DIFFERENCES OF CORTICAL EXCITABILITY BETWEEN PARKINSON'S DISEASE PATIENTS AND HEALTHY SUBJECTS. A COMPARATIVE TMS STUDY

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ABSTRACT

Transcranial magnetic stimulation (TMS) is a neurophysiological technique employed to assess the functional cortico-spinal integrity of healthy subjects, as well as the changes occurred due to various pathologies (multiple sclerosis, stroke, amyotrophic lateral sclerosis, agenesis of the corpus callosum, movements disorders, migraine, depression, schizophrenia). In Parkinson's disease (PD), single-pulse TMS provides valuable information on intracortical inhibition and facilitation mechanism alteration. A comparative analysis conducted on two groups of Parkinson's disease patients and healthy volunteers reveals a reduction of the electrical cortical silent period (which is an intracortical inhibition marker) and a facilitation decrease in the motor areas corresponding to the upper limbs (UL) in PD patients.

Key words: transcranial magnetic stimulation, Parkinson's disease, cortical silent period, transcallosal inhibition, intracortical facilitation

INTRODUCTION

Parkinson's disease is a neurodegenerative condition of the central nervous system, which is accompanied by the impairment of the cortico-subcortical excitation and inhibition systems, hence belonging to the involuntary movement diseases. TMS is a modern and noninvasive method used to evaluate the brain's functional status, which has also proven efficient in movement disorders (1). The purpose of our study is a comparative analysis of cortical excitability in Parkinson's disease patients against a group of healthy subjects.

MATERIAL AND METHOD

10 Parkinson's disease patients and 10 healthy volunteers age- and sex-matched were included in the study (Table 1). Informed consent was obtained from all participants and the study was approved by the Clinical Rehabilitation Hospital Ethical Committee.

PDG inclusion criteria:

- Hoehn and Yahr stages I-III under medication;
- "on" phase upon examination;
- stable cardiovascular and neurologic status.

Table 1. *Description of groups*

Characteristics		Parkinson's disease patients group (PDG)	Healthy subjects group (HSG)	Statistical significance
Gender (F/M)		5/5	5/5	-
Age - group (years)	Total	67.30 ± 10.34	56.00 ± 14.20	t=2.03; p>0.05
	Female	64.20 ± 9.78	58.80 ± 15.19	t=0.67; p>0.05
	Male	70.40 ± 10.99	53.20 ± 14.27	t=2.14; p<0.05

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PDG exclusion criteria:

- atypical parkinsonism;
- secondary parkinsonism;
- parkinsonism related to other neurodegenerative diseases;
- vascular, tumoral, traumatic, congenital, infectious or autoimmune cerebral and/or medullar pathology, which involves the pyramidal and/or extrapyramidal system;
- untreated or refractory epilepsy;
- deep brain stimulation;
- cardiac pacemaker.

Transcranial magnetic stimulation was done using a Magstim Rapid® device (Magstim Co Ltd, Whitland, Dyfed, UK), connected to a 7 cm-diameter butterfly-shaped coil, able to generate a 1.2 Tesla magnetic field. Motor-evoked potentials (MEPs) were determined using 4 surface electrodes (Ag-AgCl) located symmetrically at the level of the upper (UL) or lower (LL) limbs, depending on the stimulated motor area. The motor-evoked potential of the first dorsal interosseous (FDI) muscle was recorded in the UL, as the active electrode was located on the first dorsal interosseous space of the hand, and the reference electrode was placed on the index's II/III interphalangeal articulation. In the LL, the motor-evoked potential of the tibialis anterior (TA) muscle was recorded, as the active electrode was placed at the latter's peak, and the reference electrode put on the anterolateral side of the tibia, more precisely on the spot where the upper 1/3 joins the lower 2/3. In both cases, a bracelet electrode was used for earthing, which was located in the vicinity of the recording electrodes. Elefix conductive paste was used on the electrodes placed directly on the skin. A 4-channel Nihon Kohden electromyograph was used to record EMG activity. Cerebral and medullar (C6-C7 and L2-L4) magnetic stimulation was applied to determine central (CL) and peripheral (PL) latencies, and then the central motor conduction times (CMCT) were calculated for both the UL and LL. A double cone coil was employed to stimulate the areas corresponding to the lower limbs, and a high-power 9cm-diameter circular coil, able to generate an up to 2 Tesla strength magnetic field, was preferred to stimulate lumbar and sacral motor roots (which are less accessible).

