical areas can receive inputs from the ipsilateral body half through uncrossed specific afferent pathways as well as via callosal connections. Afferent ipsilateral somatic representation is stronger for axial and proximal body parts and weaker or absent for distal extremities (Mountcastle, 1981). Homotopic and heterotopic commissural connections have been described in the somatosensory cortex of many species (see reviews by Killackey, 1985; Shanks et al., 1985; Innocenti, 1986; Cusick and

Kaas, 1986; Manzoni et al., 1989). The earlier belief that callosal connections are restricted to the representations of axial and proximal limb surfaces and avoid representations of distal extremities in all somatosensory areas (Jones and Powell, 1969; Pandya and Vignolo, 1969) has been substantially revised, since at best it applies only to the primary receiving area. The total absence of callosal connections between cortical regions representing the distal extremities would indeed be incompatible with behavioral results on somatosensory interhemispheric transfer.

As indicated previously, the era of split-brain research is thought to have begun with the famous experiment on tactile interhemispheric transfer performed by Bykov and Speranski (1924; see also Bykoff, 1924) in Pavlov's laboratory. It was known that dogs conditioned to salivate in response to tactile stimulation of a specific skin location on one side of the body were perfectly capable of transferring the response to a comparable stimulation of the corresponding point of the other side (see Pavlov, 1927). Bykov and Speranski (1924) showed that a transection of the corpus callosum suppressed contralateral generalization, and that different and independent reflexes could be established to identical stimuli applied to different sides of the body.

Confirming this pioneering study, subsequent experiments on cats trained with operant rather than classical conditioning demonstrated that callosotomy can totally abolish the normal transfer between the forelimbs of fairly simple motor responses to unilateral tactile or tactile-kinesthetic stimuli (Stamm and Sperry, 1957; Meikle et al., 1962). Abolition of the normal capacity for intermanual or interpedal transfer of unimanually or unipedally learned discriminations of several classes of somesthetic stimuli has also been generally observed in callosotomized monkeys (Glickstein and Sperry, 1960; Ebner and Myers, 1962; Lee-Teng and Sperry, 1966; Kohn and Myers, 1968; Hunter et al., 1975) and chimpanzees (Myers and Henson, 1960), but cases of persistence of somesthetic transfer after callosotomy have also been noted (Glickstein and Sperry, 1960; Ettlinger and Morton, 1966; Manzoni et al., 1972; Hunter et al., 1975). When transfer is abolished by partial callosal transections, the effective section is one which interrupts callosal fibers between the parietal lobes containing the somatosensory areas (Myers and Ebner, 1976). Direct electrophysiological recordings from callosal fibers in cats and monkeys proved that tactile and proprioceptive messages are readily transmitted across the midline upon peripheral natural or electric stimulation (Innocenti et al., 1974; Spidalieri et al., 1985; Guillemot et al., 1987b, 1988; Guandalini et al., 1989). Callosal fibers convey information from axial, proximal and distal parts of the body, but there is a relative overrepresentation of axial information, in accord with the concept of sensory midline fusion (Lepore et al., 1986a; Manzoni et al., 1989).

The persistence of transfer in callosotomized animals is most likely to depend on the incomplete crossing of the somatic sensory pathways, which allows the projection of unilateral sensory inputs to both hemispheres independent of interhemispheric connections (Ettlinger and Blakemore, 1969; Gazzaniga, 1970). Why the limited ipsilateral somatic input to each hemisphere should be used by callosotomized monkeys in some learning and/or transfer situations but not in others is not clear. Butler and Francis (1973) claimed that even normal monkeys could not transfer tactile discriminations between the hands, in spite of having an intact corpus callosum, when tactile information was carefully restricted to the fingers. Although at first sight this finding might be accounted for by the lack of callosal connections between the hand regions of the primary somatosensory cortical areas (SI) of the two sides, it is best attributed to procedural factors.

Several lines of evidence do indeed indicate that, as in the visual system, interhemispheric transfer in the somestheic system relies on cortical areas beyond the primary receiving area SI, and that the complement of callosal connections of these cortical areas is fully adequate for transfer between bilateral distal extremities such as the cat's forepaws or the monkey's hands. A most likely candidate is the second somatosensory area SII, which contains neurons with bilateral receptive fields on the distal forelimb extremities in both cat (Innocenti et al., 1973; Robinson, 1973) and monkey (Whitsel et al., 1969; Robinson and Burton, 1980). In the monkey SII these neurons are likely to receive the input from the ipsilateral hand via callosal projections from the contralateral hemisphere, since, contrary to earlier reports (Jones and Powell, 1969; Pandya and Vignolo, 1969), there is now definite anatomical evidence for a hand-related callosal input to SII from contralateral SI and SII (Manzoni et al., 1984). A section (Robinson, 1973; Guillemot et al., 1987a) or cathodal blockade of the corpus callosum (Innocenti et al., 1973) reduces, but does not annul, the number of bilateral fields in the cat SII by removing their ipsilateral input. The neurons having bilateral fields in the absence of the corpus callosum receive both their ipsilateral and contralateral inputs via the thalamus (Barbaresi et al., 1984; Manzoni et al., 1989). The effect of a callosal section on bimanual receptive fields in the monkey SII has not yet been tested; however, the important role of SII in tactile interhemispheric transfer in the monkey is indicated by the decrease in transfer after a lesion of SII (Garcha and Ettlinger, 1980; Garcha et al., 1982), in agreement with similar earlier findings in the cat (Teitelbaum et al., 1968).

Granted that in each modality sensory information is processed sequentially through a series of specific cortical areas before being relayed to the limbic system for memory storage and behavioral control, an analogy can be drawn between visual interhemispheric transfer and somatosensory transfer insofar as both depend on interhemispheric connections at levels well beyond the primary receiving cortical stages (Mishkin, 1979). Mishkin (1979) originally proposed that SII in the somatosensory system and the inferotemporal cortex in the visual system are the cortical sites specialized for interhemispheric transfer, but in more recent publications he has emphasized the primary or additional role of the insula in somesthetic perception and memory, including bilateral integration (Murray and Mishkin, 1984; Friedman et al., 1986; Pons et al., 1987). No specific function, other than a generic 'midline fusion' of right and left hemibody maps, has as yet been identified for the callosal connections of the primary somatosensory area SI. These connections appear to reinforce rather than create a bilateral representation of face and trunk which is already present at thalamic level (Barbaresi et al., 1984; Manzoni et al., 1989). It seems agreed that callosal connections are absent or sparse in the primary SI representations of those body parts which are normally used in environmental exploration, such as the whiskers in rodents and the hands in primates. The tendency of callosal connections to avoid mixing with somatic afferents having high resolving powers has been considered to be useful for the preservation of the 'purity' of basic sensory information at the first cortical processing station (Killackey, 1985; Ledoux et al., 1987; Manzoni et al., 1989).

