

Idiopathic Scoliosis: a transcranial magnetic stimulation study

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Abstract

Study design: Various neurophysiological parameters of the motor system were investigated in 43 female patients with Idiopathic Scoliosis (IS) and 31 sex and age matched controls using transcranial magnetic stimulation (TMS). **Objective:** To investigate whether asymmetries in excitatory and inhibitory brain processes, as studied by TMS, are a causative factor in IS. **Summary of background data:** Previous studies associated IS with pathological asymmetries of the cerebral cortex and the brain stem at the level of the corticospinal tracts. **Methods:** Forty-three female patients with right IS and 31 normal female subjects entered the study. Various TMS parameters, including the study of ipsilateral pyramidal tract, were studied. Electrophysiological data were correlated with clinical data, the degrees of the scoliotic curve and the Perdriolle and Nash & Moe indexes. **Results:** In upper limbs, detailed testing failed to reveal any statistically significant differences between the patient and the control group. In lower limbs, side-to-side differences of central motor conduction time (CMCT) and facilitated cortical-to-muscle latencies were increased in the scoliotic patients ($p < 0.05$). This finding correlated significantly with Nash & Moe and Perdriolle indexes (Spearman's $r = 0.406$ and 0.575 , respectively, $p < 0.05$). Following the Bonferroni adjustment, however, differences in CMCT SSDs were not statistically significant ($p > 0.05$). **Conclusion:** The present TMS data do not support the concept of a generalized brain asymmetry in IS. In lower limbs, a trend towards increased asymmetries in side-to-side differences of CMCT and cortical latencies was detected probably representing subclinical involvement of the corticospinal tracts secondary to mechanical compression. Finally, it is concluded that non-decussation of the pyramidal tracts is not involved in the pathogenesis of IS.

Keywords: Idiopathic Scoliosis, Transcranial Magnetic Stimulation, Brain Asymmetry

Introduction

Idiopathic Scoliosis (IS) is a deformity of the spine with no apparent cause apart from hereditary factors. Over the years various pathogenetic mechanisms for IS have been put forward including genetic, metabolic, endocrine and neurogenic¹. The latter was initially supported by experimental studies showing that stereotaxic destruction of the brain stem and the posterior hypothalamus were able to induce

scoliosis in bipedal rats^{2,3}. At the clinical level, several neuroradiological^{4,5} and neurophysiological studies, involving electroencephalogram (EEG)^{6,7}, evoked potentials⁸ and dichotic listening tests⁹, reported pathological cerebral asymmetries and suggested that the cause of Idiopathic Scoliosis may involve the Central Nervous System (CNS). In addition, recent studies revealed uncrossed corticospinal pathways in the rare syndrome of familial horizontal gaze palsy and progressive scoliosis¹⁰ as well as in two cases of congenital scoliosis^{11,12} raising the possibility of a similar association between uncrossed pyramidal tracts and IS.

The present study was designed to address the issue of CNS involvement in IS by investigating the motor system of scoliotic patients with transcranial magnetic stimulation (TMS). A brief comment on the rationale of choosing TMS for this purpose amongst other available techniques, such as transcranial electric stimulation (TES) of the motor cortex, is warranted. First, TMS is considered to be the method of

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choice for probing the excitability of the motor cortex¹³ because, for reasons related to the physics of magnetic stimulation, TMS excites pyramidal neurons trans-synaptically whereas TES tends to recruit output neurons directly. In addition, TMS is painless, in contrast to TES, permitting a detailed investigation of excitatory and inhibitory brain mechanisms in conscious subjects.

Materials and methods

Forty-three female, neurologically normal patients with right Idiopathic Scoliosis (mean age=13±2 years) and 31 normal female subjects (mean age=12±2 years) entered the study. Two of the scoliotic patients were left-handed whereas all normal subjects were right-handed. The scoliotic curves in all patients were between 20-40°.

