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Inhibitory and excitatory interhemispheric transfers between motor cortical areas in normal humans and patients with abnormalities of the corpus callosum

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Summary

Transcranial magnetic stimulation of the motor cortex was performed in 10 normal subjects and 10 patients with radiographical abnormalies of the corpus callosum. Seven patients had a complete or partial agenesis or hypoplasia of the corpus callosum, two had a thin corpus callosum due to hydrocephalus or white matter degeneration and one had a circumscript contusion lesion of the corpus callosum. The patients served as a clinical model to investigate transcallosal influences on excitatory and inhibitory effects of motor cortex stimulation and to assess the potential diagnostic use of interhemispheric conduction studies and the contribution of interhemispheric interaction on transcranially elicited contralateral excitatory and inhibitory motor responses. Stimulation over one motor cortex suppressed tonic voluntary electromyographic activity in ipsilateral hand muscles in all subjects with preserved anterior half of the trunk of the corpus callosum. Since this suppression was lacking or had a delayed onset latency in patients with absence or abnormalities of the anterior half of the trunk of the corpus callosum it can be concluded that it is due to a transcallosal inhibition (Ti) of the opposite motor cortex mediated by fibres passing through this part of the corpus callosum. In normal subjects Ti had an mean onset latency of 36.1±3.5 ms (SD) and a duration of 24.5±3.9 ms. The calculated mean transcallosal conduction time was 13 ms. The threshold of Ti recorded in muscles ipsilateral to stimulation tended to be higher than the one for eliciting excitatory contralateral motor responses (56±6% versus 46±10% maximum stimulator output). Cortical thresholds (at rest) for contralateral excitatory hand motor responses were higher in patients with developmental abnormalities of the corpus callosum than in normals (66±17% versus 46±10% maximum stimulator output), which probably reflects also a facilitatory transcallosal interaction of both motor cortices in normals. In contrast, facilitation of cortically elicited motor responses in one hand by strong contraction of the other hand was the same in the patients with agenesis of the corpus callosum and normals, which suggests that this facilitatory spread takes place on a spinal rather than on a cortical level. Central motor latencies and amplitudes of contralateral hand motor responses were the same in patients with developmental abnormalities of the corpus callosum and normals (6.1±0.7 ms versus 6.3±0.7 ms and 6.7±2.4 mV versus 6.6±2.9 mV) so that callosal transfers do not seem to influence corticospinal conduction properties. Furthermore, the inhibition of tonic electromyographic activity following the cortically elicited contralateral response, which we refer to as postexcitatory silent period (Pi), was investigated. When about the same stimulus intensity was used, the Pi was shorter in the patients with developmental defects of the corpus callosum. This could be compensated for by increasing the stimulus intensity in the patients, which might hint at some callosally mediated enhancement of inhibition in the late phase of the Pi. Since transcranial stimulation of one motor cortex reproducibly elicited a transcallosal inhibition of the other motor cortex in normal subjects, this approach might be of diagnostic value for studying callosal conduction and intracortical inhibitory mechanisms.

Keywords: human transcranial magnetic stimulation; motor cortex; corpus callosum; agenesis of the corpus callosum; interhemispheric inhibition

Introduction

Transcranial magnetic brain stimulation has introduced the possibility of investigating interhemispherical connections in unanaesthetized man. Two transcallosal effects have been shown for magnetic stimulation. First, magnetic stimulation over the frontal cortex was followed by an evoked potential over the homologous frontal cortex of the other hemisphere, which had an onset latency of 8–9 ms and a duration of 7–15 ms (Cracco *et al.*, 1989). The authors presumed that the recorded surface positive wave reflected either an orthodromic or antidromic transfer along callosal fibres. Secondly, a strategy was employed to limit the investigation to motor cortical areas by applying magnetic conditioning stimuli over the motor areas of one hemisphere prior to conditioning stimuli given to the contralateral motor cortex (Ferbert *et al.*, 1992). The conditioning stimuli reduced the excitatory effect of the test stimuli when the conditioning-test interval was 5–6 ms or longer. When studying single motor unit responses instead of surface electromyographic responses, minimal interstimulus intervals with suppression effects were 9–12 ms. Furthermore, it was observed that magnetic conditioning stimuli suppressed ongoing voluntary electromyographic activity in small hand muscles ipsilateral to brain stimulation. This inhibition began 10–15 ms after the minimum corticospinal conduction time to the recorded hand muscle and had a duration of ~30 ms (Ferbert *et al.*, 1992). The authors could show that the observed inhibitory effect most likely occurred at the level of the cerebral cortex and suggested that it was probably conducted along a callosal pathway.

With the aim of defining the pathways involved in interhemispheric inhibition, we investigated patients with developmental abnormalities of the corpus callosum by using the paradigm of interhemispheric inhibition of tonic electromyographic activity. This patient model was also used to explore whether callosal transfers have influence on the susceptibility of the motor cortex to transcranially applied stimuli and on the inhibition of tonic voluntary activity following the contralateral excitatory response. We shall refer to this later inhibition as postexcitatory inhibition or the postexcitatory silent period (Pi; Wilson *et al.*, 1993) in this paper. Since the end of the excitatory response preceeding the inhibitory period cannot be determined exactly, the Pi was measured from the onset of the excitatory response to the end of the inhibition. At low stimulus intensities an inhibition of tonic voluntary electromyographic inhibition could sometimes be evoked without a preceeding excitation. However, as this phenomenon was inconsistant we only measured the Pi at high stimulus intensities.

Furthermore, the patient model was used to investigate whether facilitatory effects of muscle contraction on homologous muscles of the other hand are due to callosal transfers. A spread of facilitatory effects between hand muscles has previously been reported which was still present when a patient with an above-elbow amputation imagined the contraction of hand muscles in the phantom limb. The effect consisted of an increase in the amplitude and a reduction in the onset latency of transcranially elicited motor responses of the opposite arm (Hess *et al.*, 1986, 1987).