Information about the role of the mammalian forebrain commissures in olfaction is limited to the demonstration of the primary importance of the anterior commissure for interhemispheric transfer. Afferent pathways from the olfactory mucosa in each nostril travel to ipsilateral olfactory centers, and the inter-nostril transfer of odorous information requires a cross-midline integration. Cutting the anterior commissure abolishes the inter-nostril transfer of olfactory discriminations in rats (Teitelbaum, 1972). Inter-nostril transfer of olfactory information used for orientation by homing pigeons has similarly been found to be absent after sectioning the anterior commissure (Foà et al., 1985). A normal inter-nostril transfer of habituation to odorous stimuli has instead been reported in pigeons with a section of the anterior commissure (Gagliardo and Teyssèdre, 1988).

Studies on the interhemispheric integration of auditory information in man have revealed an important role of the corpus callosum in performing dichotic listening tasks which involve a competition between different simultaneous inputs from the two ears. Because of the partial crossing of the auditory pathways in the brain stem, each cerebral hemisphere receives information from both ears, hence section of the forebrain commissures is plainly insufficient to separate the two monaural inputs into different hemispheres. However, there is evidence from both normal and brain-damaged subjects that at least under conditions of dichotic competition the crossed afferent pathway from each ear is functionally superior to the uncrossed pathway (Kimura, 1967; Sidtis, 1984). It appears that in these conditions transmission of information along the weaker uncrossed ascending pathway is virtually suppressed by the stronger crossed pathway, so that the corpus callosum becomes necessary for conveying the input from each ear to the ipsilateral hemisphere (Milner et al., 1968; Sparks and Geschwind, 1968). Does the corpus callosum subserve a comparable function in animals?

Among the scanty studies of the effects of commissurotomy on auditory perception in animals (see Wegener, 1965, for an earlier discussion), only one experiment employed dichotic stimulation. Kaas et al. (1967) trained cats to recognize a specific tonal change in one ear while disregarding different tonal changes occurring simultaneously in the other ear. Removal of the auditory cortex contralateral to the 'attentive' ear led to loss of the habit, whereas removal of the ipsilateral auditory cortex did not. If, however, the corpus callosum was sectioned prior to training, cortical ablation contralateral to the attentive ear did not abolish the habit, suggesting a compensation by the auditory cortex of the other hemisphere. It follows that in the intact brain the corpus callosum prevented rather than favored the access of the input from the attentive ear to the ipsilateral hemisphere. No confirmation of this putative role of the corpus callosum in audition in animals has so far been provided.

The concept that each hemisphere has a preferential or exclusive association with the contralateral auditory hemispace rather than with the contralateral ear (Jenkins and Masterton, 1982) may aid in investigating the participation of the corpus callosum to audition. Pavlov's (1927) claim that dogs conditioned to differentiate between sounds coming from the left and the right lost this ability after callosotomy could not be supported by Neff (1961), and the lack of effects from callosotomy on sound localization in cats has been reiterated in more recent investigations (e.g. Moore et al., 1974). It must be pointed out, however, that the above experiments employed rather crude tests of sound localization which have been shown to be inadequate for a precise mapping of the cerebral substrates of this ability (Masterton and Jenkins, 1982), and the possible contribution of the corpus callosum to sound localization should be reinvestigated by using several sound sources rather than only two. By analogy with the visual system, the hypothesis can also be made that auditory commissural connections are instrumental in uniting hemispace representations into whole-space representations. In the barn owl, for example, bilateral auditory space representation in the inferior colliculus appears to rely on commissural connections of this structure (Takahashi et al., 1989). It does not seem implausible that the mammalian corpus callosum may be similarly involved in unifying the right and left auditory hemispaces and more generally in transferring spatial auditory information between the two hemispheres. In this context it is noteworthy that callosal connections are concentrated in cortical regions which represent the midline of the sound space and contain neurons nonselective for sound direction, whereas cortical areas representing the contralateral sound space have few or no callosal connections (Imig et al., 1986). No physiological evidence as to the effects of a callosal section on the response of auditory cortical neurons to sound stimuli is yet available to match and interpret the above anatomical information.

Bilateral motor interactions

On the assumption of a complete crossing of the motor pathways, a visual input restricted, say, to the right hemisphere can guide the motility of the left half of the body by an intrahemispheric visuomotor integration, while an interhemispheric interaction is required for the same input to guide motor responses on the right half of the body. In a split-chiasm animal a visual input from the right eye should elicit left-sided motor responses intrahemispherically and right-sided responses interhemispherically. To the extent that visuomotor control depends on cortico-cortical interactions, split-chiasm animals with an additional section of the cortical commissures should show impairments in the visual guidance of movements on the side of the eye receiving the input. Yet it has been found in split-brain cats that visual inputs to either eye could guide either foreleg in an essentially normal fashion (Schrier and Sperry, 1959; Voneida, 1963). Varying degrees of effective control over the motility of an arm by visual inputs to the ipsilateral eye have also been reported in split-brain monkeys (Downer, 1959; Myers et al., 1962; Gazzaniga, 1964; Hamilton, 1967; Lehman, 1968; Lund et al., 1970; Brinkman and Kuypers, 1973; Keating, 1973).

The cross-cuing model of Gazzaniga (1969) can account at least in part for the fact that commissurotomy does not abolish monocular visual reaching with the ipsilateral forelimb in split-chiasm animals. If in response to a visual input from the right eye the right hemisphere orients the head toward the visual target, bilaterally distributed spatial information from neck proprioceptors can then cue the 'blind' left hemisphere to align the right hand with the target. Gazzaniga (1969) saw that a mechanical immobilization of the head and the consequent blockade of the orienting reaction did indeed interfere with the ability of split-brain monkeys to reach with one hand under the visual guidance of the ipsilateral eye.