EMG responses, following magnetic stimulation of the motor cortex, were recorded from upper and lower limbs. In the upper limbs, recordings were made with surface electrodes from the 1st dorsal interosseous muscles bilaterally, thereby allowing the detection of contralateral as well as ipsilateral responses to unilateral hemispheric stimulation. A four-channel EMG system (Neuropack 4, Nihon-Kohden, Tokyo) with a sampling rate of A/D conversion up to 3.3 kHz per channel served as the recording unit. Analysis time was set at 50-500 and cut-off frequency filters at 20 Hz and 3 kHz. Transcranial magnetic stimulation was performed with a Magstim 200 stimulator (Magstim, Dyfed, Wales) and a 70 mm diameter figure-of-eight coil (Magstim type 9925). In this particular coil model the center of the linear contiguous segment of the coil is located 3 cm from its midanterior edge and maximum current intensity is induced at a point which is marked with a – sign on the coil case and is located on the midline 12 mm away from its midanterior edge. The center of the linear contiguous segment of the coil was placed 5 cm lateral to the vertex on the interaural line and then the coil was angled 45° to the parasagittal level so that the current in the central segment flowed toward to the midline. It has previously been shown that this positioning and orientation is the optimum for the excitation of the motor hand area¹⁴.

In lower limbs, recordings were made with surface electrodes from the abductor hallucis muscles and stimulation was performed with a double cone coil (Magstim type 9902), centered over the vortex.

The investigated TMS parameters included corticomotor threshold, silent period (SP), cortex-to-muscle latency, CMCT, F- and M-wave latencies and amplitude and area of MEPs.

Corticomotor threshold was defined at rest in 1% steps using the method of Mills & Nithi¹⁵ which determines two stimulus intensity levels designated lower (LT) and upper (UT) threshold. Briefly, LT corresponds to the highest intensity which evokes motor-evoked potentials (MEPs) with a probability of zero whereas UT is the lowest intensity which evokes MEPs with a probability of one. Mean threshold (MT) is the arithmetic mean of UT and LT.

	Patients		Controls		
	x	SD	x	SD	
L MT	39.76	7.78	43.35	5.49	n.s.
R MT	40.38	7.89	43.67	8.47	n.s.
SSD MT	4.39	3.06	4.16	2.99	n.s.
L UT	44.14	8.40	48.15	6.33	n.s.
R UT	45.23	8.81	48.10	8.81	n.s.
SSD UT	4.10	3.01	4.45	2.34	n.s.
L LT	35.38	7.35	38.50	4.83	n.s.
R LT	35.52	7.58	39.25	8.30	n.s.
SSD LT	4.29	3.41	4.56	2.95	n.s.
L Ampl -R	0.24	0.20	0.21	0.19	n.s.
R Ampl-R	0.23	0.19	0.27	0.18	n.s.
L Ampl-F	3.46	1.14	3.30	1.16	n.s.
R Ampl-F	3.82	1.63	3.32	1.66	n.s.
L CMCT	3.83	0.84	3.83	0.66	n.s.
R CMCT	3.77	0.63	3.64	0.65	n.s.
L iSP	35.9	6.6	35.8	10.4	n.s.
R iSP	36.3	6.7	36.2	10.0	n.s.

Table 1. Main neurophysiological findings in upper limbs. x=mean, SD=Standard Deviation, L=Left Hemisphere, R=Right Hemisphere, n.s.=non-significant, MT=Mean Threshold, UT=Upper Threshold, LT=Lower Threshold, SSD=Side-to-Side Difference, Ampl-R=Amplitude under Resting condition, Ampl-F=Amplitude under Facilitated condition, CMCT=Central Motor Conduction Time, iSP=Ipsilateral Silent Period.

