Abnormal Cingulate and Prefrontal Cortical Neurochemistry in Major Depression After Electroconvulsive Therapy

Angela Merkl, Florian Schubert, Arnim Quante, Alexander Luborzewski, Eva-Lotta Brakemeier, Simone Grimm, Isabella Heuser, and Malek Bajbouj

Background: Metabolic changes after electroconvulsive therapy (ECT) have been described in depressed patients, but results are heterogeneous. To determine the concentrations of N-acetyl-aspartate (NAA), choline-containing compounds, creatine + phosphocreatine (tCr), and glutamate in the left dorsolateral prefrontal cortex (DLPFC) and left anterior cingulum of depressed patients before and after ECT, we used proton magnetic resonance spectroscopy.

Methods: Metabolite concentrations in the DLPFC and anterior cingulum were determined in 25 patients with major depressive disorder (MDD) and 27 healthy control subjects using the point resolved spectroscopy sequence. Neuropsychological and clinical parameters were determined before and after nine sessions of right unilateral ultrabrief pulse ECT.

Results: In the cingulum, baseline glutamate and NAA levels were decreased in depressed patients. High glutamate at baseline predicted a greater treatment response. After ECT, increased NAA levels were observed in responders to treatment and tCr levels were significantly decreased across all depressive patients. In the left DLPFC, NAA levels were significantly decreased in responders to ECT compared with nonresponders. Autobiographic memory was deteriorated in all patients after ECT.

Conclusions: Low glutamatergic state in depressive patients emphasizes the role of dysfunctional glutamatergic neurotransmission in the pathophysiology of MDD. The low NAA level at baseline in the patients supports neurodegenerative changes in MDD. N-acetyl-aspartate levels might serve as early surrogate marker for dynamic metabolic changes due to ECT, reflecting both neuroprotection and lowered neuronal viability. The tCr decrease in the cingulum suggests altered mitochondrial energy metabolism.

Key Words: Anterior cingulum, dorsolateral prefrontal cortex, electroconvulsive therapy, glutamate, major depressive disorder, N-acetyl-aspartate

Electroconvulsive therapy (ECT) is the most effective treatment in terms of speed of action and response rates in major depressive disorder (MDD) (1), but information about the underlying neurobiological mechanisms of action is still sparse. The safety of ECT has been improved by introducing new parameters like ultrabrief pulse and right unilateral (RUL) electrode placement (2). Nevertheless, despite its strong antidepressant effect and efficacy even better than or comparable with pharmacotherapy (3) and recent advances in safety, ECT can produce reversible cognitive deficits (4). In animal models, neuroprotective effects of electroconvulsive shock (ECS) treatment have been found in the hippocampus (5), the cingulum, and frontal cortices (6). However, in humans, these processes involved in ECT are difficult to detect in vivo. Proton magnetic resonance spectroscopy (1H MRS) constitutes a unique tool for noninvasive in vivo brain imaging that can detect changes in brain biochemistry in MDD. Resonance lines in the 1H MRS spectrum can be reliably quantified for a number of metabolites including N-acetyl-aspartate (NAA), which serves as an early functional marker (7). Reduced NAA levels in the caudate, bilateral dorsolateral prefrontal cortex (DLPFC), and hippocampus in MDD have been observed using MRS (8). Further, the excitatory amino acid glutamate (Glu) and the glial cell reservoir storage form of glutamate, glutamine, and the sum of Glu and glutamine (Glx) have been studied with 1H MRS. There is evidence for a crucial role of brain glutamate for etiologic mechanisms in depression (9), supported by the observation that drugs altering glutamate neurotransmission, like ketamine and riluzole, have antidepressive potential (10). In severe MDD, a reduction of Glx in the anterior cingulate cortex (ACC) (11,12), DLPFC (13), and in the dorsoanterolateral prefrontal cortex (PFC) and ventromedial PFC (14) have been described, indicating that neuronal glial cell function is impaired in MDD. In turn, reduced Glx levels in depressive patients normalized in ECT responders compared with healthy control subjects (12). Finally, creatine + phosphocreatine (tCr) as a measure of energy utilization and choline related compounds (tCho), including glycerophosphocholine, phosphocholine, and acetylcholine, which are involved in membrane metabolism, can be investigated by 1H MRS. For tCho, an increase in hippocampus and frontal regions, as well as nonsignificant differences (12,13), have been reported in severely depressed patients (15,16). Lower levels in tCho in the hippocampus before ECT and a normalization in depressed patients after ECT have been observed (17).