However, cross-cuing is not the only mechanism involved in successful ipsilateral eye-arm visuomotor control after commissurotomy. Anatomical, functional and clinical evidence suggests that the crossing of the central motor pathways for distal hand and finger muscles is virtually complete, whereas both crossed and uncrossed motor pathways can control axial and proximal limb muscles (Kuypers, 1981). Lund et al. (1970) observed motor abnormalities in the use of a hand ipsilateral to the seeing eye in monocularly occluded split-chiasm callosotomized monkeys, and argued that in the ipsilateral eye-hand condition of the experiment the corpus callosum is required for linking the visual input to the crossed corticospinal system, thus giving dexterity to visually controlled finger movements. These findings were confirmed and extended by Brinkman and Kuypers (1973), who found that on monocular tests of visual reaching with the forelimb ipsilateral to the seeing eye, split-brain monkeys could direct the arm toward the target, but were unable, if unaided by tactile cues, to make the discrete manual and digital actions required for the precise gripping of a small object. Such precise visually guided digital prehensions could, however, be accomplished successfully with the hand ipsilateral to the open eye by split-chiasm monkeys with an intact callosal splenium, as well as by both split-chiasm and split-brain monkeys using the hand contralateral to the open eye. These findings strongly support the notion that a visual input restricted to one hemisphere can access an uncrossed motor system of the same hemisphere for controlling the ipsilateral arm at proximal joints, but must be relayed via the corpus callosum to a crossed motor system in the other hemisphere for guiding the ipsilateral hand and fingers (Brinkman and Kuypers, 1973). Several portions of the corpus callosum in addition to the splenium are likely to subserve this interhemispheric transfer (Lehman, 1968).

Brinkman and Kuypers (1973) and Haaxma and Kuypers (1974) emphasized the importance for visuomotor guidance of a multi-stage serial cortico-cortical pathway between striate and motor cortex, with intermediate stations at prestriate, parietal and premotor cortex, and callosal connections linking up bilateral stations at all levels of the pathway. By contrast Glickstein (1989; see also Glickstein and May, 1982) has argued for an essential involvement of cortico-subcortical-cerebellar pathways in visual guidance of movements. These pathways run from many visual cortical areas, particularly in the parietal lobe, and from superior colliculus alike to ipsilateral pontine nuclei and thence to ipsilateral and contralateral cerebellum. Considering that each hemicerebellum has a predominant relationship with the musculature on the same side of the body, the pathway to a hemicerebellum from the ipsilateral cortex or colliculus could account for sight-guided movements of the ipsilateral forelimb when visual information is restricted to that side by forebrain commissurotomy (Glickstein, 1989). Cortico-ponto-cerebellar connections could also account for the surprisingly normal between-hand coordination that has been described in split-brain monkeys performing object manipulations and other skilled acts (Mark and Sperry, 1968), if one grants the cerebellum the ability to infer the position of either hand from the corollary discharges of cortical motor commands to the hand muscles, as well as to signal the inferred position of each hand to the other even in the absence of the commissures (Glickstein, 1989). Finally, in view of its role in various forms of learned visuomotor adjustments (Lisberger, 1988), the cerebellum could be involved in bilateral transfer of motor adaptation to a distorted unihemispheric visual input. A split-brain monkey wearing a light-deflecting prism in front of the open eye and trained to reach for a target with one arm transferred the learned motor adaptation between the eyes but not between the arms (Hamilton, 1967). The successful interocular transfer may be due to a convergence of binocular information, not disrupted by commissurotomy, onto cerebellar neurons feeding visual information into arm-specific neural substrates of motor learning.

Electrical microstimulation of the rostral corpus callosum in the cat induced discrete unilateral or bilaterally symmetrical movements of shoulder, whisker or eyelid muscles (Spidalieri and Guandalini, 1983). This pattern of motor responses from callosal stimulation was subsequently shown to be subject to a gradual postnatal maturation (Guandalini et al., 1989). The motor effects can only in part be attributed to orthodromic activation of callosal fibers synapsing on corticofugal neurons in motor cortex, since similar, though weaker, movements could be obtained through stimulation of a callosal stump after a chronic callosal section, or by callosal stimulation after unilateral motor cortex removal (Spidalieri et al., 1986). Motor responses observed under these conditions were attributed to an activation of motor cortex neurons pursuant to an antidromic excitation of surviving callosal fibers and a consequent orthodromic excitation of their recurrent collaterals. The pattern of results suggests that callosal connections of the motor cortices in the cat serve to ensure a self-strengthening bilateral activation of cortical motor neurons controlling axial and proximal muscles (Spidalieri et al., 1986).

Combined cortical stimulation and indentification of sites of callosal connectivity in primary and supplementary motor cortex and in frontal eye fields of the owl monkey revealed a rather diffuse callosal connectivity in the latter two areas. In the primary motor cortex, dense callosal connections tended to be associated with sites whose stimulation produced movements of axial and proximal body parts , and sparse callosal connections tended to be associated with sites whose stimulation produced movements of distal limbs. However, such relations were by no means exclusive, since the same body part, whether axial, proximal or distal, could be represented in both callosal and acallosal regions (Gould et al., 1986). In theory these callosal connections of motor cortical areas may serve (1) to mediate interhemispheric sensory guidance of unilateral movements, as discussed previously in relation to visuomotor control, (2) to help bilateral coordination during associated synchronous and symmetric movements of corresponding effectors on the two sides of the body, and/or (3) to allow an orderly dissociation between corresponding contralateral effectors during bilateral actions that require coordinated but different movements on the two sides.

Behavioral commissurotomy findings by Brinkman (1984) point to a clear-cut associative function of motor cortical callosal connections. A unilateral removal of the supplementary motor area in monkeys caused a chronic impairment in bimanual coordination, consisting in a tendency to make the same actions with the two hands in tasks which instead required an intermanual uncoupling and differentiation of labor. Since the deficit was alleviated or relieved by a subsequent callosal section, it was ascribed to a callosally transmitted influence of the intact supplementary motor area, overriding residual systems for motor control in the damaged hemisphere and imposing its own motor programs upon them. By inference it can be suggested that in the intact brain each supplementary motor area can function as an independent program generator for motor systems in the same hemisphere, but at the same time it can use callosal connections to make its activities known to its counterpart and related motor systems in the other hemisphere for the purpose of bilateral coordination (Brinkman, 1984). How interhemispheric influence of the supplementary motor areas can precisely interact with intrahemispheric influences in the target areas remains to be determined.

