Exp Brain Res (2000) 133:249–253
Digital Object Identifier (DOI) 10.1007/s002210000428

RESEARCH ARTICLE

M.C. Ridding · B. Brouwer · M.A. Nordstrom

Reduced interhemispheric inhibition in musicians

Received: 11 June 1999 / Accepted: 7 March 2000 / Published online: 3 May 2000

Abstract In vivo magnetic resonance imaging has revealed that the anterior half of the corpus callosum is larger in musicians trained intensively from an early age than in untrained subjects. The corpus callosum is crucial for the coordination of bimanual motor activity, but neurophysiological correlates of morphological differences in the corpus callosum of musicians are not known. In the present study we have used transcranial magnetic stimulation (TMS) to assess interhemispheric inhibition in six adult professional musicians who began musical training at an early age. Conditioning TMS was applied to the hand area of the motor cortex of one hemisphere, followed 4–16 ms later by a test stimulus applied to the other hemisphere. Tests were performed at rest, and with the first dorsal interosseous muscle contralateral to the conditioning hemisphere voluntarily active. Conditioning TMS in musicians was 29% less effective at reducing the size of the test MEP at rest, and 63% less effective in the active condition, compared with control subjects. We conclude that transcallosal interhemispheric inhibitory circuits activated by TMS are less effective in musicians than in controls.

Key words Inhibition · Motor cortex · Corpus callosum · Musicians

Introduction

The corpus callosum forms the major interhemispheric fibre tract for transfer of sensory and cognitive information (Seymour et al. 1994). In humans, the corpus callosum is one of the last fibre tracts to be myelinated (Rakic and Yakovlev 1968; Cowell et al. 1992), with its maturation around 10 years of age coinciding with adult levels of bimanual coordination and control (Jeeves et al. 1988b). Functional deficits in the performance of unilateral and coordinated bimanual tasks associated with immaturity, agenesis, or lesion of the corpus callosum suggest that this structure plays an important role in fast and complex motor tasks involving the hands in humans (Preilowski 1975; Nass 1985; Jeeves et al. 1988a, 1988b; Meyer et al. 1998). Both facilitatory and inhibitory effects can be produced in pyramidal tract neurons by electrical stimulation of the opposite motor cortex in cats (Asanuma and Okuda 1962). Similar effects are seen with transcranial magnetic stimulation (TMS) in humans (Ferbert et al. 1992; Ugawa et al. 1993), and these effects also appear to be mediated via the corpus callosum (Schnitzler et al. 1996; Meyer et al. 1995, 1998). It has been proposed that interhemispheric facilitation or inhibition of the opposite motor cortex via the corpus callosum may assist in performance of symmetrical and asymmetrical bilateral movements of the hands, as well as suppressing unwanted movements with the opposite hand during unilateral tasks (see Schnitzler et al. 1996).

In humans, perhaps the pinnacle of bimanual motor coordination is seen in the performance of an expert musician. Using in-vivo magnetic resonance imaging, Schlaug et al. (1995) reported that the mid-sagittal cross-sectional area of the anterior half of the corpus callosum was larger in professional musicians who began their musical training before 7 years of age, compared with professional musicians who began their training later and non-musician control subjects.

One possible neurophysiological correlate of a larger corpus callosum in musicians is an alteration in the effectiveness of transcallosal interhemispheric inhibition. In the present study we have used TMS to examine interhemispheric inhibition (Ferbert et al. 1992) in musicians who began their training at an early age, and non-musician control subjects. We provide evidence for altered in-

M.C. Ridding
Department of Medicine, Royal Adelaide Hospital, Adelaide, Australia 5000

M.C. Ridding · M.A. Nordstrom
Department of Physiology, University of Adelaide, Adelaide, Australia 5005

B. Brouwer
School of Rehabilitation Therapy, Queen's University, Kingston, Ontario, Canada K7L 3N6

terhemispheric communication between motor cortices in the musicians, in whom the interhemispheric inhibitory circuits were less effective.

