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Antipsychotic effect of electroconvulsive therapy is related to normalization of subgenual cingulate theta activity in psychotic depression

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ABSTRACT

Objective: Electroconvulsive therapy (ECT) is one of the most effective options available for treating depressive and psychotic symptoms in a variety of disorders. While the exact mechanism of ECT is unclear, it is known to increase metabolism and blood flow specifically in the anterior cingulate cortex (ACC). The ACC is a cortical generator of theta rhythms, which are abnormal in patients with depression and psychotic disorders. Since patients with psychotic depression are known to respond particularly robustly to ECT, we investigated whether the therapeutic effect of ECT in this population was related to normalization of abnormal theta activity in the ACC.

Method: We obtained 19-lead electroencephalography (EEG) data from 17 participants with psychotic depression before and 2–3 weeks after a full course of ECT. EEG data was analyzed with quantitative measures and low-resolution electromagnetic tomography (LORETA) compared to an age-adjusted normative database.

Results: Quantitative EEG analyses revealed that theta band (4–7 Hz) activity was the only frequency band that changed with ECT. LORETA analyses revealed that the primary site of theta activity change was within the subgenual ACC (Brodmann area 25). There was a positive association between increased subgenual ACC theta activity and decreased psychotic symptoms. The degree of low theta activity in the subgenual ACC prior to ECT predicted the antipsychotic response of ECT.

Conclusions: The antipsychotic effect of ECT is related to normalization of subgenual ACC theta hypoactivity.

1. Introduction

Electroconvulsive therapy (ECT) is the most effective antidepressant treatment available and has a 95% efficacy rate in the treatment of psychotic depression specifically (Petrides et al., 2001). ECT was actually initially used to treat psychosis and is still an accepted treatment for resistant psychotic symptoms in schizophrenia spectrum disorders (Chanpattana and Andrade, 2006). Even though ECT has been used as a treatment for depression and psychosis in the United States since 1939, its precise mechanism and location of action remain unclear. Neuroimaging studies on the effects of ECT indicate that there is an initial decrease of blood flow in the ventral portion (i.e., subgenual region) of the anterior cingulate cortex (ACC) during (Takano et al., 2007) and immediately after ECT treatment (Scott et al., 1994). These results, when combined with other imaging studies that show decreased regional blood flow at the site of seizure focus (Zubal et al., 1999), suggest that the seizure focus from ECT is in the subgenual ACC. The post-ictal decrease in metabolic activity specifically in the ventral portion of the ACC is temporary and normalizes within a few days to weeks after the last ECT treatment (Awata et al., 2002; Bonne et al., 1996). While some studies suggest that greater than normal metabolic and theta activity in the rostral ACC predicts response to psychotropic medication in non-psychotic depression (Mayberg et al., 1997; Mulert et al., 2007; Pizzagalli et al., 2001), lower than normal blood flow/metabolic activity specifically in the subgenual ACC is known to occur in major depression with psychotic features (Skaf et al., 2002) and increase or normalize within 2–3 weeks after a course of ECT when compared to the pre-ECT state (Awata et al., 2002; Bonne et al., 1996; Bonne and Krausz, 1997; McCormick et al., 2007; Milo et al., 2001; Vangu et al., 2003). While major depression is a heterogeneous disease with many different causes and potentially different treatments, patients with psychotic depression are thought to have a unique syndrome with some features that overlap with both major depression and schizophrenia (Keller et al., 2007).

Based on a growing body of literature suggesting that abnormality in the subgenual ACC is related to non-psychotic major

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depression, Mayberg et al. (2005) have reported on a small clinical trial of deep brain stimulation of this region with continuous electrical activity. Because the subgenual ACC has connections with various other parts of the limbic system involved in affect regulation, correction of electrical abnormalities in this region is hypothesized to bring about downstream changes in other related areas of the brain (Johansen-Berg et al., 2007). Animal studies using direct electrode recording and low-resolution electromagnetic tomography analysis (LORETA) have revealed that the ACC is a generator of theta frequency activity that increases with certain behavioral and cognitive tasks (Ishii et al., 1999; Sauseng et al., 2007; Toth et al.,2007; Tsujimoto et al., 2006). Abnormally high theta activity in the rostral ACC has been found in depressed patients (without psychotic features) and the degree of abnormality has been used to predict response to antidepressant medication (Pizzagalli et al., 2001). A similar study has also found that higher than normal theta activity in the subgenual ACC predicts response to repetitive transcranial magnetic stimulation in vascular depression (Narushima, submitted for publication).

