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"Hemispheric control of unilateral and bilateral responses to lateralized light stimuli after callosotomy and in callosal agenesis"

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Hemispheric control of unilateral and bilateral responses to lateralized light stimuli after callosotomy and in callosal agenesis

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Abstract. Normally, simple digital or manual responses to a light stimulus in the right or left visual hemifields are performed faster with uncrossed hand-field combinations than with crossed hand-field combinations. Because of the organization of visual and motor pathways, the integration of uncrossed responses is assumed to occur within a single hemisphere, whereas a time-consuming interhemispheric transfer via the corpus callosum is considered to be necessary for the integration of crossed responses. However, callosal transfer may be dispensable for those crossed responses which can be controlled through ipsilaterally descending motor pathways by the hemisphere receiving the visual stimulus. We investigated crossed-uncrossed differences (CUDs) in speed of simple visuomotor responses to lateralized flashes in one subject with total section of the corpus callosum and two subjects with complete callosal agenesis. We recorded the reaction times as well as the premotor times, as indicated by the electromyographic latencies of the prime movers, of three types of responses: a distal response involving a thumb flexion, a proximal response chiefly involving a forearm flexion and an axial response involving a shoulder elevation. Further, the three types of responses to a single lateralised flash were performed both unilaterally and bilaterally. The three acallosal subjects showed CUDs greatly exceeding normal values on distal responses, either unilateral or bilateral, and on unilateral proximal responses. These abnormally long CUDs stood in sharp contrast to the insignificant CUDs exhibited by the same subjects on bilateral proximal responses and on unilateral and bilateral axial responses in agreement with correspondingly insignificant CUDs reported for normal subjects. These results confirm that a callosal contribution is important for the execution of fast distal and unilateral proximal responses to a visual stimulus directed to the hemisphere ipsilateral to the responding hand. By contrast, the other types of crossed responses appear to be efficiently coordinated across the midline without the aid of the corpus callosum. This is in keeping with the hypothesis that they are governed by a bilaterally distributed motor system which is preferentially activated for the execution of symmetrical bilateral movements, employing axial and proximal limb muscles.

Key words: Visuomotor integration – Interhemispheric communication – Callosotomy – Callosal agenesis – Man

Introduction

In higher mammals including man, the organisation of the optic pathways is such that visual inputs from either visual hemifield are projected solely to the contralateral cerebral hemisphere. Most of the central motor pathways are also crossed. Hemispheric interaction is obviously needed for those visuomotor interactions involving the production of a motor output from one hemisphere in response to a visual input directed to the other hemisphere. However, exclusive motor control by one hemisphere over contralateral muscles applies only to a few types of movement. In the macaque monkey, it is the fractionated motility of the distal extremities, especially the fingers, which is subject to a strictly contralateral control via crossed cerebro-spinal pathways including direct corticomotoneuronal connections. In contrast, bilaterally distributed motor systems originating from each hemisphere are available for the activation of axial and proximal limb muscles involved in global body movements, general postural adjustments and integrated synergistic limb-body movements. Prominent among these bilateral systems are the ventral pyramidal tract and the cortico-reticulo-spinal pathway. Unlike motoneurons for distal muscles, motoneurons for axial and proximal limb muscles receive their major inputs from the motor cortex via relays in the brainstem and/or in the spinal interneuronal pools, rather than through direct corticomotoneuronal connections (Kuypers 1987; 1989).

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Clinical and experimental evidence suggests that the organisation of the motor pathways in man is basically similar to that of the macaque monkey (Freund 1987; Palmer and Ashby 1992), although, unlike the macaque, the motoneurons of virtually all striate muscles of man can be assumed to receive a direct corticomotoneuronal input (Colebatch et al. 1990). Indeed, it appears to be true for man as well as macaque monkey that the motility of intrinsic hand muscles depends almost exclusively on a contralateral cortical control, whereas that of proximal and axial mucles relies also on bilateral cortical and subcortical controls (Freund 1987; Colebatch and Gandevia 1989; Müller et al. 1991). Thus, it is theoretically possible for a visual input channelled into a single hemisphere to directly initiate and guide axial and proximal limb movements on both sides of the body, in addition to individual movements of the contralateral distal extremities, without accessing the other hemisphere. On the contrary, a visual input limited to one hemisphere (e.g. the left hemisphere) requires interhemispheric cooperation in order to govern individual movements of the ipsilateral (i.e. left) intrinsic hand muscles. The forebrain commissures, especially the corpus callosum, are crucially important for this cross-midline visuomotor integration. Interhemispheric, but not intrahemispheric, visual guidance of precise digital grasping is virtually lost in "split-brain" macaque monkeys (Lund et al. 1970; Brinkman and Kuypers 1973; Keating 1973); similarly, praxic imitation of finger postures visually projected to the hemisphere ipsilateral to the performing hand is severely defective, compared to contralateral hand control in patients submitted to forebrain commissurotomy for treatment of otherwise uncontrollable epilepsy (Gazzaniga et al. 1967; Volpe et al. 1982).

All of the above post-commissurotomy deficits of interhemispheric visuomotor integration have been found where relatively complex motor responses must be shaped and/or continuously guided by the visual stimulus as actually perceived or remembered. Fewer studies have considered the involvement of interhemispheric transfer in more elementary forms of visuomotor integration, for example where the visual stimulus merely acts as a trigger for simple motor responses which, once initiated, can proceed unaided by visual perception or memory. At least the fastest of these responses can be emitted in a reflex-like fashion, such that the underlying neural circuits are likely to involve relatively fixed and straightforward connections between visual and motor centres, at both cortical and subcortical levels. The results in animals have suggested that even drastic surgical disconnections of the two hemispheres, entailing the complete severing of both cortical and subcortical commissures, do not abolish the ability to make simple movements with effectors on either side of the body in response to visual stimuli lateralized to one or the other hemisphere (Gazzaniga 1970; Glickstein 1990). However, the persistence of this ability after interhemispheric disconnection does not itself exclude that at least some of these responses may normally benefit from efficient hemispheric interactions ensured by intact commissures. Where visuomotor interhemispheric integration is normally required, the production of simple motor outputs in response to visual stimuli channelled into one hemisphere may become abnormal after commissurotomy, solely as a consequence of increasing the time between stimulus and response.

Chronometric analysis of the speed of detection of simple lateralised light stimuli in normal man has revealed laterality effects which can be related to interhemispheric transfer and integration. Following Poffenberger (1912), it has been repeatedly demonstrated that reaction time (RT) for detection of a lateralised light flash is slightly but significantly faster (about 2–3 ms) for responses made with the hand on the same side as the flash (uncrossed responses, i.e. left hand responding to a left field flash and right hand responding to a right field flash) than for responses made with the hand on the side opposite to the flash (crossed responses, i.e. right hand responding to a left field flash and left hand responding to a right field flash) (Tassinari et al. 1983; Levy and Wagner 1984; St. John et al. 1987; Vallar et al. 1988; Clarke and Zaidel 1989; Milner et al. 1989; Saron and Davidson 1989; Aglioti et al. 1991; Marzi et al. 1991; Di Stefano et al. 1992; for earlier studies see the review by Bashore 1981). In agreement with the above considerations, a parsimonious anatomofunctional explanation for this difference assumes that uncrossed responses can be rapidly integrated within a single hemisphere, i.e. the hemisphere contralateral to both flash and responding hand; instead, for crossed responses some extra time must be spent in an interhemispheric transfer translating the input into the output, since the hemisphere receiving the flash is different from the hemisphere producing the response. The direct relation of the difference between RTs of crossed and uncrossed responses (CUD) to interhemispheric transfer is supported by findings of abnormal, exceedingly long CUDs for cases of defective interhemispheric communication, such as subjects with callosal agenesis (Jeeves 1969; Reynolds and Jeeves 1974; Milner 1982; Milner et al. 1985; Di Stefano et al. 1992) and patients with complete forebrain commissurotomy (Sergent and Myers 1985; Clarke and Zaidel 1989) or partial callosotomy (Di Stefano et al. 1992). It must be realized that virtually all studies on CUD, in normals as well as in subjects with commissural defects, have employed distal responses, i.e. responses that are under the control of the contralateral motor cortex.

