Corticospinal excitability in patients with secondary dystonia due to focal lesions of the basal ganglia and thalamus

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Highlights

- Corticospinal excitability is increased in secondary dystonia due to lesions in putamen and caudate nuclei.
- Putamen and caudate nuclei are involved in the appearance of dystonic spasms in secondary dystonia.
- In patients with unilateral secondary dystonia intracortical inhibition is bilaterally reduced.

Abstract

Objective: To investigate the possible correlations between clinico-radiological features and pathophysiological mechanisms in patients with dystonia secondary to focal brain lesions.
Methods: single and paired-pulse transcranial magnetic stimulation was used to assess corticospinal excitability in ten patients (4 females; mean age 61) and a group of normal controls. Active threshold, latency and amplitude of motor evoked potentials (MEPs), silent period (SP) duration and short-interval intracortical inhibition (SICI) were evaluated.
Results: Patients with lesions involving the putamen and caudate presented with dystonic postures at rest. TMS assessment in these subjects showed increased MEP amplitude on the affected side and a bilateral decrease of SP duration and SICI. When the lesion spared the putamen and caudate, mainly involving the thalamus, the clinical picture was dominated by slow repetitive involuntary movements and tremor. In the affected side of these subjects the MEP amplitude was reduced and the MEP threshold was increased.
Conclusions: when putamen and caudate were lesioned, the patients presented with dystonic postures at rest; furthermore the patients showed changes of corticospinal excitability in comparison to both healthy subjects and other dystonic patients.
Significance: there are correlations between type of dystonia, site of the lesion and neurophysiological findings.

Introduction

Dystonia refers to a syndrome of sustained muscle contractions usually producing twisting and repetitive movements or abnormal postures (Fahn et al., 1998). While secondary dystonia is associated with a variety of identifiable causes and develops mainly as a result of brain insult (Calne & Lang, 1988), primary dystonia has no identifiable cause and is generally referred to a genetic abnormality (Bressman et al., 1998).

Since most lesions responsible for unilateral secondary dystonia are usually confined to the putamen, caudate, globus pallidus and thalamus (Marsden et al., 1985), it is widely held that a dysfunction of the basal ganglia or their connections plays a major role in the pathogenesis of dystonia through the induction of an excessive motor cortical activation (Berardelli et al., 1998).

Transcranial magnetic stimulation (TMS) is largely used to investigate the physiology of motor cortical areas and several paradigms have been proposed to trace corticospinal excitability changes following basal ganglia dysfunction (Abbruzzese & Trompetto, 2002).

TMS has been extensively applied to study patients with primary dystonia (Tinazzi et al., 2009), showing that the excitability of intracortical inhibitory circuits is decreased (Abbruzzese et al., 2001; Filipović et al., 1997; Ridding et al., 1995) and corticospinal excitability is increased (Ikoma et al., 1996; Mavroudakis et al., 1995). Overall, these findings support the hypothesis that dystonia is due to inappropriate disinhibition of the motor cortex leading to an increased activation of motor cortical output (Marsden et al., 1985). On the contrary, there are only two case reports, to our knowledge, dealing with TMS and secondary dystonia due to a focal lesion involving basal ganglia circuits (Hanajima & Ugawa, 2000; Trompetto et al., 2006). There are two reasons for this discrepancy. First, secondary dystonia is much less common than primary dystonia. Second, lesions causing secondary dystonia usually involve the corticospinal tract and this makes the use of TMS unsuitable to test motor excitability.

Distinct forms of dystonia have been described in patients with focal brain lesions. When the putamen and caudate are affected, the clinical picture is often dominated by sustained muscle

contractions causing abnormal postures (Lehéricy et al., 1996). Thalamic lesions, instead, have been linked to myoclonus dystonia (Ghika et al., 1994; Lehéricy et al., 1996) or hand dystonia with or without tremor (Dejerine & Roussy, 1906; Kim, 1992). The pathophysiology of these two forms is likely to be different (Krystkowiak et al., 1998; Lee & Marsden, 1994; Lehéricy et al., 1996).

The aim of this study was to examine corticospinal excitability in a group of patients with secondary dystonia due to a focal lesion in the contralateral basal ganglia and thalamus, investigating possible correlations between type of dystonia, site of the lesion and excitability changes.

