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Original article

MEG evaluation of Parkinson's diseased patients after external magnetic stimulation

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Abstract

Magnetoencephalographic (MEG) recordings of Parkinson's diseased (PD) patients were obtained using a whole-head 122-channel magnetometer and analyzed with Fourier statistical analysis. External transcranial magnetic stimulation (TMS) in the order of pico Tesla was applied on the above patients with proper field characteristics (magnetic amplitude : 1-7.5 pT, frequency : the α-rhythm of the patient : 8-13 Hz) which were obtained prior to TMS. The MEG recordings after the application of TMS showed a rapid attenuation of the high abnormal activity followed by an increase of the low frequency components toward the patients' α-rhythm. The patients responded to the TMS with a feeling of relaxation and partial or complete disappearance of tremor, muscular ache and levodopa induced dyskinesias as well as rapid reversed visuospatial impairment, which were followed by a corresponding improvement and normalization of the MEG.

Key words : 122-channel magnetometer ; PD ; TMS ; frequency analysis.

Introduction

The current pathophysiological concept of Parkinson's disease (PD) postulates alterations of the interactions within the basal ganglia complex due to the loss of dopaminergic projections from the substantia nigra to the striatum (Obeso *et al.*, 2000). According to this model, pathological hyperactivity of the subthalamic nucleus drives the internal globus pallidus, which leads to an inhibition of the 'motor thalamus' (ventro-lateral and ventro-anterior nuclei). Consequently, the output of the thalamus to the sensorimotor cortex is reduced, resulting in hypokinesia. The involvement of other brain areas such as the supplementary and cingulate motor areas, premotor cortex, sensory cortices and the cerebellum remains unclear in the described model. However, in the last years, this pathophysiological concept of PD was corroborated by the successful treatment of a variety of PD symptoms by lesioning of the subthalamic nucleus in a primate model of PD and, subsequently, by high-frequency stimulation of the subthalamic nucleus in PD patients, resulting in a remarkable reduction of symptoms (Krack *et al.*, 2000 ; Volkmann *et al.*, 2001).

The subthalamic nucleus has a key-role in the pathophysiology of PD and is the primary target for high-frequency deep brain stimulation. The subthalamic nucleus rest electrical activity in PD, however, is still unclear. Priori *et al.* (2004), have tested the hypothesis that pharmacological modulation of subthalamic nucleus activity has rhythm specific effects in the classical range of EEG frequencies, below 50 Hz, and concluded that in the human subthalamic nucleus there are at least two rhythms below 50 Hz, that are separately modulated by antiparkinsonian medication : one at low frequencies (2-7 Hz) and one in the beta range (20-30 Hz). Power changes elicited by antiparkinsonian medication in the alpha band were not significant. So, we have chosen alpha rhythm to apply external magnetic stimulation in our settings.

The availability of MEG systems covering the whole scalp and methodological advances (Gross *et al.*, 2001) now allow investigation in more detail of the oscillatory network and mechanisms involved in PD tremor (Timmermann *et al.*, 2003).

Clinical applications of transcranial magnetic stimulation (TMS) were first reported by Baker *et al.* (1984) and has been widely used to assess possible changes secondary to PD. The use of single- and paired-pulse TMS, two varieties of the original technique, disclose multiple functional alterations of the corticospinal pathway (Cantello *et al.*, 2002). The use of TMS in PD investigations began about 10 years ago. Then it had become clear that TMS could provide information not only on the conductivity of corticospinal neurons, but also on other properties of the primary motor cortex, such as excitability (Cantello *et al.*, 1991). In turn, basic evidence strongly suggested that excitability was under the influence of multiple afferences to the motor cortex itself, among which those arising

from the basal ganglia (Porter and Lemon, 1993). Hence, a new insight arose into the pathophysiology of PD as well as of other movement disorders. TMS has provided substantial new pathophysiological insights, which point to a central role of the primary motor cortex in the movement disorder typical of PD. Recently several clinical trials have suggested the therapeutic efficacy of repetitive TMS (rTMS) in patients with PD (Berardelli *et al.*, 1999 ; Siebner *et al.*, 2000 ; Strafella *et al.*, 2001 ; Wassermann and Lisanby 2001 ; Khedr *et al.*, 2003).