If proximal responses on either side of the body can be emitted by either hemisphere, CUDs may not be found with these responses, since crossed as well as uncrossed responses can be initiated by the hemisphere receiving the flash. Di Stefano et al. (1980) compared in normal subjects the CUD on a distal response, consisting of a keypress by a flexion of the thumb, with the CUD on a proximal response, consisting of 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 et al. (1989) 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. However, Di Stefano et al.(1980) described an annulment 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 lateralised 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. Quite recently, Aglioti et al. (1991) reported the absence of any CUD for a response consisting of a unilateral flexion of the big toe, and we have found a similar absence of a CUD for a response consisting of a unilateral elevation of the shoulder (Aglioti et al., in preparation). Since the subjects of these studies showed significant CUDs on distal manual responses, the results argue for a possibility of bilateral control of the toe and shoulder responses, even when made unilaterally. Congruent with this interpretation is the recent report of a bilateral motor cortex activation, as indicated by local increases in blood flow during unilateral shoulder movements, contrasting with the unilateral motor cortex activations associated with movements of the contralateral hand or digits (Colebatch et al. 1991).

No information is available on CUDs for RTs of axial and proximal upper limb muscles compared to distal muscles in commissurotomized and acallosal patients, nor have differences between CUDs for unilateral and bilateral responses been investigated in commissurotomy patients. In the present study, we assessed CUDs for distal, proximal and axial responses to lateralized light flash, made unilaterally or bilaterally, in one epileptic patient with a total section of the corpus callosum. Further, we checked in the same patient the influence of other experimental conditions, such as foreknowledge of stimulus position, eccentricity of light stimulus in the visual field and spatial compatibility between stimulus and response on the CUDs observed in the absence of the corpus callosum. Finally, we obtained additional evidence about the relationship between CUDs and interhemispheric transfer, by assessing CUDs on unilateral and bilateral responses of different effectors in two subjects with a complete agenesis of the corpus callosum. Parts of the results have been preliminarily published as an abstract (Tassinari et al. 1990).

Materials and methods

Subjects

The callosotomy subject M.E., born in 1970, was an 8-year-old boy of apparently normal development when he was submitted to removal of a right frontal, subdural hematoma and partial right, frontal polectomy after being hit by a car. Three years later, he started suffering from daily complex, partial seizures with secondary generalization which proved totally resistent to pharmacological therapy. In February 1989 he was admitted to the Neurosurgical Institute of the Catholic University in Rome, where he underwent a further resection of the right frontal lobe and a longitudinal section of the anterior third of the corpus callosum. Since there was no improvement in his condition, in June 1989 the rest of the corpus callosum was sectioned in the same Institute, resulting in a marked favourable change in both severity and frequency of the seizures. Pharmacological treatment with Phenobarbital and Phenytoin was continued throughout the postoperative period. At the times of testing for RT (April and October 1990, June and December 1991), standard clinical examinations revealed a stationary condition with no neurological deficits, except for a severe left-hand ideomotor dyspraxia on verbal command (but not on imitation), a left-hand anomia and alexia in the left hemifield. The patient is right-handed (laterality index +16, according to the criteria of Briggs and Nebes 1975). The completeness of the callosal section and the integrity of the anterior commissure were confirmed in October 1990 by magnetic resonance imaging (MRI, Fig. 1). MRI also revealed a large defect in right prefrontal cortex consisting of a fluid-filled cavity continuous with the frontal horn of the lateral ventricle, but completely sparing the premotor and motor cortices, the basal ganglia and the internal capsule.

R.B., a male born in 1976 after a normal pregnancy and a normal delivery, was first diagnosed by MRI as congenitally lacking the corpus callosum and having dilatation of the posterior portions of the lateral ventricles in March 1988. Since he was 6 years of age he has suffered episodically from cervico-occipital headaches, eyelid fluttering and occasional falls from fainting. His intelligence is within normal limits, as judged from his satisfactory scholastic performance in a technical high school. Because his father and paternal grandmother are affected by a form of hereditary optic subatrophy, his visual capacities have been tested repeatedly both clinically and electrophysiologically (electroretinography, photically evoked potentials), always with normal results. His RTs have been assessed in our laboratory between July and December 1991. Standard neurological examinations carried out during this period have revealed no clear manifestations of interhemispheric disconnection, although subtle signs of defective visual communication between the hemispheres have been found using special experimental tests in another laboratory (Fiorentini et al. 1992). The patient, who is left-handed (laterality index −14 according to Briggs and Nebes 1975), was under no medication throughout the period of RT testing.

P.M. is a right-handed male born in 1961 after a dystocic delivery with forceps. At present he is fruitfully employed as a mechanic. Since he was 10 years old he has suffered from four episodes of involuntary movements of the left hemisoma, occurring on awakening and not impairing consciousness, for which he is treated with carbamazepine. His left hemisoma is slightly hypotrophic. An MRI examination performed in July 1991 has shown a complete congenital absence of the corpus callosum as well as a porencephalic cyst in the right fronto-parietal cortex. His RTs were assessed in November 1991.

Apparatus

Each patient was comfortably seated in a partially sound-proofed cubicle facing an arc perimeter 57 cm in radius hung against a white tangential screen. The cubicle was dimly illuminated from above; the luminance measured at the screen was 0.15 cd/m^2. The patient's head was positioned in a head and chin rest so that the midpoint between the eyes was at the perimeter's centre of curvature. A fixation mark was provided on the perimeter just in front of the headrest, and two solid state miniature bulbs (TIL 222) were fastened to the perimeter, one on the left and the other on the right, equidistant from the fixation mark. From the patient's viewpoint, the angular distance between the fixation mark and each bulb was 10 deg. The callosotomised patient M.E. was also tested in some sessions with the bulbs placed at 35 and/or 70 deg from the fixation point, as specified later. Each bulb could be lit individually by a 5 ms square pulse of current, producing a gallium phosphide green flash with the same duration and an intensity of about 1000 μcd. Three response devices were provided on each side of the patient: a button key which was to be pressed with the tip of the thumb; a lever acting on

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Fig. 1. Midsagittal view of the brain of subject M.E. showing absence of corpus callosum. The completeness of the callosal section was independently ascertained on these and other sagittal, transverse and coronal sections by two experienced radiologists who were unaware of the patient's history

a spring, which was to be pulled by means of a flexion of the elbow and an abduction of the shoulder; and another button key which was to be pressed by elevating the shoulder. The button keys for the thumb responses and the levers for the forearm response were positioned on each side of the subject, 29 cm from the midsagittal plane, 16 cm below the fixation point and 22 cm in front of the screen. The button keys for the shoulder responses were mounted on a metallic support suspended behind the subject in such a way that on each side the button key rested over the acromion. Pressing either key with a force of 0.06 kg or pulling the lever with a force of 3.5 kg closed three separate electrical contacts. However, the shoulder response required a wider movement compared to the thumb response, because the contact between key and effector was not as tight on the former response as on the latter. Regardless of the response required of him, the subject's elbows were rested on supports that also acted as restraints for the forearms, thus facilitating, stabilizing and standardizing the response movements. The task consisted of pressing the thumb-key or the shoulder-key, unilaterally or bilaterally, or in pulling the lever again unilaterally or bilaterally, as soon as possible following the occurrence of a light flash. The thumb key-pressing response was selected as involving distal muscles, the lever-pulling response was selected as involving proximal arm muscles, and the shoulder key-pressing response was selected as involving mostly axial muscles. Accordingly, the three types of response and the corresponding effectors will be called distal, proximal and axial. The time elapsing between the onset of the flash and the closing of the contact(s) by the key(s) or the lever(s) was electronically measured to the nearest millisecond.

General features of the procedure

Testing was performed over two or more days during repeated, relatively short sessions of about 20 min separated by rest periods commensurate with individual fatigability. Each subject was accustomed to the various experimental situations by running several practice trials at the beginning of testing. Data from these trials were excluded from analysis. Data for analysis were provided by experimental sessions, each of which included one or more blocks of 30–50 trials. On any given block of trials, subjects were instructed to respond as fast as possible to the flash with a previously specified unilateral or bilateral response. Each flash was preceded by an auditory tone pip, 100 ms in duration, delivered via an earphone set. The interval between the auditory warning signal and the flash varied randomly from 1 to 3 s, and the inter-trial interval was about 1 s. Subjects were instructed to fixate the central mark on hearing the warning signal and maintain fixation until after performing the response. Eye position and maintenance of fixation were monitored by television, and trials with failures to fixate were aborted and repeated. The presentation of the stimuli and the recording of the RT data were automatically controlled by a computer which rejected RTs shorter than 150 ms or longer than 989 ms, and replaced the rejected trials later in the sequence.

Specific procedures of experiments on M.E.

Four experiments were run with subject M.E.

