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"Corpus Callosum and Simple Visuomotor Integration"

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CORPUS CALLOSUM AND SIMPLE VISUOMOTOR INTEGRATION*

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Abstract—Malcolm Jeeves was the first to demonstrate lengthened interhemispheric transmission times in subjects with agenesis of the corpus callosum by using a simple reaction time paradigm with lateralized unstructured light stimuli and crossed and uncrossed hand responses. Uncrossed responses can be integrated within one hemisphere, whereas crossed responses require a communication between the two hemispheres. In the normal brain this communication is effected rapidly by the corpus callosum, whereas in the acallosal brain it must occur much more slowly by way of less efficient alternative interhemispheric pathways. Using a similar experimental paradigm we have studied normal subjects, subjects with a complete callosal agenesis and epileptic patients with surgical callosal sections, either complete or partial. All subjects with complete callosal defects showed much lengthened interhemispheric times compared to normal controls. Virtually normal interhemispheric transmission times were found in subjects with partial callosal defects, whether anterior or posterior, suggesting a possible equipotentiality of different portions of the corpus callosum in the mediation of crossed manual responses. In both normals and acallosals there were no crossed–uncrossed differences in reaction time when responses were made unilaterally with lower limb effectors or para-axial upper limb effectors, as well as bilaterally with upper-limb proximal and para-axial effectors. Since these effectors can be controlled directly from either side of the brain via bilaterally distributed motor pathways, crossed responses using them, unlike crossed manual responses, do not require an interhemispheric integration.

Key Words: corpus callosum; callosal agenesis; split-brain; visuomotor integration; bilateral motor coordination.

INTRODUCTION

The corpus callosum is by far the largest fiber tract in the brain of placental mammals. It provides the most direct anatomofunctional link between the neocortical areas of the two hemispheres. Its physiological significance has been revealed by the epoch-making studies of Roger Sperry on the behavioral and psychological effects of sectioning the corpus callosum in experimental animals as well as in patients submitted to callosotomy for the treatment of otherwise uncontrollable epileptic conditions [62]. Each of the disconnected hemispheres can be shown to retain all or most of its functional abilities and specializations, but percepts and memories engendered in one hemisphere are generally excluded from the

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*This paper is dedicated to Professor Malcolm A. Jeeves, CBE, FRSE.

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conscious awareness of the other hemisphere. "Split-brain" patients can be said to possess two largely separate and independent neural systems for cognition, one of which is specialized for linguistic, analytic and sequential processing and resides in the left hemisphere, whereas the other is specialized for non-verbal, holistic and parallel processing and dwells in the right hemisphere. The integrative action of the corpus callosum is indispensable for the unification of these specialized processes in the normal brain [62].

In stark contrast with callosotomy patients, subjects with an inborn lack (agenesis) of the corpus callosum do not exhibit the most conspicuous signs of interhemispheric disconnection which become apparent after callosal section. In the absence of accompanying extracallosal malformations of the nervous system, the behavioral and psychological performance of callosal agenesis subjects seems so close to normal to suggest that, unlike in patients with acquired callosal defects, the ordinary functions of the corpus callosum can be fully substituted by alternative mechanisms which have become adapted for efficient interhemispheric communication. Due chiefly to the methodic and ingenious work of Malcolm Jeeves [31], it is now known that compensatory mechanisms in callosal agenesis, though quite powerful, are also far from complete, such that residual, usually subtle but systematic deficits of hemispheric interaction can be disclosed with appropriate specific tests. In addition to allowing an assessment of the limits of the adaptation of the brain to callosal agenesis, the analysis of these deficits affords basic information complementary to that gained from split-brain studies, thus casting further light on the normal functions of the corpus callosum.