The goal of this study is to report the beneficial effects of external TMS (in the order of pico Tesla), on PD patients using MEG measurements and statistical analytic techniques in the frequency domain.

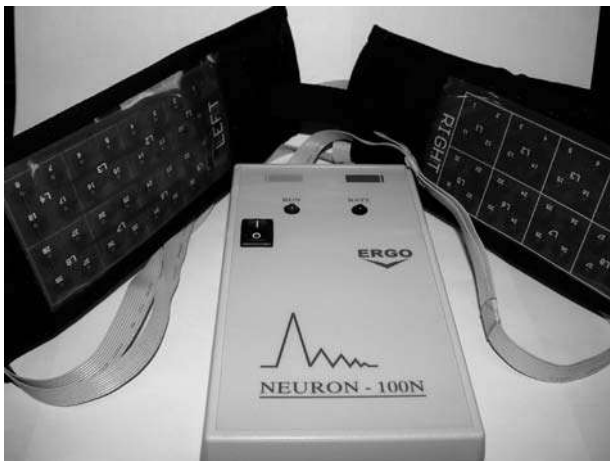

FIG. 1. — The electronic device with the coils placed in two plastic plates by which the TMS is applied to PD patients.

Methods

Thirty PD patients (22 males, 8 females ; mean age 65 years, with range 49-80 years) were referred to our laboratory by practicing neurologists from January 2002 to December 2004 with symptoms of akinesia, rigidity, or tremor and with EEG records before and after TMS. All the patients had been diagnosed to suffer from idiopathic PD on the basis of clinical observations and routine EEG recordings. The modified Hoehn and Yahr (H & Y) baseline status (Hoehn and Yahr, 1967), was stage 1.5 in 3 patients, stage 2 in 3 patients, stage 3 in 14 patients and stage 4 in 10 patients. The period from diagnosis to the beginning of this study ranged from 1 to 3 years. None of them had a history of other systemic neurological disease other than PD, or implanted devices of pacemakers and all had normal routine serum biochemical studies. Patients had a neuroimaging study i.e CT (n = 12), MRI (n = 7) or both (n = 3). In all cases written informed consent for the methodology and the aim of the study was obtained from all patients prior to the procedure. All patients were initially placed on levodopa/carbidopa (Sinemet 25/250) (1 tablet twice daily), but due to progressive deterioration in their motor disability the dosage was increased to 3 $^1/_2$ tablets/day (1/2 tablet every 2 hours). All subjects were off medication for 24 hours.

Biomagnetic measurements were performed using a whole-head Neuromag 122 MEG system in a magnetically shielded room of low magnetic noise with broadband (f > 10Hz) gradient noise 5fT/(cmHz$^{1/2}$) for the 95% of the channels and max noise 10fT/(cmHz$^{1/2}$), a broadband (1 Hz < f < 10 Hz) gradient noise 15fT/(cmHz$^{1/2}$) for the 95% of the channels and max noise 20fT(cmHz$^{1/2}$) (Timmermann *et al.*, 2003 ; Tonoike *et al.*,1998). The spontaneous MEG recordings were obtained from the PD patients using the 122-channel SQUID with sampling frequency of 256 Hz and filtered with cut – off frequencies between 0.3 to 40 Hz. The time taken for each recording was 1 min. During the MEG recordings the subject was sitting in a chair with his head covered by the helmet-shaped dewar. Four indicator coils attached to the head of the individual subject determined the exact position of the head with respect to the MEG sensors. The exact positions of the coils were determined using a three dimensional digitizer.