While the above study reported an amelioration of motor deficits by a callosal section, other studies addressing the problem of the neural organization of attention and motor intention have revealed detrimental influences of callosotomy. A severe but temporary contralateral polysensory neglect can be induced in monkeys by removal of the cortical eye field in one frontal lobe. Crowne et al. (1981) showed that section of the corpus callosum reinstated the hemineglect in monkeys which had recovered from a previous frontal lesion. This second hemineglect was also transitory. In a study by Watson et al. (1984), hemineglect from a unilateral frontal arcuate lesion was much more conspicuous in callosotomized than in callosum-intact monkeys, though the time course of the recovery was the same in the two groups. The callosal mechanisms underlying these commissurotomy findings in hemineglect are unknown, but certainly they cannot include the mutual interhemispheric inhibition postulated by Kinsbourne (1970) to account for at least some aspects of hemineglect in brain-damaged patients. On the hypothesis of a reciprocal interhemispheric inhibition a reduction or disappearance, rather than worsening, of hemineglect would indeed be expected following hemispheric disconnection. Extinction, i.e. the failure of subjects with unilateral brain damage to perceive stimuli on the affected side when another stimulus is concurrently presented to the normal side, can also be assumed to involve some kind of inhibition of the damaged hemisphere by the healthy hemisphere. Callosotomy experiments on monkeys with tactile extinction from unihemispheric lesions have shown that if such extinction does indeed involve an interhemispheric inhibition, the inhibition is *not* mediated by the corpus callosum, since its section leaves extinction unaffected (Eidelberg and Schwartz, 1971). Inhibitory side-to-side effects in visual orienting in cats with superior collicular lesions have been discovered by Sprague (1966) and replicated by Sherman (1977). Originally described as a reciprocal blocking influence between the superior colliculi via the intertectal commissure, this inhibition has now been attributed by Sprague and his colleagues to the action of non-commissural fibers decussating in the posterior part of the above commissure (Wallace et al., 1989).

Plasticity effects in commissurotomy experiments

Most commissurotomy experiments on interhemispheric transfer of learned responses have been carried out on adult animals, and one wonders whether immature animals might provide a more suitable model for revealing an experimental modifiability of the commissural substrates for transfer. An impressive amount of evidence from developmental behavioral studies in cats, reviewed by Berlucchi and Marzi (1982), leaves no doubt that the neural bases for the ability to transfer

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visual discriminations between the eyes are largely innate, and cannot be disrupted even by forcing the two eyes to receive asynchronous and incongrous information during the critical maturation period of the visual system. However, the interocular transfer examined in these developmental studies could not be taken as an index of interhemispheric transfer, since the experiments were performed on animals with an intact optic chiasm and a binocular visual input to each hemisphere. In recent studies on rats the interocular transfer of a spatial discrimination, presumably requiring interhemispheric communication, became apparent only after a postnatal practice period, suggesting that the substrates for interhemispheric transfer are provided not only by innate factors but also by a maturation process (Rudy and Stadler-Morris, 1987; Rudy and Paylor, 1987). Investigations on the influence of early experiential or direct manipulations of the nervous system on interhemispheric transfer are therefore in order.

Discordant results were obtained in four independent but similar experiments specifically designed to analyse the relative contribution of innate and experiential factors to the organization of the neural substrates for interhemispheric transfer in higher mammals, and more precisely to assess whether an early callosotomy can induce the utilization of alternative pathways for visual and tactual transfer. Jeeves and Wilson (1969) found no interpaw transfer of a tactile discrimination in cats with a neonatal section of the entire corpus callosum, although good transfer was observed in a cat with a neonatal incomplete callosal section presumably removing the interhemispheric connections between somesthetic cortical areas. They concluded that if a reorganization of the pathways for interhemispheric transfer is induced by an early callosal section, the section must be partial and the reorganization must affect the remaining portions of the corpus callosum itself rather than noncallosal commissures. Yamaguchi and Myers (1972) saw that forebrain commissurotomy blocked the interhemispheric transfer of brightness, color and pattern discriminations in split-chiasm macaques tested as adults, regardless of whether commissurotomy had been performed soon after birth or later in life. Ptito and Lepore (1983) compared interhemispheric transfer of visual pattern discriminations in two groups of cats, the corpus callosi of which had been sectioned at 20 days of age in one group and 45 days in the other. On anatomical and physiological criteria it was thought that maturation of the commissural connections was incomplete in the first age group and nearly complete in the second group. All cats were submitted to section of the optic chiasm and tested for interhemispheric transfer as adults. While there was no evidence for interhemispheric transfer in the group callosotomized at 45 days of age, the group with an earlier callosotomy proved to be endowed with some capacity for transfer. The hypothesis that this capacity was due to plasticity and reorganization of immature subcortical commissures pursuant to callosal disconnection must undergo further experimental confirmation and scrutiny in view of an opposite result reported by Mascetti (1983). He found that interhemispheric visual transfer was as bad in cats that had been callosotomized between the 22nd and the 28th postnatal day as in cats callosotomized as adults.

Elberger (1982, 1986) has described a series of behavioral and electrophysiological visual deficits in cats submitted to neonatal callosotomy. These deficits include a reduction in visual acuity, a reduction in cortical binocular interactions and a reduction in extent of visual field, and are probably due to the lack of a normal organizing action of the callosal connections on the functional architecture of the primary visual ,cortex. This organizing action occurs during an early postnatal period, because no such detrimental effects on visual behavior and electrophysiology occur in cats callosotomized as adults. An influence of the corpus callosum on the reorganization of the lateral visual suprasylvian cortex following early ablation of contralateral cortical areas 17, 18 and 19 has been reported by Tong et al. (1987). They found that in cats undergoing such unilateral cortical lesion at 8 weeks of age a callosal section interfered

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with the recuperation of directionally selective and binocularly driven neurons in the lateral suprasylvian area in the intact hemisphere.