In humans, key findings of brain imaging studies concern abnormalities in blood flow and metabolism in DLPFC and ACC in depression (18). Structural abnormalities are reported in the ACC (19), the right dorsomedial PFC, and bilateral DLPFC (20). Postmortem analyses indicate a reduction in glial cell number and neuronal cell body size in the prefrontal and orbitofrontal cortices (21,22). In turn, these neuronal and glial alterations are

From the Department of Psychiatry (AM, AQ, AL, IH, MB) Charité–Universitätsmedizin, Campus Benjamin Franklin, Berlin; Cluster of Excellence "Languages of Emotion" and Dahlem Institute for Neuroimaging of Emotion (AM, SG, MB), Freie Universität Berlin, Berlin; Department of Psychiatry (E-LB), Universitätsklinik für Psychiatrie und Psychosomatik, Freiburg; and Physikalisch-Technische Bundesanstalt (FS), Berlin, Germany.

Address correspondence to Angela Merkl, M.D., M.A., Charité–Universitätsmedizin, Campus Benjamin Franklin, Department of Psychiatry, Eschenallee 3, 14050 Berlin, Germany; E-mail: angela.merkl@charite.de.

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associated with biochemical changes, shown for the density and size of γ-aminobutyric acid (GABA)ergic interneurons (23). The aim of the present study was to examine absolute levels of NAA, tCr, tCho, and Glu at baseline and after nine treatments with ultrabrief ECT in a priori defined regions, namely the left DLPFC and anterior cingulum. We hypothesized that patients with depression would have lower levels of glutamate and N-acetylaspartate when compared with healthy control subjects. In addition, we hypothesized an increase in these metabolites after successful antidepressant treatment.

Methods and Materials

Participants

A total of 27 patients fulfilling the diagnostic criteria for MDD (DSM-IV) and referred to ECT due to clinical indication and 27 healthy sex-matched control subjects were enrolled from January 2005 to December 2008. Diagnoses were established by two independent experienced psychiatrists based on a clinical interview following DSM-IV criteria. Patients with a medical history of alcohol und drug abuse, schizophrenia, or dementia were excluded. Medication resistance was measured with the medication resistance was measured with the Modified Antidepressant Treatment History Form (24). Response to antidepressant therapy was defined as a 50% reduction in the Hamilton Depression Rating Scale (HDRS) 17-item version. Psychometric ratings were performed at baseline, to which we refer as time point 0 (T0); after nine ECTs, here denoted as time point acute (T_acute); and at complete end (after full response) of ECT, referred to as time point 1 (T1). Self-ratings, Beck Depression Inventory (German Version) (25) and the Montgomery Åsberg Rating Scale were used (Table 1). After a detailed description of the study protocol to the patients, written informed consent was obtained. The protocol was approved by the local University Ethics Committee of the Charité Berlin, and the study was carried out in accordance with the declaration of Helsinki. Healthy control subjects gave written informed consent, and a semistandardized interview was performed to rule out any underlying psychiatric or neurological condition. Magnetic resonance spectroscopy (MRS) datasets of two patients and two control subjects in the cingulum were discarded due to head moving artifacts in the scanner.