SIMPLE REACTION TIME AS A MEANS TO STUDY INTERHEMISPHERIC COMMUNICATION

In one of his most productive lines of investigation, Jeeves has asked the question of how the brain, and particularly the acallosal brain, translates a visual input directed to one hemisphere into a motor response emitted by the other hemisphere. He has done so especially by examining elementary instances of visually guided behavior in which the visual stimulus merely acts as a trigger for simple ballistic motor responses. At least the fastest of these forms of visuomotor integration are likely to depend on relatively fixed and straightforward connections between visual and motor centers, at both cortical and subcortical levels. In 1969 Jeeves [30] published the results of the first comparison between callosal agenesis subjects and normal controls in a simple reaction time task (RT) based on the Poffenberger paradigm. Poffenberger [53] had shown in normal subjects that RT to a brief flash of light presented to one hemifield, and thus projected to the contralateral hemisphere, is shorter for responses made with the hand ipsilateral to the stimulus (uncrossed responses) than for responses made with the other hand (crossed responses). As argued by Poffenberger [53], the simplest explanation for this effect is offered by neuroanatomy: since spinal motoneurons for hand movements are controlled by the contralateral motor cortex, uncrossed responses can be directly initiated by the hemisphere receiving the visual stimulus, whereas crossed responses should call for a time-consuming transfer of information between the hemisphere receiving the visual input and that controlling the responding hand. In the normal brain, the interhemispheric transfer should be rapidly effected by the corpus callosum, and the difference between crossed and uncrossed responses (CUD for short) should thus be regarded as a measure of callosal interhemispheric transfer time.

Accordingly, Jeeves predicted that the CUD should be considerably greater in callosal agenesis subjects than in normal subjects, since transfer of information along indirect extracallosal pathways for cross-midline intercortical communication is bound to be less efficient and expeditious than the direct callosal transfer. The prediction was confirmed by his original finding that while the mean CUD in six groups of normal subjects varied between 1.3 and about 3.0 msec, three callosal agenesis subjects had CUDs of 19.5, 14.5 and 61.3 msec, that is well outside the normal range [30].

The findings of a small but significant CUD in normals and a much larger CUD in subjects with callosal agenesis have been repeatedly confirmed in Jeeves' laboratory and many other laboratories alike [4, 6, 11–13, 18, 19, 23, 24, 40, 42, 43, 45–48, 55, 58, 61, 64, 67, 72; for other studies see the review by Bashore, 8]. In normal subjects, the CUD has been found to be relatively constant despite gross variations in the strength of visual input, as can be induced by changes in light intensity and stimulus eccentricity, suggesting that callosal interhemispheric transfer time may be invariant [3, 11, 12, 46, 48]. This statement requires some qualifications. When CUDs assessed with the Poffenberger paradigm are equated with interhemispheric transfer time, it should be made clear that the equation is valid only for the specific type of visuomotor integration required by the paradigm, i.e. the performance of simple manual RTs to lateralized unstructured visual stimuli. The range of fiber diameters in the human corpus callosum is enormous—from a fraction of μm to 6–8 μm—and a non-negligible percentage of the population—from 5 to 40%—is made up by non-myelinated fibers [1, 56]. Theoretical calculations by Ringo *et al.* [56] indicate that conduction times along callosal fibers may vary from less than 5 msec up to 300 msec, depending on fiber length and diameter, and presence or absence of a myelin sheath. Thus callosal transfer time as measured in the Poffenberger paradigm appears to be an instance of the fastest possible interhemispheric communication. We do not know whether callosal fibers with different sizes have different functions, but there is no doubt that very different estimates of interhemispheric transfer time can be obtained with different experimental tasks which require more elaborate cognitive decisions and motor performances, and, consequently, more complex exchanges between the cerebral hemispheres. However, such estimates are liable to be contaminated by the influence of complicating factors such as stimulus–response compatibility, hemispheric specialization, attentional biases, and the like [8]. For example, if a choice between hands must precede a speeded manual response to a lateralized light stimulus, the spatial stimulus–response compatibility effect does not allow one to assess the interhemispheric transfer time [6, 11]. On the contrary, go–no go RT paradigms with lateralized stimuli, which do not require a choice between the hands, have yielded estimates of interhemispheric transfer time comparable to those obtained with the typical Poffenberger paradigm [6, 11, 18].

In what follows we will review a number of our own and other studies which have used lateralized stimuli for examining the role of interhemispheric transfer in various types of visuomotor integration in both normal and acallosal subjects.