Afterwards, external TMS in the order of pico Tesla was applied to PD patients with proper field characteristics (magnetic intensity : 1-7.5 pT ; frequency : the α-rhythm of the patient : 8-13 Hz), which were obtained prior to TMS using an electronic device (Anninos and Tsagas 1995 ; Anninos *et al.*, 1999 ; 2000 ; 2003). The coils of this device were placed on the patient's scalp and weak magnetic fields, were applied for 6 minutes in total (2 minutes over each of the following areas : left and right temporal regions, frontal and occipital regions, and over the vertex). This device consists of a generator to produce square waves of low frequencies magnetic field in the range from 2-13 Hz to a group of coils of 1cm in diameter. The coils are enclosed between two parallel plane surfaces in such a way that their axis is situated perpendicular to these surfaces. The time between the first MEG and the MEG obtained after the application of TMS was about an hour.

To confirm that the responses to TMS were reproducible, the patients were instructed to apply TMS with the same characteristics (2 times a week, for 6 min total duration) nightly at home with the electronic device (Fig. 1). In all patients placebo tests were also performed before the TMS and without energizing the device in order to evaluate the influence of the TMS. None of the patients experienced any side effects during or after the procedure. The statistical analysis of the results was obtained using the chi-square test and paired t-test.

Table I

Individual clinical data for each PD patient (N = 30). (A : abnormal ; P : partial normal ; N : normal diagnosis ; BTMS : before TMS ; ATMS : after TMS)

SUBJECTS	AGE	AGE START	EEG BTMS	EEG ATMS	MEG BTMS	MEG ATMS	H & Y stages BTMS	H & Y stages ATMS	IMPROVEMENT (YEARS)
MEN	77	55	P	N	A	A	1.5	1.5	2
	61	52	P	N	A	N	2	2	2
	79	58	N	N	A	N	2	1.7	3
	57	63	P	N	A	A	3	2.7	3
	69	57	P	N	A	A	3	2.7	3
	71	52	P	N	A	N	3	2.8	3
	49	45	P	N	A	N	3	2.9	2
	55	48	P	N	A	N	4	3.7	2
	67	63	P	P	A	N	3	2.9	3
	66	61	N	N	A	N	1.5	1.5	2
	58	50	P	N	A	N	3	2.8	3
	80	64	P	N	A	N	3	1.4	2
	76	65	P	N	A	N	3	1.5	2
	58	66	A	N	A	N	3	1.4	3
	58	50	N	N	A	N	3	1.3	2
	66	60	P	N	A	A	3	1.1	3
	78	58	N	N	A	N	3	3.7	2
	75	52	P	N	A	A	4	3.8	3
	51	48	P	N	A	N	4	2.4	2
	64	59	P	N	A	N	1.5	1.3	2
	73	55	P	N	A	N	4	3.8	3
	54	45	A	N	A	N	4	2.3	3
WOMEN	58	47	P	N	A	N	2	2	2
	72	67	P	N	A	N	3	1	3
	62	55	A	N	A	N	3	1	2
	76	61	P	N	A	N	4	2.5	2
	58	50	P	P	A	N	4	1.2	3
	52	50	P	N	A	A	4	1	2
	68	58	A	P	A	A	4	1.2	2
	65	49	P	N	N	N	4	1	2