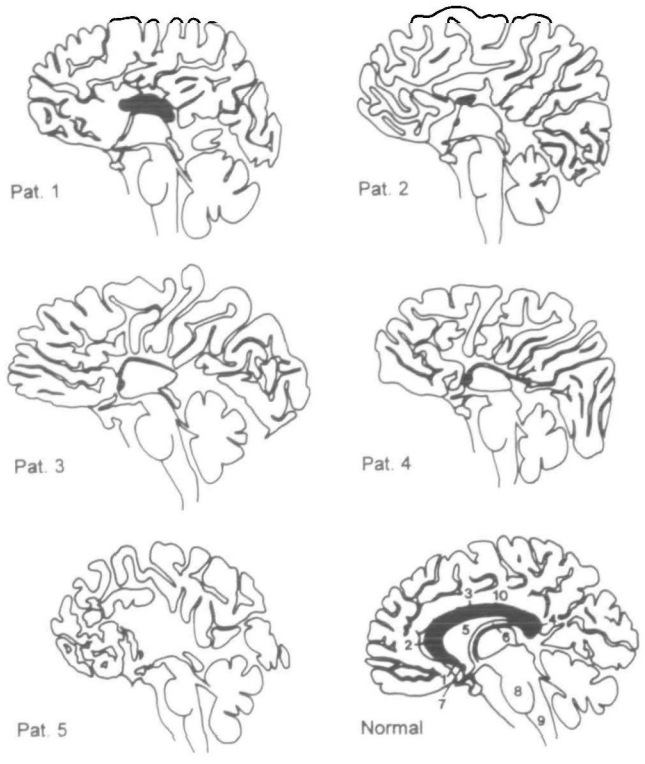

Fig. 1 Anatomical parasagittal slices of five investigated patients (Pat. 1–5) with partial or complete agenesis of the corpus callosum drawn after corresponding T_1-weighted MRIs. In none of the patients could an interhemispheric inhibition following magnetic stimulation over the motor cortex be detected (*see* also Fig. 7). For comparison normal anatomical conditions are shown for one subject. 1 = rostrum corporis callosi, 2 = genu corporis callosi, 3 = truncus corporis callosi, 4 = splenium corporis callosi, 5 = septum pellucidum, 6 = fornix, 7 = commissura anterior, 8 = pons, 9 = medulla oblongata, 10 = gyrus cinguli.

Material and methods

Ten normal subjects (age range 24–38 years, mean 28 years; five woman, five men) and seven patients (patients 1–7) with congenital abnormalities of the corpus callosum were investigated. Three patients had complete agenesis (patients 3–5), three partial agenesis of the corpus callosum (patients 1, 2 and 6), and one had hypoplasia of the corpus callosum (patient 7). The callosal abnormalities were diagnosed on the basis of magnetic resonance imaging (MRI) scans. Midsagittal slices of the brains of the patients were constructed from the corresponding MRI scans and are shown in Figs 1 and 2. For localization of the depicted defects of the corpus callosum in the patients, the topography of the callosal fibres is shown in Fig. 3 as it was constructed from data obtained by autoradiograms of the corpus callosum after injecting

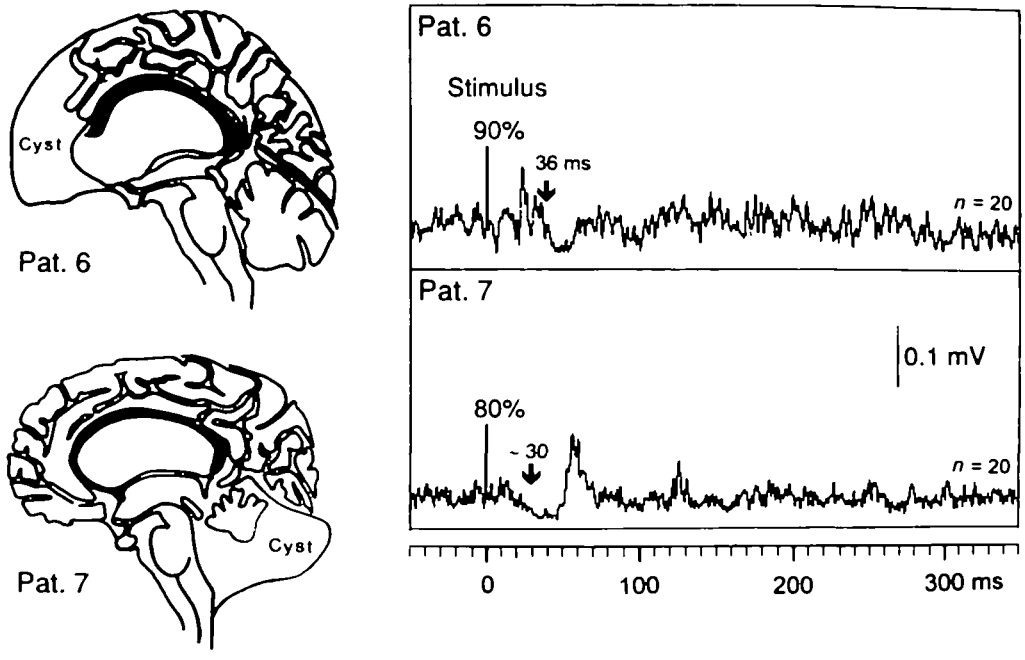

Fig. 2 Transcallosal inhibition with a normal onset latency in a patient with holoprosencephaly and agenesis of the rostrum and genu corporis callosi (Pat. 6) and a patient with Dandy Walker syndrome and hypoplasia of the corpus callosum (Pat. 7). Comparing the findings in patient 6 with patient 1 (cf. Figs 1 and 7) with absent interhemispheric inhibition, it can be concluded that the callosal transfer mainly passes through the anterior half of the trunk of the corpus callosum. Despite the normal onset latency of transcallosal inhibition in patient 6, its depth is less than in normal subjects. The stimulation conditions are similar to those in Figs 6 and 9.

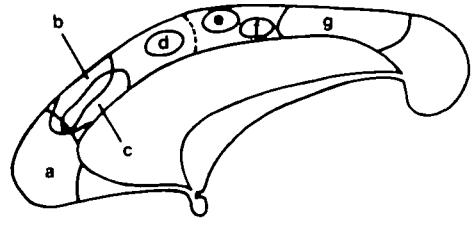

Fig. 3 Schematic topography of callosal fibres constructed from data obtained by labelling studies in the monkey (from Pandya and Seltzer, 1986). a = prefrontal area, b = premotor area, c = supplementary motor area, d = primary motor area, e = primary somatic sensory area, f = second somatic sensory area, g = posterior parietal area.

radiolabelled amino acids into various discrete sectors of the cerebral cortex in the rhesus monkey (Pandya and Seltzer, 1986). In some of the patients agenesis of the corpus callosum was associated with other developmental defects such as holoprosencephaly (patient 6) or agenesis of the cerebellar vermis (patient 7). Wide sulci were observed in patients 1–5 and probably reflect diminished volume of the white brain matter due to the reduced number of callosal fibres. Special attention was paid to the question as to whether this increased the distance between the coil on the scalp and the underlying motor cortex, since this might influence the effectiveness of stimulation. A thorough analysis of the MRI scans revealed no such significantly increased distance.

Additionally, three patients with acquired abnormalities of the corpus callosum were investigated (patients 8–10). Their MRI scans are shown in Fig. 4. Patient 8 had a leukencephalopathy and atrophy of the corpus callosum, patient 9 had a thin corpus callosum due to hydrocephalus aresorptivus and patient 9 had a circumscript contusion lesion within the first half of the trunk of the corpus callosum. Table 1 gives details of the patients ages, sexes and the clinical and radiographical findings. All patients and normal subjects gave informed consent to participate in this investigation.