Material and Methods

Subjects

Ten patients were enrolled in the study (4 females; mean age 61 ± 12 years) according to the following criteria: (i) secondary dystonia defined according to the criteria proposed by Fahn (Fahn et al., 1998); (ii) unilateral distribution, with a main involvement of upper limb; (iii) magnetic resonance imaging (MRI) or computed tomographic (CT) scan showing a single lesion in the basal ganglia and/or thalamus contralateral to the clinically involved side; (iv) no other cause of dystonia revealed by investigation; (v) no treatment with botulinum toxin or last treatment at least 8 months before the enrolment; (vi) no contraindication to the use of TMS.

Twenty healthy controls were also recruited (8 females; mean age, 54 years ± 16 years). The study was approved by the local Ethical Committee. Subjects gave their written informed consent to participate.

Electromyography (EMG) recordings and TMS

EMG activity was recorded bilaterally from first dorsal interosseous (FDI) muscle using surface electrodes placed in a tendon belly arrangement. TMS was performed with two Magstim 200 stimulators connected to the same figure-of-eight shaped coil (external loop diameters 9 cm) through a Bistim module (Magstim Co. Ltd Whitland, UK). The coil was placed over the “hot spot”

for contralateral FDI with the handle pointing backwards and laterally at a 45º angle to the sagittal plane. EMG signals were amplified and filtered (20 Hz to 1 kHz) with a D360 amplifier (Digitimer Limited, Welwyn Garden City, UK). The signals were sampled at 5000 Hz, digitised using a laboratory interface (Power1401, Cambridge Electronics Design (CED), Cambridge, UK) and stored on a personal computer for display and later off-line data analysis. Each recording epoch lasted 600 ms, of which 100 ms preceded TMS.

Active motor threshold (AMT) was determined at 40-60% of maximum voluntary contraction (MVC) and was defined as the minimum intensity eliciting a clear-cut contralateral MEP in 5 out of 10 consecutive trials using a display gain of 0.5 mV/cm. AMT values were expressed as a percentage of maximum stimulator output (MSO).

Both motor cortices were stimulated in succession in patients with secondary dystonia, while only the dominant (left) hemisphere was evaluated in healthy controls.

Single-pulse TMS

The stimuli were delivered through the Bistim module with the first stimulator set at 0% of MSO. The following three stimulation intensities were used: AMT + 10% of MSO; AMT + 20% of MSO; AMT + 30% of MSO. Patients were instructed to maintain a steady contraction (40-60% of MVC) before and after the stimulus. At each stimulation intensity 20 trials were recorded and the following 4 parameters were measured in the FDI contralateral to the stimulated hemisphere: 1) area of the rectified EMG activity in the 100 ms preceding TMS (pre-stimulus EMG activity); 2) MEP latency; 3) MEP peak-to-peak amplitude; 4) silent period (SP) duration (from stimulus artefact to the reappearance of EMG).

Paired-pulse TMS

Short-interval intracortical inhibition (SICI) (Kujirai et al., 1993) was investigated at rest using the inter-stimulus interval (ISI) of 3 ms. Conditioning stimulus (CS) intensity was changed in a range from AMT to AMT - 15% of MSO in 5% steps. Test stimulus (TS) intensity was adjusted to obtain

unconditioned MEPs in contralateral FDI ranging from 0.5 to 1.5 mV peak-to-peak amplitude. In each subject, at least 10 conditioned and 10 unconditioned trials for each CS intensity were randomly collected and the ratio *conditioned MEP amplitude / non-conditioned MEP amplitude* was calculated. The lowest ratio (among the four CS intensities used) was called maximal-SICI (Trompetto et al., 1999).

Statistical analysis

According to clinical and MRI findings dystonic patients have been separated in two groups: patients 1-5 and patients 6-10. To test the normal distribution we submitted all data to Kolmogorov-Smirnov test, that resulted not significant ($p>0.05$). Therefore we submitted all data to parametric tests. For comparison of AMT, MEP latency and maximal-SICI, a one way Analysis of Variance (ANOVA) was performed with GROUP (controls, patients 1-5 and patients 6-10) as main factor. For pre-stimulus EMG activity, MEP peak-to-peak amplitude and SP duration, a repeated measure (RM) ANOVA was performed with INTENSITY (AMT +10%, AMT + 20% and AMT +30% of MSO) as within subject factor and GROUP (controls, patients 1-5 and patients 6-10) as between subject factor. For both one-way and RM ANOVAs, GROUP factor was run twice, once comparing controls (dominant side) *vs* the affected side of patients 1-5 and patients 6-10 and then comparing controls (dominant side) *vs* the unaffected side of patients 1-5 and patients 6-10. We applied Bonferroni correction for multiple comparisons (the level of significance was set at 0.025).