Methods

Six musicians and six age- and gender-matched controls were studied. All subjects were right-handed. The musician group (five females, one male; age 21.5±1.0 years, mean ±SD) consisted of five pianists and one classical guitarist. All musicians had commenced their musical training at an early age (5.8±1.7 years, range 4–9 years), and were professional-level performers. The time spent practising their instrument ranged from 17.5 to 28.0 h per week. The control group consisted of five females and one male (mean age: 26.0±6.0 years) with no history of any special training for skilled use of their hands. All protocols were approved by the Human Research Ethics Committee of the University of Adelaide.

Recording techniques

Surface electromyographic (EMG) recordings were made from both first dorsal interosseous (FDI) muscles using surface recording electrodes. EMG signals were amplified (1000×), filtered (10 Hz–2 kHz) and fed via a CED (Cambridge Electronic Design, Cambridge, UK) laboratory interface (sampling frequency 5 kHz per channel) to a computer for storage and off-line analysis.

Magnetic stimulation techniques

TMS was delivered using two Magstim 200 stimulators (The Magstim Co., Dyfed, UK) and two figure of eight coils (external diameter of wings 9 cm). The optimal scalp site for evoking responses in the contralateral resting FDI muscle was determined for each hemisphere, and the resting threshold (T), defined as the minimal stimulus intensity necessary to evoke five responses in the resting contralateral muscle of at least 50 μV in amplitude in a series of ten consecutive stimuli, was determined at these sites.

Interhemispheric inhibition

Interhemispheric inhibition was assessed as previously described (Ferbert et al. 1992). Briefly, TMS was delivered to the motor cortex bilaterally through two figure-of-eight stimulating coils. A conditioning stimulus to one hemisphere was followed by a test stimulus applied to the other hemisphere. Conditioning and test stimuli were given at the optimal site on the scalp for evoking responses in their respective contralateral FDI muscles. The intensities of both the conditioning and test stimuli were adjusted to elicit motor evoked potentials (MEPs) of approximately 1 mV peak-to-peak amplitude in their respective contralateral FDI muscles. The following conditioning-test (C-T) interstimulus intervals were examined: 4, 6, 8, 10, 12, and 16 ms. Single data blocks consisted of 40 pseudo-randomly presented trials consisting of ten trials in each of the four conditions: test stimulus alone, and the test stimulus preceded by a conditioning stimulus at one of three different C-T intervals. C-T intervals were varied between blocks until ten trials of each C-T interval of interest had been investigated.

Experimental protocol

First, two blocks of data were collected with both FDI muscles relaxed (relaxed condition). Visual feedback of the EMG was given to ensure subjects remained completely relaxed during this series of measurements. A second set (active condition) of trial results were collected while subjects maintained a low level (1 N) isometric contraction of the FDI muscle contralateral to the conditioning stimulus. Visual feedback of the index finger abduction force and the target force was provided to subjects throughout the experimental procedure. In this active condition, the intensities of both test and conditioning stimuli were adjusted to maintain the size of responses elicited in the respective contralateral FDI muscles at approximately 1 mV peak-to-peak amplitude. For each subject, the entire protocol was repeated after transposing the conditioning and test stimuli to the opposite hemisphere.

The EMG data collected by computer were averaged for each C-T interval condition, and peak-to-peak amplitude of the averaged MEP was measured with custom software. The amplitude of the conditioned MEP was expressed as a percentage of the size of the unconditioned MEP in both the relaxed and tonically active conditions (see Ferbert et al. 1992). Significant reduction of MEP amplitude with conditioning was assessed using one-sample *t*-tests with Bonferroni adjustment to the critical value of α for the number of contrasts performed within the data set. Repeated measures ANOVA was used to assess the effects of Group (Musician, Control), Condition (relaxed or active FDI contralateral to the conditioned hemisphere), Hemisphere stimulated (left, right) and C-T interval (4, 6, 8, 10, 12, 16 ms) on the size of the conditioned MEP.

Results

TMS thresholds

Threshold TMS intensities for an MEP in relaxed FDI are summarised in Table 1. There were no significant differences in relaxed TMS threshold for musicians and controls ($F_{1,16}$=0.019, P>0.5). or between left and right hemispheres ($F_{1,16}$=0.98, P>0.3).