The regular stimulation intensity amounted to 120% of the motor threshold (MT), which is a parameter defined as the lowest TMS intensity capable of eliciting small motor-evoked potentials, meaning more than 50 μV in amplitude in muscle at rest in at least five out of 10 trials (2). The spot where the motor threshold was reached (hot spot, HS) was marked on a silicon helmet put on the patient's head. The MEP amplitude was measured in the hot spot both at rest and after facilitation, by minimum target muscle contraction. The contralateral electrical silent period (CSP) was measured on the EMG between the last MEP wave and voluntary electromyographic activity reoccurrence, while the target muscle was subject to a submaximal contraction (20-50%) (3). Transcallosal inhibition (TI)/ipsilateral silent period (ISP) was determined when the stimulation intensity was ≥ 80%, and the tonic contraction of the small muscles of the hand ipsilateral to the stimulated hemisphere was ≥50%; the EMG revealed a temporary contractile activity suppression (4). The following parameters were measured on each hemisphere of the subjects:

- the MEPs' central and peripheral latencies, corresponding to the UL and LL;
- the central motor conduction times, motor threshold, hot spot amplitudes with and without facilitation, cortical silent period, latency (LTI) and duration (DTI) of the transcallosal inhibition corresponding to the UL.

The SPSS 17 (Statistical Package for the Social Sciences) software was used for statistical data processing.

RESULTS

As shown in tables II and III, the mean values of the MEP and CMCT latencies were approximately equal in Parkinson's disease patients and healthy volunteers.

Table 2. *Latencies and central motor conduction times of the upper limbs*

Upper limbs		N	Mean (ms)	Std. Deviation	Std. Error Mean	Test t-Student
LC	PDG	10	21.0	1.08	0.34	t = 0.105
	HSG	10	20.9	2.80	0.88	p = 0.917
LP	PDG	10	13.3	0.63	0.20	t = 0.328
	HSG	10	13.4	1.30	0.41	p = 0.747
TCMC	PDG	10	7.7	1.18	0.37	t = 0.317
	HSG	10	7.4	2.19	0.69	p = 0.755

Table 3. *Latencies and central motor conduction times of the lower limbs*

Lower limbs		N	Mean (ms)	Std. eviation	Std. Error Mean	Test t-Student
LC	PDG	10	30.4	2.58	0.81	t = 0.991
	HSG	10	29.2	2.82	0.89	p = 0.335
LP	PDG	10	13.4	2.00	0.63	t = 1.447
	HSG	10	12.3	1.24	0.39	p = 0.165

Lower limbs		N	Mean (ms)	Std. eviation	Std. Error Mean	Test t-Student
TCMC	PDG	10	17.0	1.99	0.63	t = 0.133 p = 0.896
	HSG	10	16.9	2.03	0.64	

The mean value of the motor thresholds of the UL was higher in the PDG than in the HSG (table 4).

Table 4. *Motor thresholds of the upper limbs*

Motor threshold MS	N	Mean (%)	Std. Deviation	Std. Error Mean	Test t-Student
PDG	10	64.7	10.22	3.23	t = 2.039 p = 0.056
HSG	10	57.2	5.55	1.75	

MEP amplitude in the hot spot without facilitation was high in the PDG. Maximum amplitude increased by 6% in Parkinson's disease patients, and by 75% in healthy subjects, after facilitation (table 5).

