Evidence for Impaired Cortical Inhibition in Patients with Unipolar Major Depression

Malek Bajbouj, Sarah H. Lisanby, Undine E. Lang, Heidi Danker-Hopfe, Isabella Heuser, and Peter Neu

Background: *Several lines of evidence suggest that central cortical inhibitory mechanisms, especially associated with gamma-aminobutyric acid (GABA) neurotransmission, may play a role in the pathophysiology of major depression. Transcranial magnetic stimulation is a useful tool for investigating central cortical inhibitory mechanisms associated with GABAergic neurotransmission in psychiatric and neurological disorders.*

Methods: *By means of transcranial magnetic stimulation, different parameters of cortical excitability, including motor threshold, the cortical silent period, and intracortical inhibition/facilitation, were investigated in 20 medication-free depressed patients and 20 age- and gender-matched healthy volunteers.*

Results: *Silent period and intracortical inhibition were reduced in depressed patients, consistent with a reduced GABAergic tone. Moreover, patients showed a significant hemispheric asymmetry in motor threshold.*

Conclusions: *This study provides evidence of reduced GABAergic tone and motor threshold asymmetry in patients with major depression.*

Key Words: Unipolar major depression, transcranial magnetic stimulation, GABA, intracortical inhibition, intracortical facilitation, silent period

Several lines of evidence in preclinical and clinical studies suggest that the gamma-aminobutyric acid (GABA) neurotransmitter system is involved in the pathophysiology of major depression. Animal studies report decreased GABA concentration and receptor function after both acute and chronic stress (Acosta et al 1993; Acosta and Rubio 1994). Anticonvulsants that elevate GABA in humans have antidepressant as well as mood stabilizing and anxiolytic properties (Calabrese et al 1999). Moreover, GABA levels have been reported as decreased in the cerebrospinal fluid of patients with melancholic subtype of depression in some but not in all studies (Gold et al 1980; Roy et al 1991). Consistent with these findings, brain imaging studies using proton magnetic resonance spectroscopy demonstrated lower GABA concentrations in depressed patients than in healthy subjects (Sanacora et al 1999, 2004). Finally, benzodiazepine and GABA-A receptor radioligand binding in relation to chronic stress shows either no changes (Kugaya et al 2003) or a globally decreased GABA-A receptor binding in depressed patients (Northoff et al 1999).

In addition to these neurochemical changes, the results of Northoff et al (1999) suggest that depressed patients with psychomotor retardation may also have asymmetries in GABA-A receptor binding. Previous work suggests that depressed patients may have structural as well as functional asymmetries in limbic-thalamic-cortical networks hypothesized to modulate mood states. Early and recent neuroanatomical studies in depressed patients revealed asymmetries in several structures such as frontal and temporal lobe (Kumar et al 2000). Moreover, functional neuroimaging studies have shown functional asymmetries in brain metabolism (Brunswick et al 2003), especially in the prefrontal cortex (Kocmur et al 1998; Baxter et al 1989).

Transcranial magnetic stimulation (TMS) is a noninvasive investigational tool that provides ways to directly measure the excitability of the human motor cortex. A variety of TMS motor cortex excitability measures are available, each with a distinct anatomy and neurophysiological underpinnings. Motor threshold, or the lowest intensity required to elicit a motor evoked potential (MEP) of a designated amplitude in 5 of 10 trials, has been associated with membrane excitability of cortical motor neurons. Cortical silent period follows the contralateral motor evoked potential and refers to a silence in the electromyograph (EMG) following the MEP. It depends, at least in part, on GABAergic neurotransmission (Reis et al 2002). Intracortical inhibition and facilitation as measured by the paired pulse technique have been associated with the balance of GABAergic, dopaminergic, and glutamatergic tone. These parameters are of special interest in the context of our study since they are strongly influenced by the GABAergic system and are capable of investigating laterality differences (for review, Sanger et al 2001; Daskalakis et al 2002).

Previous studies have explored single aspects of motor cortical excitability in patients with major depression. Reid et al (2002) showed in depressed patients a reduced postexercise facilitation as compared with healthy control subjects. Steele et al (2000) reported a prolonged silent period in depressed patients. In a recent study by Grunhaus et al (2003), no differences in motor threshold between patients and control subjects were reported. In all three studies, patients were receiving psychotropic medication, which may have influenced the measures. Maeda et al (2000) found in a small sample of unmedicated patients an interhemispheric asymmetry of motor threshold and parameters of the paired-pulse curves indicating a decreased excitability on the left hemisphere. Finally, Fitzgerald et al (2004) recently replicated the finding of a decreased left hemispherical excitability in a sample of medicated patients with major depression.

The aim of the present study was to compare all mentioned parameters of motor cortical excitability in 20 medication-free patients with unipolar major depressive disorder and healthy control subjects. It was hypothesized that patients with major depression would show differences consistent with reduced GABAergic activity and evidence of hemispheric asymmetry.

From the Department of Psychiatry (MB, UEL, HD-H, IH, PN), Charité University Medicine Berlin, Berlin, Germany; Brain Stimulation and Neuromodulation Division (SHL), Columbia University; and Department of Biological Psychiatry (SHL), New York State Psychiatric Institute, New York, New York.

Address reprint requests to Malek Bajbouj, M.D., Department of Psychiatry, Charité University Medicine Berlin, Campus Benjamin Franklin, Eschenallee 3, 14050 Berlin, Germany; E-mail: malek.bajbouj@charite.de.

