

# Effects of right unilateral electroconvulsive therapy on motor cortical excitability in depressive patients

Malek Bajbouj <sup>a,\*</sup>, Undine E. Lang <sup>a,b</sup>, Ludwig Niehaus <sup>c</sup>, Florence E. Hellen <sup>a</sup>,  
Isabella Heuser <sup>a</sup>, Peter Neu <sup>a</sup>

<sup>a</sup> Department of Psychiatry, Charité – University Medicine Berlin, Campus Benjamin Franklin, Eschenallee 3, 14050 Berlin, Germany

<sup>b</sup> Department of Neurology, University of Tuebingen, Germany

<sup>c</sup> Clinic of Neurology II, Otto-von-Guericke-University, Magdeburg, Germany

Received 5 April 2005; received in revised form 7 July 2005; accepted 8 July 2005

## Abstract

Electroconvulsive therapy (ECT) is a widely acknowledged effective treatment for severe major depression. ECT produces considerable anticonvulsant effects that may be related to an increased GABA-ergic neurotransmission. We aimed to explore whether motor cortical excitability as assessed with single and paired pulse transcranial magnetic stimulation (TMS) could be used to investigate these anticonvulsant effects. Therefore, parameters of motor cortical excitability were investigated in 10 patients before and after 10 sessions of right unilateral ECT. After 10 sessions of right unilateral ECT, an enhanced activity of inhibitory circuits in human motor cortex had been observed, as measured by both increased intracortical inhibition and cortical silent period duration, whereas intracortical facilitation and resting motor threshold remained unchanged. The reduction of seizure duration in the course of ECT was associated with clinical improvement and an increase in intracortical inhibition. We interpret this finding as further indirect evidence for changes in inhibitory circuits in the course of ECT in patients with major depression.

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**Keywords:** Major depressive disorder; Electroconvulsive therapy; Cortical excitability

## 1. Introduction

Electroconvulsive therapy (ECT) continues to have an established and important role in the management of treatment-resistant depression (Eranti and McLoughlin, 2003). A compensatory increase in the function of the inhibitory neurotransmitter  $\gamma$ -aminobutyric acid (GABA) has been suggested as one possible mechanism contributing to both the anticonvulsant and antidepressant actions of ECT (Sackeim, 1999).

Transcranial magnetic stimulation (TMS) has been introduced as a powerful tool to explore the integrity

and excitability of the corticospinal system in patients with neurological and psychiatric diseases (Puri and Lewis, 1996; Fitzgerald et al., 2002). A variety of TMS motor cortex excitability measures are available, each with a distinct anatomy and neurophysiological underpinning. Resting motor threshold has been associated with the membrane excitability of cortical motor neurons. The cortical silent period succeeds the contralateral motor evoked potential (MEP) and refers to a silence in the EMG following the MEP. It depends, at least in part, on GABA-ergic neurotransmission (Reis et al., 2002). Intracortical inhibition and facilitation as measured by the paired pulse technique have been associated with the balance of GABA-ergic, dopaminergic, and glutamatergic tone. All these parameters are of special interest in the context of the investigation of ECT effects

\* Corresponding author. Tel.: +49 30 8445 8622; fax: +49 30 8445 8233.

E-mail address: [malek.bajbouj@charite.de](mailto:malek.bajbouj@charite.de) (M. Bajbouj).

since they are strongly influenced by the GABA-ergic system (for review, see Daskalakis et al., 2002).

An investigation of a single patient with major depression showed changes of motor cortex excitability in the ECT course (Sommer et al., 2002). In a previous work, enhanced activity of inhibitory circuits in human motor cortex following a single ECT session has been observed (Bajbouj et al., 2003). Finally, a recent study reported an association of the antidepressant effect of bilateral ECT and left hemispheric excitability (Chistyakov et al., 2005).

To our knowledge, changes of all four mentioned TMS measures in the course of a right unilateral ECT treatment have not been studied so far. Therefore, the present study aims to clarify the effect of 10 sessions of electroconvulsive therapy on these TMS parameters associated with central GABA-ergic neurotransmission.