INTERHEMISPHERIC TRANSFER AND THE ORGANIZATION OF THE MOTOR SYSTEMS

The Poffenberger paradigm is based on the assumption of a complete crossing of the motor pathways mediating the response. In fact only a few types of movements on one side of the body are controlled exclusively by the opposite hemisphere. Experiments in man and non-human primates suggest that a strictly contralateral control via crossed cortico-spinal pathways is required solely for the fractionated motility of the distal extremities, especially the fingers. Axial and proximal limb muscles involved in global body movements, general postural adjustments, and integrated synergistic limb–body movements are instead under the control of bilaterally distributed motor systems, such that each hemisphere can activate these muscles on either side of the body without the assistance of the corpus callosum or other interhemispheric pathways [9, 16, 21, 36, 37, 39, 41, 49]. Thus it is possible in principle that the Poffenberger paradigm fails to yield CUDs with responses made with these effectors, since crossed as well as uncrossed responses can be initiated by the hemisphere receiving the flash. Di Stefano *et al.* [23] compared in normal subjects the CUD on a distal response, consisting in a keypress by a flexion of the thumb, with the CUD on a proximal response, consisting in a leverpull by a flexion of the forearm. They found indistinguishable significant CUDs for both types of response, but only when the responses were made unilaterally. A comparable result was reported by Milner [47] who found no differences in the CUD between a finger–thumb apposition response and an index lifting response presumably involving a movement of the whole hand. By contrast, Di Stefano *et al.* [23] described an abolition of the CUD on proximal responses (but not on distal responses) when such responses were executed bilaterally in reaction to a single lateralized flash. it would appear therefore that unilateral crossed responses to the flash, both distal and proximal, are elicited from the contralateral motor cortex and thus require an interhemispheric integration; in contrast, bilateral proximal responses to a lateralized flash are actuated by a bilaterally distributed motor system which ensures an approximate simultaneity of crossed and uncrossed reactions without the aid of interhemispheric integration. Further, a complete absence of a significant CUD was found when the response consisted in a unilateral elevation of the shoulder (Aglioti *et al.*, unpublished), suggesting the possibility of a bilateral control of this response even when made unilaterally. Congruent with this interpretation is the finding that during unilateral shoulder movements there is a bilateral motor cortex activation, as indexed by local increases in blood flow, in contrast with the unilateral motor cortical activations associated with movements of the contralateral hand or digits [20].

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One can thus distinguish between two classes of responses on the basis of the presence or absence of a significant CUD. One class includes unilateral and bilateral distal responses and unilateral proximal responses of the upper limb, which being associated with significant CUDs presumably require interhemispheric cooperation in the crossed condition. The other class includes bilateral proximal responses and unilateral and bilateral axial responses of the upper limb, which being associated with null CUDs presumably never require an interhemispheric cooperation. The prediction following from this distinction is that impairment of interhemispheric transfer by callosal defects should considerably increase the CUDs associated with the first class of responses, while it should not alter the null CUDs associated with the second class of responses.

We have tested this prediction in a male patient with a complete section of the corpus callosum, aged 20–21 years at the time of testing, as well as in two male subjects with a total callosal agenesis. The first subject, born in 1970, was submitted to a complete section of the corpus callosum at the Neurosurgical Institute of the Catholic University in Rome (Prof. G. F. Rossi). Callosotomy was performed in two stages (February and June 1989) in an attempt to control a form of post-traumatic epilepsy with complex partial seizures and secondary generalization which had proved totally resistant to pharmacological therapy as well as to a removal of a focus in the right prefrontal cortex. Callostotomy has resulted in a marked favorable change in both severity and frequency of the seizures. Pharmacological treatment with Phenobarbital and Phenytoin has been continued throughout the postoperative period. The other two subjects have been diagnosed by MRI as congenitally lacking the corpus callosum. At the time of testing they were 16 and 31 years old, were free from major neurological symptoms and appeared to have normal intelligence.