In experiment 1, only distal responses were studied with the aims of confirming the post-callosotomy prolongation of the CUD and of assessing its possible dependence on stimulus eccentricity and/or foreknowledge of stimulus position. The experiment included 12 blocks, each consisting of 50 trials. Stimuli could be presented at 10, 35 and 70 deg of visual angle from the fixation point along the horizontal meridian in either hemifield. Stimulus eccentricity was held constant in each of the 12 blocks. Six blocks were allocated to a condition called random, in which the occurrence of the stimulus in the right or left hemifield could not be predicted with certainty, and six blocks were allocated to a condition called "blocked," in which the position of the stimulus on each trial was known in advance. In the random condition, stimulus occurrence within each block was alternated randomly between hemifields with the constraint that stimulus frequency was the same in the two hemifields, i.e. 25 stimuli per hemifield per block. Two blocks were allocated to each of the three stimulus eccentricities, and with each stimulus eccentricity one block was performed with the right hand and the other with the left hand. In the blocked condition, two blocks were again allocated to each of the three stimulus eccentricities; one block for the right hand and the other for the left hand. In each block, the stimulus appeared constantly in one hemifield on the first 25 trials and in the other hemifield on the remaining 25 trials. The subject was informed about the hemifield in which the stimulus would appear, both before the beginning of each block and before the beginning of the 26th trial. Alternations between different eccentricities, hands, hemifields and conditions were effected according to a Latin square design.

Experiment 2 was aimed at assessing the CUD for each of the three types of effector – distal, proximal and axial – and as a function of the unilaterality or bilaterality of response. It involved 27 blocks, each consisting of 30 trials, and in each block 15 right hemifield stimuli were randomly interspersed with 15 left hemifield stimuli. Eighteen blocks were allocated to unilateral responses, and nine blocks were allocated to bilateral responses. Among the 18 blocks with unilateral responses, six blocks were performed with distal responses, six with proximal responses and six with axial responses. With each type of unilateral response, three blocks were performed with the effector on the right side and three blocks were performed with the effector on the left side; in each case, on two of these three blocks the stimulus appeared at 10 deg from fixation, whereas it appeared at 70 deg from fixation on the third block. Similarly, the nine blocks with bilateral responses were divided into three blocks with distal responses, three blocks with proximal responses and three blocks with axial responses, and in each group of three blocks two were run with the stimulus at 10 deg from fixation and one was run with the stimulus at 70 deg from fixation. The number of trials in the bilateral condition was half the number of trials in the unilateral condition, because each trial of the first condition yielded two data; one for the uncrossed response and the other for the crossed response. Types of effectors, sides of responding effectors, unilateral and bilateral conditions and eccentricities were alternated according to a Latin square design.

In experiment 3, only unilateral responses with the three types of effectors were studied. The purpose of this experiment was to compare RTs with corresponding latencies of activation of the prime movers, i.e. the muscles primarily involved in the performance of each response, as indicated by their electromyographic (EMG) activities. Behavioural RT can be divided into a premotor time, i.e. the lag between the stimulus and the first EMG activation of the prime movers, and a motor time, i.e. the differential between RT and premotor time (Botwinick and Thompson 1966). Only premotor time can serve as a reliable direct indicator of the temporal course of central neural processes, since motor time is mainly determined by the speed in attaining the force value necessary for overcoming the inertial load of the response device (Tomberg et al. 1991). Concurrent measures of EMG latencies and RTs of crossed and uncrossed responses allow one to evaluate the relative contributions of central and peripheral factors to CUDs. Premotor times of crossed and uncrossed responses with the three effectors were assessed by recording the EMG with surface silver electrodes attached to the skin overlying, respectively, the thenar muscles, the biceps brachii and the trapezius of either side. EMG responses were displayed trial by trial on an oscilloscope screen which allowed a semi-automatic reading of the latency of the response onset following the occurrence of each flash. EMG latencies thus measured were then manually fed into the computer, while the corresponding RTs were recorded automatically. There were six blocks of 30 trials altogether, two of which were allocated to each type of effector, one block for each side. Each block included 15 right hemifield stimuli and 15 left hemifield stimuli intermixed according to a quasi-random sequence: the eccentricity of the stimulus was in all cases 10 deg from fixation. The alternation between different effectors and different sides was randomized according to a Latin square design.

Experiment 4 was aimed at assessing the possible influence of spatial compatibility on the CUD for distal responses. Two blocks of 30 trials each were run in the usual way, with the patient pressing the right key with the right thumb and the left key with the left thumb. In two other blocks, again of 30 trials, the patient held the responding arm across the midline in order to press the right key with the left thumb and the left key with the right thumb so that uncrossed responses were performed with the hand in the hemispace contralateral to the visual stimulus, and crossed responses were performed with the hand in the hemispace ipsilateral to the visual stimulus. In each block of both conditions (the normal hand-position condition and the reversed hand-position condition), the location of the visual stimulus varied randomly between 10 deg to the right and 10 deg to the left of fixation, with the constraint that each block included 15 right and 15 left stimuli. In each condition, the trials of one block were performed with the right hand and those of the other block were performed with the left hand. The order of presentation of the four blocks was decided on a random basis according to a Latin square design.

Experiments on R.B. and P.M.

The two subjects with callosal agenesis were tested with the general procedure used with the callosotomized subject M.E. in experiment 2, except that stimuli were presented only at 10 deg from fixation. P.M. was tested in nine blocks of 30 trials each; three blocks were allocated to each effector, two for the unilateral response condition, one for the left and one for the right, and one for the bilateral response condition. R.B. performed on 18 blocks of 30 trials because there were two blocks for each effector for each response condition. For each of the two subjects the alternation between variables was randomized according to a Latin square design.

Analysis of data

Results from each experiment on each subject were subjected to analyses of variance (ANOVAs) for completely randomized designs involving two or more fixed-effect variables and using data from individual trials as the random-effect variable. Selected comparisons were made by t-tests for unpaired samples, using the Bonferroni correction for repeated contrasts. Side-by-side correlations on bilateral trials were examined by linear regression analysis (Myers 1979).

Comparisons with data from normals

The CUDs of the three acallosal subjects could be compared and contrasted with corresponding CUDs of normal controls tested with the same apparatus in almost identical experimental conditions in two other studies (Di Stefano et al. 1980; Aglioti et al. 1991). The study of Di Stefano et al. (1980) provided data on unilateral and bilateral proximal and distal responses from 12 normal males aged between 21 and 43 years. They were tested with visual stimuli presented at 15 deg from fixation, but this procedural difference from the present study can be ignored as CUDs of normals are known to be invariant across retinal eccentricities (Berlucchi et al. 1971, 1977; St.John et al. 1987). In the present study, this proved to be true also in callosotomized subject M.E. (see Results). CUDs on unilateral and bilateral axial responses of normal subjects for comparison with those of the three subjects of the present study were obtained by Aglioti et al. (in preparation) on 12 normal males ranging in age from 26 to 34 years.

Results

General considerations

The callosotomized subject M.E. when tested initially tended to neglect stimuli in the left hemifield, but with practice he quickly overcame this tendency so that during the experimental sessions he responded regularly to stimuli in both hemifields. However, RTs to left hemifield stimuli were consistently longer than RTs to right hemifield stimuli, an effect probably due to the presence of a right prefrontal lesion. In general, in the experimental sessions described below, the three subjects lacking the corpus callosum made so few anticipations and errors of omissions that data analysis was limited to RTs. The fact that RTs of M.E. and P.M. were considerably longer than those of normals may depend partly on anti-epileptic medication. Further, P.M. was consistently slower with left than with right effectors, probably in connection with the presence of a porencephalic cyst in the right hemisphere and the slight degree of left hemisoma atrophy. The differences between right and left hemifields in M.E. and between right and left effectors in P.M. will not be considered in detail as they are not relevant to the purpose of the present study, i.e. to the analysis of the interactions between the side of stimulus and the side of the responding effector as reflected in the CUD. Since the CUD was computed in each subject for each effector as the difference between the mean of the two crossed hemifield/effector combinations and the mean of the two uncrossed hemifield/effector combinations, it should be independent of RT per se, and unaffected by systematic side differences between hemifields and/or effectors because these were bound to cancel each other in the computation.