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Table 1. Demographic and Clinical Characteristics of Patients with Unipolar Depression and Healthy Control Subjects

	Patients with Major Depression		Healthy Control Subjects	
	Mean	SD	Mean	SD
Age (years)	42.9	11.9	44.0	14.6
N (Female/Male)	20	(6/14)	20	(6/14)
EHS	26.9	4.4	25.9	3.8
HRSD (24)	21.1	6.0		—
Duration Index Episode (Weeks)	21.3	20.8		
Duration All Episodes (Months)	12.7	10.4		
Number of Episodes	2.6	1.2		
Total Length of Illness (Years)	.9	.7		
CORE: Noninteractiveness	6.9	3.3		
CORE: Motor Retardation	8.9	3.9		
CORE: Agitation	2.3	1.7		
CORE: Total	18.1	7.0		

EHS, Edinburgh Handedness Scale; HRSD, Hamilton Rating Scale for Depression.

Methods and Materials

Patients and Healthy Control Subjects

The study was approved by the Ethics committee of the Benjamin Franklin University Hospital of the Free University of Berlin. Inpatients and outpatients with a major depressive episode meeting the DSM-IV criteria were recruited from the Department of Psychiatry, Free University of Berlin. Out of a larger sample of 84 patients, 20 were free of antidepressants, anticonvulsants, mood stabilizers, or benzodiazepine treatment for at least 4 weeks due to intolerance or nonresponse. These patients were included in this study and gave written informed consent. Healthy participants were recruited by newspaper advertisements. All participants, who were of German descent, were interviewed by a research psychiatrist with structured clinical interviews, the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al 1998) in healthy subjects and Structured Clinical Interview for DSM-III-R Axis I (SCID-I) in patients (Spitzer et al 1992). Exclusion criteria were Axis I or Axis II disorders (except major depression for the patient group), hearing disorder, concurrent psychiatric or neurological illness, seizure disorder, or any clinically relevant abnormalities in blood chemistry or other laboratory tests (patients). We studied 20 right-handed patients with major depressive episode (6 women, 14 men). Clinical symptoms were assessed using the 24-item Hamilton Rating Scale for Depression (HRSD) (Hamilton 1967) and CORE criteria (Parker et al 1995) prior to the TMS procedures. The CORE rating consists of 18 signs that are summed into three dimensions, noninteractiveness, retardation, and agitation (for further clinical data, see Table 1).

The control group was comprised of 20 age-matched and gender-matched, right-handed healthy volunteers, who underwent a Mini-Structured Clinical Interview for DSM-III-R (Mini-SCID). Since it is known that sex hormones may influence cortical excitability (Smith et al 1999), the comparison group was matched for the number of female participants (6), number of postmenopausal women (4), and menstrual cycle phase at time of testing (luteal). In both healthy volunteers and patients, handedness was assessed with the Edinburgh Handedness Scale (Oldfield 1971). Demographic and clinical data are summarized in Table 1.

TMS and EMG Recording

General Procedure. Focal TMS with monophasic pulses was performed with a figure-eight coil (MC-B70) of the Maglite stimulator with the Twin Top option (Dantec Medtronic, Skovlunde, Denmark), with the coil's center (contact point of both half-coils) placed over the optimal site for hand area of the motor cortex. For each subject, the stimulation point for eliciting maximal hand motor responses was determined individually and was, 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 mm^2) was recorded bilaterally from the first dorsal interosseus (FDI) muscle. Data were amplified, bandpass filtered (20 Hz to 2 kHz), digitized (sampling rate 5 kHz), and stored on a personal computer for off-line analysis with the BrainVision Analyzer software (Fa. Brain Products, Munich, Germany).

Cortical Excitability Measures. To control for the stability of coil positioning, motor evoked potentials amplitudes were measured at the beginning and end of each cortical excitability assessment at 125% of resting motor threshold. Ten sweeps of data were measured and then averaged.

All off-line EMG analysis was performed masked to group and all clinical variables. The 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 .05 mV occurred in at least 5 of 10 trials.

Single-pulse TMS was then performed during maximal tonic hand muscle contraction. A high level of muscle contraction was chosen to reduce variability of cortical silent period (CSP) duration (Mathis et al 1998). The stimuli were applied over each hemisphere at an intensity of 40% above resting motor threshold. The duration of the cortical silent period was measured from the onset of the corticospinal mediated EMG response to the end of the silent period, which was defined as the point where the averaged tonic EMG activity again reached the amplitude of the mean EMG activity before TMS. To assess inhibitory effects, 20 consecutive EMG signals elicited by stimulation over each hemisphere were rectified. The duration of the CSP in each trial was measured and then averaged.

Intracortical inhibition (ICI) and intracortical facilitation (ICF) were investigated with the previously described paired-pulse technique (Kujirai et al 1993). Since it was known from previous studies that short interstimulus intervals (ISI) (2 and 3 milliseconds) have an inhibitory effect and long ISIs (10 and 15 milliseconds) 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 (accepted range: .8–1.2 mV). After 10 trials of the test stimuli, 10 paired-pulse stimuli of each ISI were recorded and delivered 10 seconds apart in random order. The peak-to-peak amplitudes of the conditioned response were averaged and expressed as a percentage of the average of the test response amplitudes.

Statistical Methods

An a priori sample size calculation with the silent period (SP) as the primary outcome variable revealed that 20 patients and 20 volunteers are enough to get a statistically significant result with