Earlier assessments of CUDs for unilateral manual responses in commissurotomy patients had yielded CUD values even greater than those of callosal agenesis subjects [19, 61]. We confirmed these results in our completely callosotomized subject, who showed CUDs on unilateral and bilateral distal responses and on unilateral proximal responses that were at least an order of magnitude greater than the typical 2–3 msec corresponding CUDs of normal subjects. However, in the conditions which yielded null CUDs in normal subjects [23], i.e. bilateral proximal responses and both unilateral and bilateral axial responses, this subject also exhibited insignificant or downright null CUDs [3, 10, 13]. The pattern of CUDs in the two callosal agenesis subjects agreed with that of the callosotomy patient insofar as the CUD tended to decrease along a distal–proximal–axial gradient, and to be greater for unilateral than for bilateral responses [3].

It has been suggested that long CUDs of acallosal subjects are due to spatial stimulus–response compatibility rather than the absence of the corpus callosum [35]. Spatial compatibility effects are observed in tasks in which the subject has to choose between hands before responding to a lateralized stimulus the side of which is unpredictable. They consist in a speed advantage for responding when stimulus and response are matched for side, as compared to responding when the sides of stimulus and response are opposite, regardless of whether each hand responds in the ipsilateral or contralateral hemispace [see 71]. In simple RT tasks in which the same hand is used in one block of trials, thus eliminating the task of choosing response effectors, CUDs in normals [6, 11], callosal agenetics [43, 45] and partial callosotomy patients [24] remain the same regardless of whether each hand responds in the ipsilateral or contralateral hemispace, hence these CUDs are based on anatomy rather than spatial compatibility. This conclusion has been extended to our patient with complete callosotomy by showing that his CUD on unilateral manual responses was also unaffected by the spatial relations between the position of the visual stimulus and that of the responding hand [3, 10, 13]. Moreover, electromyographic recordings from prime movers showed that CUDs in this patient were entirely accounted for by cross–uncrossed differences in premotor times, meaning that they arose prior to the activation of motoneurons [3, 13].

Several considerations suggest that the long crossed manual responses of acallosals are best explained by an extracallosal interhemispheric transfer [3, 19, 44–46, 48]. The anterior commissure does not seem to be involved in the transfer because CUDs are no shorter in acallosal subjects with an intact anterior commissure than in subjects with a section of both callosum and anterior commissure [3, 19, 44, 61]. The extracallosal transfer appears to occur by way of subcortical commissures and other brainstem routes for indirect communication between the cortices of the two sides. These indirect cross-midline routes have been postulated to account for other aspects of interhemispheric interaction in visually guided behavior which persist in callosal agenesis and after forebrain commissurotomy [15, 25, 28, 50, 59, 60, 68].

CROSSED–UNCROSSED DIFFERENCES IN FOOT RESPONSES

Aglioti *et al.* [4] measured R of a distal foot response (a plantar flexion of the big toe) to lateralized light stimuli in two groups of normal subjects ($N = 48$ and 12, respectively). The CUDs found in the two groups were 0.90 and 0.85 msec; both values were not significantly different from 0. The first group was also tested with a manual response, and the test yielded a significant CUD of 7.4 msec. According to the argument put forward in the previous section, the failure of Aglioti *et al.* [4] to find a significant CUD for distal foot movements suggests that these muscles, unlike distal hand movements, enjoy a bilateral motor control, and thus can be activated from the ipsilateral hemisphere as rapidly as from the contralateral hemisphere without the aid of the corpus callosum. The possibility that central motor pathways for distal foot movements are bilaterally distributed is also suggested by clinical evidence that after extensive motor cortex lesions sparing or recovery of motility is possible for both distal and proximal muscles of the contralesional lower limb, but only for proximal muscles of the contralesional upper limb [2, 21]. This finding is congruent with the notion that an intact hemisphere can exert a full motor control over the ipsilateral lower limb, as opposed to a control limited to proximal muscles in the upper limb. All these data make one predict an absence of a significant CUD for foot responses in acallosal subjects, but in a preliminary experiment on our completely callosotomized the CUD for distal foot responses was almost as great as that for manual responses (Aglioti *et al.*, unpublished). The reasons for this discrepancy are under investigation.