Silent period (SP) measurements were done using a standardized protocol and included the study of contralateral as well as ipsilateral SPs. Contralateral SPs were elicited using stimuli of 130% MT stimulus intensity (SI) whereas for ipsilateral SPs stimuli of 100% maximum SI were used. Subjects performed an isometric contraction at 50% MVC and were specifically instructed to maintain the force constant after the magnetic stimulus until the order to relax¹⁶. Stimuli were given 3 s after the target force was attained and were repeated every 15 s. To measure the duration of SP its onset was defined as the onset of the MEP and the endpoint coincided with the reoccurrence of EMG activity in individual trials¹⁷.

Cortex to muscle latency (Cx-M) represented the mean latency of eight responses and was measured both under resting (Cx-R) and under facilitated conditions (Cx-F), with facilitation performed as previously described for SP measurements.

Central motor conduction time (CMCT) was calculated using the F-wave method and using the formula:

$$\text{CMCT (ms)} = \text{Minimal Cx-F} - \frac{F+M-1}{2}$$

where F and M represent the F-wave and the CMAP latency, respectively¹⁸.

The *amplitudes* of MEPs were measured from baseline to peak both under resting and facilitated conditions. It is well

	Patients		Controls		
	x	SD	x	SD	
L Cx-M-R	38.69	2.39	38.79	1.96	n.s.
R Cx-M-R	39.48	2.50	39.2	2.98	n.s.
SSD Cx-M-R	1.56	1.08	1.28	1.09	n.s.
L Ampl-R (Log e)	-2.49	1.42	-2.06	1.02	n.s.
R Ampl-R (Log e)	-2.31	1.18	-1.74	1.40	n.s.
SSD Ampl-R (Log e)	-0.18	0.81	-0.20	1.40	n.s.
L Cx-F	37.78	2.94	37.90	3.03	n.s.
R Cx-F	38.23	2.68	37.61	2.85	n.s.
SSD Cx-F	1.87	1.34	1.02	1.15	p<0.05
L Ampl-F (Log e)	-1.84	1.38	-1.87	1.05	n.s.
R Ampl-F (Log e)	-1.87	1.16	-1.73	1.29	n.s.
SSD Ampl-F (Log e)	0.02	0.89	-0.10	1.60	n.s.
L CMCT	12.40	2.82	13.58	1.37	n.s.
R CMCT	13.95	3.16	13.20	1.81	n.s.
SSD CMCT	1.82	1.08	0.97	0.64	p<0.05
L Tib F-wave	45.51	3.83	45.98	4.13	n.s.
R Tib F-wave	44.75	3.84	45.83	3.53	n.s.
SSD F-wave	1.1	0.57	1.51	0.68	n.s.

Table 2. Main neurophysiological findings in lower limbs. x=mean, SD=Standard Deviation, L=Left Hemisphere, R=Right Hemisphere, n.s.=non-significant, Cx-M-R=Cortical-to-Muscle latency under Resting condition, Cx-F=Cortical-to-muscle latency under Facilitated condition, MT=Mean Threshold, UT=Upper Threshold, LT=Lower Threshold, SSD=Side-to-Side Difference, Ampl-R=Amplitude under Resting condition, Ampl-F=Amplitude under Facilitated condition, CMCT=Central Motor Conduction Time, Log e=logarithmic transformation, R and L Tib=Right and Left posterior Tibial nerve.

known that amplitude and *area* measurements are quite variable. Accordingly, the mean values of these parameters were determined, at each condition, after collecting 8 individual MEPs.

A primary objective of the study was to investigate whether pathological cerebral asymmetries are implicated in the pathogenesis of IS. Therefore for all neurophysiological parameters, asymmetries between the two hemispheres (termed side-to-side differences, SSDs) were calculated.

Electrophysiological data were correlated with several clinical characteristics including the degrees of the scoliotic curve and the Perdriolle and Nash indexes (which are measures of the rotational deviation of the spine).