All statistical analysis were conducted with SPSS 13.0.

Results

Clinical and imaging findings

Clinical features of the patients are summarised in Table 1. With the exception of patient 8, in whom dystonia developed gradually without a preceding acute event, all the patients presented a

delayed-onset posthemiplegic dystonia, occurring when the patients had almost recovered from hemiplegia, with a mean interval of 15 months from the acute event.

Dystonia in the lower limb was similar in all the patients, consisting in hyperextension of the great toe and claw-like flexion of the interphalangeal joints of the other toes during walking. In addition, subject 8 showed an exaggerated leg extension during walking. On the contrary, dystonic features in the upper limb differentiated the first five patients from the remaining five. In subjects 1-5 dystonic spasms leading to dystonic postures (lasting from a few seconds to several minutes) were spontaneously present at rest and worsened by active movement, emotional or mechanical stimuli. On the other hand, patients 6-10 did not present dystonic postures at rest. They had repetitive, slow and small amplitude flexion movements of the fingers and wrist at rest, with inconstant extension of the fingers. When the patients moved the unaffected upper limb, the involuntary movements in the affected arm increased: beside wrist and fingers flexion motions, elbow flexion and forearm pronation became evident, together with the appearance of dystonic flexion posture of fingers, wrist and forearm. A jerky tremor resembling myoclonus was present during voluntary movements of the affected limb and when it was held outstretched. Surface EMG analysis revealed the presence of co-contraction of forearm antagonist muscles. None of the patients showed sensory abnormalities except for a slight impairment of the two-point discrimination in patients 7 and 10.

Brain imaging (Table 1) showed the involvement of the putamen and caudate nuclei in the first five subjects, with the exception of patient 1, in whom the lesion was confined to the putamen. The putamen and caudate nuclei were instead spared in the last five subjects, the lesion affecting the thalamus (subjects 7-10) or the globus pallidum, substantia nigra and subthalamic area (subject 6).

TMS study

1) Controls vs patients' affected side

No differences were found for MEP latency (one way ANOVA, GROUP F (2,29): 2.63, p=0.091) and pre-stimulus EMG activity (GROUP F (2,27): 2.79, p=0.08; GROUP * INT F (4,54): 0.088, p=0.97).

AMT was different between groups (GROUP F (2,29): 10.32, p<0.0001); *post hoc* analysis showed that AMT value was higher in patients 6-10 with respect to controls (p=0.004) and patients 1-5 (p<0.0001) with no difference between patients 1-5 and controls (p=0.17).

Regarding MEP amplitude, a main effect of GROUP was found (F (2,27): 28.2, p<0.0001). *Post hoc* analysis showed that MEP amplitude of patients 1-5 was greater than that of patients 6-10 (p<0.0001) and controls (p<0.001), while MEP amplitude of patients 6-10 was smaller than that of controls (p=0.012) (Figure 1).

Further a significant effect of GROUP was also found for SP (GROUP F (2,27): 4.31, p=0.022) and *post hoc* analysis showed that SP was shorter in patients 1-5 *vs* controls (p=0.012) with no difference between patients 1-5 and patients 6-10 (p=0.31) and between patients 6-10 and controls (p=0.18) (Figure 1).

Maximal-SICI was different among groups (one way ANOVA, GROUP F (2,27): 4.89, p=0.016); *post hoc* analysis showed that SICI was reduced in patients 1-3 in comparison to controls (p=0.005) and patients 6-10 (p=0.015), while no difference was found between patients 6-10 and controls (p=0.97) (Figure 2).

2) Controls vs patients' unaffected side

No differences were found for MEP latency (one way ANOVA, GROUP F (2,29): 2.71, p=0.084), AMT (GROUP F (2,29): 2.69, p=0.86), and pre-stimulus EMG activity (GROUP F (2,27): 3.15, p=0.06; GROUP * INT F (4,54): 0.160, p=0.96).

While no differences were found for MEP amplitude (GROUP F (2,27): 1.73, p=0.196), a significant effect of GROUP for SP duration was found (F (2,27): 11.89, p<0.0001); *post hoc* analysis indicated that SP was shorter in patients 1-5 *vs* controls (p=<0.0001) and patients 6-10 (p=0.014) without difference between patients 6-10 and controls (p=0.14) (Figure 3).