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ASYMMETRY IN CALLOSAL TRANSFER

Marzi *et al.* [42] have done a metanalysis of 16 studies reporting CUDs for manual responses in normal right-handers. After subdividing the CUDs into their components and conflating that data across studies, they found that the advantage for uncrossed over crossed responses was significantly larger for the right visual field (5.8 msec) than for the left visual field (2 msec), and significantly larger for the left hand (5.3 msec) than for the right hand (2.3 msec). Further, the differences between CUD components were shown to be accompanied by a significant advantage of the left hemifield over the right, and a significant advantage of the right hand over the left. These hemifield and hand asymmetries were first reported by Jeeves and Dixon [32] and Jeeves [30], who attributed them to a superiority of the right hemisphere for light detection and the left hemisphere for motor output. The differences in CUD components analyzed by Marzi *et al.* might in principle be caused by the pattern of hemispheric asymmetries suggested by Jeeves and Dixon [32] and Jeeves [30], but an alternative explanation has been offered by Marzi *et al.* [42]. According to their argument the differences between CUD components may depend on a slight asymmetry in callosal transfer, the transfer being faster from the right hemisphere to the left than in the opposite direction. In a metanalytic examination of the literature Marzi *et al.* have found no evidence for similar directional asymmetries between CUD components in left-handers as well as in subjects with total congenital or acquired absence of the corpus callosum [40]. As it stands this evidence suggests that the corpus callosum is responsible for the hypothesized asymmetry in interhemispheric transfer found in normal right-handers, but it must be corroborated with further studies because the samples of acallosal subjects so far examined are much smaller than those drawn from the normal right-handed population. A step in this direction has been taken

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by Bisiacchi *et al.*, who have confirmed the left–right asymmetry of callosal transfer in normal human subjects [14].

Meanwhile the hypothesis of an asymmetric callosal transfer receives support from electrophysiological investigations. In a recent metanalysis of 18 experiments in which interhemispheric transfer time was assessed with visual evoked potentials, Brown *et al.* [17] found a significant faster transfer in the right-to-left direction than in the contrary direction. Twelve out of the 18 experiments showed a faster right-to-left transfer, the advantage over the opposite transfer ranging from 2 to 16 msec. The asymmetry in transfer could not be related to a systematic asymmetry between visual fields. Further, Brown *et al.* [17] confirmed the asymmetrical transfer by recording potentials evoked at parietal sites by visual stimuli during the performance of a letter recognition task.

Since the tasks employed in the experiments on visual evoked potentials are usually different from and more complex than the simple Poffenberger paradigm used for assessing CUDs, one cannot be certain that the transfer asymmetries found in electrophysiological data correspond to the transfer asymmetries suggested by RT data. If the asymmetry in interhemispheric transfer suggested by the differences in the CUD components and evoked potentials is indeed related to a better capacity of the corpus callosum to transmit the relevant signals from right to left than in the opposite direction, then it becomes important to look for possible anatomical substrates of the hypothesized directional asymmetry in callosal transfer. The examination of the anatomical organization of major projection tracts, such as the pyramidal tracts, in the human nervous system has revealed systematic side asymmetries which can be at least tentatively related to functional right–left asymmetries like handedness [51]. While it is possible in principle that at least for certain cortical areas the callosal projections originating from one hemisphere are more numerous than those originating from the other hemisphere, the task of demonstrating such asymmetries in the human corpus callosum does not seem feasible at present.

SYNCHRONIZATION OF BILATERAL RESPONSES

Another pioneering contribution by Jeeves to the understanding of the neural bases of simple visuomotor integration comes from a study of RT of *bilateral* symmetric responses. He found that CUDs were still present in normal subjects as well as callosal agenetics when they responded *bimanually* to a single lateralized flash [30]. This finding, which was replicated in subsequent investigations [23, 45], is consistent with the view that simple speeded manual responses to light flashes are subserved by relatively fixed neural pathways, and that there is an irreducible difference in length between the relatively 'long' pathway for crossed responses and the relatively 'short' pathway for uncrossed responses. Moreover, CUDs of acallosal subjects are much greater than those of normal subjects also in the bimanual condition, as expected from the substantial increase in length of the pathway for crossed responses dependent on the absence of the corpus callosum. Finally, acallosal and normal subjects alike show a 40–60% reduction of the CUD in the bimanual compared to the unimanual responding condition, suggesting that in spite of the irreducible difference in length between the pathways for crossed and uncrossed responses, both groups possess functional mechanisms which in the bimanual condition tend to synchronize the motor outputs on the two sides. This is attested also by a correlational analysis according to which manual crossed and uncrossed RTs are strongly correlated even though the former RTs are systematically longer than the latter [23, 45].