Callosotomised patient

Experiment 1: *effects of stimulus eccentricity and random versus blocked presentations on CUDs for distal responses.* This experiment tested distal responses only. Each hemifield/hand combination yielded 25 RTs for each of the three stimulus eccentricities (10, 35 and 70 deg from fixation) in each of the two conditions (blocked vs randomised stimulus presentation). The results were analysed by an ANOVA with hemifield, hand, eccentricity and condition as main factors. The following main factors proved significant: (a) hemifield ($P < 0.0001$), the right hemifield RT (349.1 ms) being faster than the left hemifield RT (539.6 ms); (b) eccentricity ($P < 0.0001$), RT being fastest at 10 deg (395.6 ms), intermediate at 35 deg (450.5 ms) and slowest at 70 deg (487 ms), in agreement with the well-known changes in retinal sensitivity along the horizontal meridian (e.g. Chelazzi et al. 1988); and (c) condition ($P = 0.0005$), the RT in the blocked condition (422.3 ms) being faster than the RT in the random condition (466.4 ms). Significant among the two-way interactions were: (a) the hemifield/hand interaction ($P < 0.0001$), with uncrossed RTs significantly shorter than crossed RTs in both hemifields, resulting in an overall CUD of 84.7 ms; (b) the hemifield/eccentricity interaction ($P = 0.003$), the increase in RT with eccentricity being greater in the left hemifield than in the right; and (c) the hemifield/condition interaction ($P < 0.0001$), the advantage for RT of the blocked over the random condition being limited to the right hemifield. In the blocked condition, both crossed and uncrossed responses to stimuli in the right hemifield were faster than the corresponding responses in the random condition, as expected from the effect of foreknowledge of stimulus location on RT (Posner et al. 1982); the differences between the blocked and random conditions in the left hemifield were more complex, since only crossed responses were comparatively shorter in the former condition than in the latter, whereas uncrossed responses were paradoxically faster in the random than in the blocked condition. Finally the three-way hemifield/hand/condition interaction was also significant ($P = 0.0004$), reflecting the fact that a CUD occurred in both the random and the blocked condition in the right hemifield, but only in the random condition in the left hemifield (Fig. 2).

Figure 2 shows uncrossed and crossed RTs as a function of stimulus eccentricity, as well as of foreknowledge of the stimulus position. In both the blocked condition and the random condition, the CUDs did not appear to vary with stimulus eccentricity in agreement with the statistical insignificance of the hemifield/hand/eccentricity interaction. However, the mean of the CUDs across eccentricities was much larger in the random condition (130.4 ms) than in the blocked condition (30 ms), and in fact in the latter condition the difference between crossed and uncrossed RTs did not reach statistical significance. As shown in Fig. 2, the reduction of the CUD in the blocked condition compared to the random condition was at least partly due to the absence of a CUD in the left hemifield in the former condition.

In conclusion, the experiment confirmed the occurrence of an abnormally prolonged CUD for distal responses following callosotomy, supporting earlier results of Sergent and Myers (1985) and Clarke and Zaidel (1989). The independence of the CUD from stimulus eccentricity in our callosotomized patient agrees with findings in one commissurotomy patient of Clarke and Zaidel (1989), who was tested with stimuli at 4 and 10 deg of eccentricity. However, this independence is at variance with findings in three more commissurotomy patients from the same study who had significantly larger CUDs for stimuli at 10 deg eccentricity than at 4 deg eccentricity. The reasons for these discrepancies within and between studies in the effects of stimulus eccentricity on post-callosotomy CUDs are unclear, and are thus worthy of further investigation in a large sample of subjects.

In callosotomized patient M.E., the CUD was shorter with blocked than with random presentations of the visual stimulus, but the interpretation of this finding is dubious because the difference was limited to the left hemifield. However, even the shortest CUD of 30 ms observed in this patient in the blocked condition was more than four times greater than the largest CUD (7 ms) found in a group of normal subjects tested in the same apparatus by Di Stefano et al. (1980).

Experiment 2: *comparison between CUDs for distal, proximal and axial responses in unilateral and bilateral response conditions.* The main purpose of this experiment was to compare CUDs of different effectors on unilateral and bilateral responses. A preliminary inspection of the

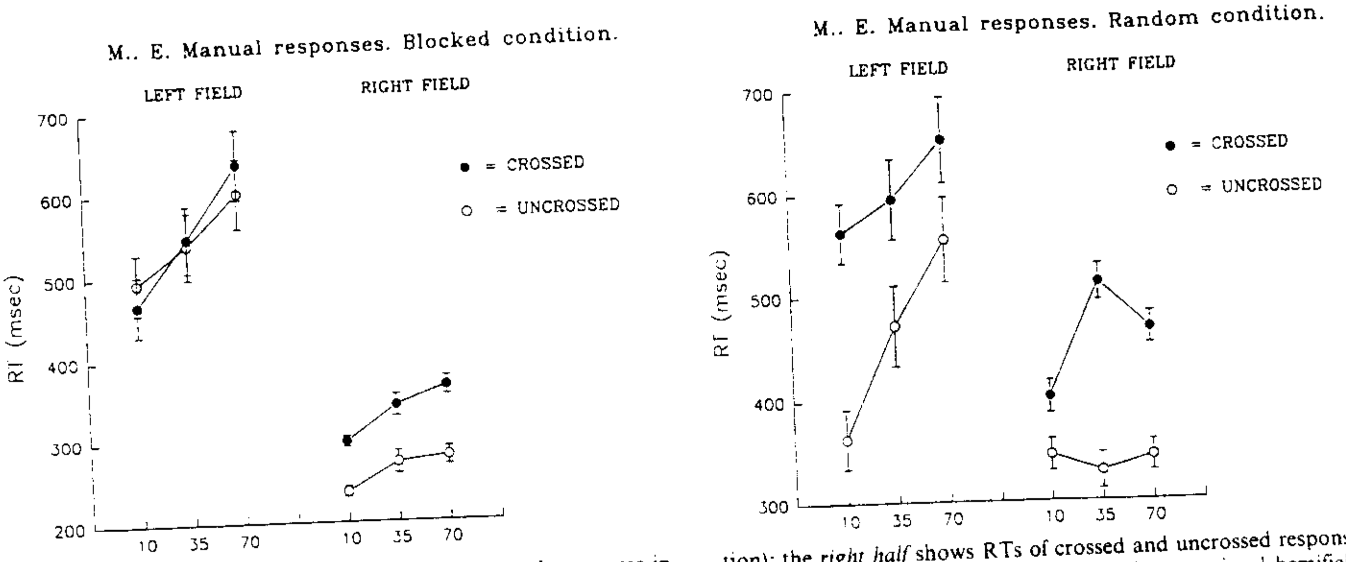

Fig. 2. Reaction times (RT) of crossed and uncrossed responses in callosotomised subject M.E. as a function of the eccentricity of the visual stimulus and of foreknowledge of stimulus position. Stimulus eccentricity is indicated on the abscissae as angular distance from the fixation point along the horizontal meridian. The *left half* of the figure shows RTs of crossed and uncrossed responses to visual stimuli the position of which was known in advance (blocked condition); the *right half* shows RTs of crossed and uncrossed responses to visual stimuli occurring randomly in the two visual hemifields (random condition). Overall RT increases with stimulus eccentricity, while the crossed-uncrossed difference (CUD) remains constant across eccentricities. The CUD is smaller in the blocked condition than in the random condition, mainly in the left visual hemifield

data confirmed that RTs were longer with stimuli at 70 deg than with stimuli at 10 deg from fixation, but since stimulus eccentricity did not appear to interact with other factors, and since as in Experiment 1 CUDs did not appear to vary with stimulus eccentricity, data were pooled across eccentricities. Each hemifield/effector side combination yielded 45 RTs for each of the three effectors in each of the unilateral and bilateral conditions. RT data were divided in six groups corresponding to the effector/condition combinations, and the data from each group were separately submitted to ANOVAs having hemifield and side of effector as main factors. Relevant to present purposes is the fact the hemifield/effector side interaction was highly significant in the ANOVAs for unilateral and bilateral distal responses and for unilateral proximal responses ($P \leq 0.02$ in each case), whereas it was completely insignificant in the ANOVAs for bilateral proximal responses and unilateral and bilateral axial responses. These differential effects of the hemifield/effector side interaction were accounted for by changes in the CUD across effectors as well as between unilateral and bilateral trials, as can be evaluated from the display of uncrossed and crossed RTs as a function of effector type and condition in Fig. 3. Several trends are apparent from this figure.

First, there were differences in RT between the three effectors which may be chiefly attributed to the mechanics of the response devices (rather than to physiological differences between the effectors themselves), as shown by the EMG findings of experiment 3 described below. Second, in the unilateral condition, there was a CUD with all effectors, but the difference in favour of uncrossed over crossed RTS was large and significant for the distal (69.6 ms, $P<0.001$) and proximal effectors (60 ms, $P=0.003$), and smaller and insignificant for the axial effector (34.6 ms). Third, in the bilateral condition, there was a small and insignificant CUD with either proximal (CUD 1.4 ms) or axial effectors (CUD 1.0 ms), whereas with distal responses uncrossed RT was still 37.9 ms shorter than crossed RT ($P=0.02$).

Figure 4 offers a different graphical representation of the above differences based on the cumulative frequency distributions of all RTs for each of the three effectors in the unilateral and bilateral response conditions. While CUDs are simply differences between the means of crossed and uncrossed RTs, Fig. 4 allows a general comparison between the two classes of reactions over their entire RT ranges.