Other authors have reported more general effects of early commissural sections. Sechzer et al. (1977) have argued that a neonatal callosal section in kittens results in widespread behavioral symptoms resembling those of the so-called minimal brain dysfunction syndrome in children. Denenberg (1981; see also Denenberg et al., 1986) has suggested that the corpus callosum is the agent of massive interhemispheric facilitations and inhibitions which may play a crucial role in the development of functional hemispheric specializations during the maturation of the brain in rats. Given that (a) the precise morphological brain changes attending neonatal callosotomy have not yet been worked out, (b) the possibility of a functional lateralization in the brain of non-human animals is a largely unsolved issue (see Glick, 1985; Hamilton and Vermeire, 1988, 1989), and (c) the basic physiology of the interhemispheric mechanisms presumably contributing to hemispheric specialization is unknown, the issue of the participation of the corpus callosum in the development and maturation of the rest of the central nervous system is completely open to further experimentation.

Commissurotomy effects in animal models of experimental epilepsy

Experimental epilepsy has been an active field of research in the neurosciences for well over a century (for a historical review see Moruzzi, 1950), and commissurotomy has consistently occupied a prominent position in it as an effective tool for investigating the mechanisms of epileptogenesis and the spread of epileptic activity through nervous tissue. The following discussion will be centered on the forebrain commissures and especially on the corpus callosum because of their major importance for experimental epilepsy.

It is essential to distinguish between three possible roles of the forebrain commissures in epileptic events. First, the commissures can almost instantaneously transmit epileptic discharges from a unilateral focus to healthy regions of the other hemisphere, thus arousing hypersynchronous activities in them. This is an important component of the mechanism for the generalization of an epileptic seizure. Second, if the projected discharges are prolonged and repeated, the commissures conveying them can inflict enduring damaging effects on their targets, with a resulting development of secondary autonomous foci. This induction of new foci is called secondary epileptogenesis. Third, the commissures can mediate interactions between independent foci of the two sides, usually generating a bilateral synchrony of ictal and interictal activity which increases the severity of the condition.

The role of the commissures in the rapid cross-midline projection of epileptic activities is well illustrated by the acute focal discharge model. Massive hypersynchronous firing of populations of neurons, resembling the ictal discharges of human epileptic attacks, can be promptly induced in discrete brain foci, such as circumscribed areas of neocortex or regions of hippocampus, either by direct tetanic electric stimulation or by local application of fast-acting chemical irritants. The tendency of the evoked discharges to outlast the triggering stimulus in a self-sustained fashion is expressed by the term ‘afterdischarge’. A common feature of focal epileptic seizures, long known from both clinical practice and experimental investigations, is that they can quickly propagate from their primary location not only to adjacent tissue, as exemplified by the so-called Jacksonian march, but also to quite distant regions of the nervous system. That this long-distance fast propagation occurs chiefly over specific anatomic pathways is proven by the fact that it can be blocked by cutting the appropriate connections between the primary focus and its projection targets. Basically the mechanism of the propagation does not differ from the normal orthodromic conduction and transsynaptic transmission of impulses along the affected pathways, but some contribution from antidromic excitation and ephaptic transmission is probable (see below). The interhemispheric spread of discharges and afterdischarges has been tested repeatedly before and after total or partial and selective commissurotomy.

Although early observations (reviewed by Spiegel, 1931) indicated that unilateral tetanic stimulation of the motor cortex in dogs could give rise to convulsions on both sides of the body even after a complete transection of telencephalic, diencephalic and mesencephalic commissures, suggesting that bilateralization of seizure discharges in the central nervous system normally relies on ponto-bulbar or even spinal mechanisms rather than on direct interhemispheric connections, this view was radically revised after the application of electroencephalography (EEG) to the study of experimental epilepsy. Pioneering studies by Gozzano (1935) and Moruzzi (1939) led to the discovery that EEG epileptic discharges induced in the motor cortex of one side by local application of strychnine or tetanic electric stimulation promptly spread to the contralateral motor cortex with a latency that was compatible with the conduction speed of callosal fibers. Section of the corpus callosum abolished the appearance of epileptic activities in the EEG of the motor cortex contralateral to the side of stimulation. These results were soon replicated in macaque monkeys by Erickson (1940), who showed that the intactness of the corpus callosum was indispensable for the propagation of electrically evoked EEG afterdischarges from sites in the motor cortex in one hemisphere to mirror-symmetric cortical points in the other hemisphere. In addition to the EEG findings, this conclusion was also arrived at on the basis of behavioral and cerebral blood flow indexes of convulsive activity. The behavioral analysis revealed that after the callosal section typical tonic-clonic movements were no longer bilateral. Indeed they occurred solely in muscles contralateral to the side of stimulation, in contrast with the ipsilateral side, which exhibited only tonic contractions restricted to axial and proximal muscles. In good accord with present-day views about the organization of the cortico-spinal motor systems (Kuypers, 1981), Erickson (1940) attributed the ipsilateral tonic phenomena not abolished by callosotomy to the existence of uncrossed cortical motor pathways to motoneurons for muscles of the trunk and proximal limb segments, but not to motoneurons for distal muscles.

The early discoveries of Gozzano, Moruzzi and Erickson were later extended to several animal species as well as to a variety of cortical areas, firmly establishing the principle that direct commissural pathways are the preferential if not the exclusive route for the transfer of acutely induced epileptic activities from a cortical site in one hemisphere to a corresponding site in the other hemisphere. Evidence was obtained in cats, monkeys and chimpanzees (Bailey et al., 1941, 1943; McCulloch and Garol, 1941; Garol, 1942; Rosenblueth and Cannon, 1942) for a locus-specific, usually homotopic interhemispheric transfer of epileptic discharges following unilateral strychninization or electrical stimulation of neocortical areas endowed with abundant callosal connections. This contrasted with an absence of transfer between bilateral cortical areas lacking commissural connections. Interhemispheric transfer of seizures between acallosal temporal areas linked across the midline via the neocortical component of the anterior commissure was found to be mediated by the latter commissure (Bailey et al., 1941, 1943; McCulloch and Garol 1941; Garol, 1942; Poblete et al., 1959). In this vein, the method of 'strychnine physiological neuronography', assessing the existence of direct connections between two brain regions based on the possibility of firing one region by strichninizing the other (Dusser de Barenne and McCulloch, 1939), came to be regarded as a useful complement to classical neurohistology for mapping the exact origin and termination of callosal and other commissural fibers within various neural centers.