ECT Procedure

Right unilateral (RUL) ECT was administered 3 times a week with a customized square-wave, ultrabrief pulse, constant-current device (Mecta 5000Q, Somatics, Inc., Lake Bluff, Illinois). We applied

Table 1. Clinical Characteristics Across Subjects Groups

	Patients with MDD[a] ($n = 25$)					
Characteristics	Depressives (Responders) 68% ($n = 17$)	Depressives (Nonresponders) 32% ($n = 8$)	Control Subjects ($n = 27$)	F	df	p Value
Age (Years)	51.76 ± 13.16	46.38 ± 12.93	36.30 ± 13.98	1.15	50	.001[b]
				$\chi^2 = 10.284$	2	.006[c]
Gender (% Female)	88.2	62.5	74.1	$\chi^2 = -2.242$	2	.33[c]
Axis I Comorbidity	2 (BP-II, OCD)	1 (BP-I)	—			
Duration of Current Episode (Weeks)	48.1 ± 61.6	91.4 ± 97.4	—	10.42	23	.28
Number of Depressive Episodes	7.1 ± 3.8	6.0 ± 4.6	—	.15	23	.53
BDI T0	31.8 ± 10.8	34.6 ± 11.1		.02	21	.58
BDI (T_acute)	26.4 ± 13.9	20.4 ± 10.2		.57	18	.28
BDI T1	15.3 ± 10.0	23.1 ± 9.9		.002	20	.11
HDRS-28 T0	32.2 ± 8.9	33.4 ± 7.7		.001	21	.75
HDRS-28 T1	14.3 ± 9.6	23.1 ± 8.9		.39	21	.05
HDRS-17 T0	24.5 ± 5.0	23.0 ± 5.6		.21	23	.52
HDRS-17 (T_acute)	14.6 ± 4.9	18.7 ± 6.4		.12	20	.11
HDRS-17 T1	9.7 ± 5.2	17.2 ± 4.7		.35	23	.002
MADRS T0	33.2 ± 7.0	31.5 ± 6.3		.02	19	.58
MADRS (T_acute)	24.9 ± 8.5	29.3 ± 8.3		.001	15	.32
MADRS T1	16.9 ± 8.5	18.9 ± 10.7		.48	19	.66
Number ECT for Response (T1)	20.3 ± 5.9 (range 12–32)	18.6 ± 5.9 (range 12–32)		.63	1	.43[d]
ATHF[e]	12.9 ± 4.9	15.3 ± 8.5		2.168	22	.41

Values are mean ± SD if not otherwise specified.

ATHF, Modified Antidepressant Treatment History Form; BDI, Beck Depression Inventory; BP-I, bipolar disease type I; BP-II, bipolar disease type II; ECT, electroconvulsive therapy; HDRS-17, 17-Item Hamilton Depression Rating Scale; HDRS-28, 28-Item Hamilton Depression Rating Scale; MADRS, Montgomery Åsberg Rating Scale; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; T0, time point 0 or pre-ECT baseline; T1, time point 1 or at complete end (after full response) of ECT; T_acute, time point acute or after nine ECTs.

[a]Patients received concomitant medication, dosage being kept constant in all patients during ECT. Treatment comprised different antidepressants with add-on therapy; serotonin-norepinephrine reuptake inhibitors (52%), noradrenaline-dopamine reuptake inhibitors (12%), selective serotonin reuptake inhibitors (52%), tricyclic antidepressants (20%), or atypical neuroleptics (20%). Seven patients were augmented with mood stabilizers (29.4% of the responders; using lithium carbonate with lithium plasma levels lower than .8 mmol/L). Benzodiazepines were used as pharmacotherapy in 24 patients (94%). Eighteen patients (72%) were medication resistant (60).

[b]*t* test for independent samples; comparison of all depressive patients versus healthy control subjects.

[c]Comparison of depressive patients who responded to ECT versus nonresponders versus healthy control subjects.

[d]Kruskal-Wallis nonparametric test.

[e]Medication resistance was measured with the ATHF.