Results

Table I shows each patient's clinical report and their response to TMS. Based on an independent chart review, they were divided into two groups according to the degree of their responsiveness to TMS. The first group included patients who exhibited only partial response (PR) to TMS (i.e., their tremor or muscular ache or dyskinesias recurred within 12 months after TMS and partial appearance of α-rhythm in their EEG denoted by low amplitudes). The second group included patients who demonstrated a favorable response (FR) to TMS (i.e., they were free from the above symptoms for at least one year after TMS and the appearance of α-rhythm in their EEG denoted by high amplitudes). Using the above mentioned criteria table II was formed. Twelve patients (40%) were classified as partial responders (PR) and the remaining 18 (60%) exhibited a favorable response (FR) to TMS (table II). Among the partial responders to TMS (41.67%), normal EEG (i.e., the appearance of high amplitude of power spectrum in the α-rhythm frequency) was seen only in 5 patients, whereas 16 out of 18 patients who showed a favorable response to TMS (88.88%) had normal EEG (i.e., the appearance of very high amplitude power spectrum in the α-rhythm frequency). The difference was of statistical significance ($p < 0.01$, chi-square = 7.64). The EEG and the MEG diagnosis before and after TMS is based on the appearance of α-rhythm amplitude in their power spectra amplitude distribution (tables I, II). Neuroimaging studies demonstrated diffuse cerebral atrophy in 5 patients and cortical atrophy in one. Two patients exhibited small ischemic infracts in the temporal lobes. No other abnormalities were detected. After 1-2 months of TMS, the H & Y stages showed significant decreases when compared with the baseline status. Three patients showed no change of their H & Y status. They were stage 1.5 (2 of them) and stage 2 (the remaining one). The scores of one patient stage 1.5, one patient stage 2, seven patients stage 3, and four patients stage 4 decreased to averages 1.2 ± 0.3. One patient stage 2 score decreased to 1.7. Five patients stage 3, and three patients stage 4 scores decreased to averages 1.6 ± 0.2. Two patients stage 3, and three patients stage 4 scores decreased to averages 1.9 ± 0.1. The difference in the H & Y status before and after TMS was of statistical significance for the whole study group ($p < 0.0001$, paired t-test). Surprisingly, from the random choice

Table II

Classification of the examined PD patients according to their EEG and MEG diagnosis and their response to TMS ($p < 0.01$, chi-square = 7.64)

Response	NORMAL EEG	ABNORMAL EEG	TOTAL
PR	5	7	12
FR	16	2	18
TOTAL	21	9	30

of the patients only 4 of the 30 had abnormal EEG BTMS, whereas the MEG BTMS was abnormal for 29 out of 30 patients (table I).

Discussion

The primary pathology of Parkinson's disease (PD) is located in basal ganglia (DeLong, 1990). However TMS studies have demonstrated altered excitability of the motor cortex in PD. Studies using electrical and magnetic stimulation techniques have shown that the corticomotor neuron connection is normal in PD (Dick *et al.*, 1984). This means that bradykinesia is not primarily the result of any deficit in the final output pathways of the motor areas of the cortex. Most authors reported that the motor cortex of patients with PD has the same threshold for stimulation as in healthy subjects (Ridding *et al.*, 1995). However, when the patients are tested at rest, the slope of the input-output relationship between stimulus intensity and response size is steeper than normal. Perhaps as a result of this, voluntary contraction facilitates responses less than for normal subjects (Valls-Sole *et al.*, 1994). Although this could be the result of a primary basal ganglia deficit, it seems probable that it could also be an attempt to compensate for the slow recruitment of commands to move by making it easier to recruit activity from a resting state (Berardelli *et al.*, 2001).