The chief contribution of the forebrain commissures to the contralateral spread of epileptic discharges was also demonstrated in com-

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missurotomy studies employing gradually developing unilateral foci generated by the local application of slowly acting irritants such as aluminum hydroxide (e.g. Kopeloff et al., 1950) and penicillin (e.g. Isaacson et al., 1971), as well as in the reflex epilepsy model. Reflex epilepsy is usually induced through the summation of natural peripheral stimuli in one modality with subliminal local strychninization of the primary receiving cortical area in the same modality (Moruzzi, 1950). In a much-studied model of reflex epilepsy, the photosensitive baboon *Papio papio*, treatment of the cortex is not required for the triggering of seizures because of an inherent, probably innate epileptogenic tendency of the frontorolandic cortex. An ictal EEG symptomatology can be unleashed in this species by a 15 Hz intermittent light stimulation, and includes bisymmetrical and bisynchronous spike-and-waves, polyspikes and waves initially restricted to the frontorolandic cortex but subsequently diffusing to subcortical centers and other cortical areas. Generalized seizures which tend to outlast the light stimulation and eventually to recur spontaneously are thus generated, and are accompanied by myoclonic ocular, facial, collic and somatic contractions which may possibly give way to a grand-mal attack. Fukuda et al. (1988) saw that bilateral and bisynchronous EEG seizures could be precipitated by appropriate light stimulations in baboons with intact forebrain commissures, regardless of whether stimulation was delivered to the full visual field an thus to both hemispheres, or restricted to the right or left visual field and thus channeled into the contralateral hemisphere. Section of the anterior two-thirds of the corpus callosum and hippocampal commissure did not change the bilateral EEG pattern of photosensitive epilepsy upon full field stimulation; however, separate stimulation of each visual hemifield largely confined seizures to the contralateral hemisphere. It follows that upon stimulation of a single hemifield in intact baboons the anterior corpus callosum and possibly the hippocampal commissure are instrumental for projecting the seizure from the hemisphere receiving the visual input to the other hemisphere (Fukuda et al., 1988).

The old claim that the interhemispheric spread of epileptic events in the acute unilateral focus model may utilize extracommissural pathways (Spiegel, 1931) was reaffirmed based on findings of persisting contralateral afterdischarges in callosotomized cats after unilateral electric tetanization of motor (Hoefer and Pool, 1943) and ectosylvian cortex (Straw and Mitchell, 1967). The occurrence of an extracommissural interhemispheric spread after callosotomy might well depend on a very high intensity of the epileptic discharge (Hoefer and Poole, 1943), but in the case of the ectosylvian cortex it is likely that a noncallosal but commissural transfer was mediated by additional interhemispheric connections via the anterior commissure (Straw and Mitchel, 1967). A possible extracommissural pathway for the interhemispheric projection of epileptic discharges in the cat has been suggested by the discovery of an interhemispheric delayed response evoked in a cortical point by a single-shock stimulation of the corresponding point in the contralateral cortex. The response persists after a callosal section and is probably mediated by a multisynaptic pathway that may course through the brainstem reticular formation (Rutledge and Kennedy, 1960, 1961). However, the interhemispheric delayed response appears to be largely restricted to cortical regions in the suprasylvian gyri, thus making it unlikely that the pathway subserving it is an important component in the mechanisms for the interhemispheric propagation of epileptic discharges to all other cortical areas. Alternative cortical-subcortical-cortical routes for an interhemispheric epileptic spread in the absence of the forebrain commissures have also been suggested in other species (Isaacson et al., 1971; Nie et al., 1974) and in other experimental conditions (Kusske and Rush, 1978).

Secondary epileptogenesis can usually be subdivided into three stages: a first stage in which discharges at the secondary site are simple, synaptically mediated, responses to abnormal volleys from the discharging primary focus, as described previously; a second stage in which abnormal electrogenesis begins to develop at the secondary site, even in the absence of seizures within the primary focus, but subsides permanently following removal of the latter focus; and a final stage in which epileptic activity within the secondary site, now secondary focus, can no longer be suppressed by removing the primary focus or by disconnecting the two foci (see Moruzzi, 1950; Morrell, 1960, 1985). For still unknown reasons, secondary epileptogenesis is very often mediated in all its stages by interhemispheric pathways, and in accord with the predominantly homotopic character of these connections the most frequent localization of a secondary focus is at a specular position across the midline from the primary focus: the mirror focus. Among the interhemispheric pathways, the corpus callosum is a preferred route for the generation of a mirror focus in the hemisphere contralateral to that containing the primary focus, as proven by the fact that callosotomy performed soon after the establishment of the primary focus can prevent the development of a mirror focus, while a later callosotomy cannot (Morrell, 1960, 1985; McQueen and Dow, 1979). The hypothetical participation of non-commissural immunity-dependent mechanisms in the genesis of mirror foci (Ettlinger, 1979) is still to be proven.

Conceptually similar to secondary epileptogenesis is kindling. In this model, originally proposed by Goddard (1967, 1983; Goddard et al., 1969; see also Racine 1972a,b; Racine et al., 1972), an enduring predisposition to epilepsy is engendered by the stimulation of discrete telencephalic and diencephalic sites with recurring trains of electrical pulses of constant intensity. Although initially these stimuli are not strong enough to bring about behavioral or electric signs of epilepsy, they become overtly epileptogenic in the course of several days as a result of repeated intermittent applications separated by one or two days. Kindling stimulation is most effective within the limbic system, particularly in the amygdala and the hippocampus. The development of kindling is signalled by a gradual propagation of the electrical afterdischarge from the kindled site to increasingly more diffuse portions of cortex and subcortical centers, as well as by a progression of behavioral symptoms from focal to generalized, e.g. from facial twitching, head-turning and circling to jumping and standing, and eventually to falling down with diffuse clonic or clonic-tonic-clonic convulsions. Complete or even partial commissurotomies have been repeatedly observed to prevent or retard the bilateralization of electrical and clinical ictal phenomena evoked from a unilateral kindling site in rats (McCaughran et al., 1977, 1978; McIntyre and Stuckey, 1984; McIntyre et al., 1986; McIntyre and Edson, 1987), cats (Wada and Sato, 1975; Wada et al., 1982; Fukuda et al., 1987; Hiyoshi and Wada, 1988a,b), baboons (Wada and Mizoguchi, 1984; Wada and Komai, 1985) and macaques (Wada et al., 1978 , 1981). A positive interhemispheric transfer effect of kindling consists in a facilitation of kindling of a unilateral site such as the amygdala after kindling of the corresponding contralateral site. In contrast with the generation of cortical mirror foci, the interhemispheric transfer of kindling at limbic sites does *not* utilize the corpus callosum, but rather the hippocampal commissure (McIntyre and Edson, 1987; Fukuda et al., 1987) and/or the thalamic massa intermedia (Hiyoshi and Wada, 1988a,b). However, in the generalized seizures induced by kindling limbic stimulations a callosal section reduced the bilaterality and severity of ictal phenomena (Wada and Komai, 1985).