Table 5. *MEP amplitude in the HS further to 120% MT stimulation*

MEP amplitude in the HS	without facilitation (μV)	with facilitation (μV)
PDG	2364.4 ± 1146.2	2508.7 ± 1129.9
HSG	1155.3 ± 1245.8	3430.1 ± 1641.2

The contralateral cortical silent period was considerably shorter in the PDG than in the HSG; yet the transcallosal inhibition latency and duration were approximately the same in the two groups (table 6).

Table 6. *Cortical silent period, transcallosal inhibition latency and duration*

Upper limbs		N	Mean (ms)	Std. Deviation	Std. Error Mean	Test t-Student
cSP	PDG	10	72.3	16.92	5.35	t = 7.026 p < 0.001
	HSG	10	117.9	11.60	3.67	
LTI	PDG	10	31.3	3.19	1.01	t = 0.122 p = 0.904
	HSG	10	31.1	2.21	0.69	
DTI	PDG	10	25.4	1.57	0.49	t = 0.090 p = 0.929
	HSG	10	25.4	0.76	0.24	

The correlation between motor threshold and age was moderately direct in Parkinson's disease patients (r = + 0.20), whereas the same parameters were independent in healthy volunteers (r = +0.05) (Fig. 1 a, b).

According to our findings, the aging process was accompanied by higher intracortical (CSP) and interhemispheric (LTI, DTI) inhibition values and lower cortical facilitation (Fig. 2, 3).