Only a trend for the effect of GROUP was found for maximal-SICI taking into account that we set the level of significance at 0.025 (one way ANOVA, GROUP F (2,27): 3.69, p=0.04) (Figure 2).

Discussion

All the patients in this study were characterized by the occurrence of dystonia secondary to focal brain lesions. However, they could be differentiated on the basis of clinical features and MRI findings. A group of patients (cases 1-5) presented with dystonic postures at rest which were worsened by voluntary movements. A similar clinical pattern has been previously reported in patients whose lesions were centred in the putamen, often extending to the caudate and, less frequently, to the external globus pallidus (Denny-Brown, 1962; Dooling & Adams, 1975; Krystkowiak et al., 1998; Lehéricy et al., 1996; Oppenheimer, 1967; Pettigrew & Jankovic, 1985). In accordance with these previous observations, the putamen alone (patient 1) or the putamen and caudate (patients 2-5) were affected in these subjects. A second group of patients (cases 6-10) presented with absent or mild dystonia at rest; during voluntary activation slow repetitive movements and tremor were more prominent than abnormal dystonic postures. Both putamen and caudate nuclei were spared in these subjects, while the focal lesions mainly involved the thalamic nuclei (subjects 7-10) or the subthalamic region, the globus pallidus and the substantia nigra (subject 6). Lesions in these brain areas have been previously reported in patients with secondary dystonia (Marsden et al., 1985; Pettigrew & Jankovic, 1985; Krauss et al., 1992; Momjian-Mayor et al., 2008; Münchau et al., 2000).

TMS results were different in the two groups of patients. On the affected side, MEP amplitude of patients 1-5 was larger than in controls, while MEP amplitude in patients 6-10 was smaller than in controls. Furthermore, SP duration were reduced in patients 1-5 *versus* controls and SICI was reduced in patients 1-3 *versus* controls and patients 6-10. On the unaffected side, SP duration was shorter in patients 1-5 in comparison to both controls and patients 6-10.

The reduced MEP amplitude, associated with an increased MEP threshold, in the affected side of patients 6-10 was an expected finding, as it was found in hemiparetic subjects with a subcortical lesion (Liepert et al., 2005).

For the same reasons, the larger MEP amplitude in the affected side of patients 1-5, which reveals a condition of increased corticospinal excitability (Abbruzzese & Trompetto, 2002), was a surprising result. A possible explanation might be that the lesion of the caudate and putamen had played a role in the development of this increase of excitability through a "distortion" of the thalamo-cortical output in the presence of a pre-existing deficit of intracortical inhibition, in line of what has been said in primary dystonia (Tinazzi et al., 2009) and in line with our SP and SICI findings. It is also possible that the increased corticospinal excitability represents, at least partially, a consequence of the prolonged muscle spasms, as in healthy subjects it has been shown that prolonged muscle activation can increase the MEP size (Balbi et al., 2002; Lentz & Nielsen, 2002). Whatever the case, the mechanisms underlying the increased corticospinal excitability in these patients seem to be very powerful, as they were able to reverse the expected MEP decrease due to the impairment of the central motor pathways.

Pharmacological studies indicated that the SP reflects a long-lasting cortical inhibition mediated by $GABA_B$ receptors (Inghilleri et al., 1996; Siebner et al., 1998; Ziemann et al., 1996). The duration of SP in patients 1-5 was reduced in comparison to healthy subjects on both sides. It is interesting to note that the reduction of SP duration in the affected hand was observed despite the presence of an increased MEP amplitude, which in itself could lead to a SP elongation (Ghosh et al., 1988; Ikoma et al., 1996; Trompetto et al., 2001). Our SP results are in line with previous findings in patients

with primary dystonia, in whom it has been reported that SP can be reduced in affected and unaffected body parts (Tinazzi et al., 2009).

SICI, which probably relies upon the activation of $GABA_A$ receptors, is another parameter reflecting the excitability of inhibitory circuits at the level of the motor cortex (Kujirai et al., 1993). SICI was not different from healthy controls in patients 6-10. While in these patients we found no difficulty in studying SICI in conditions of muscle relaxation, the presence of dystonic spasms made this assessment extremely difficult in patients 1-5. In order to investigate SICI in these subjects, we used the relaxing periods between involuntary muscle spasms. This makes the assessment very difficult and long-lasting, also because the muscular twitch evoked by cortical stimulation was often able to trigger dystonia. As a matter of fact, we could study SICI at rest only in the first three subjects (patients 1-3). In the other two patients (cases 4 and 5), SICI in the affected side was absent, but unfortunately we could not avoid the presence of involuntary EMG activity in most of the collected trials. Since the presence of activation of the corticospinal tract is known to reduce and even to eliminate SICI in healthy subjects (Buccolieri et al., 2004), the data of these two patients were not included in statistical analysis. In the affected side of patients 1-3 SICI was reduced both *vs* healthy control subjects and patients 6-10. However, considering the small number of patients, this finding should be considered with extreme caution.