Magnetic stimulation and recording

Motor cortex stimulation was performed with a focal 8-shaped coil (outside diameter of one half-coil 8.5 cm) of the Magstim 200 stimulator (2-Tesla version; Magstim Company Ltd, Dyfed, UK) with the centre (contact point of both half-coils) placed tangentially on the skull over the motor cortex. For each subject, the stimulation point for eliciting maximal hand motor responses was determined individually and lay on average 6 cm lateral to the vertex and 1 cm anterior to the interaural line. For optimal stimulation, the coil currents were directed anteroposteriorly (with the handle of the coil pointing backwards) and the induced currents posteroanteriorly. The elicited electromyographic responses were recorded bilaterally from the first dorsal interosseus muscle with surface electrodes (area 70 mm^2). The electromyographic signals were amplified by a Tönnies DA II electromyograph (formerly Tönnies, Freiburg im Breisgen,

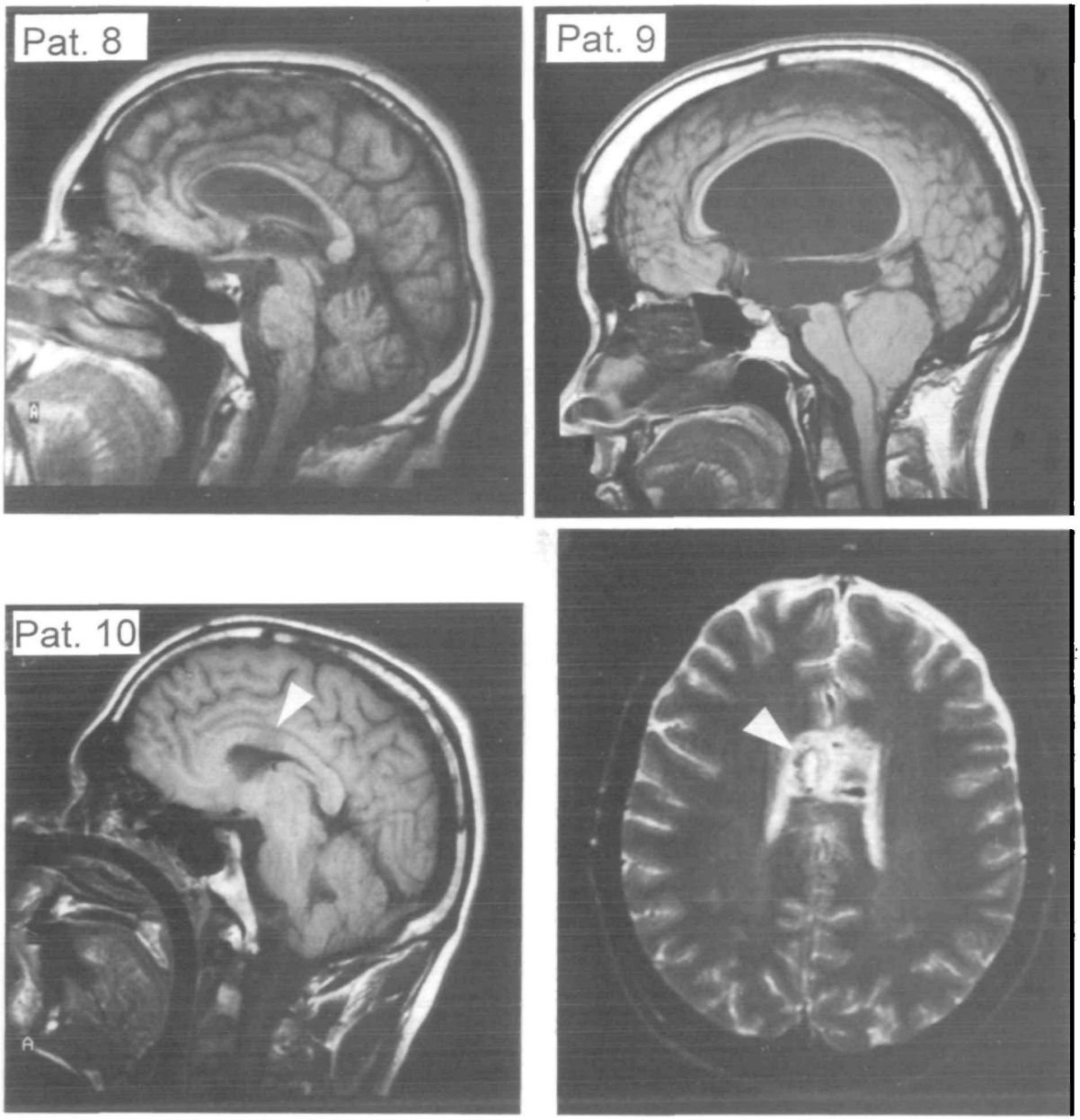

Fig. 4 MRIs of patients with present but abnormally late transcallosal inhibition. Parasagittal slices of the brain in a patient with atrophy of the corpus callosum due to leukencephalopathy (Pat. 8; TR 621 ms/TE 20 ms); a patient with thin corpus callosum due to hydrocephalus (Pat. 9; TR 0.5 s/TE 20 ms); and a patient with a circumscript contusion lesion in the anterior half of the trunk of the corpus callosum (Pat. 10; sagittal slice: TR 621 ms/TE 20 ms; axial slice: TR 3.6 s/TE 2.1s). The corresponding electrophysiological recordings concerning transcallosal inhibition are shown in Fig. 8.

Germany) with band-pass filtering between 20 and 3000 Hz. Data were collected with a Tandon personal computer using a CED 1401 interface and a data collection program (SIGAVG, sampling frequency of 5000/s/channel).

Experimental procedures

Response thresholds for transcranially elicited electromyographic compound potentials were determined with the muscle at rest. Relaxation was monitored by using a high gain display and auditory feedback of the electromyographic activity in patients and normal subjects. Conduction studies were carried out with slight tonic contraction (~10% of the maximal tonic force) of the hand muscles and stimulus intensities of 70% in the normal subjects (1.5 times the excitation treshold at rest) and with 90% in the patients 1, 2, 3 and 5 (~1.4–1.6 times the excitation threshold at rest), to correct for threshold differences. In patient 4 the threshold at rest was already 95% so that maximal stimulus intensities had to be used. Central motor latency times (CMLs) were calculated by subtracting the peripheral conduction time from the cortically evoked motor response with the shortest onset

Table 1 *Clinical and radiographical findings in patients with abnormalities of the corpus callosum*

Pat.	Sex	Age (years)	Radiographical findings			Clinical findings
			Corpus callosum	Anterior commissure	Associated malformations or diseases	Abnormalities of the motor system/other signs or symptoms
1	F	30	Partial agenesis with preserved middle trunk	Absent	Cortex heterotopias, hypoplastic left hemisphere	Migraine-like headache, grand maux, anticonvulsive medication
2	M	62	Partial agenesis with preserved part of the middle trunk	Present	Suspected early stage of motoneuron disease	Generalized weakness
3	M	51	Complete agenesis	Present		Pressure-like headache
4	M	52	Complete agenesis	Present		Clumsiness of fine finger movements
5	M	21	Complete agenesis	Present		Impaired bimanual interaction when visual control was excluded, dysdiadochokinesia of the left arm, bilaterally increased reflexes in the the lower extremity
6	M	56	Partial agenesis with preserved trunk and splenium	Absent	Large frontal cyst (holoprosencephaly)	Clumsiness of fine finger movement
7	F	27	Hypoplasia of the whole corpus callosum	Present	Aplasia of the caudal lobe of the cerebellar vermis, open connection between 4th ventricle and cerebello-medullary cistern (Dandy Walker syndrome)	Headache, dizziness, upbeat spontaneous nystagmus
8	F	56	Atrophy of the whole corpus callosum	Present	Leukencephalopathy	Dementia
9	M	32	Thin corpus callosum	Present	Hydrocephalus aresorptivus	Gait ataxia, double vision
10	M	29	Contusion lesion in the anterior half of the trunk of the corpus callosum	Present		Gait ataxia, disturbed bimanual interaction, disturbed mirroring Dizziness

latency. The peripheral motor latency time was obtained by magnetic stimulation of spinal nerve roots with a large circular stimulation coil placed over the cervical spine in such a way so that the coil currents flowed tangentially to the nerve course.

