Research report

Are autonomic signals influencing cortico-spinal motor excitability?
A study with transcranial magnetic stimulation

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Abstract

In order to investigate the role of visceral afferent inputs flowing along autonomic fibers on corticospinal tract excitability, the variability of Motor Evoked Potentials (MEPs), elicited by Transcranial Magnetic Stimulation (TMS), was analysed during simultaneous monitoring of electrocardiogram (EKG) phases, breathing phases and sudomotor skin responses (SSRs) in a group of 10 healthy subjects. A cascade of at least 60 consecutive magnetic stimuli, with an interstimulus interval randomly varying between 20 and 40 s, was acquired. At the end of the recording session, the subject was asked to make at random five not consecutive self-paced forced inspirations. TMS was carried out at an intensity 10% above motor threshold excitability via a circular coil placed over the motor area of the right hemisphere. MEPs were recorded from the contralateral abductor digiti minimi muscle (ADM). Sudomotor Skin Responses (SSRs) were recorded on both hand palms. MEPs latency and amplitude did not show significant correlation with any of the EKG and respiratory phases. During forced inspiration, a significant latency shortening was found. TMS elicited SSRs, whose amplitudes were not correlated with MEP parameters. During forced inspiration a significant SSR amplitude increment, not correlated with MEP latency shortening, was also observed. These results assign a minor if any role to the considered autonomic parameters in modulating corticospinal motor excitability. © 2000 Elsevier Science B.V. All rights reserved.

Theme: Motor system and sensorimotor integration

Topic: Cortex

Keywords: TMS; MEP; Cortical excitability; Autonomic system; Skin test

1. Introduction

Motor evoked potentials (MEPs) from resting muscles produced in response to TMS, show a high degree of amplitude variability even with apparently stable stimulus and subject’s condition. This variability appears to be generated spontaneously [8] and has no known cause. It could result from physical changes in the parameters of stimulation or from neurophysiological changes in the excitability of the corticospinal pathway [5].

Previous reports have emphasized the role of mental activity, background EEG oscillating rhythms and sensory feed-back as causes of the variability of motor cortex excitability [7,16,17,20,21].

TMS is supposed to activate the cortico-spinal fibers mainly through cortico-cortical connections after one or more synaptic interruptions; therefore, threshold for MEPs excitation is profoundly influenced by the level of cortical activation. In fact, mental activity with a low-voltage (desynchronized EEG) is facilitating larger MEPs during TMS, while EEG rhythms in \( \alpha \) range, during relaxed wakefulness with closed eyes, are associated to MEPs amplitude reduction [17].

The time-varying fluctuations of MEPs amplitude may also reflect modulation of cortical and spinal \( \alpha \) motoneurons excitability by somatic afferent inputs [9,20].

The possible influence of visceral inputs, travelling along autonomic fibers, on corticospinal descending vol-
leys has not yet been investigated in detail. The simultaneous analysis of motor cortical outputs in the Central Nervous System (CNS), as studied with TMS, and of some functional parameters under the control of Autonomic Nervous System (ANS) could therefore shed light on the potential interactions between the two systems, classically thought as anatomically and functionally independent.

In the present study we aimed to investigate the interactions between MEP latency and amplitude and phasic changes of some autonomic parameters, such as cardiac cycle, respiratory phases and sudomotor activity in a group of healthy subjects. This is in order to verify whether these ANS parameters play some role on cortical excitability fluctuations.

2. Materials and methods

The study was performed in 10 healthy subjects, including the authors, (4 males, 6 females; mean age 33.4 ± 5.15 years).

The examined subject was lying fully relaxed on a bed with the eyes open in a quiet room. Care was taken to avoid sleep or drowsiness.

Poligraphy was carried out as follows:

Electrocardiogram (EKG) recorded by means of two Ag/AgCl electrodes filled with conductive jelly, placed on both wrists. The cardiac cycle was analyzed with respect to the different phases: P wave, QRS complex, ST tract, T wave, TP tract (interval from the end of the preceding T to the P wave of the next phase).

Heart Rate (HR) was measured in the 5 s preceding and following TMS.

Pneumogram recorded by means of a band tight round the thorax connected to a mechanical transducer sensitive to thoracic excursions and through a mask connected to a transducer sensitive to the air in and out flow during respiratory phases.

Sudomotor skin response (SSRs) recorded by means of Ag/AgCl exploring electrodes placed on both hand palms, referred to the hand dorsum (0.01–10 Hz-3 dB/oct) with an amplification level ranging from 200 to 500 μV/div, individually determined for each subject at the beginning of the recording session.

All these parameters (EKG, Pneumogram, SSRs) were recorded together with the TMS trigger on paper at a velocity of 15 mm/s. The magnetic stimulus produced an artifact that allowed the evaluation of the chronological correlation between MEPs and the EKG phase, the respiratory phase (inspiration/expiration), the SSR amplitude (see Fig. 1).