In the model with bilateral foci, if two independent epileptic foci are active in bilateral cortical sites interconnected by direct commissural pathways, mutual facilitation mediated by these pathways should be expected to result in an interfocal synchronization of epileptic discharges. Mattson and Bickford (1961) were the first to confirm this expectation by showing that pairs of epileptic foci acutely established by strychnine application in corresponding points of the two hemispheres of the cat cortex tended to produce bilaterally synchronous EEG spikes. Bilateral synchrony depended on a precise spatial symmetry between the foci and was disrupted by sectioning the corpus callosum. However, bilateral EEG coupling could be reestablished after callosotomy by increasing the depth of barbiturate anesthesia, obviously because of the recruitment of unknown extracallosal mechanisms for interhemispheric synchronization. The corpus callosum has long been suspected to be involved in the fine bilateral synchronization of normal EEG activities (Bremer and Stoupel, 1957; Berlucchi, 1966), but not in the gross bilateral symmetry of the EEG signs of the sleep-wake cycle (Berlucchi, 1966; Batini et al., 1967). Recent work on coherence patterns of the sleep EEG in infants with agenesis of the corpus callosum is in line with the old animal findings (Kuks et al., 1987).

The model with symmetrical foci has been most extensively utilized by Marcus and his associates (Marcus and Watson, 1966, 1968; Marcus et al., 1968; Marcus, 1985) in cats and monkeys with bilateral and symmetric topical application of estrogens or other fast-acting convulsants to several pairs of cortical areas. The resulting bilateral spike-slow wave complexes were found to be well synchronized in pairs of areas with abundant commissural connections, such as the frontal, precentral and parietal areas in monkeys, whereas in the same animals bilateral synchrony was less pronounced or absent in pairs of areas with few commissural connections, such as the primary visual cortex or the middle superior temporal area. In both cats and monkeys section of the forebrain commissures left each side with the capacity to produce independent discharges, but the discharges of the two sides were largely asynchronous. Occasional bilateral couplings of EEG spikes seen after complete forebrain commissurotomy were on a much coarser temporal scale than before commissurotomy: 40 – 200 ms as opposed to 0 – 20 ms (Marcus, 1985). In both cats and monkeys good and persistent bilateral synchrony was noted between EEG discharges of opposite foci established in cortical slabs surgically isolated from subcortical centers, but maintaining reciprocal interconnections via an intact corpus callosum. The dominant role played by the corpus callosum in the interactions between bilateral cortical foci was also supported by the failure of large diencephalic and mesencephalic lesions to disrupt bilateral synchrony of discharges in the presence of intact commissures (Marcus and Watson, 1966; Marcus et al., 1968; Marcus, 1985).

Results comparable with those of Marcus and coworkers were obtained by Isaacson et al. (1971) in rats with bilateral implants of penicillin into the cortex. Spike discharges in the two hemispheres were correlated within 20 ms of each other, the leading spike originating at random from either hemisphere. After a complete callosal section spike discharges from the two hemispheres became asynchronous and remained so for 75 minutes. Afterwards bilateral synchrony tended to reappear, but the time between correlated discharges in the two hemispheres increased to 80 – 100 ms. Musgrave and Gloor (1980) similarly described an uncoupling by callosotomy of bilateral epileptic activities induced by systemic injection of penicillin in cats.

However, there must exist a neural substrate for the partial synchronization of discharges of bilateral foci which occurs in commissurotomized animals. Ottino et al. (1971) proposed a thalamic and/or midbrain reticular substrate for this function. They established parallel foci in the sensorimotor cortex (anterior sigmoid gyrus) of the two sides of cats by local application of penicillin and/or strychnine. The continuous bilateral synchrony of discharges characterizing the preparation with intact commissures was markedly disrupted by severing the corpus callosum and the hippocampal commissure. The inconstant bilateral synchrony seen after this operation – covering on average 13% of the recording time – depended on a high intensity of the focal discharges, as signalled by the amplitude and frequency of the EEG epileptiform waves and by the appearance of clonic contractions of the limbs, as well as on a spread of the seizures from cortex to ipsilateral intralaminar thalamic nuclei and midbrain reticular formation. Bilateral synchrony was further reduced by an additional section of the anterior commissure and midline division of thalamus and hypothalamus, and permanently abolished by splitting the midbrain tectum and tegmentum.

A model with bilateral *asymmetric* foci, involving cortical sites not directly connected by commissural pathways, has been employed by Mutani and coworkers in cats (Mutani et al., 1972, 1973; Mutani and Durelli, 1980). Acute foci were induced by local applicaton of conjugated estrogens to the sigmoid gyrus on one side and the lateral gyrus on the other (Mutani et al., 1972; Mutani and Durelli, 1980); chronic foci were induced with intracortical injections of cobalt-alumina into the same areas (Mutani et al., 1973). While bilateral asynchrony was the rule for discharges from acute foci (Mutani et al., 1972; Mutani and Durelli, 1980), a clear-cut electric coupling between chronic foci of the two sides began to develop 5 – 7 days following treatment and became complete within 20 – 25 days. Each side could lead the other in random alternation by a time lag of 50 – 100 ms (Mutani et al., 1973). In keeping with the results with symmetric foci (Marcus, 1985), the bilateral coupling between asymmetric foci was lost upon sectioning the corpus callosum and the hippocampal commissure. The physiological mechanisms for this interhemispheric coupling between cortical areas lacking *direct* commissural connections remain to be clarified.

In summary, animal models of experimental epilepsy indicate that forebrain commissurotomy can (1) hinder the immediate bilateralization of initially unilateral seizures, (2) abolish or reduce the transhemispheric secondary epileptogenesis, i.e. the establishment of secondary mirror foci, and (3) decrease the severity of seizures in cases of bilateral symmetric or asymmetric foci by disrupting bilateral synergy and synchrony. To the extent that the results from animal models of experimental epilepsy are applicable to epilepsy in man, these effects of commissurotomy justify the employment of this surgical procedure for controlling drug-resistant forms of the disease in human patients. However, in addition to beneficial effects of callosotomy, the findings from models of experimental epilepsy may also reveal some limited adverse effects of the operation (e.g. Mutani and Durelli, 1980; Wada and Komai, 1985). While on balance the experimental evidence suggests that callosotomy may reasonably be regarded as a definite therapeutic possibility in carefully selected cases of human epilepsy, the final word on the advisability of its employment on a large scale will have to come from further clinical trials (e.g. Spencer, 1988).