## 2. Methods

### 2.1. Subjects

The study was approved by the Ethics committee of the Benjamin-Franklin-University Hospital of the Free University of Berlin. All subjects gave written informed consent. Hospitalized patients meeting the DSM-IV criteria for major depression were studied. Diagnosis was made in accordance with the attending physician and a senior house officer. The exclusion criteria for patients were other significant psychiatric or neurological disorders such as epilepsy, mental retardation, personality disorder, and alcohol or substance abuse within one year of the study. We studied 10 right-handed patients (seven women and three men, aged  $54.1 \pm 15.2$  years) with unipolar major depression with a mean episode duration of  $28.7 \pm 18.4$  weeks. Patients had  $4.3 \pm 3.4$  prior episodes, an illness duration of  $5.9 \pm 4.6$  years and  $3.9 \pm 2.5$  prior antidepressant treatment trials. Patients received the following antidepressant medication, which was taken constantly four weeks prior to investigation and during ECT treatment: venlafaxine (five patients, dose range from 150 to 225 mg/day), tranylcypromine (five patients, dose range from 20 to 40 mg/day). No patient received anticonvulsants or mood stabilizers. Since it is known that sexual hormones may have an influence on cortical excitability (Smith et al., 1999), the stage of investigation was controlled with respect to the menstrual cycle in female patients. Five of the female patients were postmenopausal and in one patient the investigation was performed in the luteal phase. Clinical symptoms were assessed using the Hamilton Depression Scale (HAMD) (Hamilton, 1967) and the Beck Depression Inventory (Beck et al., 1961) at baseline and after 10 treatments.

### 2.2. Transcranial magnetic stimulation

Focal TMS with monophasic pulses was performed with a figure-of-eight-shaped coil (MCB70) of the Mag-lite stimulator with the Twin Top option (Dantec Medtronic, Skovlunde, Denmark), with the centre of the coil (contact point of both half-coils) placed over the hand-associated motor cortex. For each subject, the stimulation point for eliciting maximal hand motor responses was determined individually and lay, on average, 6 cm lateral to the vertex and 1 cm anterior to the interaural line. For optimal stimulation, the induced currents were directed posteroanteriorly. The elicited surface compound muscle action potential (electrode area  $28 \text{ mm}^2$ ) was recorded bilaterally from the first dorsal interosseus (ID) muscle. Data were amplified, bandpass filtered (from 20 Hz to 2 kHz), digitized (sampling rate 5 kHz) and stored on a personal computer for offline-analysis.

TMS was performed one day before and 24 h after the 10th session of ECT. The second time point of investigation was chosen because it was assumed that most of the patients would show an antidepressant effect at this time point.

The resting motor threshold (percentage of maximum stimulator output) for eliciting contralateral hand motor responses was determined for the relaxed hand muscles and defined as the stimulus intensity at which responses of at least 0.05 mV occurred in about half of 10 trials.

Cortex stimulation was then performed during maximal tonic hand muscle contraction. The stimuli were applied over each hemisphere at an intensity of 40% above resting motor threshold. The duration of cortical silent period was measured from the onset of the corticospinally mediated EMG response to the end of the silent period, which was set at a point where the averaged tonic EMG activity again reached the amplitude of the mean EMG activity before the cortex stimulus. To assess inhibitory effects, 20 consecutive EMG signals elicited by stimulation over each hemisphere were rectified. The duration of each trial was then measured and then averaged.

Intracortical inhibition (ICI) and intracortical facilitation (ICF) were investigated, using the previously described paired-pulse technique (Kujirai et al., 1993). Since it was known from previous studies that short interstimulus intervals (ISIs), of 2 and 3 ms, have an inhibitory effect and long ISIs, of 10 and 15 ms, have a facilitatory effect, intracortical inhibition and facilitation were calculated across these intervals respectively. The intensity of the conditioning stimulus was adjusted to 80% of the resting motor threshold, and the intensity of the test stimulus was set so that the test stimulus alone produced a response of about 1 mV peak-to-peak amplitude. Ten trials of the unconditioned control single test stimuli and 10 paired pulse stimuli of each ISI were recorded, delivered 10s apart in random order. The

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