TMS intensities and size of test MEPs

TMS intensities employed are summarised in Table 1. There was no significant difference in the intensities em-

Table 1 Summary of stimulus intensities and MEP size. Values are mean ±SE

	Controls R+L hemi (n=12)	Musicians R+L hemi (n=12)	All (n=24)
Relaxed threshold (% max. output)	40.4±2.5	40.0±1.0	40.3±1.3
Test intensity (% max. output)			
Rest	48.8±3.0	51.8±2.1	50.3±1.8
Active	46.3±3.0	50.2±1.0	48.3±1.6
Conditioning intensity (% max. output)			
Rest	47.6±3.3	50.4±1.8	49.0±1.9
Active	37.1±2.5	40.1±1.1	38.6±1.4*
Test MEP amplitude (mV)			
Rest	0.99±0.15	0.98±0.18	0.98±0.11
Active	0.97±0.10	1.01±0.11	0.99±0.07
Conditioning MEP amplitude (mV)			
Rest	0.83±0.11	0.86±0.01	0.84±0.07
Active	0.82±0.09	1.03±0.11	0.92±0.07

*Significant difference, rest vs active (P<0.001)

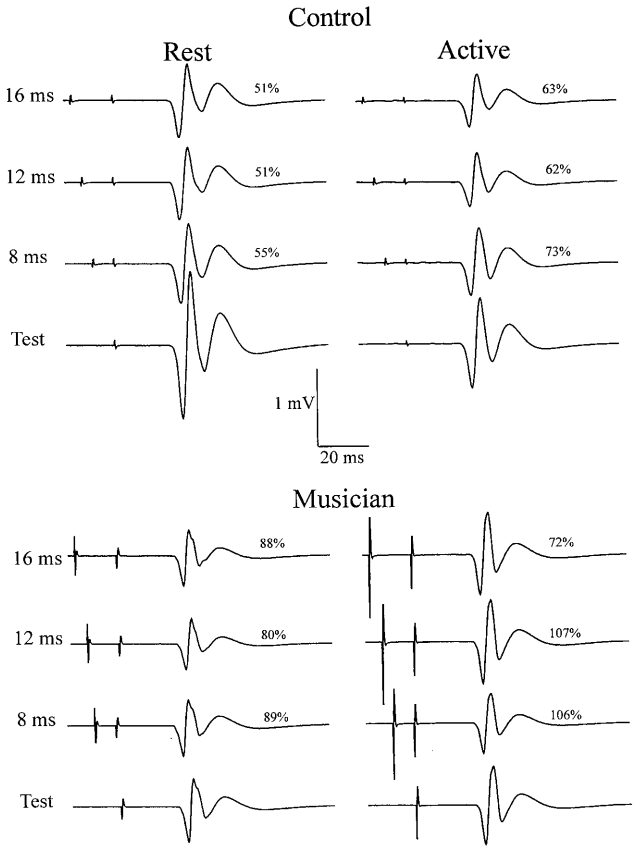

Fig. 1 Representative examples showing test and conditioned MEPs for a control subject (*top*) and a musician (*bottom*). Data for three C-T intervals (8, 12 and 16 ms) and the unconditioned test MEP are shown. *Numbers* above the traces indicate the amplitude of the conditioned MEP as a percentage of the unconditioned test response. For the control subject in the relaxed state (*top left*), the conditioned MEP amplitude was reduced to 51–55% of the test response with these C-T intervals. Conditioning was less effective with the muscle active (*top right*), but still reduced the MEP by 27–37%. In the musician, conditioning was less effective at reducing the MEP amplitude than in the control subject, for both the resting and active conditions

ployed between controls and musicians [ANOVA effect of Group ($F_{1,94}$=0.53, P=0.5)] or between hemispheres [ANOVA, effect of Hemisphere ($F_{1,94}$=0.057, P=0.82)]. None of the interaction terms involving Group or Hemisphere stimulated were significant in the ANOVA.

MEP amplitudes are summarised in Table 1. ANOVA demonstrated no main effects of Group, Hemisphere stimulated, Stimulus Type, or Condition. This indicated that the TMS intensities used during the experiments produced MEPs of comparable size in the contralateral FDI for musicians and controls under all test conditions.