In the present context it may be worthwhile to consider the possible cellular mechanisms which underlie commissurotomy effects in models of experimental epilepsy. As already mentioned, electrophysiological evidence undoubtedly indicates that callosal neurons are in all cases facilitatory to their immediate target neurons (Naito et al., 1970; Toyama et al., 1974; Innocenti, 1986), a characteristic which can reasonably be extrapolated to neurons of the anterior and hippocampal commissures. Callosal neurons most probably use excitatory amino acids as transmitters (Barbaresi et al., 1987; Conti et al., 1988). The various types of cortical neuron that project to the corpus callosum do not include the non-spiny stellate neurons belonging to the major GABAergic category of inhibitory cortical elements (Voigt et al., 1988). Inhibition of cortical neurons by callosal afferents can of course be mediated by interneurons (Naito et al., 1970; Toyama et al., 1974; Innocenti, 1986). Many callosal fibers give rise to recurrent collaterals which return to the cortex containing their parent cell bodies, and these collaterals may exert both inhibitory (Feeney and Orem, 1971) and facilitatory effects (Spidalieri et al., 1986). The conduction along callosal fibers of impulses underlying projected epileptic discharges is usually orthodromic, but there is some indication that callosal fibers terminating in, or running through, an epileptic focus can also be stimulated antidromically (Schwartzkroin et al., 1975). On these grounds, the following speculations can be offered. (1) The interhemispheric projection of epileptic discharges and the synchronization of bilateral epileptic activities can be ascribed to orthodromic transmission of predominantly facilitating callosal influences. (2) Occasional increases in partial epileptic seizures following callosal section (e.g. Mutani and Durelli, 1980; Wada and Komai, 1985; Spencer et al., 1988) may be due to a functional suppression of inhibitory recurrent actions of callosal fibers pursuant to axotomic depression of neurons projecting to the corpus callosum. (3) Secondary epileptogenesis may derive not from impulse conduction along commissural fibers, but from a secretion of toxic factors by these fibers. The establishment of mirror foci has indeed been reported to occur when axonal flow along callosal fibers is normal, but impulse generation is chemically prevented (Morrell, 1985). Experiments prompted by these speculations can increase our knowledge of both physiological and pathophysiological mechanisms of commissural activities.

Epilogue

The two facets of research on the effects of commissurotomy in animals – one concerned with physiological hemispheric interactions and the other with pathological epileptic mechanisms – are not as disparate as it may seem at first sight. It is a truism, but nevertheless true, that in every epoch of science researchers tend to produce results that fit the systems of ideas prevailing in the contemporary scientific community. When many decades ago the neuroscientific community seemed ready to substitute central nervous system models couched in terms of orthodox anatomical circuitry with field theories borrowed from physics, the alleged absence of dysfunctions produced by commissural section was as much a product of that frame of mind as an inspiration for it. Convinced that neural integration must be carried out *solely* by diffuse networks of short-axoned neurons, Lashley affirmed in 1951: "There are, of course, long association tracts in the cortex, such as the corpus callosum, the superior longitudinal fasciculus, and the temporo-frontal tracts. Once, 26 years ago, I suggested facetiously that these might be only skeletal structures, since I could find no function for them. No important functions of these tracts have yet been demonstrated. Section of the corpus callosum produces only a slight slowing of reaction time, ipsilateral as well as contralateral (Akelaitis, 1941) . . .".

Yet the patients studied by Akelaitis had had their forebrain commissures surgically transected, in an attempt to control their severe epileptic conditions, because animal experiments had already substantiated the involvement of the great cerebral commissures in the propagation of epileptic seizures. The latter notion was so solidly entrenched in neurological thinking that McCulloch could write in 1949: "I have laughingly said that, so far as I can see, it is the only demonstrable function of the corpus callosum, to spread seizures from one side to the other. I still do not know of anything else we can attribute to it safely." However, well before the times of Lashley and McCulloch's writings neurophysiologists had collected strong evidence that the separation between physiological and abnormal, epileptic, activities of the commissures was artificial and unwise, if not downright wrong. In 1939 Moruzzi had clearly shown in the rabbit that the masticatory cortex of each side normally exerted a physiological facilitatory action on the corresponding contralateral cortex via the corpus callosum, and had convincingly argued that the transhemispheric spread of epileptic discharges between the masticatory cortices of the two sides was due merely to an exaggerated intensification of the normal callosal activity. The fundamental notion that physiological and epileptogenic commissural actions differed in degree rather than kind, and that there could be a gradual transition between the two types of action, was extended to the entire cortex by Bremer (see Bremer et al., 1956) and elaborated into a conception of the forebrain commissures as key elements in the 'cerebral dynamogenesis'.

These germs for a paradigmatic shift in the way of thinking about commissural function were brought to fruition when Sperry, a staunch advocate of brain models founded on a strict selectivity of connections, and his student Myers combined proper behavioral tests with good neurosurgical techniques for linking the interhemispheric transfer of habits with specific commissural pathways in animals. From this Sperry and his colleagues went on to show that commissural section in epileptic human patients blocks normal interhemispheric communication as well as transhemispheric generalization of seizures. While the spectacular success, both clinical and scientific, of commissurotomy work on man is dealt with in other chapters of this volume, it is this writer's hope that the present review can provide the reader not with a complete survey of the field of commissurotomy studies in animals, which would be impossible anyway, but just with an impression of the magnitude and richness of the developments that have occurred in the 36 years following Myers and Sperry's publication of 1953. If, however, the review is to end on an advisory note, the message is that the search for the functional significance of the commissures and its place in an overall theory of the brain has still a long way to go, and the experimental uses of commissurotomy are by no means exhausted. Hypotheses about hemispheric interaction will have to be increasingly inspired by anatomy, physiology, neurochemistry, and even molecular biology, rather than by analysis of behavioral commissurotomy effects, but the latter analysis will continue to serve as the ultimate test of every assumption about commissural function.

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