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Research paper

Influence of GRIK4 genetic variants on the electroconvulsive therapy response

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HIGHLIGHTS

- GRIK4 variants modulate ECT outcome.
- Kainate receptor modulation in ECT.
- Genetic factors & ECT.

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ABSTRACT

Several lines of evidence have shown the involvement of the glutamatergic system in the function of electroconvulsive therapy (ECT). In particular, patients with treatment resistant depression (TRD) and chronic depression have lower levels of glutamate/glutamine than controls, and ECT can reverse this deficit. Genetic factors might contribute to modulating the mechanisms underlying ECT.

This study aimed to evaluate the relationship between three polymorphisms (rs1954787, rs4936554 and rs11218030) of the glutamate receptor ionotropic kainate 4 (GRIK4) gene and responsiveness to ECT treatment in a sample of one hundred individuals, TRD or depressive Bipolar Disorder patients resistant to pharmacological treatments.

The results revealed that GRIK4 variants were significantly associated with the response to ECT. In particular, we found that patients carrying the G allele of the GRIK4 rs11218030 had a significantly poorer response to ECT ($p = 2.71 \times 10^{-4}$), showing five times the risk of relapse after ECT compared to the AA homozygotes. Analogously, patients carrying the GG rs1954787 genotype and rs4936554 A allele carriers presented a double risk of lack of response after ECT ($p = 0.013$ and $p = 0.040$, respectively).

In conclusion, the current study provides new evidence, indicating that some GRIK4 variants modulate the response to ECT in patients with depression resistant to treatment, suggesting a role for kainate receptor modulation.

1. Introduction

Electroconvulsive therapy (ECT) is a safe and well-established effective treatment option for severe depression that was introduced in 1938 by Bini and Cerletti. Despite controversial issues, ECT remains one of the most eligible therapies among Treatment Resistant Depression (TRD) patients or those intolerant to antidepressant medications or when a rapid and definitive response is required (e.g., because of psychosis or a risk of suicide) [1–3]. Furthermore, ECT is the most powerful antidepressant treatment strategy available today with success rates higher than pharmacological treatment in patients affected by refractory unipolar or bipolar depression [4–8].

Although the exact mechanism of the action of ECT is not entirely known, changes in neuroplasticity and in the activity of certain neurotransmitter systems have been reported [9–11]. More and

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Table 1
Socio-demographic, clinical and pharmacological features for the TRD patients undergoing to ECT, and relative responder and non-responder subgroups differences.

Characteristics	TRD patients (N = 100)	ECT responders (N = 69)	ECT non-responders (N = 31)	*p*-value
Age (years), mean (SD)	56.3 (13.5)	55.7 (14.2)	57.8 (11.9)	0.47
% Gender (F)	70.0	72.5	64.5	0.42
Education (years), mean (SD)	8.5 (3.6)	8.2 (3.6)	9.1 (4.8)	0.27
% Smokers	31.6	31.3	32.3	0.93
MADRS at T0, mean (SD)	33.3 (6.3)	33.0 (6.3)	33.9 (6.3)	0.48
% of ΔMADRS, mean (SD)	60.2 (34.7)	80.8 (14.8)	14.4 (18.5)	**<0.001**
Age of onset (years), mean (SD)	36.4 (14.8)	36.8 (15.5)	35.9 (13.3)	0.83
% psychotic symptoms	69.0	71.0	64.5	0.52
% comorbidity with personality disorders	25.0	20.3	35.5	0.11
% comorbidity with anxiety disorders	32.0	29.0	38.7	0.34
% comorbidity with alcohol abuse	2.0	1.4	3.2	0.56
Number of treatments, mean (SD)	7.6 (2.5)	7.2 (1.9)	8.3 (3.3)	**0.03**
% administration of typical antipsychotics[a]	55.1	60.9	40.0	0.07
% administration of atypical antipsychotics[a]	58.4	57.8	60.0	0.85
% administration of SSRIs[a]	61.8	67.2	48.0	0.09
% administration of SNRIs[a]	29.2	28.1	32.0	0.72
% administration of TCAs[a]	41.6	40.6	44.0	0.77
% administration of NaSSAs[a]	27.0	29.7	20.0	0.36
% administration of benzodiazepines[a]	93.3	93.8	92.0	0.77
% administration of mood stabilizers[a]	16.9	15.6	20.0	0.62
% administration of antiepileptics[a]	11.2	7.8	20.0	0.10