Altogether, our SP and SICI findings suggest a bilateral deficit of intracortical inhibition in the patients with a lesion involving the caudate and the putamen (cases 1-5).

Correlations between clinical features and TMS findings

All the present anatomo-clinical correlations, made by MRI or CT assessment, cannot exclude a spread of the pathology beyond the boundaries of the lesion displayed by brain images.

With this limit, it seems that when the putamen and caudate were involved by the lesion, either alone or in combination with other nuclei, the clinical picture was dominated by spontaneous muscle spasms leading to dystonic postures at rest. TMS assessment showed an increased

corticospinal excitability on the affected side and a bilateral decrease of the excitability of intra-cortical inhibitory circuits. When the lesion spared the putamen and caudate, being centred on the thalamus or in the globus pallidus and subthalamic region, the clinical picture was dominated by slow repetitive involuntary movements and tremor. In these patients TMS results showed a decreased excitability of the affected corticospinal system, in line with the impairment of the central motor pathways.

Relevance of the present results

There is a substantial analogy between the present TMS results in dystonic patients with a lesion involving the putamen-caudate complex and those obtained in patients with primary dystonia affecting the upper limb. Also in primary dystonia TMS abnormalities consist in a bilateral reduction of intra-cortical inhibitory circuits (Filipović et al., 1997; Ridding et al., 1995), associated with an abnormally enhanced MEP facilitation on the affected side (Ikoma et al., 1996; Mavroudakis et al., 1995). This analogy endorses the notion that the pathogenetic mechanisms underlying primary dystonia are likely to involve the putamen and caudate (Burton et al., 1984; Fross et al., 1987; Marsden et al., 1985).

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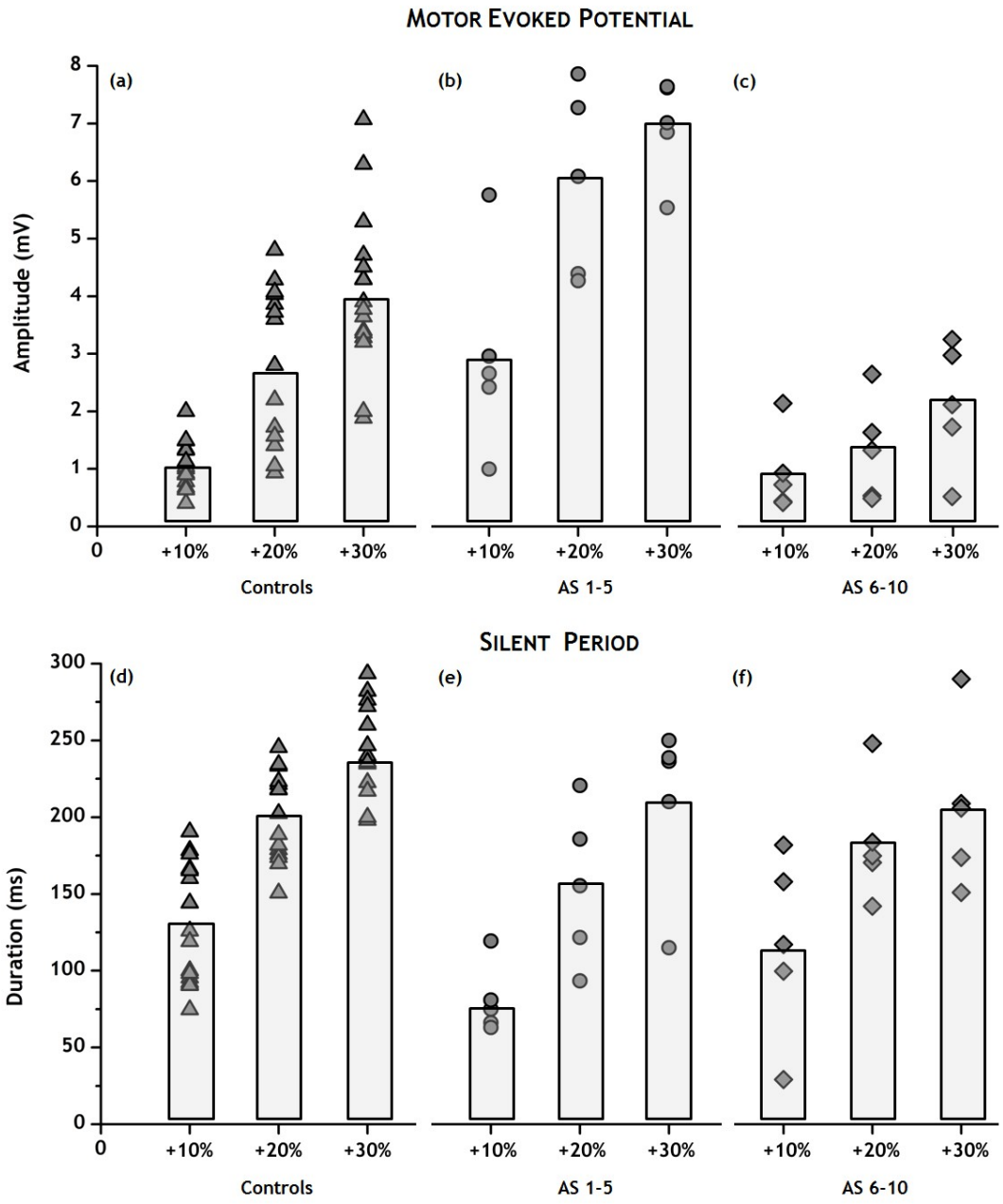