Interhemispheric inhibition

Repeated measures ANOVA revealed significant effects of Group ($F_{1,240}$=11.3, P<0.001), Condition ($F_{1,240}$= 26.8, P<0.001), and C-T interval ($F_{5,240}$=11.0, P<0.001) on the size of the conditioned MEP. The hemisphere stimulated had no significant effect on the size of the conditioned MEP ($F_{1,240}$=0.06, P=0.81). None of the interaction terms in the ANOVA were significant. As there was no difference in the effectiveness of conditioning stimuli applied to the left or right hemisphere, the data obtained by stimulating each hemisphere were pooled for all subsequent analyses.

Typical examples of MEPs for a control subject and a musician are shown in Fig. 1. Conditioning stimuli were significantly less effective at reducing the size of the test MEP in musicians compared with controls ($F_{1,264}$=12.0, P<0.001). At rest, mean (±SE) amplitude of conditioned MEPs in controls was 65.8±3.7% of the unconditioned MEP amplitude (data pooled across all conditioning-testing intervals), compared with 75.5±3.9% in musicians. Corresponding values for the active condition were 81.3±2.7% vs 93.0±3.0%, respectively. Conditioning stimuli were significantly less effective in the active con-

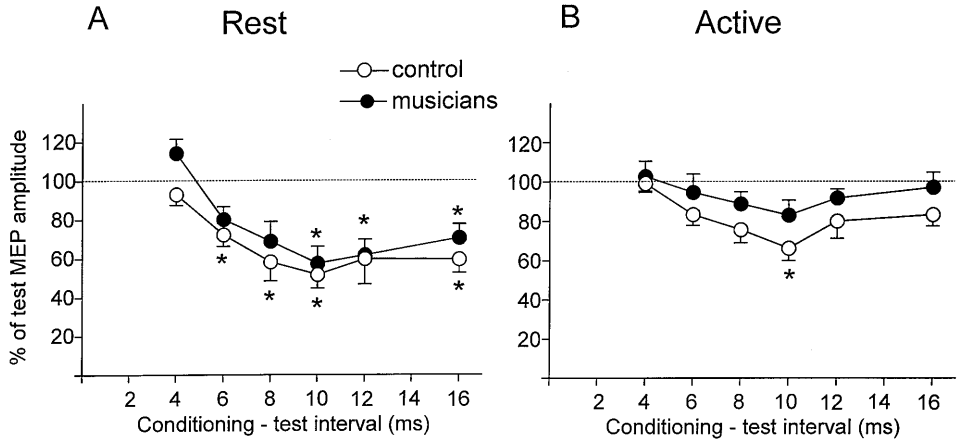

Fig. 2 Effect of C-T interval on suppression of the MEP with interhemispheric conditioning in controls and musicians. Mean (±SE) amplitude of conditioned MEPs is expressed as a percentage of unconditioned response size, and is shown for musicians (*filled circles*) and control subjects (*open circles*) at each C-T interval for rest (**A**) and active (**B**) conditions. *indicates that the amplitude of the conditioned MEP is significantly different from 100% (Bonferroni *t*-tests; P<0.002). Conditioning was less effective at reducing the size of the MEP in musicians compared with controls at all C-T intervals, under both rest (ANOVA; P<0.05) and active conditions (ANOVA; P<0.01). In all cases, a C-T interval of 10 ms was the most effective at suppressing the test MEP

dition compared with the resting condition ($F_{1,264}$=28.3, P<0.001).

The effect of C-T interval on the size of the conditioned MEP is shown for controls and musicians in Fig. 2. In both the rest and active conditions the conditioned MEPs were smaller in controls than in musicians at each C-T interval, and differences between groups were significant overall (Rest, $F_{1,132}$=4.14, P<0.05; Active, $F_{1, 132}$=8.81, P<0.01). The interaction term (Group * C-T interval) in the ANOVA was not significant (Rest, $F_{5, 132}$=0.31, P>0.05; Active, $F_{5, 132}$=0.21, P>0.05), indicating that the effect of C-T interval on MEP suppression was similar in musicians and controls.