What are the mechanisms which tend to synchronize bimanual responses to a lateralized visual stimulus? Granted that the time for interhemispheric transfer is fixed, an approximation to synchrony of the outputs from the two hemispheres can be achieved by increasing the speed of the slower (crossed) responses, or by decreasing the speed of the faster (uncrossed) responses. The tendency to coupling of bimanual movements can be sustained by both central (e.g. cerebellar) and peripheral (proprioceptive) regulations [27, 29, 65]. In our completely callosotomized patient the CUD was reduced on bimanual compared to unimanual responding because uncrossed responses were retarded so that their RT approximated that of crossed responses [3, 10]. A similar effect is seen when normal subjects carry out dual tasks calling for highly differentiated actions of the two hands: the hand performing the easier task slows down as if waiting for the other hand to catch up with it [65]. Other experiments indicate that acallosal subjects possess mechanisms for gross synchronization and equalization of bilateral symmetrical movements [69] or for simple postural adjustments of one hand in anticipation of a movement of the other hand [73].

By contrast, in patients with hemiparesis or hemianaesthesia from lateralized brain damage, the advantage of the RT of the normal hand over the RT of the affected hand was shown to diminish on bilateral compared to unilateral responding because the disadvantaged response was speeded up selectively in the bimanual task, as if its execution were aided in some way by the concurrent motor command from the undamaged hemisphere to the normal side [34]. Since proximal upper limb responses were examined in that study, the simplest explanation for this effect is that these responses can be issued after one motor command from a single hemisphere, as already mentioned before. An additional assumption is that unilateral proximal responses of the upper limb are effected through a crossed pathway, whereas the same responses, when made bilaterally, engage a different, bilaterally distributed motor system, which ensures a yoked movement of the two sides.

The fact that the CUD may vary depending on the responses being unilateral or bilateral indicates that RT measures can only afford approximate estimates of interhemispheric transfer time in each experimental condition. What seems to be of importance for the interpretation of callosal function in interhemispheric transfer is that even in those conditions which minimize CUD values in normal controls, the acallosals' CUDs are still significantly prolonged.

In summary, speeded bilateral symmetrical responses to visual inputs restricted to one hemisphere can never be perfectly synchronous if the neural pathways mediating the responses on the two sides differ in length. When the two responses are emitted by different hemispheres, as occurs with distal hand movements, there is an irreducible advantage in speed for the response emitted by the hemisphere which receives the visual stimulus. However this advantage is minimized by the corpus callosum which allows an efficient interhemispheric communication for the fast integation of the disadvantaged response. This synchronizing callosal influence is inferred from the increased asynchrony of bilateral hand responses which occurs in the absence of the corpus callosum, whether congenital or acquired. However, the persistence of strong temporal correlations between bilateral hand responses to lateralized visual stimuli in acallosal patients suggest a not-negligible contribution of extracallosal mechanisms to the bilateral temporal coordination of the motor outputs from the two hemispheres. These extracallosal mechanisms for bilateral temporal coordination of hand responses are not yet understood. More information is available as to the mechanisms which ensure the bilateral synchronization of responses effected with axial and proximal arm muscles. Each hemisphere can control these responses on both sides of the body, so that the synchronization between the two sides is made possible by the shared origin of the motor commands and by the bilateral distribution of the pathways transmitting them. In this case bilateral synchronization is totally independent from the corpus callosum.