TMS was performed using a flat positioned regular round coil lateralized on the right hemiscalp until overlying the right motor strip (Cadwell MES-10 stimulator; I.D. 5 cm). The site was carefully located where MEPs with the lowest intensity and with minimal latency could be elicited in the contralateral abductor digiti minimi (ADM). Intensity of TMS was 10% above the threshold, defined — following international standards [19] — as the intensity which elicits reproducible MEPs of above 50% μV in amplitude, in 50% of 10 consecutive stimuli.

A continuous sequence of at least 60 magnetic stimuli,
with an average interstimulus interval of 30 s, was acquired and stored on floppy disk for off-line analysis.

During the recording session the subject was asked to make maximal inspirations, randomly intermingled with physiological respiratory phases, and at the moment of the maximal thoracic excursion the magnetic pulse was delivered.

MEPs were recorded throughout the experiment with a 50 ms analysis time, 5–5000 Hz bandpass filters, 5000 Hz sampling rate and a 200 µV/div amplification. Trials contaminated by even minimal EMG activity were discarded from further analysis. MEPs selected on the polygraphic recordings were retrieved from floppy disk for detailed analysis of latency/amplitude characteristics.

2.1. Data analysis

Amplitude values of MEPs and SSRs were measured between the two largest peaks of opposite polarity and were analyzed after logarithmic transformation, in order to achieve a better fit to normal distribution. MEP latencies were measured at the onset of the initial reproducible deflection.

Since a large inter-individual variability was observed, z-scores were computed both for MEP parameters (latency and amplitude) and for SSR amplitude.

The relationship between MEP and cardiorespiratory parameters was investigated by means of ANOVA and graphically represented by error bars (95% confidence intervals).

Pearson’s r correlation index was used to assess the possible correlation between MEPs and SSR amplitudes during maximal inspiration. The chronological behavior of the MEP and SSR amplitudes during the recording session was analyzed by regression techniques with time as independent variable; the correlation index (Pearson’s r) was calculated both for each subject and for the whole sample.

Throughout the statistical analysis, the significance level was set at 0.05.

3. Results

Table 1 summarizes latency, log amplitude values and excitability thresholds for each subject. The reported statistics were computed without including data recorded during maximal inspiratory effort. All values were transformed to obtain the z-scores.

Table 1

<table>
<thead>
<tr>
<th>Subject</th>
<th>MEP latency (ms)</th>
<th>MEP amplitude (log microV)</th>
<th>SKIN ipsi (microV)</th>
<th>SKIN contra (microV)</th>
<th>Excitability threshold (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>s1</td>
<td>Mean 21.8</td>
<td>7.5</td>
<td>118.8</td>
<td>118.8</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>S.D. 0.5</td>
<td>0.4</td>
<td>84.7</td>
<td>91.6</td>
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<tr>
<td></td>
<td>N 57</td>
<td>57</td>
<td>36</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>s2</td>
<td>Mean 23.5</td>
<td>5.3</td>
<td>574.0</td>
<td>822.8</td>
<td>60</td>
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<tr>
<td></td>
<td>S.D. 0.8</td>
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<td>521.3</td>
<td>909.3</td>
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<tr>
<td></td>
<td>N 60</td>
<td>60</td>
<td>34</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>s3</td>
<td>Mean 21.9</td>
<td>6.6</td>
<td></td>
<td></td>
<td>45</td>
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<tr>
<td></td>
<td>S.D. 1.1</td>
<td>0.7</td>
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<td></td>
<td>N 61</td>
<td>61</td>
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<tr>
<td>s4</td>
<td>Mean 27.0</td>
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<td>48</td>
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<td>N 69</td>
<td>69</td>
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<td>143.3</td>
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<td></td>
<td>N 59</td>
<td>59</td>
<td></td>
<td></td>
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</tr>
<tr>
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<td>48</td>
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<tr>
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<td>113.8</td>
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<td>N 59</td>
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<td>68</td>
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</tr>
<tr>
<td>s10</td>
<td>Mean 22.1</td>
<td>7.1</td>
<td>93.4</td>
<td>83.8</td>
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<td>13.1</td>
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<td>N 54</td>
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</table>
MEP latency and amplitude did not show significant relationship with any of the EKG phases ($F=0.56; df=5.524; P=0.730$ NS; see Fig. 2).

Similarly, physiological breathing phases (inspiration and expiration) did not influence MEP parameters. On the other hand, during forced maximal inspiration a significant MEP latency shortening was found ($F=14.3, df=2.481 P=0.001$; Fig. 2), without any related amplitude modification ($F=1.3, df=2.481 P=0.256$; Fig. 3).

SSRs were present in all the tested subjects. However in five of them SSR rapidly attenuated and disappeared. In the remaining five subjects a reliable (>60%) number of SSRs to TMS was recorded.