Figure 1. Motor evoked potential amplitudes and silent period durations in normal controls and in the affected side of patients.

Amplitude (mV) of motor evoked potentials (MEPs) (a-b-c) and duration (ms) of silent periods (SPs) (d-e-f) in controls (grey triangles), affected side (AS) of patients 1-5 (grey circles) and affected side of patients 6-10 (grey diamonds) at the three intensity levels of stimulation (x-axis): active motor threshold (AMT) + 10%, AMT + 20% and AMT + 30% of maximum stimulator output (MSO). Each point corresponds to the mean value of a single subject. In each panel columns represent mean value of MEP amplitude (a-b-c) and SP duration (d-e-f).

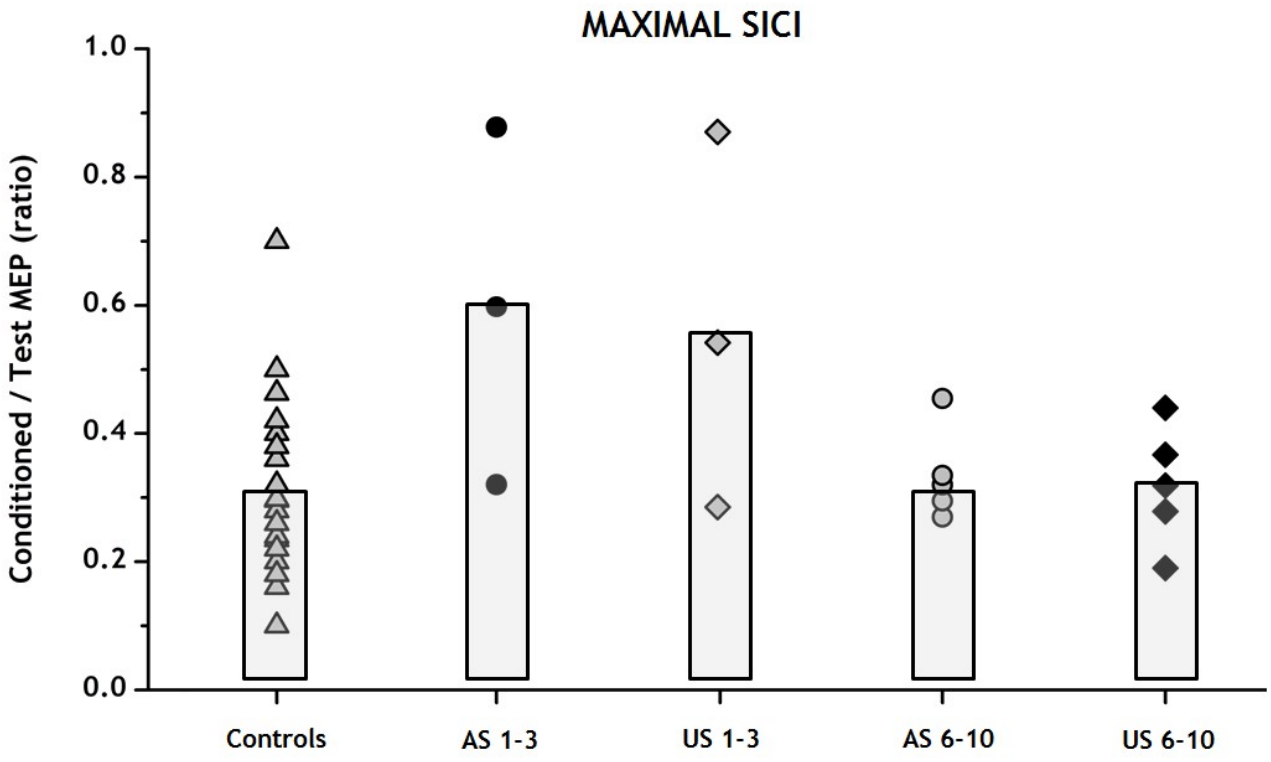

Figure 2. Maximal short-interval intracortical inhibition in controls and in the patients.

Maximal short-interval intracortical inhibition (maximal-SICI), at the inter-stimulus interval of 3 ms, in controls (grey triangles), affected side of patients 1-3 (AS 1-3, black circles), unaffected side of patients 1-3 (US 1-3, grey diamonds), affected side of patients 6-10 (AS 6-10, grey circles) and unaffected side of patients 6-10 (US 6-10, black diamonds). SICI (y-axis) is expressed as: mean conditioned / mean test motor evoked potential (MEP) amplitude. Each point corresponds to the mean value of a single subject. Columns represent mean value of maximal-SICI.