Discussion

The principal finding of the present study is that conditioning TMS applied to one hemisphere is less effective at reducing the size of responses evoked by TMS applied to the opposite hemisphere in musicians compared with control subjects. Conditioning was equally effective when applied to the left or right hemisphere.

Ferbert et al. (1992) demonstrated that the level of interhemispheric inhibition was dependent on the intensity of both the conditioning and test stimuli, and size of the test MEP. There were no significant differences in these variables between groups in the present study (Table 1). If anything, conditioning intensities were slightly higher in the musicians. If this were to have an effect it should have resulted in an *increased* level of inhibition in the musicians (Ferbert et al. 1992). We conclude that methodological factors were not responsible for the reduced transcallosal inhibition in the musicians.

In primates, the cortical motor areas of proximal muscles are more richly innervated by transcallosal fibres than the distal muscles (Cusick and Kaas 1986), but there is anatomical and physiological evidence for transcallosal connections between distal forelimb cortical areas (Matsunami and Hamada 1984; Gould et al. 1986). Both facilitatory and inhibitory effects can be produced on pyramidal tract neurons by electrical stimulation of the opposite motor cortex in cats (Asanuma and Okuda 1962). Facilitatory effects are restricted to stimulation of a small area of homotopic contralateral cortex, while inhibitory effects are seen with stimulation of the surrounding area. TMS has been used in humans to demonstrate comparable interhemispheric facilitatory (Ugawa et al. 1993) and inhibitory (Ferbert et al. 1992) effects between the hand areas of motor cortex. Interhemispheric facilitation is only seen with weak conditioning TMS of the homotopic area of the contralateral motor cortex (approximately active threshold for contralateral FDI); stronger conditioning TMS at the same site produces interhemispheric inhibition which overwhelms the facilitation (Ugawa et al. 1993). Inhibition presumably predominates at higher intensities because the stimulus activates a surrounding area of cortex with inhibitory effects on the homotopic target area of contralateral cortex which receives point-to-point facilitation with weak stimulation (Ugawa et al. 1993). The inhibition seen with this technique is critically dependent upon activity in transcallosal projections (Ferbert et al. 1992; Schnitzler et al. 1996). Our results show that these interhemispheric inhibitory circuits are less effective in musicians, both at rest and with voluntary activation of the FDI muscle controlled by the hemisphere receiving the conditioning stimulus.

Our findings could be explained by changes in excitability of neurons in either the conditioned motor cortex or the motor cortex receiving the artificially generated transcallosal volley. There is little evidence to guide us on this point. At present there are no data in musicians on the operation of local intrahemispheric circuits that may form part of the pathway involved in the generation of transcallosal inhibition of corticospinal neurons. It would be of interest in this regard to examine within-hemisphere intracortical inhibition (Kujirai et al. 1993) in musicians in a future study.

There is now anatomical and physiological evidence for altered communication between hemispheres via the corpus callosum in musicians trained from an early age. The increased size of the corpus callosum (Schlaug et al. 1995) and reduced transcallosal inhibition (present study) in the musicians may reflect plastic changes brought about by intensive practice, or could reflect genetic traits predisposing to an ability to play the musical instruments. We do not know whether the anatomical and physiological findings in musicians are linked. A change in excitability of neurons involved in the generation of transcallosal inhibition of corticospinal neurons would not produce an anatomical correlate in the corpus callosum. It should be noted that many fibres in the anterior corpus callosum connect other frontal regions of cortex (De Lacoste et al. 1985). Increased interhemispheric facilitatory connections between motor cortices could contribute to the anatomical differences in the corpus callosum described by Schlaug et al. (1995), and might produce a net reduction in transcallosal inhibition following TMS. Our protocol did not allow us to address this specifically, but this could be done in a future study using the protocol of Ugawa et al. (1993).

It has been proposed that interhemispheric facilitation or inhibition of the opposite motor cortex via the corpus callosum may assist in performance of symmetrical and asymmetrical bilateral movements of the hands, as well as suppressing unwanted movements with the opposite hand during unilateral tasks (see Schnitzler et al. 1996). A functional correlate of reduced interhemispheric inhibition in musicians is unclear. Future studies are required to determine what contribution, if any, is made to the extraordinary bimanual coordination of musicians by a reduced effectiveness of transcallosal inhibitory circuits operating between motor cortex of each hemisphere.