Intensities of TMS (and the related acoustic noise) were not significantly different between the group with a reliable number of SSRs and the other one ($t$-test, $P=0.595$; see Table 1). Concerning the former group, neither the SSR presence–absence nor their amplitudes correlated with MEP parameters. In these subjects, no clear pattern of SSR changes was identifiable during the recording session, not allowing detecting an adaptation or a facilitation process as a function of the time. Therefore, the large standard deviation (shown in Table 1) could not be accounted for by any of the considered parameters. In addition, no significant SSR amplitude differences were observed between the side contralateral and ipsilateral to TMS. During forced maximal inspiration SSRs were significantly larger in amplitudes compared to those recorded in the physiological respiratory phases, but without any evident correlation with MEP latency.

TMS did not induce any significant HR modification. In addition, the HR measured before and after each TMS stimulus was constant throughout the experiment.

In addition, no significant changes could be observed in MEP parameters in the course of the recording session. The lack of significance found in bivariate analyses was also confirmed when simultaneous effects were taken into account.

4. Discussion

Results of the present study show a lack of correlation between MEP parameters and cardiac cycle, sudomotor skin responses and respiratory phases. On the other hand, during maximal inspiratory effort, a significant, but independent MEP latency decrement and SSR amplitude increment, were observed.

These data seem to suggest that visceral signals originating from the mechanical cyclic impact of the heart action and chest expansion do not significantly influence motor excitability either at the cortical or at the spinal levels.

It is known that somatosensory mechanoreceptors in the chest pick up the cyclic impact of the heart muscle on the surrounding tissue and that mechanoreceptors, located near the large arteries, are stimulated by small translocations of tissues induced by the pulse wave [14]. All these signals, originating at different locations in the body, could flow synchronously with each heart action and have been associated to a heart action-related EEG potential in frontal and parietal regions [3]. It remains an open question whether the above mentioned visceral inputs can modulate the motor outputs.

Connections of the cerebral cortex with the heart, blood vessels and viscera are well known. Frontal lobe, insular cortex and limbic areas establish a rich mutual exchange of information with vegetative centers located in the brain stem and medulla [1,12,25]. Results of stimulation and lesion studies suggest that insular cortex is involved in heart rate (HR) and blood pressure regulation [12,13].
According to these results, repetitive TMS induced a clearly marked autonomic response with HR acceleration and decrease in blood pressure in normal subjects [6].

At more fundamental anatomic levels, it has been shown that noradrenergic fibers have a global extent in the animal cortex. They form through the neocortex a three-dimensional matrix, where multiple contacts are possible, permitting a synchronous modulation of afferent neuronal activity throughout this network [10].

All the above observations suggest the potential for the autonomic afferent fibers to modulate cortical and/or spinal motor excitability.

Our findings show a significant reduction of MEP latencies during forced inspirations. It has been previously demonstrated that hyperventilation increases motor cortical excitability [15,22], as measured with TMS, and that this effect is related to a reduction in pCO2.

On the other hand, in the present study, reduced levels of pCO2 can not account for the finding of MEP latency decrement, since our subjects did not hyperventilate and it is known that pCO2 becomes significantly lower only after 5 min of hyperventilation [22].

Therefore, a possible explanation for the latency shortening during forced inspirations could be referred to an increase of afferent inputs from cardiopulmonary system to the cerebral cortex and spinal motoneurons. In fact, inflation of lungs is known to activate pulmonary stretch receptors of tracheobronchial tree [24], that could target the motor centers, influencing their excitability. In this context, it has been demonstrated an interaction between vagal afferent fibers and spontaneous electroencephalographic (EEG) activity of the sensorimotor cortex, evident during the mechanical activation of pulmonary afferents [2]. However, a spread of motor cortical excitability due to the voluntary act of inspiration, as well as the involvement of unspecific factors, such as an arousal reaction, during self-paced maximal inspiration can not be excluded. Moreover, since maximum voluntary inspiration is a voluntary act, it might induce a transient spread of cortical excitability similar to the one induced by voluntary contraction of muscles of the hand or foot opposite to the one where MEP are recorded from [23].

In the present study, TMS was able to elicit a sympathetic skin reflex (SSR) in both contralateral and ipsilateral hands. This finding confirms previous reports showing an SSR induced by TMS of the motor area in normal subjects [4,18]. This response has been explained by the activation of cortical structures influencing palmar and generalized sweating. Therefore, the significant SSR amplitude increment observed during phases of deep breathing probably reflects a combined summation of two stimuli (TMS and deep breathing), each individually able to elicit this response.

In our study, SSR amplitudes were similar in the side contralateral and ipsilateral to TMS. This finding is in line with previous data [11], showing that SSR amplitudes are independent of the cortical region and the brain hemisphere underlying the stimulating coil.

In conclusion, our study suggests that the investigated autonomic parameters have a minor influence in modulating motor cortical and/or spinal excitability. Although a large amount of data was collected for each subject and we never found a clear pattern of influence on motor excitability, a limit of the present study is the small number of recruited subjects, which is a very critical point especially for ‘negative’ results.

In addition, the approach adopted was limited to a description of autonomic function in normal subjects, in a state of equilibrium. For a more complete knowledge on this topic to occur, future research should include the study of patients with selective autonomic disorders, in whom the altered balance between somatic and visceral inputs could reveal other contributions of autonomic signals to cortical and spinal excitability.

References