The aims of this study were to characterize the electrophysiological changes that occur in the brain after an effective course of ECT in psychotic depression and to identify potential predictors of response to the antidepressant and/or antipsychotic aspects of ECT. Since ECT is known to decrease electrical activity in the brain post-ictally for several days, we aimed to reduce the influence of immediate post-ictal slowing by assessing electrophysiological changes associated with symptom change and/or cognitive and memory changes at 2–3 weeks post-ECT. We used both quantitative EEG and LORETA to assess electrophysiological changes from ECT. Since reduced subgenual ACC volume has been found in psychotic depression (Coryell et al., 2005) and reduced overall ACC volume may be related to psychotic symptoms (Wang et al., 2007), the *a priori* hypothesis was that this area would exhibit abnormal electrical activity that normalizes with ECT. Furthermore, since abnormal theta activity in the rostral portion of the ACC has been shown to predict response to psychotropic medication in major depression (Pizzagalli et al., 2001), we hypothesized that baseline theta activity in this brain region could also be used to predict response to ECT.

Table 1
Subject demographics and clinical symptoms before and after ECT

		Admission (pre-ECT)
Age (years)		45.6 (9.99)
Education (years)		13.9 (2.78)
Gender		
Female		10 (59%)
Male		7 (41%)
Duration of episode (months)		5.3 (8.31)
Days between EEG testing		69.1 (54.46)
Treatment setting		
Inpatient		15 (88%)
Outpatient		2 (12%)
ECT history		
Previous ECT course(s)		8 (47%)
ECT-naïve		9 (53%)
Initial electrode placement		
Bilateral (BL)		1 (6%)
Right unilateral (RUL)		16 (94%)
Overall electrode placement		
Pure BL		1 (6%)
Pure RUL		9 (53%)
Switched from RUL to BL		7 (41%)
Number of ECT treatments		
Total		12.4 (7.05)
Bilateral		4.9 (5.95)
Right unilateral		7.5 (3.41)
	Admission (pre-ECT)	2–3 weeks post-ECT
Medications[a]		
Antidepressant	16 (94%)	15 (94%)
Antipsychotic*	13 (76%)	8 (50%)
Anxiolytic	4 (24%)	2 (13%)
Lithium	1 (6%)	1 (6%)
HDRS**	39.1 (5.69)	15.2 (10.36)
BDI**	40.6 (11.40)	19.1 (15.24)
HARS**	27.6 (7.19)	12.2 (7.63)
SANS**	13.1 (3.99)	5.1 (4.22)
SAPS (psychosis)**	3.2 (1.79)	1.0 (1.84)
SF-36 Mental health**	12.5 (7.41)	57.0 (30.03)

Note: HDRS, hamilton depression rating scale; BDI, beck depression inventory; HARS, hamilton anxiety rating scale; SANS, scale for assessing negative symptoms; SAPS, scale for assessing positive symptoms; SF-36, short form-health survey.
* $p < 0.05$.
** $p < 0.01$.
[a] Post-ECT medication data was not obtained for one patient.

2. Materials and methods

2.1. Participants

This study included seventeen participants (seven males and 10 females) with a mean age of 45.6 ± 9.99 years (range 22–63) who met DSM-IV criteria for major depression with psychotic features and completed EEG before and after ECT (Table 1). Fifteen participants (88%) underwent inpatient hospitalization at the University of Iowa Hospitals and Clinics and were referred for ECT by their psychiatrist on clinical grounds; the other two participants (12%) had been referred for outpatient ECT treatment. All participants had a pre-ECT score of at least 30 on the 28-item hamilton depression rating scale (HDRS) and had at least one psychotic or delusional symptom. The hamilton anxiety rating scale (HARS) assessed anxiety symptoms, whereas positive and negative symptoms were measured with the scale for the assessment of negative and positive symptoms (SANS/SAPS) (Andreasen, 1990). Psychotic symptoms, derived from the SAPS, were based on global scores of hallucinations and delusions (scale 0–10). The most common psychotic symptom was delusional guilt. Negative symptoms were based on global scores of alogia, affective flattening, avolition-apathy, anhedonia-associality, and attention (scale 0–25). Quality of life was assessed with the short Form 36 (SF-36) Health Survey (Bouchet et al., 2000). Participants were excluded if they had a diagnosis of bipolar disorder or schizophrenia, met criteria for alcohol or illicit drug abuse or dependence within the past 3 months, or had been treated with ECT within the past three months. The medication regimens of all participants before and after ECT are listed. Six of the participants enrolled in this study overlapped with participants who also had metabolic assessments done before and after ECT as reported elsewhere (McCormick et al., 2007). All participants also underwent cognitive testing with the repeatable battery for the assessment of neuropsychological status (RBANS). After complete description of the study to the participants, written informed consent was obtained. This study was approved by The University of Iowa Institutional Review Board.

2.2. Procedures

All participants had clinical and EEG assessments before and 2–3 weeks after a course of ECT. The mean time between assessments was 69.1 ± 54.46 days (range: 24–205).

2.3. ECT treatment

ECT was administered with a constant current, brief-pulse device (MECTA Spectrum 5000Q). Medications at ECT were benztropine (0.4 mg), methohexital (1 mg/kg), and succinylcholine (1 mg/kg), with dose adjustment after the first treatment. Motor