Acknowledgements This work was supported by the Australian Research Council. MCR is supported by a Royal Adelaide Hospital Florey Post Doctoral Research Fellowship. BB was a Visiting Fellow supported in part by the Association of Commonwealth Universities. We thank Dr. Timothy Miles for helpful comments on a draft of the manuscript.

References

Asanuma H, Okuda O (1962) Effects of transcallosal volleys on pyramidal tract cell activity of cat. J Neurophysiol 25:198–208

Connolly K, Stratten P (1968) Developmental changes in associated movements. Dev Med Child Neurol 10:49–56

Cowell PE, Allen LS, Zlatimo NS, Denenberg VH (1992) A developmental study of sex and age interactions in the human corpus callosum. Dev Brain Res 66:87–192

Cusick CG, Kaas J (1986) Interhemispheric connections of cortical sensory and motor representations in primates. In: Lepore F, Ptito M, Jasper HH (eds) Two hemispheres – one brain. Functions of the corpus callosum. Alan R Liss, New York, pp 83–102

De Lacoste MC, Kirkpatrick JB, Ross ED (1985) Topography of the human corpus callosum. J Neuropathol Exp Neurol 44: 578–591

Ferbert A, Priori A, Rothwell JC, Day BL, Colebatch JG, Marsden CD (1992) Interhemispheric inhibition of the human motor cortex. J Physiol (Lond) 453:525–546

Gould HJ, Cusick CG, Pons TP, Kaas JH (1986) The relationship of corpus callosum connections to electrical stimulation maps of motor, supplementary motor, and the frontal eye fields in owl monkeys. J Comp Neurol 247:297–325

Jeeves MA, Silver PH, Jacobson I (1988a) Bimanual co-ordination in callosal agenesis and partial commissurotomy. Neuropsychologia 26:833–850

Jeeves MA, Silver PH, Milne AB (1988b) Role of the corpus callosum in the development of a bimanual motor skill. Dev Neuropsychol 4:305–323

Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A, Wroe S, Asselman P, Marsden CD (1993) Corticocortical inhibition in human motor cortex. J Physiol (Lond) 471:501–519

Matsunami K, Hamada I (1984) Effects of stimulation of corpus callosum on precentral neuron activity in the awake monkey. J Neurophysiol 52:676–691

Meyer BU, Roricht S, Grafin von Einseidel H, Kruggel F, Weindl A (1995) Inhibitory and excitatory interhemispheric transfers between motor cortical areas in normal humans and patients with abnormalities of the corpus callosum. Brain 118:429–440

Meyer BU, Roricht S, Woiciechowsky (1998) Topography of fibres in the human corpus callosum mediating interhemispheric inhibition between the motor cortices. Ann Neurol 43:360–369

Nass R (1985) Mirror movement asymmetries in congenital hemiparesis: the inhibition hypothesis revisited. Neurology 35:1059–1062

Preilowski BFB (1975) Bilateral motor interaction: perceptual-motor performance of partial and complete “split-brain” patients. In: Zulch KJ, Creutzfeld O, Galbraith GC (eds) Cerebral localization. Springer Berlin Heidelberg New York, pp 116–131

Rakic P, Yakovlev PI (1968) Development of the corpus callosum and cavum septi in man. J Comp Neurol 132:45–72

Schlaug G, Jancke L, Huang Y, Staiger JF, Steinmetz H (1995) Increased corpus callosum size in musicians. Neuropsychologia 33:1047–1055

Schnitzler A, Kessler KR, Benecke R (1996) Transcallosally mediated inhibition of interneurons within human primary motor cortex. Exp Brain Res 112:381–391

Seymour SE, Reuter-Lorenz PA, Gazzaniga MS (1994) The disconnection syndrome. Basic findings reaffirmed. Brain 117: 105–115

Ugawa Y, Hanajima R, Kanazawa I (1993) Interhemispheric facilitation of the hand area of the human motor cortex. Neurosci Lett 160:153–155