It is clear from the figure that the distributions of crossed and uncrossed RTs were neatly separated over the whole range as far as unilateral and bilateral distal responses and unilateral proximal responses are concerned, whereas distributions of crossed and uncrossed reactions overlapped virtually completely for all other kinds of responses. Figure 4 also shows that the CUD decrease in the bilateral compared to the unilateral distal responses was entirely due to a shift in the distribution of ipsilateral RTs toward longer values, the distribution of contralateral RTs being virtually the same in the unilateral and bilateral condition.

A regression analysis of the bilateral distal and proximal responses showed that crossed and uncrossed RTs were linearly related in both types of reactions. Correlation coefficients for the proximal responses were 0.97 for the left hemifield and 0.98 for the right hemifield. These values compare with those found in 12 normal controls by Di Stefano et al. (1980) who reported a mean of 0.97 with a range of 0.95–0.98. Like normals, M.E. showed lower correlation coefficients for distal than for proximal responses. His coefficients on distal responses were 0.78

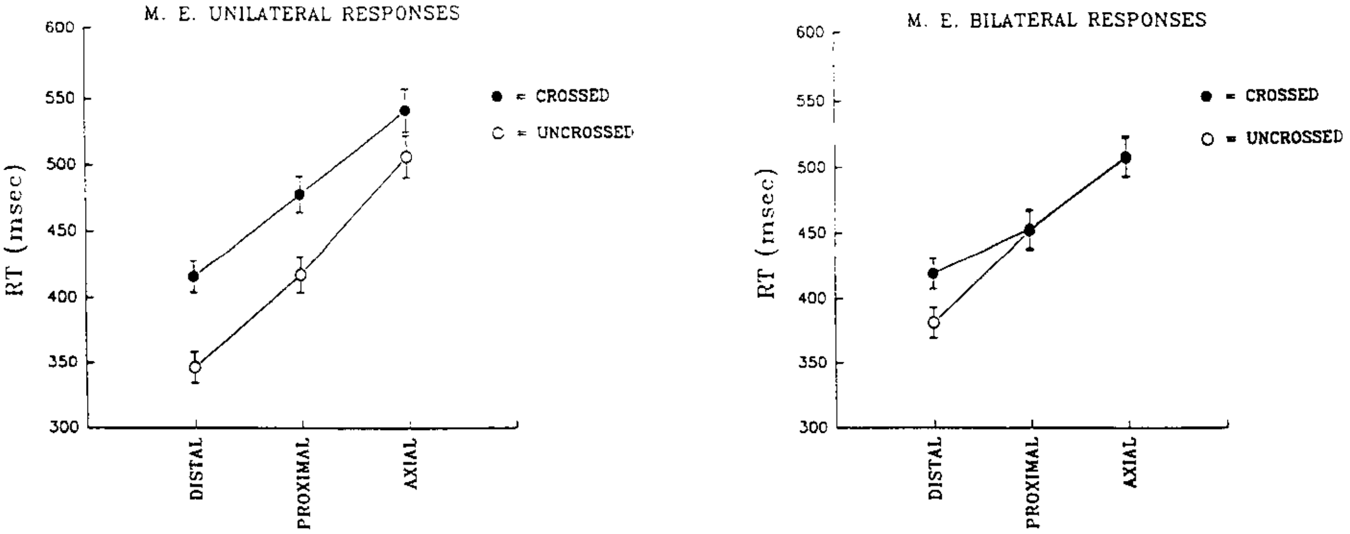

Fig. 3. Reaction time (RT) of callosotomized subject M.E. as a function of different response effectors and unilaterality or bilaterality of response. In the unilateral response condition (*left*), uncrossed responses are faster than crossed responses with all types of effectors, but the difference between crossed and uncrossed RTs is not significant for the axial response. In the bilateral response condition (*right*), there is a significant difference between crossed and uncrossed RTs on distal responses, but not on proximal and axial responses

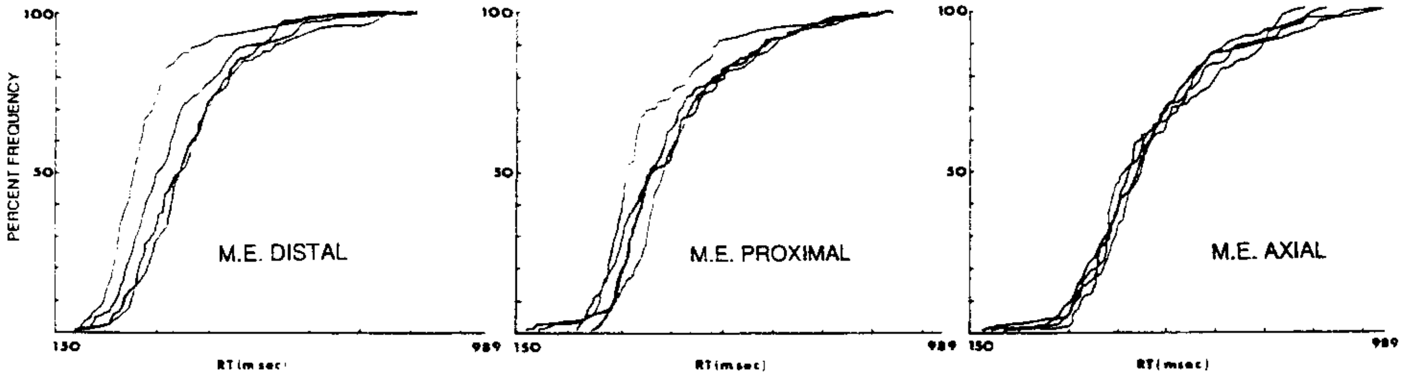

Fig. 4. Comparison between crossed and uncrossed RTs in the unilateral and bilateral response conditions. Cumulative percent frequency distributions of RTs of distal (*left*), proximal (*centre*) and axial responses (*right*). Each curve includes 90 RTs. Uncrossed RTs in the unilateral and bilateral response condition are shown in *blue* and *black* respectively; unilateral and bilateral crossed RTs are shown in *red* and *green* respectively. Note that for proximal and especially distal responses the uncrossed RT curve in the bilateral condition is shifted to the right (i.e. toward longer RTs) relative to the uncrossed RT curve in the unilateral condition. This rightward shift accounts for the reduction of the CUD for distal responses in the bilateral compared to the unilateral condition and for the absence of a CUD on bilateral proximal responses. The curves of unilateral crossed RTs overlap with those of bilateral crossed RTs, regardless of the responding effector; all curves, crossed and uncrossed, bilateral and unilateral, overlap in the case of the axial effector.

with stimuli in the left hemifield and 0.74 with stimuli in the right hemifield. They are lower than the corresponding mean value of 0.91 found in normals by Di Stefano et al. (1980), but fall within the 0.73–0.96 normal range reported by the same authors. In M.E., the uncrossed RT led the crossed RT on 73.4% of the trials on distal responses, as opposed to only 46.6% on proximal responses.

Experiment 3: comparison of CUDs for RTs and EMG latencies. As in experiment 2, the three types of effectors were used in this experiment, but only in the unilateral response condition. There were 15 premotor times (PMTs = EMG latencies) and 15 matched motor times (MTs) for each hemifield/effector side combination for each effector, MT being defined as the differential between each RT and the corresponding PMT. An ANOVA was run with hemifield, type of effector, side of effector and type of response as main factors, the levels of the last factor being PMT and MT. The important significant interactions in the ANOVA were: (a) the hemifield/effector side interaction ($P < 0.01$), uncrossed combinations yielding values significantly shorter than those for crossed combinations ($P < 0.01$); (b) the hemifield/effector side/effector type interaction ($P = 0.003$), the difference between uncrossed and crossed combinations being highly significant for the distal and proximal effectors ($P < 0.01$ in both cases), and insignificant for the axial