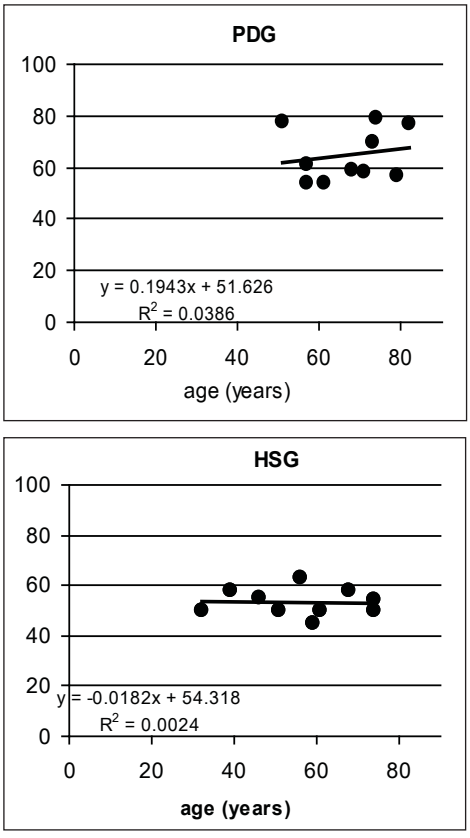

Figure 1. *Correlation between motor threshold and age*

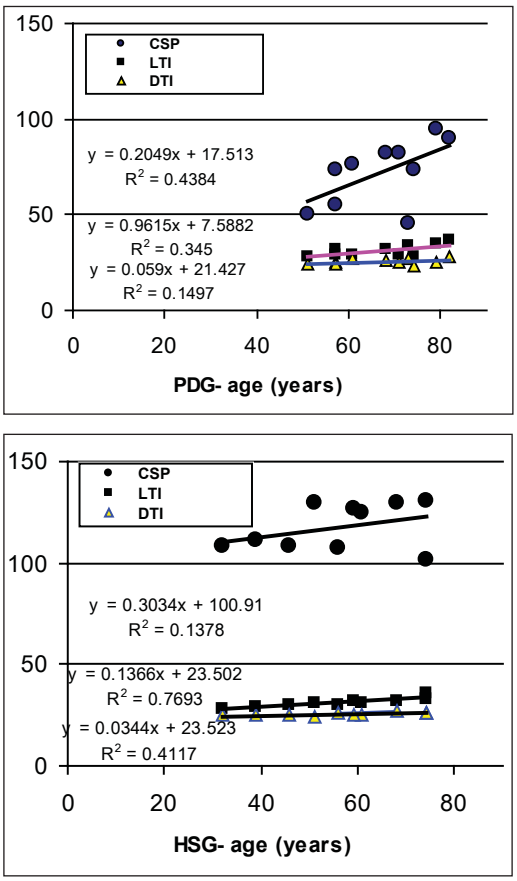

Figure 2. *Correlation between cortical inhibition markers and age*

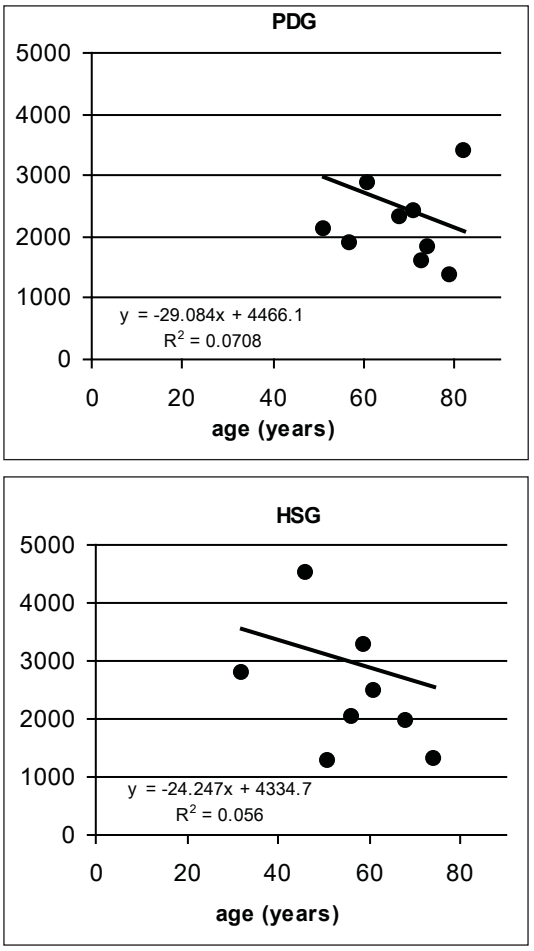

Figure 3. *Correlation between cortical facilitation and age*

DISCUSSIONS

Our results support the results of similar previous studies.

The pyramidal tracts are not impaired in pure Parkinson's disease. Therefore, the values of the MEP latencies and central motor conduction times are normal (2).

The diffuse degenerative process (which impairs the dopaminergic, serotoninergic, noradrenergic and cholinergic neurons) disorganizes the motor activity control system in the basal ganglia (corticostriatopallidal circuits). The direct tract (association areas → substantia nigra- D1 dopaminergic receptors → putamen → inner globus pallidus → ventral anterior and ventral lateral nuclei of the thalamus → motor cortex) is inhibited, whereas the indirect tract (substantia nigra- D2 dopaminergic receptors → putamen → outer globus pallidus → subthalamic nucleus → inner globus pallidus→ thalamus→ premotor cortex) is over activated; the disinhibition of Luys' subthalamic nucleus triggers exacerbated inhibitory phenomena in the pallido-thalamo-cortical circuit, which, clinically speaking, results in brady- and hypokinesia (5, 6).

The mean motor threshold value was slightly higher in the studied group than in the control group (64.2% *vs.* 57.2%). This may be accounted for by the fact that parkinsonian patients suffering from pronounced bradykinesia have lower excitability of the motor cortex (7). Nonetheless, most of the patients included in the PDG suffered from a mixed form of disease, as no precise distinction between the predominantly tremorigenic and bradykinetic-rigid types was made. There are numerous other studies (8, 9, 10) that support an increase in the cortical excitability in PD, which is related to the length of the disease (the motor threshold is lower in patients whose disease duration is $\geq$ 5 years) and which is partially corrected, in its early stage, by dopamine.