MODALITIES OF CALLOSAL TRANSFER

It has been suggested that there are two ways in which the corpus callosum can mediate crossed visuomotor reactions in normal subjects. It can do so by transmitting a replica of the visual input from the receiving hemisphere to the hemisphere controlling the motor output. Or, alternatively, the visual input may be conveyed to premotor and motor areas in the receiving hemisphere, leaving to the corpus callosum the task of relaying a trigger signal from these areas to corresponding contralateral areas for the emission of the response [12, 19, 44, 48]. The hypothesis that a purely visual callosal transfer underlies crossed responses is made unlikely by the already mentioned invariance of the CUD across major variations in the strength of the visual input and, consequently, of absolute RT. The alternative hypothesis of a callosal transfer of a trigger signal at a premotor or motor stage of the stimulus–response translation process implies that the transfer is effected by non-visual callosal routes, with the anterior and/or middle callosal portions interconnecting areas of the frontal lobes being perhaps the most likely candidates for this function. Indirect support for the latter possibility has come from the demonstration that the CUD is matched by interhemispheric differences in latencies of potentials evoked by lateralized visual stimuli at central rather than occipital sites [57], and from the finding of abnormally prolonged CUDs in patients with frontal but not occipital lesions [72]. On the other hand, the posterior parts of the corpus callosum, including the splenium, contain not only the interhemispheric connections of purely visual occipital areas, but also those of posterior–inferior parietal areas [22] which are known to be involved in the initiation of oculomotor and skeletomotor responses to visual stimuli [5]. Very long CUDs have been reported not only in patients with frontal lesions, as mentioned above, but also in patients with parietal lesions [7], hence it is conceivable that posterior callosal connections of parietal cortical areas may also play a role in the integration of crossed responses.

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On the assumption that a specific contingent of callosal fibers mediates crossed responses, an abnormal increase of the CUD should follow from a selective callosal defect interrupting the specific pathway. In a partial attempt to test this possibility we have measured the CUDs in six subjects with an anterior section of the corpus callosum sparing the splenium [66]. They had been suffering for several years from drug-resistant forms of epilepsy, and had been submitted to section of the anterior and middle corpus callosum at the Institute of Neurosurgery of the Catholic University in Rome in an effort to reduce the severity of their condition. Objective assessments based on magnetic resonance imaging (MRI) show that in five of these patients the extent of the callosal section varies from the anterior third to the anterior four fifths of the corpus callosum, the splenium being spared in all cases. In the remaining patient the commissural section was evaluated at operation by the neurosurgeon to include the anterior one third of the corpus callosum. We also assessed the CUD of a non-epileptic patient recruited at the Neurosurgical Department of the General Hospital of Verona where she had been diagnosed to have a congenital absence of the posterior third of the corpus callosum including the splenium because of the obstructive presence of an arterovenous malformation attached to the vein of Galen. The rest of the corpus callosum appears normal on MRI. The grand mean of the CUDs of the six callosotomy patients was equal to 3.3 msec (±2.8 msec, S.E.M.). This value can be compared with grand CUD means of 2.2±0.4 msec, and 2.7±1.3 msec found in 12 and 8 normal subjects tested with the same apparatus [see 23, 67]. All the CUDs of callosotomy patients fell within the range of individual CUDs of normal subjects. There was no correlation between the magnitude of the CUD and the extent of the callosal section. The CUD of the patient with the obstructive posterior callosal dysgenesis was 11.8 msec; this relatively high value still lies within normal limits, and is considerably smaller than the CUDs of subjects with total callosal defects, whether congenital or acquired [~~2, 63~~]. The 3, 61 finding of normal CUD in six patients with anterior callosotomies would seem to outweigh the opposite evidence of an abnormal CUD in a single case with a similar splenium-sparing anterior callosotomy [24]. It implies that interhemispheric connections running in the posterior corpus callosum of these patients suffice for mediating fast crossed reactions. Yet neither was there a noticeable CUD prolongation in the patient with an agenetic defect of the entire splenium, suggesting that in this case a normal or near-normal CUD was ensured by the anterior and middle callosal portions as well. Data from this patient must of course be interpreted with caution not only because they come from a single case, but also because the topographic organization of her incompletely developed corpus callosum may be abnormal. For example, the anterior portions of her corpus callosum may contain at least part of the fibers that would normally run in the splenium. Experiments on mice with congenital deficiencies of the corpus callosum have indeed suggested that callosal fibers can reach their appropriate targets even when they have to follow devious growth pathways in order to avoid abnormal blockades at the midline [52]. However callosal connections in our patients with the AV malformations are clearly abnormal insofar as, in contrast with her normal CUD, she exhibits clear signs of visual and tactile interhemispheric disconnection such as left-hand anomia and left-hemifield alexia.