The amplitude of cortically evoked motor responses was determined 'peak-to-peak', i.e. as the difference from the maximal negativity to the maximal positivity of 20 averaged consecutive responses. The duration of the Pi was measured during maximal tonic muscle contraction from the onset of the cortically elicited excitatory response to the end of the silent period of 20 rectified and averaged consecutive contralateral responses (Fig. 9). The end of Pi was set at a point where the averaged electromyographic activity exceeded ~0.2 times the amplitude of the averaged electromyographic activity before the magnetic stimulus. For the same stimulation and recording conditions we investigated whether a transcallosal inhibition (Ti) in hand muscles ipsilateral to the stimulated motor cortex occurred (Figs 2 and 5–9). Averages were performed offline from single sweeps. Recordings were discarded in which the degree of muscle activation did not meet the postulated conditions. By this procedure the variability of the evaluated motor responses could be kept low.

To investigate potential spread of facilitatory effects between muscles of both hands, cortex stimulation was performed with 1.2 times the response threshold for the relaxed muscle. The amplitudes of the cortically elicited responses were determined for the target muscle at rest and maximally tonically contracted, and for maximal tonic

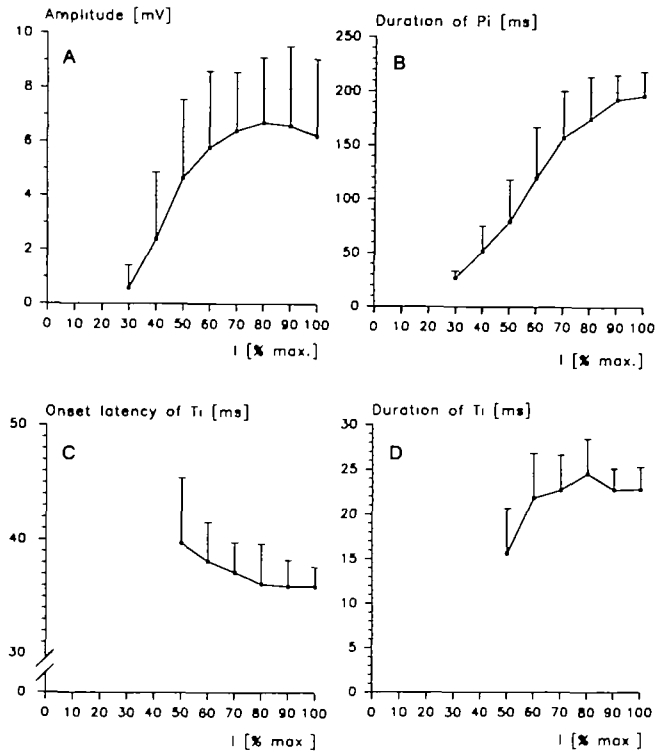

Fig. 5 Changes in different parameters of motor responses in the first dorsal interosseus muscle following transcranial magnetic brain stimulation with different stimulus intensities. Stimulation was performed with a focal coil over the hand-associated motor cortex with coil currents flowing in an anteroposterior direction. In muscles contralateral to the stimulated hemisphere the amplitude (**A**) and the duration (**B**) of the Pi and in muscles ipsilateral to stimulation the onset latency time (**C**) and duration (**D**) of the Ti were measured. Mean values ±SD (bars) for 10 averaged consecutive responses in 20 hands of 10 different normal subjects are given.

contraction of the same muscle of the contralateral hand while the target muscle was at rest (Fig. 10). Only patients without interhemispheric inhibition (patients 1–5) were investigated, to make sure that there was no callosal interaction between the motor cortices of both sides.

The controls were 10 normal subjects who were investigated in the same way as the patients. Furthermore, the stimulus intensity-dependent changes of the Pi and Ti were investigated systematically in the normal subjects (Fig. 5).

Results

Interhemispheric inhibition

While at stimulus intensities of 80% of the maximal output of the stimulator an early phase of ipsilateral inhibition with a mean onset latency of 36.1±3.5 ms (mean±SD, range 30.6–44.0 ms) and a duration of 24.5±3.9 ms (range 12.6–29.0 ms) occurred in all healthy subjects at stimulus intensities of 80% of the maximal stimulator output (Fig. 5C), a second and third later phase of inhibition occurred irregularly at

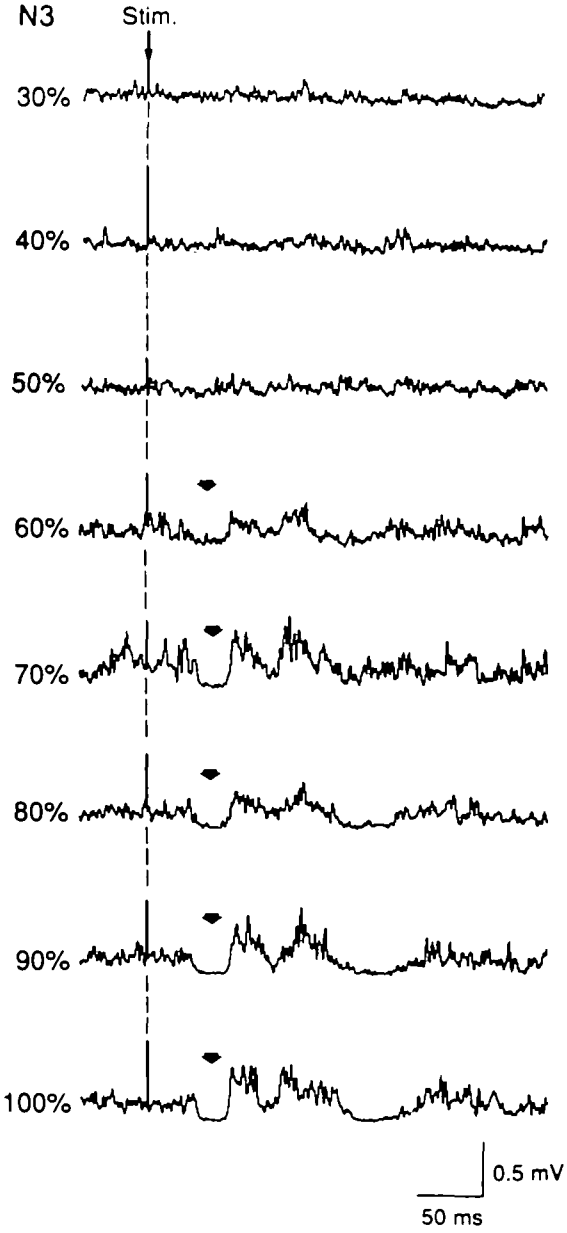

Fig. 6 Effect of stimulus intensity on interhemispheric inhibition in a normal subject (N3, *see* also Fig. 7). Transcranial magnetic stimulation was performed with a focal stimulation coil over the left motor cortex while electromyographic recordings were taken from the left first dorsal interosseus muscle during maximal voluntary tonic contraction. Twenty consecutive rectified electromyographic traces were averaged. It can be seen that the early transcallosal inhibition between 36 and 61 ms had a lower threshold of ~60–70% maximum than later inhibitory phases which clearly occurred only at maximal stimulus intensities.