The occurrence of peripheral tremor leads to permanent stimulation of the cerebral cortex. Dopamine secretion diminution is accompanied by intracortical inhibitory mechanism alteration. Hence an excessive response to single-pulse stimulation in Parkinson's disease, the consequence of which is the increase of the motor-evoked potential amplitude (9, 10, 11). However, cortical excitability disturbance is not univocal. Unlike healthy subjects, in whom any slight contraction of the target muscle is accompanied by a 2-5 times increase in response amplitude (12), in PD amplitude increases very little or even decreases further to facilitation (13, 14, 15). This was also revealed by our study (6% in the PDG *vs.* 75% in the HSG).

Intracortical and interhemispherical inhibition has been thoroughly studied by both single-pulse TMS, and especially paired-pulse TMS. In Parkinson's disease, the electrical cortical silent period, which is the direct intracortical inhibition marker, is reduced, just like short-interval intracortical inhibition (SICI), whereas long-interval intracortical inhibition (LICI) is exaggerated, normal or reduced (16, 17). It is well-known that gamma-aminobutiryc acid (GABA) is the main inhibitory neurotransmitter in the central nervous system. While $GABA_A$ receptors are mostly postsynaptic, $GABA_B$ receptors are both presynaptic and postsynaptic. SICI commonly activates postsynaptic $GABA_A$ receptors and results into fast inhibitory postsynaptic potential (IPSP) (≈20 ms). LICI basically acts through $GABA_B$ receptors and determines slow IPSP (≈150-200 ms) postsynaptically, while inhibiting SICI presynaptically (18). Presynaptic $GABA_B$ receptors are GABA release inhibition mediators. LICI action on SICI by presynaptic $GABA_B$ receptors activation consists of the secondary decrease in GABA

release and it corresponds to a period of late cortical disinhibition, the consequence of which is a net increase in corticospinal excitability (18, 19). LICI normally inhibits SICI. In PD, presynaptic inhibition in the motor cortex is impaired, SICI inhibition by LICI is decreased, and this is probably why SICI is decreased. This may be a nondopaminergic feature of this disease (17). Just like LICI, CSP is mediated by postsynaptic $GABA_B$ receptors, whereas TI is mediated, like SICI, by $GABA_A$ receptors. CSP shortening suggests hypoactivity of inhibitory interneurons in the motor cortex (1). Two other parameters determined by paired-pulse TMS, i.e. interhemispheric inhibition (IHI) and intracortical facilitation (ICF), are reduced in PD patients without mirror movements (2, 11). Although IHI is mediated by transcallosal inhibition and subcortical circuits (20), it seems that TI is normal in Parkinson's disease. This is what distinguishes it from other parkinsonian syndromes, such as corticobasal degeneration and progressive supranuclear palsy, in which TI is shorter due to corpus callosum atrophy (2).

Cortical excitability decreased (MT increase, facilitation phenomenon diminution), and both intracortical (CSP) and interhemispheric (LTI, DTI) inhibition increased with age, in the two groups under survey, i.e. both in volunteers and in Parkinson's disease patients (fig. 1, 2, 3). This is due to increased GABAergic inhibition in older adults (increased SICI, LICI and CSP) and decreased glutamatergic facilitation (decreased ICF) (21).

CONCLUSIONS

MEP latencies and central motor conduction times are normal in parkinsonian patients, as long as their pyramidal tracts are intact.

Resting motor threshold may be increased in bradykinetic patients.

The cortico-subcortical excitatory and inhibitory circuits are deeply altered. Subcortical inhibition in the pallido-thalamo-cortical circuit coexists with intracortical disinhibition, which is proven in single-pulse TMS by higher amplitude values in the hot spot and by CSP diminution. Also, cortical facilitation is disrupted, whereas voluntary muscle activation elicits a smaller MEP amplitude increase in PD patients than in normal subjects. The enhancement of excitability at rest and weak energization during voluntary muscle activation suggest that motor system excitability control is abnormal in Parkinson's disease.

Cortical excitability is an age-related characteristic. Parkinson's disease patients, just like normal older adults, exhibit more intracortical inhibition and less intracortical facilitation than young adults.

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