Bold numbers indicate significant *p*-values (<0.05).
[a] The total number could exceed the number of subjects due to the presence of multiple drugs administration.

more studies show evidence that neurotrophic factors are related to ECT function and/or to its effectiveness [12–17]. Converging data obtained from biological and imaging studies support findings related to the enhancement of serotonergic neurotransmission and the activation of the mesocorticolimbic dopamine system after ECT [18].

Increasing evidence indicates the relevant involvement of the glutamate system in the neurobiology and treatment of Major Depressive Disorder (MDD) with imbalances in glutamate and GABA (γ-amino-butyric acid) metabolism and region-specific alterations of these neurotransmitters [19–21].

Several glutamate receptor genes have been investigated in antidepressant-treatment outcome. One of the most studied is the Glutamate Receptor Ionotropic Kainate 4 (GRIK4) gene, which encodes the kainate receptor subunit KA1 and is predominantly expressed in the hippocampus [22], exerting a modulatory effect on synaptic plasticity [23,24]. In particular, several GRIK4 single nucleotide polymorphisms (SNPs) were initially found to be associated with a non-response to antidepressant therapy in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study [25]. However, these results were partly or none at all replicated in further studies [26–30]. In our previous study, we found that two GRIK4 variants were associated with the risk of developing psychotic symptomatology during a depressive episode [30]. This is of particular importance because the presence of psychotic symptoms is one of the strongest negative predictive factors of response to treatment in MDD [31,32].

ECT results in a normalisation of glutamate deficits [33,34] by modifying the inhibitory neurotransmitter systems and by affecting neurogenesis through the increase of neurotrophic factors [9,13,14,17,35,36].

The genetic factors associated with the ECT response are poorly known and, to date, few studies have been conducted [37–43] and none have investigated the glutamatergic system.

The data concerning the GRIK4 gene and treatment outcome in depression combined with the evidence that ECT affects the glutamatergic pathway provide the grounds for hypothesising a possible association between the GRIK4 gene and the ECT response. In particular, we focused on the three most significant polymorphisms (rs1954787, rs4936554 and rs11218030) found to be associated with treatment outcome in the STAR-D cohort [25].

2. Methods

2.1. Sample

One hundred individuals were voluntarily enrolled in the study, which was approved by the local ethics committee (Ethics Committee of the province of Verona N: 4997/09.11.01), and written informed consent was obtained. The group was made of 92 MDD and 8 Bipolar Disorder (BD) patients, in accordance with the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) classification system criteria. All of the BD patients were in a severe depressive state. The diagnoses were confirmed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) diagnostic scale. The exclusion criteria were as follows: (a) mental retardation and cognitive disorders; (b) a lifetime history of schizophrenic or schizoaffective disorder; (c) personality disorders, obsessive compulsive disorder, post-traumatic stress disorder, substance abuse or dependency as a primary diagnosis; and (d) comorbidity with eating disorders.

All of the patients were referred to the Psychiatric Hospital "Villa Santa Chiara", Verona, Italy, and they were scheduled to undergo ECT because they had been evaluated as treatment-resistant patients. TRD was defined as at least the failure of the patient to respond to two or more adequate trials of two or more different classes of antidepressants and to an adequate trial of a tricyclic (TCA) drug referred to as the Stage III of Thase and Rush Staging Method [44]. Treatment nonresponsiveness in the patients with bipolar depression was defined as the failure to respond to at least three mood disorder treatments, comprising an adequate trial with a TCA, and/or a combination with a mood stabiliser(s) [45].

Illness severity and the outcome of ECT were assessed using the Montgomery and Asberg Depression Rating Scale (MADRS) before the treatment (T0) and about one month after the end of ECT (T1). In the month after the end of ECT, the pharmacological treatment was maintained the same with only a possible light reduction in the dosage. All of the socio-demographical, clinical and pharma-