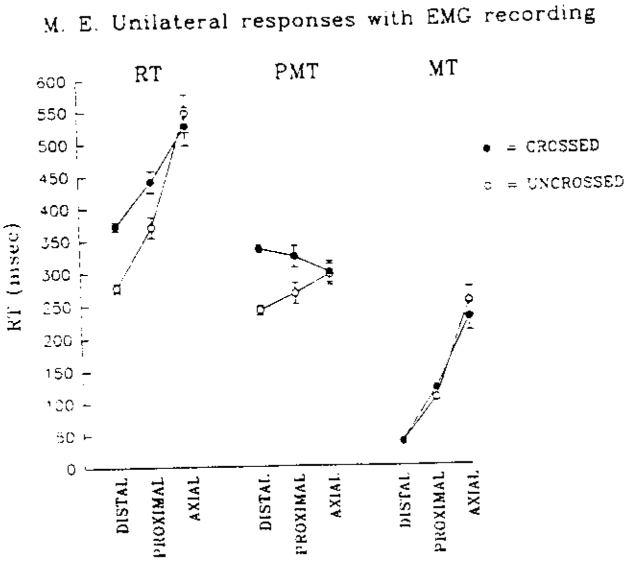

Fig. 5. Central origin of the CUD in callosotomized subject M.E. Reaction time (RT) of crossed and uncrossed distal (hand), proximal (arm) and axial (shoulder) responses, shown on the *left*, is divided into premotor time (PMT, centre), elapsing between stimulus and initial EMG reaction of the prime mover, and motor time (MT, *right*), elapsing between the initial EMG reaction of the prime mover and the activation of the response device. All responses ($n = 180$) were made unilaterally, half on the right and half on the left. Note that crossed RTs and PMTs are longer than uncrossed RTs and PMTs, respectively, for distal and proximal but not axial responses. There is no difference between crossed and uncrossed MTs for any response

effector; (c) the hemifield/effector side/response type interaction ($P < 0.0001$), depending on the fact that uncrossed PMT (267.1 ms) was significantly shorter than crossed PMT (318.4 ms, $P < 0.001$), whereas uncrossed MT (130.7) was statistically indistinguishable from crossed MT (128.1 ms). The four-way interaction almost reached significance ($P = 0.06$), reflecting the presence of significant differences between crossed and uncrossed PMTs, but not between crossed and uncrossed MTs of both distal and proximal effectors, and the absence of significant differences between crossed and uncrossed PMTs as well as between crossed and uncrossed MTs of the axial effectors.

A separate ANOVA carried out on RTs showed that both the hemifield/effector side interaction and the hemifield/effector side/effector type interaction were highly significant ($P < 0.005$ in each case).

Figure 5 presents a summary of the results by showing uncrossed and crossed RTs, PMTs and MTs as a function of effector type. These results provide a general confirmation of those from experiment 2 with some important additions and qualifications. First, RT increased considerably along the distal-proximal-axial gradient. Second, CUDs were large and comparable for the distal and proximal effectors (respectively 94.9 ms and 71.2 ms), while, on the contrary, the axial response exhibited a negative CUD (–20 ms). Third, a comparison between RTs, PMTs and MTs indicated that the large distal-proximal-axial increase in RT was entirely accounted for by a corresponding increase in MT, while there was no such gradient in the PMTs. Fourth, the differences between crossed and uncrossed RTs of each effector were exactly matched by the differences between corresponding crossed and uncrossed PMTs, thus explaining the coincidence between crossed and uncrossed MTs of each effector.

Taken together, the statistically insignificant negative CUD for the unilateral axial response in experiment 3 and the similarly insignificant positive CUD for the same response in experiment 2 suggest the absence of a systematic CUD with this type of response, in keeping with results in normals (Aglioti et al., in preparation). On the other hand, experiments 2 and 3 are fully concordant in demonstrating large significant CUDs for unilateral responses of proximal and distal effectors, thus pointing to an effective difference between such effectors and the axial effectors in relation to the CUD. Finally, the EMG findings prove that the differences between crossed and uncrossed RTs expressed in the CUDs must arise in the central nervous system, prior to the activation of the motoneurons, and thus cannot be accounted for by differences at the peripheral neuromuscular level. On the contrary, peripheral differences must be responsible for the changes in overall RT across different effectors seen in experiments 2 and 3, undoubtedly as a result of the different mechanical properties of the response devices described in Materials and methods.

Experiment 4: independence of the CUD from spatial stimulus-response compatibility. This experiment used distal responses and yielded 15 RTs for each hemifield/hand combination in each of two hand-position conditions, normal and reversed. The results were analysed by an ANOVA with hemifield, hand and condition as factors. The hemifield/hand interaction was highly significant ($P = 0.002$), while the three-way interaction was far from significant. Figure 6 shows RT as a function of hemifield, hand and condition.

The advantage of uncrossed RT over crossed RT was significant and similar in both hemifields and in both conditions, with a CUD of 78 ms in the normal hand-position condition and a CUD of 60 ms in the reversed hand-position condition. The right hand responded faster than the left hand to stimuli in the right hemifield, and the left hand responded faster than the right hand to stimuli in the left hemifield, regardless of whether each hand worked in the ipsilateral or contralateral hemispace. Thus, the abnormal prolongation of the CUD in the callosotomised subject ME did not depend on the functional relations between the side of the stimulus and the side of the response, as it occurs in spatial stimulus-response compatibility effects, but rather on the anatomical relations between the visual hemifields, the cerebral hemispheres and the hands.

Experiments on acallosal subjects R.B. and P.M.

As in experiment 2 performed on M.E., CUDs were assessed on unilateral and bilateral responses of the three different effectors. R.B. produced 30 RTs and P.M. pro-

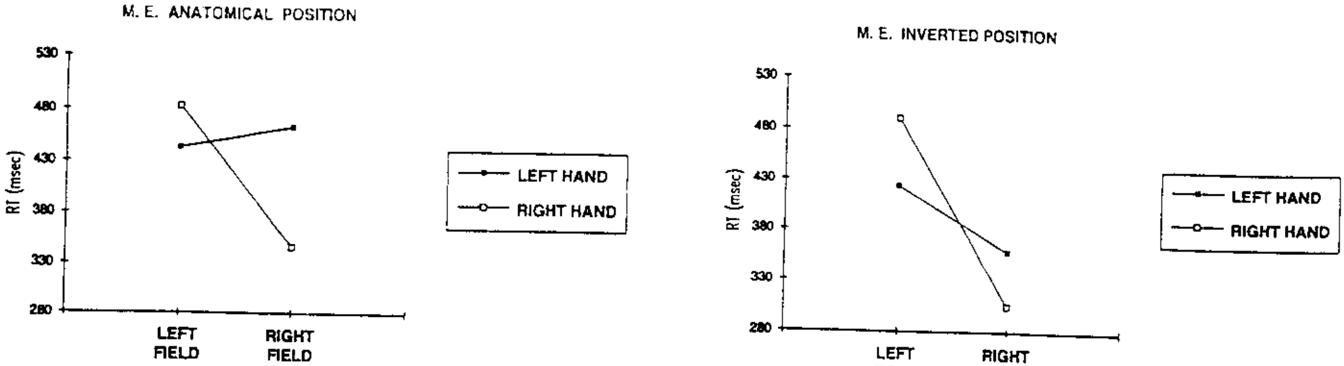

Fig. 6. Differentiation of the CUD from a spatial compatibility effect. RTs of callosotomized subject M.E. are shown as a function of the hemifield containing the visual stimulus and the responding hand in the anatomical (*left diagram*) and reversed position (*right diagram*). In the anatomical position the right hand responded in the right hemispace and the left hand responded in the left hemispace; in the inverted position each hand responded in the opposite hemispace. Uncrossed responses, made with the hand attached to the side of the body ipsilateral to the visual stimulus, are faster than crossed responses, made with the hand attached to the side of the body contralateral to the visual stimulus. in both right and left hemifields, and regardless of the anatomical or inverted positions of the hands. The CUD is invariant across the two hand positions

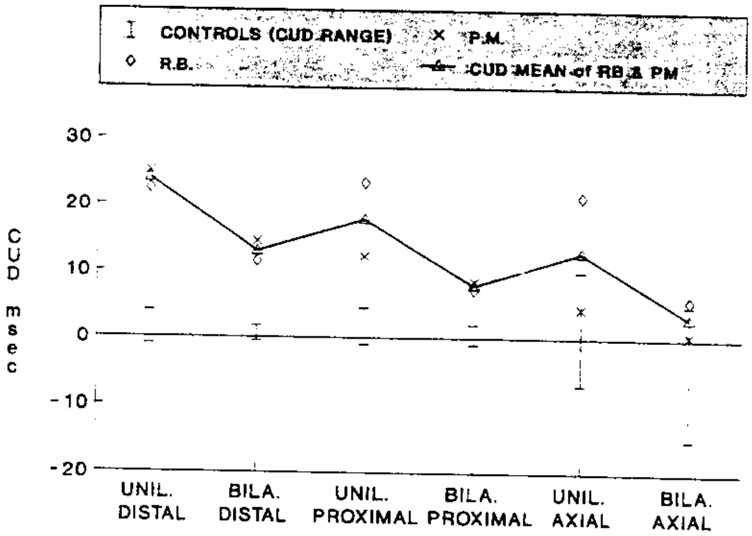

Fig. 7. CUDs in callosal agenesis. The intersubject means and individual values of CUDs of acallosal subjects R.B. and P.M. are shown for the different effectors and response conditions. The *vertical bars* represent the ranges of corresponding CUDs of two different groups of 12 normal controls from the studies of Di Stefano et al. (1980) and Aglioti et al (in preparation). Note that the CUDs of the two acallosals are much longer than the upper values of the normal ranges with all types of responses, unilateral (unil.) and bilateral (bila.), distal and proximal, but not with unilateral and bilateral axial responses