Data analysis. Normality of data distribution was tested using the Kolmogorov-Smirnov test. The amplitudes and areas of MEPs were not normally distributed. For this reason the data were subjected to natural logarithmic transformation before any further parametrical statistical analysis. For all variables, mean differences between the scoliotic and the control group were assessed with unpaired t-tests. In order to control for the effect of multiple comparisons, the Bonferroni adjustment was applied. The proportions of sub-

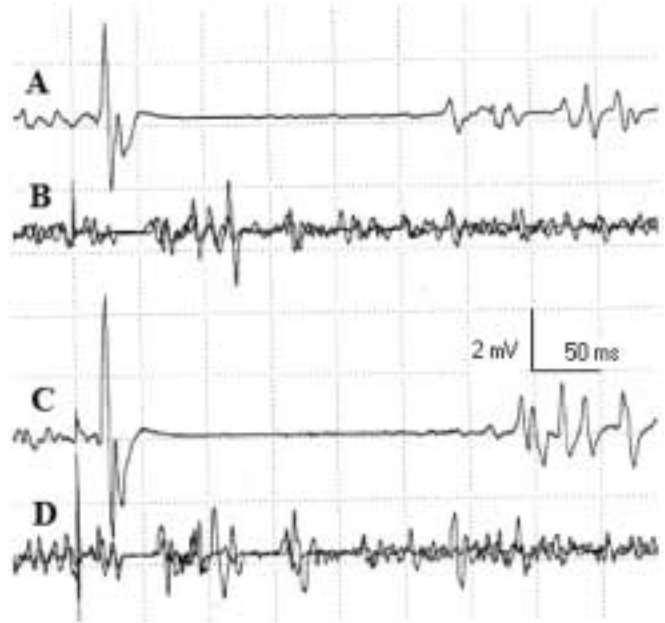


Figure 1. Representative waveforms of contralateral (A, C) and ipsilateral (B, D) silent periods obtained after stimulation of the right hemisphere with a figure-of-eight coil at 100% stimulus intensity in a scoliotic patient (A, B) and a control subject (C, D). In B, D: three superimposed responses are displayed. MEP=Motor Evoked Potential, cSP=contralateral Silent Period, iSP=ipsilateral Silent Period.

jects with ipsilateral MEPs in the two groups were compared with Fisher's exact test. The covariance of neurophysiological data and the Perdriolle and Nash indexes was investigated with Spearman's correlation test. For all tests $p < 0.05$ was the level of significance.

Results

The patient and the control group were matched for various important clinical variables including age (13 ± 2 vs. 12 ± 2 years, respectively) and height (161 ± 7 vs. 163 ± 5 cm, respectively, $p > 0.05$).

The main results of the neurophysiological investigation are summarized in Tables 1 & 2. Representative waveforms are shown in Figure 1.

In upper limbs, patients had a right hemisphere (R Hem) MT of 40.4 ± 7.9 (vs. 43.7 ± 8.5 in controls), a left hemisphere (L Hem) MT of 39.8 ± 7.8 (vs. 43.4 ± 5.5) and an MT asymmetry of 4.4 ± 2.4 (vs. 3.8 ± 3.5). R Hem SP duration was 124.2 ± 32.5 msec (vs. 124.05 ± 32.5), L Hem SP duration was 130.8 ± 36.9 msec (vs. 137.4 ± 35.9), R Hem CMCT was 3.8 ± 0.6 msec (vs. 3.6 ± 0.6) and L Hem CMCT was 3.8 ± 0.8 msec (vs. 3.8 ± 0.7). None of the examined parameters differed from those of the control group ($p > 0.05$).

Ipsilateral MEPs were not obtainable at rest in any subject

despite the use of 100% maximum stimulator output stimulus intensity. During facilitation, ipsilateral MEPs were observed in 6% of scoliotic and 5% of control subjects (Fisher's exact test, $p > 0.05$) (Figure 1). These potentials had a latency of 18.5 ± 1.4 msec in the patients and 18.6 ± 1.3 msec in the control subjects ($p > 0.05$). The amplitude ratio of ipsilateral/contralateral MEPs did not differ significantly between the two groups ($p > 0.05$). Finally, the duration of ipsilateral SPs was 36.1 ± 6.7 msec in scoliotic patients versus 36.0 ± 10.2 msec in controls ($p > 0.05$).