latencies of 70–85 ms and 120–145 ms, respectively (Figs 6 and 7). In seven of the 10 normal subjects later phases of inhibition occurred at 80% of the maximal stimulus intensity. In general, the later phases of suppression of tonic voluntary activity occurred at higher stimulus intensities than the early phase of inhibition.

In normal subjects, the threshold for the early phase of inhibition was 56±6% of the maximal stimulator output and

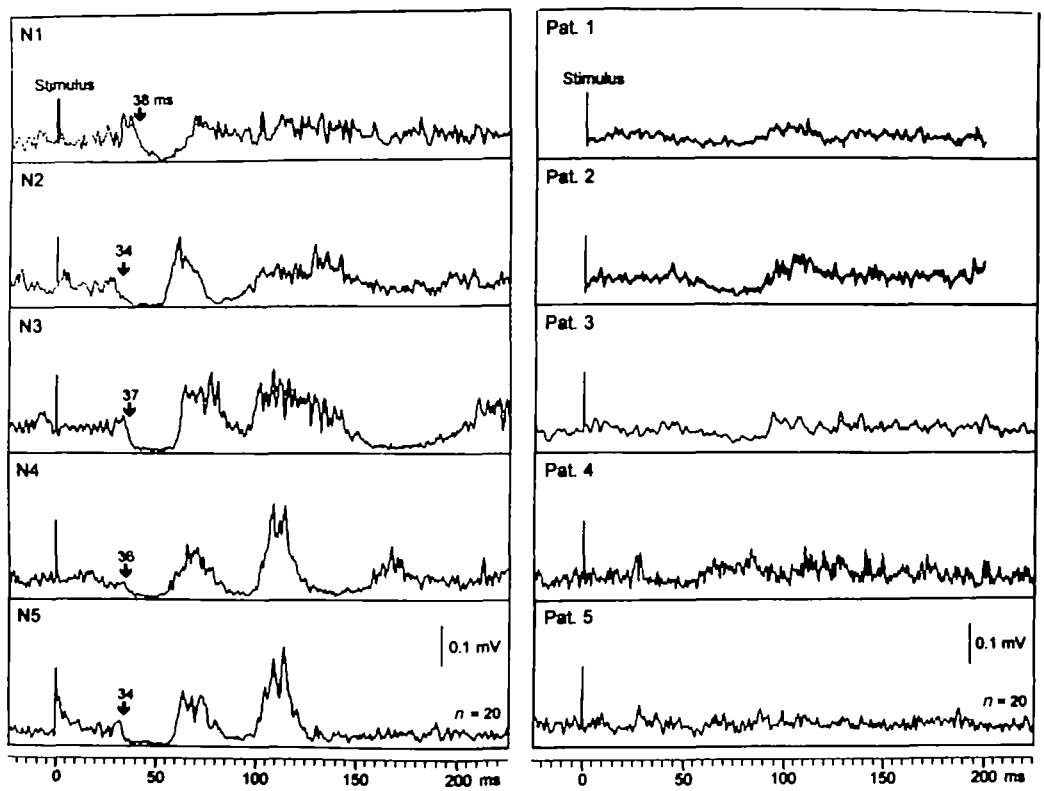

Fig. 7 Averages of consecutive traces of maximal tonic electromyographic activity in the left first dorsal interosseus muscle following transcranial magnetic stimulation over the ipsilateral left motor cortex. The recordings are from five normal subjects (N1–5) and five patients with agenesis of the corpus callosum (Pat. 1–5). The stimulation conditions were the same as in Figs 5 and 9. Stimulation was performed at 80% (normal subjects) and 90% (patients) of the maximal stimulator output. In normal subjects an early phase of inhibition always occurred which had an onset latency of 30–44 ms, the occurrence of later phases of inhibition and excitation varied between individuals. In patients with agenesis of the corpus callosum no early phase of inhibition occurred, which indicates that this phase is mediated via a callosal pathway.

consequently tended to be higher than the threshold for eliciting contralateral excitatory motor responses (46±10%). With increasing stimulus intensities, the onset of interhemispheric inhibition decreased but reached a minimum at 80% of the maximal stimulator output (Fig. 5C). The duration of this inhibition remained fairly constant at stimulus intensities higher than 60% maximum (Fig. 5D).

In patients with absence of the anterior half of the trunk of the corpus callosum (patients 1–5), no clear early interhemispheric inhibition was observed (Fig. 7). Since one patient with agenesis of the rostrum and genu, but present anterior half of the trunk of the corpus callosum (patient 6), had a weak early interhemispheric inhibition with a normal onset latency (Fig. 2), it might be assumed that the pathways connecting the primary motor cortices and being responsible for the early phase of inhibition are mainly localized in the anterior half of the trunk of the corpus callosum, which is in accordance with the findings in monkeys (Fig. 3). In patients 1–3 a slight inhibition of tonic voluntary activity occurred 60–70 ms after the ipsilaterally applied stimulus (Fig. 7) and might therefore be of spinal origin.

In patient 7 with hypoplasia of the corpus callosum the early Ti was weak but occurred at a normal latency (Fig. 2). In patient 8 with atrophy of the corpus callosum (MRI, Fig. 4) the Ti had a prolonged onset latency of 42 ms. Two pronounced later phases of increased electromyographic activity which were not separated by an inhibitory phase were present in this patient. This might hint at an alteration of inhibitory mechanisms in this patient (Fig. 8). Also in patient 9 with a thin corpus callosum due to hydrocephalus and patient 10 with a contusion lesion of the corpus callosum (*see* MRIs, Fig. 4), the Ti was weak and showed prolonged onset latencies of 51 and 46 ms (Fig. 8). From these results it is not possible to determine whether the increased onset latencies of Ti in patients 8–10 result from a reduced conduction velocity of the callosal fibres or from altered intracortical inhibitory mechanisms.