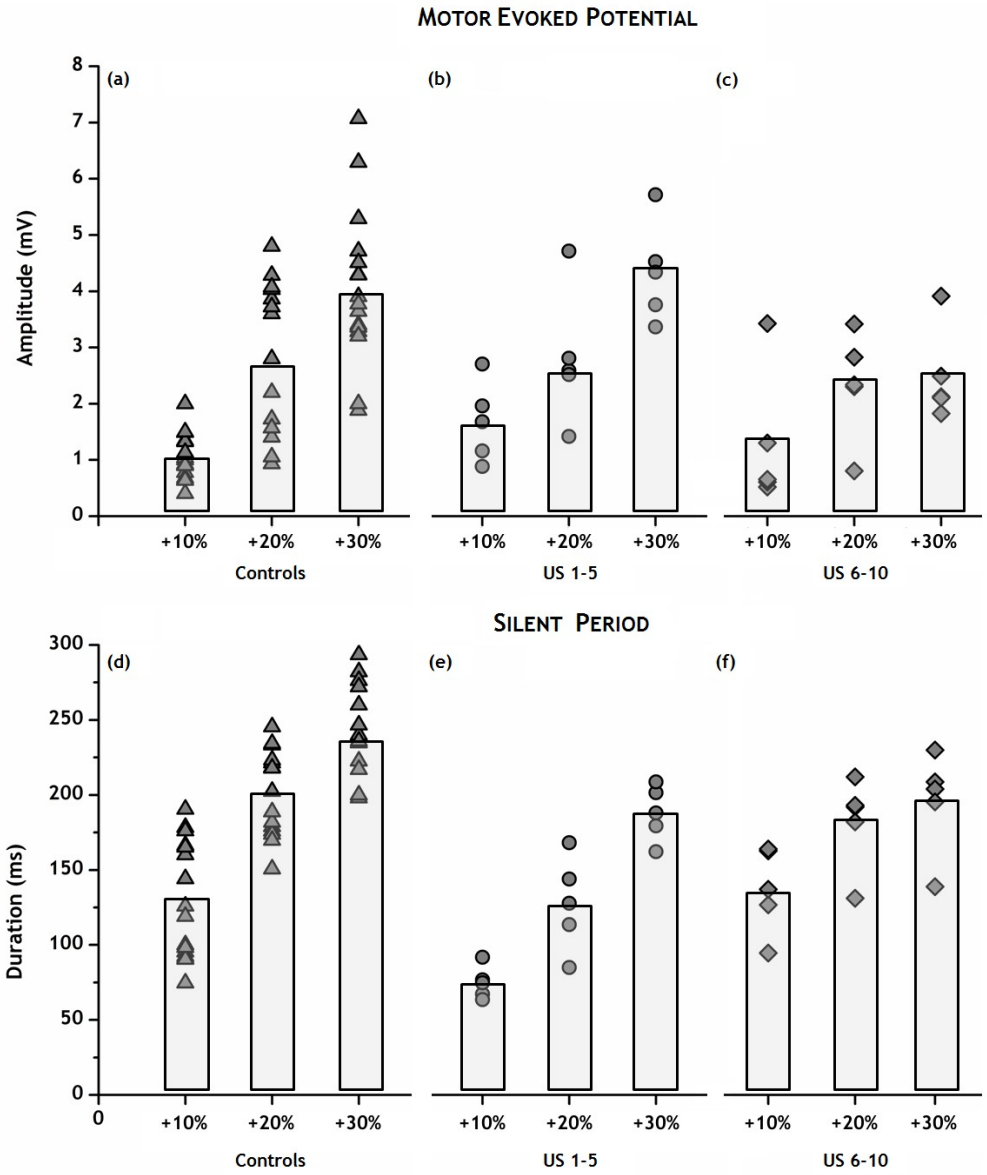

Figure 3. Motor evoked potential amplitudes and silent period durations in normal controls and in the unaffected side of patients.

Amplitude (mV) of motor evoked potentials (MEPs) (a-b-c) and duration (ms) of silent periods (SPs) (d-e-f) in controls (grey triangles), unaffected side (US) of patients 1-5 (grey circles) and unaffected side of patients 6-10 (grey diamonds) at the three intensity levels of stimulation (x-axis): active motor threshold (AMT) + 10%, AMT + 20% and AMT + 30% of maximum stimulator output (MSO). Each point corresponds to the mean value of a single subject. In each panel columns represent mean value of MEP amplitude (a-b-c) and SP duration (d-e-f).

Table 1

Patients	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***	***10***
Lesion localisation	**R** PN	**L** PN; CN	**R** PN; CN; GP; Th; IC	**R** PN; CN; IC	**R** PN; CN; IC	**L** GP; SN; subTh; IC	**R** Th; IC	**L** Th	**R** Th; IC	**L** Th; IC
Aetiology	Infarct	Vascular	Infarct	Infarct	Infarct	Haemorrhage	Haemorrhage	Infarct	Infarct	Infarct
First clinical picture	**L** hemiplegia	**R** hemiplegia	**L** hemiplegia	**L** hemiplegia	**L** hemiplegia	**R** hemiplegia	**L** hemiplegia + hemihypoesth.	**R** Upper limb dystonia	**L** hemiplegia + hemihypoesth.	**R** hemiplegia + hemihypoesth.
Age at first clinical picture	41 years	5 years	50 years	27 years	53 years	39 years	70 years	35 years	75 years	68 years