In lower limbs, the investigated neurophysiological parameters were not significantly different between the two groups ($p > 0.05$) with two exceptions. Side-to-side difference of facilitated cortical latencies (Cx-M) was 1.87 ± 1.34 msec in IS (vs. 1.02 ± 1.15 in controls, $p < 0.05$) and correlated significantly with Nash & Moe and Perdriolle indexes (Spearman's $r = 0.406$ and 0.575 , respectively, $p < 0.05$). In addition, the CMCT SSD was significantly increased in the scoliotic group (1.82 ± 1.08 vs. 0.97 ± 0.64 msec, $p < 0.05$). Following the Bonferroni adjustment, however, the SSD differences of the CMCT and cortical latencies between the two groups were not statistically significant ($p > 0.05$). It should be noted that these findings may have failed to reach statistical significance for reasons related to the size of our sample. In view of the large variance of our results, which is a well-known feature of magnetically elicited MEPs, it is probably necessary to investigate an even larger group of subjects in order to resolve this issue conclusively.

Discussion

The etiology of Idiopathic Scoliosis remains an enigma. Previous neuroradiological and neurophysiological studies^{4,9,19} have identified CNS asymmetries or abnormalities related to this disease.

From a neuroradiological point of view, two MRI studies reported asymmetries of the midbrain and hindbrain in individuals with Idiopathic Scoliosis compared to normal controls^{4,5}. Interestingly, the asymmetry was mainly localized in the ventral pons or the medulla in the area of the corticospinal tracts.

Regarding neurophysiological studies, it was initially shown that EEGs have pathological findings in up to 57% of scoliotic patients⁶⁻⁷. Somatosensory Evoked Potentials (SEPs) were abnormal in 9.8% of patients in the study of Cheng et al.⁸ and long-latency reflex testing suggested that a defect might lie in the CNS at the processing level⁹. Finally, dichotic listening testing, which examines a non-spinal, non-motor system revealed increased perceptual asymmetry and led to the conclusion that IS is associated with a fundamental right-left asymmetry in brain organization¹⁹.

With this background knowledge, we decided to investigate the CNS of scoliotic patients using Transcranial Magnetic Stimulation (TMS). This is a widely used non-invasive technique for investigating physiological brain mechanisms as well as the pathophysiology of various neuro-

logical diseases. In the present study, TMS was specifically utilized in order to investigate whether there is a subclinical involvement of the motor system in IS as would be expected from pathological alterations of the corticospinal tracts, suggested by MRI studies, or in the context of a generalized brain asymmetry suggested by neurophysiological studies. Moreover, testing the motor system in IS seems intuitively important as irrespective of its initiating factor, asymmetrical muscle action may be an additional mechanism that maintains scoliosis²⁰.

Transcranial Magnetic Stimulation has been used in a number of recent studies as a means of monitoring of the motor pathway during spinal surgery^{11,21-23}. Transcranial electrical stimulation of the motor cortex has been used, in this context, even more extensively for a number of reasons. It is more easily applied in the operating theater, it produces more clearly defined corticospinal volleys and the painless stimulation achieved by magnetic stimuli, as opposed to the painful electric ones, is not an advantage in the intraoperative setting²⁴. When trying to compare the results of these studies with the present one, it should be emphasized that they differ significantly regarding their objectives, the study design and the methodology used. First, the aforementioned studies were performed in order to determine the usefulness of magnetic or electric stimulation of the motor system as a monitoring method during spinal surgery with a view to reducing post-operative complications. As a result, they were restricted to surgical candidates, who are usually suffering from severe scoliosis, and they did not provide a comprehensive comparison of various TMS parameters between patients and controls. Second, they were performed intraoperatively and therefore their results were influenced by the administration of anesthetic drugs. These factors should be taken into account in the interpretation of relevant results. For instance, Tabaraud et al.²³ reported that the mean latency of electrical MEPs recorded from lower limbs during spinal surgery is prolonged compared to unanaesthetized controls. However, their patients suffered from severe IS and, since this is an intraoperative finding, there is also the confounding factor of anesthetic drugs.