Excitatory responses

In patients with agenesis of the anterior half of the trunk of the corpus callosum (patients 1–5) the mean response threshold for the relaxed hand muscles was 66±17% (mean±SD, n = 10 hands) of the maximal stimulator output

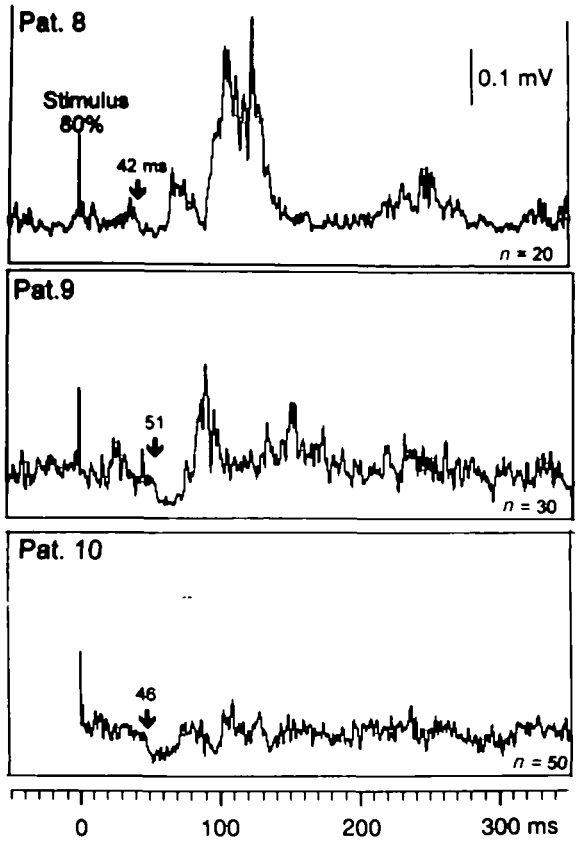

Fig. 8 Inhibition of tonic voluntary electromyographic activity in the left first dorsal interosseus muscle by transcranial magnetic stimulation over the left motor cortex in patients 8–10 whose MRIs are shown in Fig. 4. The clinical findings in the patients are given in Table 1. All three patients have a diminished transcallosal inhibition with increased onset latencies.

and therefore tended to be higher than in the control group of normal subjects (46±10%; Table 2) and in the group of patients with alterations of the corpus callosum but present anterior part of the trunk of the corpus callosum (range 38–48%). Patient 1 was on anticonvulsant medication which might reduce the excitability of the corticospinal system. Excluding him from the calculation of the mean response threshold of the patients group did not change the mean value.

When the stimulation intensity was 90–100% of the maximal stimulator output to correct for the higher response thresholds in patients 1–5, the CMLs and absolute response amplitudes (AMPs) of the investigated 10 hand muscles lay within the range determined for normal subjects with stimulus intensities of 70% (*t* test: CML, $P = 0.24$; AMP, $P = 0.69$; Table 2). These results indicate that agenesis of the corpus callosum does not affect the conduction properties of the investigated corticospinal tracts. Stimulation with 90% instead of 70% of the maximal stimulator output in normal subjects did not significantly change the CMLs and AMPs (*t* test: CML, $P = 0.62$; AMP, $P = 0.71$) due to saturation of excitatory effects (Fig. 5). Also patients 6–10 had CMLs and AMPs within the normal range.

Postexcitatory silent period

When compared with normal subjects and when using the same stimulation strengths, the duration of Pi was reduced in the patients with agenesis of the corpus callosum. In the patients, when the stimulation strengths were increased to 90–100% of the maximal stimulator output to correct approximately for the higher response thresholds, the duration of Pi matched that determined for normal subjects with stimulus intensities of 70% (*see* Table 2; *t* test, $P = 0.95$). Figure 5B shows that in normals the duration of the Pi increased proportionally with the stimulation strength, but not with the size of the evoked excitatory response which saturated at 70% of the maximal stimulator output.

Facilitation by muscle contraction

No significant differences were found for the different contraction manoevres between normal subjects and patients 1–5 with agenesis of the anterior half of trunk of the corpus callosum (Fig. 10), so that there was no evidence for a callosally mediated facilitatory interaction in this paradigm. In the following paragraph, the muscle contralateral to the stimulated motor cortex is named the target muscle. When stimulation was performed with ~1.2 times the response threshold determined for the muscle at rest, contraction of the target muscle contralateral to the stimulated motor cortex reduced the response latency on average by 2.5±1.1 ms (10 normal subjects, 20 hand muscles) and 2.6±0.9 ms (five patients, 10 hands). Concomitantly the AMP of the response in the target muscle increased by a factor of 5.2±1.8 (normal subjects) and 5.9±2.0 (patients). Maximal contraction of the homologous hand muscle ipsilateral to the stimulated motor cortex (contralateral to the target muscle activated by cortex stimulation) reduced the latency of the response in the relaxed target muscle by 0.4±0.8 ms (normal subjects) and by 0.3±1.2 ms (patients). Concomitantly the AMP of the response in the target muscle increased by a factor of 1.7±0.6 (normal subjects) and 1.8±1.3 (patients).

Discussion

Commissural fibres from a given cortical region, especially from the primary motor and somatic sensory cortex, occupy a circumscript part of the corpus callosum (Pandya and Seltzer, 1986). In the rhesus monkey, fibres from the primary motor cortex, which in man is most probably excited by transcranial magnetic stimulation, cross the midline in the second quarter of the trunk of the corpus callosum as it is shown schematically in Fig. 3. This view is compatible with the absence of interhemispheric inhibition in patient 1, who has agenesis of the rostrum, genu and anterior half of the body of the corpus callosum, and presence of interhemispheric inhibition in patient 6, who has agenesis only of the rostrum and genu of the corpus callosum. This interpretation is further supported by the finding of a weak and delayed transcallosal