duced 15 RTs for each hemifield/effector side combination for each of the three effectors in each of the unilateral and bilateral conditions. In each subject. RT data were divided in six groups corresponding to the effector/condition combinations, and the data from these groups were separately submitted to ANOVAs having hemifield and side of effector as main factors. In subject R.B., the hemifield/effector side interaction proved significant only for unilateral distal ($P < 0.05$) and proximal responses ($P < 0.005$), while in subject P.M. it was significant only for unilateral distal responses ($P < 0.005$). In all other cases. the hemifield/effector side was far from significant in both subjects. Figure 7 provides a comparison between the CUDs of the two acallosal subjects and corresponding CUDs of normal controls. The CUDs of the two acallosal subjects clearly lie outside the upper limit of the normal range. except for the CUD of the unilateral axial response in P.M. and the CUDs of the bilateral axial responses in both R.B. and P.M. On the one hand. these data clearly support previous findings of abnormally long CUDs in callosal agenesis (Jeeves 1969; Milner 1982; Milner et al. 1985). On the other hand, although the low number of RTs collected does not allow definite conclusions, the pattern of CUDs in the two acallosal subjects agrees with that of the callosotomy patient M.E. insofar as it suggests that the CUD tends to decrease along a distal-proximal-axial gradient and to be greater for unilateral than for bilateral responses.

Discussion

Forebrain commissurotomy causes a total loss of normal abilities such as reading in the left visual hemifield or naming objects felt by the left hand, implying that callosal interhemispheric transfer is indispensable for the correct execution of these tasks in normals (Sperry et al. 1969; Sperry 1984; Bogen 1987). But the understanding of commissural functions can also be aided by the analysis of less conspicuous signs or symptoms of interhemispheric disconnection, consisting for instance of the perturbation of the timing, rather than in the total suppression of certain specific actions. Using this approach, the present report provides evidence for a specific involvement of the corpus callosum in elementary forms of normal. visually guided motor behaviour. Further, it affords information on how laterality of visuomotor control changes with the axial, proximal or distal nature of the movement and in relation to the bilateral or unilateral mode of responding.

Crossed-uncrossed differences (CUDs) in simple visuomotor reaction time to lateralized visual stimuli are absent in normal subjects if the crossed responses are liable to be directly initiated by either hemisphere through bilaterally distributed motor pathways (Di Stefano et al. 1980; Aglioti et al., in preparation). These studies in normals allow a distinction between crossed responses which presumably utilize interhemispheric transfer from those which presumably do not. The first set of responses includes unilateral and bilateral distal responses and unilateral proximal responses of the upper limb, all associated with significant CUDs and reflecting dependence on interhemispheric transfer. The second set includes bilateral proximal responses and unilateral and bilateral axial responses of the upper limb, all associated with null CUDs reflecting independence from interhemispheric transfer. On these premises, impairment of interhemispheric transfer by callosal defects should alter the CUDs associated with the first set of responses, but not those associated with the second set.

The pattern of CUDs in our callosotomized subject M.E. fits this prediction very well. His CUDs on unilateral and bilateral distal responses and on unilateral proximal responses had values that were at least an order of magnitude greater than the typical 2–3 ms corresponding to CUDs of normals. The corresponding CUDs of our two subjects with callosal agenesis were smaller than those of M.E., but still completely outside the range of normals. Similarly, elevated CUDs values have been reported in previous studies on subjects with a congenital absence of the corpus callosum (Jeeves 1969; Reynolds and Jeeves 1974; Milner 1982; Milner et al. 1985; Di Stefano et al. 1992) as well as in split-brain patients (Sergent and Myers 1985; Clarke and Zaidel 1989; Di Stefano et al. 1992); however, in those studies, CUD assessments were limited to digital and/or manual reactions, or were inferred from RT differences between the visual hemifields, or lack thereof, for vocal or blowing responses. Our extension of the analysis to proximal and axial upper limb responses and our comparison between unilateral and bilateral responding modes show that, in at least some of these response conditions, acallosal subjects display insignificant or null CUDs, in sharp contrast with their abnormally long CUDs on distal responses. More specifically, the response conditions which yield null CUDs in normals also tend to yield null CUDs in acallosals.

The long CUDs of acallosals present themselves as straightforward manifestations of interhemispheric disconnection rather than as effects of spatial stimulus-response compatibility, as suggested by Ledlow et al. (1978) and Swanson et al. (1978). Spatial compatibility effects consist of a speed advantage for responding when stimulus and response are matched for side, compared with responding when the sides of stimulus and response are opposite (e.g. Umiltà and Nicoletti 1990). However, such effects are usually seen in choice RT tasks but not in simple RT tasks. Previous studies on simple manual RT have clearly shown that CUDs in normals (Anzola et al. 1977; Berlucchi et al. 1977), callosal agenetics (Milner et al. 1985; Di Stefano et al. 1992) and partial callosotomy patients (Di Stefano et al. 1992) are based on anatomy rather than on spatial compatibility. This conclusion can now be extended to patients with complete callosotomy on account of experiment 4 showing that M.E.'s CUD on unilateral distal responses was unaffected by the spatial relations between the position of the visual stimulus and that of the responding hand.

It must be emphasized that the three acallosal subjects in this study were fully capable of making all types of speeded responses both ipsilaterally and contralaterally to the visual stimulus, either unilaterally on right and left sides, or concurrently on both sides. Their strikingly long CUDs depended on a selective retardation of crossed distal responses, both unilateral and bilateral, and of crossed unilateral proximal responses, compared with corresponding uncrossed responses. Possible non-specific influences of epileptogenic pathology and/or antiepileptic medication on the performance of commissurotomized patients in RT tasks (Smith 1947) can be ruled out as causal factors of the abnormal CUDs of acallosals. First, abnormally long CUDs are found in M.E. and other callosotomized epileptics, all of whom are treated with antiepileptic drugs, as well as in subjects with callosal agenesis, who are neither epileptic nor treated with drugs (e.g. Milner et al. 1985; and present subject R.B.). Second, in another study we found an entirely normal pattern of CUDs in patients also treated pharmacologically and surgically for epilepsy, but with a more limited commissural section intended to spare the posterior corpus callosum (Tassinari et al. 1990). It must also be emphasized that the long CUDs of acallosals were in no way caused by an inflation of motor times of crossed responses, due to a slower development of force compared to uncrossed responses and a resulting delayed operation of keys and levers. Our EMG recordings from prime movers have indeed shown that these long CUDs depended on factors preceding the activation of motoneurons.

In theory, subjects with defective forebrain commissures could use various extraordinary modes of visuomotor integration in order to perform crossed responses to lateralized visual stimuli. First, extant central channels for interhemispheric communication may maintain functional cross-linkages between the hemisphere in receipt of the visual stimulus and the hemisphere which produces the motor response, although such transfer of information is bound to be more time consuming than normal interhemispheric transfer via the major commissures. Second, an even more time consuming solution may be offered by the so-called external cross-cuing strategy, by which the visually recipient hemisphere prompts the other hemisphere to emit the required response through an

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overt or covert behavioural feedback. In short, upon receiving a visual stimulus one hemisphere can bring about a mediating change in the somatosensory periphery, for example through a contraction of the neck muscles: the other hemispere can then sense this change and use it as a releaser of an action belonging in its specific motor repertoire, such as a movement of a contralateral finger (Gazzaniga 1970). Third, motor systems in the visually recipient hemisphere, i.e. the hemisphere opposite the side of the visual stimulus, may activate ipsilateral effectors through direct descending connections, thus making interhemispheric transfer unnecessary for the execution of crossed responses. In this case the speed of such responses would be determined by the efficacy of the ipsilateral motor command.

No CUD found in the acallosals of the present and previous studies (Jeeves 1969; Reynolds and Jeeves 1974; Milner 1982; Milner et al. 1985; Sergent and Myers 1985; Clarke and Zaidel 1989; Di Stefano et al. 1992), however long, is long enough to be compatible with a peripheral cross-cuing mechanism as the mediator of crossed responses. The pattern of CUDs found in these subjects must therefore be related to extracallosal pathways for interhemispheric communication and/or to uncrossed versus crossed pathways for motor control. Specifically, premotor time may be longer for crossed as compared to uncrossed responses because the former responses either require an interhemispheric transfer, or are effected by a weak ipsilateral motor system.