Delay of dystonia onset	5 months	3 months	3 months	6 months	72 months	6 months	24 months	No delay	7 months	5 months
Age at time of study	51 years	60 years	60 years	65 years	60 years	46 years	72 years	38 years	80 years	75 years
Topography of dystonia	Hemidystonia	Hemidystonia	Hemidystonia	Hemidystonia	Hemidystonia	Hemidystonia	Hand dystonia	Hemidystonia	Hemidystonia	Hemidystonia
Type of dystonia	Dystonic postures	Dystonic postures	Dystonic postures	Dystonic postures	Dystonic postures	Repetitive slow movements + tremor	Repetitive slow movements + tremor	Repetitive slow movements + tremor	Repetitive slow movements + tremor	Repetitive slow movements + tremor
Neurological signs at time of study	**L** mild hemiparesis (MRC=4)	**R** mild hemiparesis (MRC=4)	**L** mild hemiparesis (MRC=4)	**L** mild hemiparesis (MRC=4)	**L** mild hemiparesis (MRC=4)	**R** mild hemiparesis (MRC=4)	**L** mild hemiparesis + hemihypoesth. (MRC=4)	None (MRC=5)	**L** mild hemiparesis (MRC=4)	**R** mild hemiparesis + hemihypoesth. (MRC=4)

Table 1. Clinical data from the 10 dystonic patients.
R = right; L = left; PN = putamen; CN = caudate nucleus; GP = globus pallidus; SN = substantia nigra; Th = Thalamus; IC = internal capsule; subTh = subthalamic area; hemihypoesth. = hemihypoesthesia; MRC = Medical Research Council scale for muscle strength (average evaluation in the distal part of the affected upper limb).