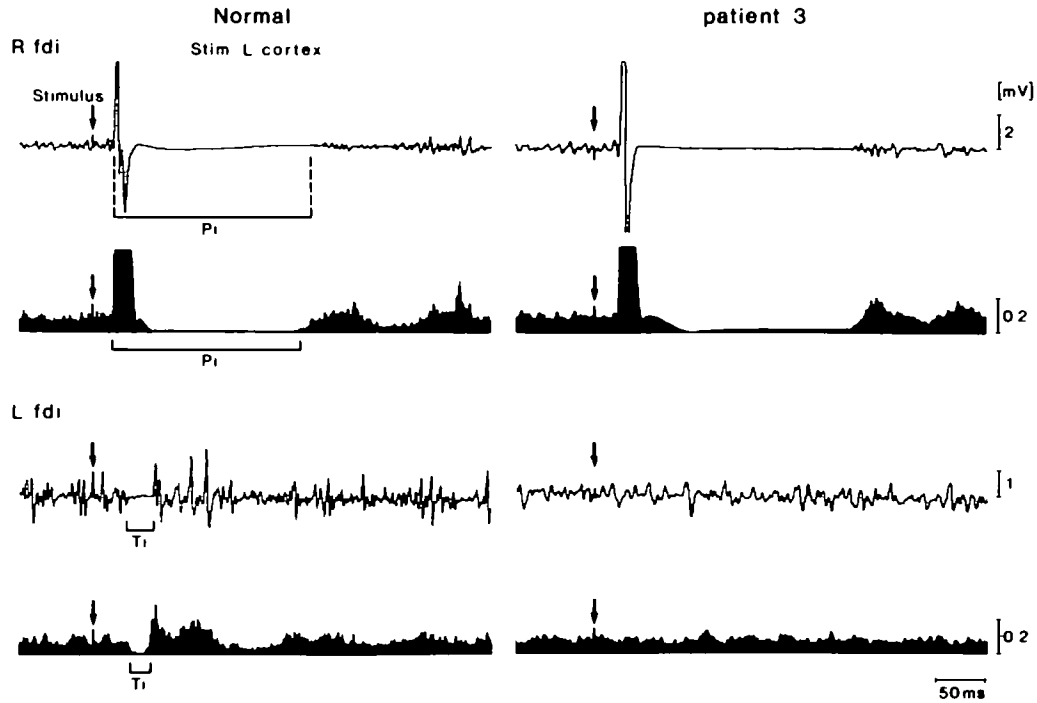

Fig. 9 Exemplary original recordings of cortically elicited, compound electromyographic activity in the first dorsal interosseus muscle (fdi). For magnetic stimulation the centre of the focal 8-shaped coil was placed over the left motor cortex 6 cm lateral to the vertex and 1 cm anterior to the interaural line. Stimulation was performed at 70% (normal subject) and 90% (patient) of the maximal stimulator output, with coil currents flowing in an anteroposterior direction. Single sweeps and the averages of 20 rectified recordings are displayed. In the patient with complete agenesis of the corpus callosum, normal contralateral excitatory responses occurred, while no inhibition of maximal tonic electromyographic activity ipsilateral to the stimulated hemisphere was seen. Pi = postexcitatory inhibition, Ti = transcallosal inhibition, R = right, L = left. The stimulation conditions are the same as in Fig. 5.

Table 2 *Response parameters of transcranially elicited hand motor responses of 10 normal subjects and five patients with partial (patients 1 and 2) or complete (patients 3–5) agenesis of the corpus callosum*

Subjects	Side	Threshold at rest (% max. I)	Stimulus intensity used (% max. I)	CML (ms)	Response amplitude (mV)	Duration of postexcitatory inhibition (ms)
Normals	R/L	46±10	70	6.4±0.7	6.5±2.2	157±43
(n = 10)			90	6.3±0.7	6.6±2.9	192±23
Minimum		30		5.4	3.0	172
Maximum		59		7.4	9.8	225
Patient 1	R	65	90	6.4	2.5	201
	L	65	90	6.0	6.4	158
Patient 2	R	50	90	6.0	7.5	160
	L	65	90	6.4	5.0	69
Patient 3	R	60	90	6.4	11.1	237
	L	60	90	4.8	9.6	206
Patient 4	R	95	100	5.4	6.6	54
	L	95	100	6.5	4.8	64
Patient 5	R	56	90	7.0	7.5	195
	L	45	90	5.8	6.3	212
Patients 1–5	R/L	66±17		6.1±0.6	6.7±2.4	156±68
Minimum		45		4.8	2.5	54
Maximum		95		7.0	11.1	237

For details of the clinical findings *see* Table 1. Responses in the first dorsal interosseus muscle following stimulation over the contralateral hemisphere. Values are given as mean±SD. Results from averages of 10 responses in each normal subject and 20 responses in each of the patients. (% max. I = percentage of maximum stimulator output; R = right; L = left; CML = central motor latency time.)

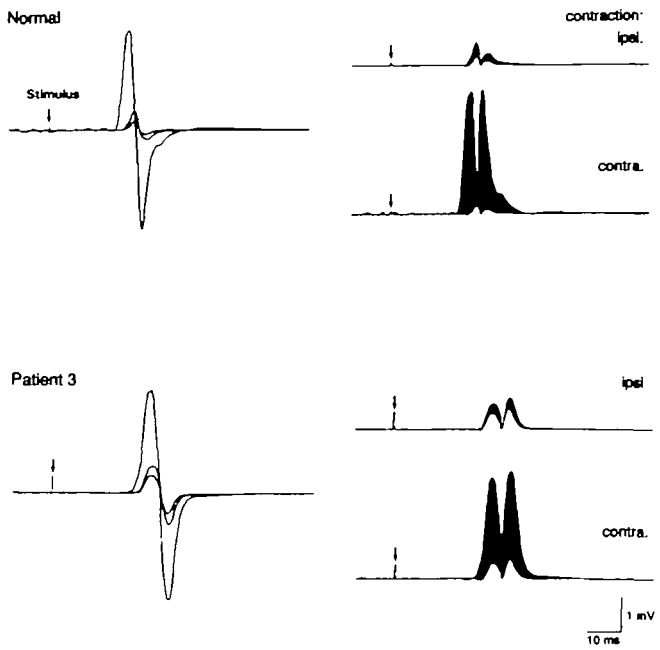

Fig. 10 Facilitation of hand motor responses by contraction of the target muscle (largest response) and the homologous contralateral muscle (second largest response) in comparison with the muscle at rest (smallest response). Examples of recordings for one normal subject and one patient with complete agenesis of the corpus callosum (Patient 3). Superimposition of 10 averaged non-rectified (*left side*) and rectified (*right side*) responses. The faciliatory effect is illustrated as the black area. No significant difference was found between the normal subject and patients with complete agenesis of the corpus callosum, so that the facilitatory effects in this paradigm seem not to be mediated by callosal fibres. ipsi = ipsilateral; contra = contralateral.

inhibition in patient 10 who has a circumscript lesion in the anterior half of the trunk of the corpus callosum. In principle, the occurrence of interhemispheric inhibition was not dependent on a normal volume of the corpus callosum, which could be shown in patients 7–9 who have hypoplastic or atrophic corpus callosum. However, the delayed onset of transcallosal inhibition might indicate reduced conduction velocities in the callosal fibres which might be diagnostically useful.

In monkeys, those areas of the motor representation of axial or midline muscles are reported to have the highest number of commissural connections, while areas representing most distal parts of the extremities often appear to have relatively few commissural connections (Curtis, 1940; Killackey *et al.*, 1983; Gould *et al.*, 1986). However, we found a strong interhemispheric inhibitory effect on hand motor responses in normal subjects, which suggests a quite direct callosal pathway connecting also the hand-associated motor areas in man. We studied the effects of stimulation over the hand-associated motor cortex, since the fast-conducting corticospinal system to hand muscles is the best-defined functional structure activated by magnetic stimulation for which a hemisphere-selective stimulation can be assumed (Day *et al.*, 1987, 1989; Hess *et al.*, 1987).

Previous studies in patients with agenesis of the corpus callosum and anterior commissurotomy have shown that anterior parts of the corpus callosum are crucial for the interhemispheric integration of motor activity during fast, bimanual motor coordination, especially under speed stress and when visual feedback is taken away (Jeeves *et al.*, 1988; Preilowski, 1975). In our study, this feature was prominent in one patient with complete agenesis of the corpus callosum (patient 5), who was sent from the army for examination because he could not take his gun apart and put it together again within a given time at night. In the other patients with agenesis of the corpus callosum, conventional neurological examination of the motor system was normal except for slight clumsiness of finger movements in two patients. The often clinically normal sensorimotor function of acallosal patients (Kretschmer, 1968; Aicardi *et al.*, 1987; Jeeves *et al.*, 1988; Lassonde *et al.*, 1991) and patients with early callosotomy is probably due to compensatory mechanisms (Lassonde *et al.*, 1991). Well-learned, bimanual motor activities such as tying shoe laces were found to be unaffected by anterior commissurotomy (Zaidel and Sperry, 1974). However, such patients normally use visual and proprioceptive feedback systems during the conventional clinical testing (Jeeves *et al.*, 1988). As in the patients of our study, agenesis of the corpus callosum is frequently associated with other malformations (Loeser and Alvord, 1968), which appear to play the dominant role in the production of symptoms.