The foregoing general pattern of results is compatible with the hypothesis that the mediation of fast crossed visuomotor responses to simple lateralized light stimuli can be coordinated by virtually all portions of the corpus callosum, in agreement with experiments on visually guided reaching in macaque monkeys [39]. The evidence is insufficient, however, to rule out another hypothesis according to which posterior callosal routes are more important than anterior ones for interhemispheric visuomotor integration. This hypothesis has been proposed to account for the fact that patients with posterior (but not anterior) callosotomies are unable to imitate with one hand finger postures visually presented to the ipsilateral hemifield [26, 74]. The relationships between the neural substrates of the simple visuomotor responses used for assessing CUDs and those of visually guided shaping of the hand remain to be determined.

CONCLUSIONS

The outcomes of most comparisons between the performances of commissurotomy patients with those of callosal agenesis subjects lead to an emphasis on the absence in the latter subjects of the interhemispheric disconnection syndrome typical of the former. While the capacity of the genetically acallosal brain to adapt to the absence of its largest connection pathway cannot be underrated, Jeeves must be credited for having systematically drawn attention to those deficits of hemispheric interaction in callosal agenesis for which there appears to be no compensation [31, 38]. These deficits are often revealed by diminished performance levels when compared with normals rather than by the complete functional losses which manifest themselves in callosotomy patients. They affect such diverse abilities as, among others, simple visuomotor integrations, binocular fusion and stereopsis, bimanual coordination in skilled actions, auditory memory, and certain aspects of language and spatial cognition [38]. Many of the tasks used to demonstrate such deficits in callosal agenesis subjects are based on procedural or implicit knowledge, i.e. operational knowledge which need not be represented in consciousness; on the contrary these subjects often perform normally on tests of hemispheric interactions which are failed by callosotomy patients and are based on declarative or explicit knowledge, i.e. factual knowledge which can be described as consciously possessed [63]. Accordingly, it seems likely that the main successful adaptations occurring in callosal agenesis are aimed at enabling the interhemispheric unification of conscious activities of the two hemispheres rather than at compensating for the lack of more automatic and unconscious aspects of hemispheric interaction. These compensations do not take place in callosotomy patients, although their behavior can at least in part be guided by information transmitted by extracallosal interhemispheric pathway. Milner [44] has argued that while interhemispheric transmission of information can occur subcortically in both callosal agenetics and split-brain patients, only in the former subjects can such information access consciousness, possibly because the necessary adaptation processes are aided ‸ time and the plasticity of the immature brain. Since procedural forms of learning and memory develop early in human infants [70], the time for compensating for the lack of the corpus callosum in these activities would be limited. By contrast, the later and prolonged development of declarative learning and memory would allow more time for functional compensation of potential deficits from callosal agenesis. A greater flexibility of the neural mechanisms of declarative vs procedural knowledge [70] may also be a factor favoring a more efficient compensation in callosal agenesis.

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According to Jeeves the normal functions of the corpus callosum can be better understood by investigating those deficits of interhemispheric communication which occur in both callosal agenetics and split-brain subjects. In this paper we have concerned ourselves with one of such deficits of visuomotor integration, namely the failure to make speeded responses with one hand to simple visual stimuli in the contralateral visual half field. In the absence of the corpus callosum, whether congenital or acquired, the ability to make such responses is not lost, but the time elapsing between stimulus and response becomes abnormally long, most probably due to a slow interhemispheric transmission by extracallosal pathways. The fast visuomotor integration of visual inputs and motor outputs dealt with by different hemispheres can thus be considered a normal function of the corpus callosum. The callosal function is not necessary when fast responses to lateralized visual inputs can be performed with proximal and para-axial muscles of the upper limb which can be guided by bilaterally distributed rather than crossed motor pathways, particularly if both limbs are used for responding. In addition, in order to enable differentiated and asymmetric activities of the two hands in skilled action [33, 54], the corpus callosum may refine the synchronization of bilateral symmetric motor activities which is ensured in part by non-callosal mechanisms.

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