A work of Brown and colleagues (Brown *et al.*, 2001) has shown that in PD patients there is a coherence between the motor cortex EEG and 15-30 Hz subthalamic nucleus (STN) local field potential oscillations. Thus the PD STN is driven by 15-30 Hz motor cortex oscillations. This leads to the hypothesis that the PD motor cortex-basal ganglia may be held abnormally in a 15-30 Hz oscillatory state ; yet these are the same coherent frequencies as those detected between motor cortex and muscle during postural maintenance in healthy humans. The study by Levy *et al.* (2002) contains a number of important insights : (i) The frequency range (15-30 Hz) of rhythms detected in STN is the same as that found in healthy humans to modulate motor unit activity during isometric muscle contraction. (ii) The 15-30 Hz frequency range is the same as the coherence found between motor cortex MEG, EEG or local field potentials and contralateral electromyogram (EMG) during steady muscle contraction in humans and primates. (iii) The 15-30 Hz STN oscillations are diminished by voluntary movement in a way analogous to the suppression of human motor cortex beta EEG oscillations and motor cortex-muscle 15-30 Hz coherence in primates and humans. (iv) Whilst we do not know if STN 15-30 Hz oscillations are present in non PD individuals. Levy *et al.* (2002) show that treatment with apomorphine and levodopa suppresses the oscillations with a time course that correlates with improvement of the "off" symptoms of PD. (v) Suppression of 15-30 Hz STN oscillations with voluntary movement occurs independently of changes in the firing rate of STN neurons, indicating that their temporal pattern of discharge conveys additional information to their firing rate. (vi) The 15-30 Hz oscillations are detected in the temporal patterning of STN neuron spike trains as well as at the level of local field potentials. (vii) The oscillations do not relate in any clear way to PD tremor and may relate more to mechanisms of akinesia. (Farmer, 2002) Coherence between STN area local field potentials and EEG is apparent in a wide range of frequencies (theta : 3-7Hz, alpha : 8-13Hz, lower beta : 14-20Hz, and upper beta : 21-32Hz) but activity in the alpha and upper beta bands dominates (Fogelson *et al.*, 2006) .

Improvements, such as those that were found in the present study, are likely to be attributed to dopamine release, which is supported by an experimental study in which repetitive TMS (rTMS) lead to increased release of dopamine in the striatum and frontal cortex (Ben-Shachar *et al.*, 1997). Strafella *et al.* (2001) showed that rTMS of the prefrontal cortex induces the release of endogenous dopamine in the ipsilateral caudate nucleus as detected by positron emission tomography in healthy human subjects. The rTMS-induced release of dopamine in the caudate nucleus could be a consequence of direct stimulation of the corticostriatal axons (Rothwell, 1997). GABA is the dominant inhibitory neurotransmitter of the motor cortex. Berardelli *et al.* (1999) recorded an increase in the duration of the TMS-evoked SP during a 20-pulse train of suprathreshold rTMS in healthy volunteers as well as in PD patients. Mally and Stone (1999) have reported sustained improvements in movement-related measures with various regiments of repeated TMS pulses administered with round coils over periods of weeks to months. Siebner *et al.* (2000) recorded an increase in the duration of the TMS-evoked SP in PD after 15 trains of 5-Hz rTMS over the hand area. This means that 5-Hz rTMS is capable of inducing short-term change in the excitability of intracortical inhibitory circuitry in PD patients. As dopamenergic drugs result in a similar modulation of the SP, the facilitatory effect

of 5-Hz rTMS on intracortical inhibition might be a candidate mechanism that mediates the beneficial effect of 5-Hz rTMS of primary motor area in PD patients (Khedr *et al.*, 2003).

In this study the patients' responses to the TMS were a feeling of relaxation and partial or complete disappearance of muscular ache and levodopa-induced dyskinesias as well as rapid reversal of visuospatial impairment. This clinical improvement was followed by a corresponding improvement and normalization of the MEG, recorded after the application of TMS. Assuming that the MEG of PD patients is a reflection of the pathogenesis in the substantia nigra, dopaminergic functions and sympathetic ganglia, it appears that the application of the TMS has an immediate and beneficial effect on the dynamic condition of these abnormally functioning neural structures (Sandyk *et al.*, 1991a ; 1991b ; 1991c ; 1991d ; 1992a ; 1992b ; 1992c ; 1992d ; 1992e ; 1992f ; 1992g ; 1992h). Although the striking beneficial effects of the application of the TMS on the clinical picture of the PD patients are well observed, the mode of action of TMS in PD remains an open question. This question is difficult to be answered given the complexity of cellular, systemic and neuroendocrine effects of TMS on biological systems and their potential impact on neurotransmitter functions. Despite all these and independent of their mechanisms of action, this method of magnetic stimulation may be considered an important non-invasive means in the management of idiopathic PD patients.

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