Inhibitory interhemispheric effects

Previously, two effects of transcranial magnetic brain stimulation have been attributed to a transcallosal pathway. Unilateral magnetic stimulation over the sensorimotor cortex produced an evoked response over the contralateral cortex which had a minimum onset latency of 8–9 ms and a duration of 7–15 ms (Cracco *et al.*, 1989). This represents qualitative reproduction of results obtained earlier in cats and monkeys, in which single electrical shocks were applied unilaterally to the pial surface of the exposed brain and were followed by evoked potentials over corresponding sites of the other hemisphere (Curtis, 1940; Chang, 1953). A second effect can be shown by using a simple paradigm: in normal subjects, stimulation over the motor cortex of one side suppressed cortical activity during tonic contraction of hand muscles ipsilateral to the site of stimulation (Ferbert *et al.*, 1992). A transcallosal pathway for this effect was assumed on the basis of findings similar to ours in a single patient with agenesis of the corpus callosum (Rothwell *et al.*, 1991). The presence of mirror movements in this patient led to the assumption that callosal inhibition might ensure strictly unilateral movements. However, the incomplete radiographical diagnosis in this patient might have led to failure to detect other cerebral defects as origins of the mirror movements, since no mirror movements were observed in any of our five patients with absence of transcallosal inhibition.

On the basis of the mean onset latency of the ipsilateral

inhibition of 36 ms and the overall corticomuscular latency of 21 ms to the same muscle, following stimulation over the contralateral motor cortex, a callosal conduction time can be calculated. When this is done two points have to be considered. First, that magnetic stimulation is thought to activate corticospinal neurons preferentially via cortical interneurons (Day *et al.*, 1987, 1989) which takes ~2 ms to activate the pyramidal neurons including 1 ms for the synaptic delay. Secondly, that the contralateral inhibitory effect might also be elicited by interneurons whose activation also could take ~2 ms. The conduction time from the axon hillock of the callosal neuron to the surface of the contralateral pyramidal tract neuron would then be ~15 ms for a pathway length of ~13 cm (Amassian and Cracco, 1987), which would lead to a conduction velocity of ~8–9 m/s. If an interneuron between the callosal neuron and the pyramidal neuron was postulated, then the callosal conduction time to this interneuron would be ~13 ms and the callosal conduction velocity ~10 m/s. Such a conduction velocity would be consistent with an activation of large-diameter callosal fibres (Tomasch, 1954). These calculations would also be valid if an interhemispheric exchange of corollary or feed-forward discharges arising directly from the motor cortical cells was assumed to be the origin of the interhemispheric inhibition (Jeeves *et al.*, 1988). A corticocortical latency time of 15 ms would be slightly longer than the transcallosal conduction time of 10.5 ms calculated for the interhemispheric spread of myoclonic activity (Thompson *et al.*, 1993), which might be explained by different populations of activated callosal fibres.

Callosal fibres mainly arise from cells in superficial cortical layers, especially from layer III of the isocortex (Jones *et al.*, 1979). The large corticospinal pyramidal neurons responsible for the direct excitatory influence on contralateral spinal motoneurons are located in the cortical lamina V and therefore lie slightly deeper than the callosal neurons. Therefore the stratigraphy of the cortex cannot explain the lower stimulus intensity required for excitatory, contralateral motor responses than for ipsilateral, inhibitory, callosally mediated effects. The higher threshold for transcallosal inhibition could result from a relatively large amount of temporo-spatial summation necessary for orthodromic trans-synaptic activation of callosal neurons or of cells in the recipient cortex, or from the need to excite a sufficient number of fibres to produce an effective antidromic activation of the corpus callosum.

Postexcitatory silent period

Transcranial magnetic stimulation of the motor cortex during tonic electromyographic activity produces a contralateral excitatory motor response followed by a silent period in the electromyogram (Valls-Solé *et al.*, 1992; Wilson *et al.*, 1993). Its duration was found to be proportional to the used stimulus intensity, but not to the activated portion of the alpha motoneuron pool as reflected by the response size. The long duration of the Pi excludes the possibility that the later phase of the Pi is due to refractory properties of cortical neurons and makes it likely that it results from various cortical inhibitory mechanisms and additional inhibitory spinal mechanisms that have already been discussed in detail elsewhere (Fuhr *et al.*, 1991; Uncini *et al.*, 1993; Valls-Solé *et al.*, 1993; Wilson *et al.*, 1993). For a given stimulus intensity the Pi was, on average, shorter in patients with agenesis of the corpus callosum and absent interhemispheric inhibition than in normal subjects. This might hint at some callosally mediated enhancement of inhibition in the late phase of the Pi.

Facilitatory transcallosal effects

When recording from cat pyramidal tract cells during stimulation of the contralateral cortex, an excitation was observed that only occurred when stimulation was performed in a very restricted homotopic cortical area. The excitation was supervened by inhibition when stimulation was extended to a larger surrounding area or was performed with higher stimulation strengths (Asanuma and Okuda, 1962). In a similar approach it could be shown that this facilitatory effect disappeared after sectioning of the corpus callosum (Bremer, 1958). Even when using the most focal magnetic stimulation coil available, the stimulated area is relatively large, which might explain why our investigation in normal human subjects only revealed a clear early inhibition phase. However, the increased response thresholds in patients with agenesis of the corpus callosum might be interpreted as an indirect indicator for interhemispheric facilitatory influences. Facilitatory interhemispheric effects have been postulated in man, since callosotomy sometimes reduced bilateral synchronous electroencephalographic discharges in patients with secondarily generalized seizures (Spencer *et al.*, 1985). On the other hand, epilepsy in patients with lipomas of the corpus callosum was thought to result from a disinhibition of an otherwise subthreshold epileptogenic lesion (Gastaut *et al.*, 1980).

In agreement with previous findings (Hess *et al.*, 1986, 1987) we observed a facilitation of motor responses in one hand by strong voluntary contraction of the other hand. This effect was quantitatively about the same in normal subjects and patients with agenesis of the corpus callosum (patients 1–5), which provides evidence that the facilitatory effect is not mediated by callosal fibres. Different routes could be suggested to account for the observed facilitation. It could originate from a subcortical source with connections to the motor cortices of both cerebral hemispheres. Furthermore it could be mediated by descending motor pathways from one motor cortex which is in contact with spinal motor neurons on both sides, or activity on one side of the spinal cord might cross to the homologous spinal motor neurons on the other side. In some patients a functional abnormality of the observed facilitatory effect could be the origin of mirror movements (Britton *et al.*, 1991).

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