The possibility that individual finger movements are initiated by the ipsilateral hemisphere can be evaluated against different kinds of clinical evidence. In hemispherectomy cases, an effective ipsilateral control of digital movements is at best feasible by means of synkinesias of the wrist and forearm (e.g. Müller et al. 1991). Crossed distal responses in our acallosals cannot be explained in this way because these synkinesias were definitely impracticable, and were not observed, in our experimental situation. On the other hand, ipsilateral motor control of the fingers may function only on a background of normal or subnormal contralateral innervation. Contrasting results have been reported in this respect in earlier studies on commissurotomized patients. Tests of imitation of lateralized pictures of finger postures have supported the conclusion that either hemisphere can control proximal limb muscles to some extent, but neither hemisphere can control ipsilateral fingers (Gazzaniga et al. 1967; Volpe et al. 1982). Trope et al. (1987) have instead claimed that in commissurotomy patients there exists some degree of motor control by each hemisphere – on at least the thumb and the index – as suggested by their ability to move a single finger indicated in a lateralized drawing of the hand. However, these results can also be explained in terms of interhemispheric transfer, or can be due to a response bias favouring the most mobile fingers.

The hypothesis that acallosal subjects can use an ipsilateral motor control for performing responses with single fingers has been challenged by Milner et al. (1985), on account of the pattern of side-to-side correlations for bilateral responses to lateralized flashes (see below). We agree with Milner et al. (1985) that crossed distal responses of acallosals are most likely to be mediated by an extracallosal interhemispheric transfer. This hypothesis is compatible with the demonstrated ability of noncallosal cross-midline pathways to transmit at least crude visual information. The main extracallosal pathways which may subserve interhemispheric transfer at the cortical level are the hippocampal commissure and the anterior commissure. The possible contribution of the hippocampal commissure to distal crossed responses of split-brain patients, including our callosotomised patient, can be disregarded because this commissure is usually sectioned along with the corpus callosum. The anterior commissure, which has been repeatedly though never conclusively implicated in interhemispheric visual and visuomotor integration in normal and acallosal people, was cut in the patients of Sergent and Myers (1985) and Clarke and Zaidel (1989), but not in our patient M.E. Since the latter patient has CUDs as long as, or even longer than those of the former patients, it follows that the putative extracallosal interhemispheric transfer for crossed responses is not speeded up significantly by having an intact anterior commissure. This conclusion is also supported by the long CUDs found in cases where callosal agenesis is associated with a normal or even hyperplasic anterior commissure (Jeeves 1990), and confirmed in our two cases also affected by callosal agenesis and also having an apparently normal anterior commissure. We therefore suggest that if an extracallosal interhemispheric transfer mediates crossed responses, this transfer occurs by way of subcortical commissures and other brainstem routes for indirect communication between the cortices of the two sides, as has been postulated to account for residual abilities for interhemispheric interaction in visually guided behaviour in callosal agenesis and after forebrain commissurotomy (Trevarthen and Sperry 1973; Milner 1982; Holtzmann 1984; Milner et al. 1985; Myers and Sperry 1985; Sergent 1986, 1987).

Earlier studies in split brain patients and callosal agenetics have suggested that the role of the corpus callosum in bilateral co-ordination may have to do with diversifying rather than equalizing bilateral responses. The absence of the corpus callosum appears to induce a disability to suppress symmetry of concurrent bimanual movements on dual tasks which call for differentiated actions of the two hands (Preilowski 1972; Jeeves et al. 1988; Tuller and Kelso 1989). Normal controls and callosal agenetics alike have been shown to display highly significant correlations between crossed and uncrossed manual responses when responding bilaterally (Di Stefano et al. 1980; Milner et al. 1985). Our finding of a similar effect in M.E. lends greater applicability to the phenomenon by extending it to the acallosal brain in general, although there are some important differences with normals. M.E. exhibited a definite tendency for synchronisation of bilateral components of motor output when he responded with both upper limbs to the lateralised flash. This tendency manifested itself in a strong reduction of the CUD on bilateral compared to unilateral distal responses, in an annulment of the CUD on bilateral proximal responses, and in the occurrence of clear-cut correlations between crossed and uncrossed RTs of distal and proximal responses. Qualitatively, the above changes in CUD mirror those observed under comparable conditions in normals by Di Stefano et al. (1980). Quantitatively, however, the CUD for the bilateral distal responses of M.E. was still much longer than those of normal counterparts, as was also previously found in callosal agenetics (Jeeves 1969; Reynolds and Jeeves 1974; Milner et al. 1985) as well as in the two subjects R.B. and P.M. of the present study, also affected by callosal agenesis. Milner et al. (1985) argued that if the same motor system in the visually recipient hemisphere of acallosals initiated manual responses on either side through ipsilateral and contralateral descending pathways, then the crossed-uncrossed correlations should be higher in acallosals than in normals, because of a stronger intra- than intersystem coupling. The fact that crossed-uncrossed correlations are similar in normals (Di Stefano et al. 1980), callosal agenetics (Milner et al. 1985) and callosotomized subjects (present results) is a further argument against ipsilateral control and in favour of interhemispheric transfer in the mediation of crossed distal responses in acallosals. Apparently, a true bilateral simultaneity of crossed and uncrossed distal responses to a lateralized flash cannot be achieved in both normals and acallosals, although there is a reduction of the CUD relative to the unilateral response mode. However, the different CUD magnitudes indicate that this failure is much more pronounced in acallosals implying that, in normals, the corpus callosum does participate in some way to bilateral synchronization of distal responses triggered by a lateralized visual input. Callosal contributions seem immaterial for bilateral synchronization of proximal and axial responses to a lateralized flash, given the absence of a CUD in acallosals and normals alike. Bilateral synchrony of symmetric proximal and axial limb responses thus appears to be brought about by a unitary motor control system without the aid of the corpus callosum.

There is a certain similarity between the present CUD modifications and the changes in RT patterns observed when patients with unilateral brain damage shift from a unilateral to a bilateral response mode. For example, Jung and Dietz (1975) found in a simple audiomotor RT task that the EMG latency of prime movers in the arm contralateral to a chronic central motor lesion was on the average about 55 ms longer than EMG latency of the corresponding muscles on the healthy side. However, when patients responded bilaterally, EMG latency on the affected side diminished considerably, so that the average difference relative to the normal side dropped to 25 ms. Likewise, in a test for simple RT of key pressing responses to a non-lateralized flash, a patient with anaesthesia of the right hand from a left parietal lesion showed a 70 ms difference in favour of the normal left hand when responding unilaterally; however, the difference reduced to only 6 ms on bilateral responding due to a slight increase in RT of the normal hand and a more marked decrease of RT in the affected hand (see Jeannerod 1988, p.82). These effects suggest that in the bilateral response mode the speed of movements on the affected side benefits from the selective activation of an ipsilateral motor command from the undamaged hemisphere, contingent on the emission by the same hemisphere of a concurrent command to the effectors of the other side.

Yet some of the data from M.E. suggest that the tendency to synchronize the two sides on bilateral trials was obtained not by speeding up crossed responses relative to uncrossed responses, but rather by slowing down uncrossed responses relative to crossed responses. This was found with both distal and proximal responses. In the case of distal responses, the partial synchronization of crossed and uncrossed responses may result from the action of a superordinate premotor centre which tends to incorporate separate motor commands from the two hemispheres into a coordinative ensemble. Alternatively, it is possible that on bilateral trials the faster motor command is delayed because of some interhemispheric extracallosal interference by the concurrent slower command. In both cases, the absence of the corpus callosum is bound to reduce the interactions between the two motor commands and thus their tendency to be synchronous. The situation may be different for bilateral proximal responses, since in this case bilateral synchronisation is likely to depend on a single motor command initiating the response on both sides. Further, the unilateral components of a bilateral response can be performed by neural systems differing at least in part from those mediating the same movements when made unilaterally, as has been shown to be the case for the facial musculature (Gazzaniga and Smylie 1990). Similarly, different motor systems can be recruited to effect the same proximal movement of the upper limb depending on whether this is performed unilaterally or bilaterally. A proximal arm movement can be triggered through the crossed corticospinal tract from the opposite hemisphere when performed unilaterally, or through the uncrossed component of the corticospinal tract and/or by the cortico-reticulo-spinal pathway from the ipsilateral hemisphere when performed bilaterally (Jung and Dietz 1975; Di Stefano et al. 1980; Kuypers 1987, 1989; Freund 1987; Benecke et al. 1991; Müller et al. 1991). Since the latter motor pathways are bilaterally distributed, bilateral responses can be generated by a single motor command from either hemisphere, hence the good crossed-uncrossed synchronization even in the absence of the corpus callosum.

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