In the present TMS study we have focused on patients suffering from mild to moderate IS, in an effort to avoid any secondary effects by mechanical distortion of the spinal cord due to exaggerated spinal curvatures. Detailed upper limb testing revealed normal findings. Therefore, our results do not support the concept of a generalized brain asymmetry in IS or the existence of pathological alterations in the corticospinal tracts to upper limbs.

During lower limb testing, investigation of mean facilitated cortical latencies and the CMCT, which reflect the activation of the fastest conducting fibers of the corticospinal tract, revealed a trend towards increased asymmetry between the two sides in the scoliotic patients which correlated weakly with measures of the rotational deviation of the spine such as the Nash & Moe and Perdriolle indexes. The pathophysiological basis of this finding is currently unknown.

Investigation of ascending neuronal pathways in Idiopathic Scoliosis with somatosensory evoked potentials revealed asymmetries in cortical latencies of a similar magnitude. For instance, Hausmann et al.²⁵ reported that interside differences of N/P37 latencies were 1.58 ± 1.28 ms in IS patients versus 0.82 ± 0.58 ms in controls ($p < 0.01$). The authors attributed this finding to a possible intrinsic neurological impairment rather than to mechanical compression of the posterior columns by the scoliotic curve because there was no correlation between interside difference and Cobb angle ($p > 0.05$). It is generally assumed that if neurological malfunction is secondary to the scoliotic deformity then it should correlate positively with the severity of scoliosis curvature²⁶. This was the case in the present study. Accordingly, our finding of increased asymmetry of cortical latency and CMCTs to lower limbs most likely represents a subclinical malfunctioning of the pyramidal system caused by mild, asymmetric compression of the cortico-spinal tract by the scoliotic curve. It is therefore an epiphenomenon rather than a cause of IS.

The present study additionally investigated the issue of uncrossed pyramidal tracts in IS. The impetus for this investigation was provided by three reports linking sensorimotor non-decussation with some forms of scoliosis. The most detailed of these studies concerns the rare syndrome of horizontal gaze palsy and progressive scoliosis (HGPS). HGPS is an autosomal recessive disorder mapping to chromosome 11q23-25 and is clinically characterized by progressive scoliosis and congenital horizontal gaze palsy with no affection of vertical gaze²⁷. MacDonald et al.¹⁰ recently brought into attention the fact that clinically unsuspected non-decussation of medial lemniscus and the corticospinal tracts may occur in association with HGPS. In addition, Hosokawa et al.¹¹ and Terakawa et al.¹² described two patients with marked congenital scoliosis in whom sensorimotor non-decussation was disclosed by ipsilateral deficits following a unilateral hemorrhagic stroke. Despite these associations, our detailed investigation of the uncrossed pyramidal tracts suggests that non-decussation is not a pathogenetic factor in IS. A limitation of our study, is that the investigation of the uncrossed pyramidal tract was limited to upper limbs only. This limitation was imposed by technical factors as currently available coils for lower limb stimulation (that is circular and double-cone coils) can not selectively excite one hemisphere and therefore can not be used in a meaningful way to investigate non-decussation in lower limbs.

In conclusion, the present TMS study does not support the concept of a generalized brain asymmetry in IS. Upper limb findings were within normal limits whereas lower limb testing revealed only a trend towards increased asymmetries of cortical latencies and CMCT. The latter finding may indicate that subclinical involvement of the cortico-spinal tracts, probably secondary to mechanical compression, occurs even in patients with mild-to-moderate IS. Finally, it is concluded that non-decussation of the pyramidal tracts is not involved in the pathogenesis of IS.

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