Impact of depressed mood on neuropsychological status in temporal lobe epilepsy

S Paradiso, B P Hermann, D Blumer, K Davies, R G Robinson

Abstract

Objectives—Depression is a common psychiatric complication of temporal lobe epilepsy. This study examined the effect of depressed mood on neuropsychological performance among patients with chronic temporal lobe epilepsy.

Methods—Seventy consecutive surgery candidates for medication resistant complex partial seizures of unilateral temporal lobe origin were assessed for psychiatric symptoms and underwent comprehensive neuropsychological assessment.

Results—Standardised psychiatric interview disclosed that 34% of the patient sample exhibited significant depression. Controlling for seizure frequency, patients with comorbid depression at the time of neuropsychological assessment exhibited significantly poorer performance on measures of intelligence, language, visuo-perceptual ability, memory, and executive function. Within lateralised temporal lobe epilepsy groups, the adverse effects of depression on cognitive function were greater in patients with left temporal lobe compared with those with right temporal lobe epilepsy. In addition, depression seemed to be underrecognised and undertreated as none of the patients with epilepsy and comorbid depression were treated for their psychiatric condition at the time of admission for monitoring.

Conclusions—Depression, a common psychiatric comorbidity among patients with chronic temporal lobe epilepsy, seems to be undertreated and to have adverse effects on cognitive functioning.

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Keywords: depression; neuropsychology; temporal lobe epilepsy

Assessment of neuropsychological status is a standard component of the preoperative assessment of patients with medically intractable complex partial seizures who are candidates for anterior temporal lobectomy.¹ Neuropsychological assessment is conducted for various purposes including provision of lateralising and localising information as well as for general determination of baseline (preoperative) neurobehavioural status.² Among patients with epilepsy, the degree to which preoperative neuropsychological assessment is influenced by concomitant psychopathology and emotional distress is largely unknown. The estimated prevalence of lifetime to date DSM axis

I disorders among patients with chronic epilepsy is about 60%,³ and prevalence of lifetime to date major depression about 30%.^{4,5} Although depressive disorders are widely appreciated to represent a significant comorbid psychiatric complication of chronic epilepsy,^{3,6} the relation between depressed mood and cognition among patients with epilepsy has not been extensively investigated.⁷ The general psychiatry literature has shown that depression with or without a demonstrable brain lesion can adversely affect a wide range of cognitive abilities.⁸⁻¹⁵

Further, some reports have suggested that the degree of neuropsychological impairment may be mediated by the laterality of lesion. For instance, among depressed patients with a cerebrovascular accident, greater cognitive impairment has been found among depressed than non-depressed patients with left cerebrovascular accident, this relation is not evident among patients with right cerebrovascular accident.^{14,15}

It is now widely appreciated in the primary care and psychiatry literature that depression is often underdiagnosed and undertreated.¹⁶⁻¹⁸ Failure to recognise and treat mood disorders adds to the suffering of patients and their families and reduces health related quality of life.¹⁹ Although there is general agreement that mood and anxiety disorders are common in epilepsy, the degree to which depression among patients with chronic epilepsy is adequately identified and treated has rarely been examined. The limited evidence to date suggests that there is underrecognition and undertreatment of comorbid psychopathology in general, and depression in particular, among patients with epilepsy.⁵

This investigation therefore examined the effects of interictal comorbid mood disorder on the adequacy of neuropsychological status among patients with chronic unilateral temporal lobe epilepsy. The issue of whether depression exerts greater adverse neuropsychological effects among patients with left versus patients with right temporal lobe epilepsy was examined, as was the degree to which depression had been recognised and treated before presentation for comprehensive evaluation.

Method

PATIENTS

The study sample was a consecutive series of 70 patients who were candidates for anterior temporal lobectomy for treatment of medication resistant complex partial seizures of unilateral temporal lobe origin who met the following criteria: (1) left hemisphere domi-

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Table 1 Demographic, clinical characteristics, and severity of depression

	Depressed (n=24)	Non-depressed (n=46)
Chronological age	31.6 (7.9)	29.0 (7.2)
Sex (% female)	66.6	33.3
Education (y)	12.4 (2.3)	13.1 (2.4)
Handedness (% right handed)	91.9	89.1
Age at onset (y)	11.3 (10.9)	10.0 (9.9)
Laterality of TLE (% left origin)	62.5	69.5
Hippocampal sclerosis (% moderate to marked)	76.7	63.1
Seizure frequency (number/month)	65.8 (125.8)*	17.5 (43.1)
Patients on two or more AEDs	8.3	18.1
CES-D	18.2 (10.5)†	10.7 (8.23)
BDI	11.0 (7.24)‡	6.0 (6.67)
MMPI-D	72.4 (13.9)§	61.3 (14.5)

Values are means (SD) or percentage of subjects. BDI=Beck depression inventory; CES-D=Centre for Epidemiological Studies-depression scale; MMPI-D=Minnesota multiphasic personality inventory depression subscale. * $t(62)=2.26$, $p<0.03$; † $F(1,63)=8.8$, $p<0.005$; ‡ $F(1,61)=5.5$, $p<0.025$; § $F(1,62)=9.3$, $p<0.004$.

nant for speech as determined by bilateral intracarotid sodium amobarbital testing (Wada test²⁰); (2) patients with tumours, cysts, cortical dysgenesis, encephalomalacia, and other lesions disclosed by MRI were excluded. The primary MRI finding was hippocampal atrophy, but there were a few with comorbid cerebellar atrophy; (3) WAIS-R full scale IQ >69; and (4) chronological age >17 years. All patients underwent continuous (24 hour) EEG monitoring of spontaneous seizures with scalp and then subdural strip electrodes.²¹ Generally, three spontaneous seizures were recorded with invasive EEG procedures, and localisation of ictal onset was determined by the electroencephalographer, blinded to the results of the neuropsychological assessment. The monitoring period lasted about 1 week. The psychiatrist and neuropsychologist conducted their evaluations independently, and both were blinded to the EEG findings and the results of each others' assessments until the final consensus conference.

NEUROPSYCHIATRIC EXAMINATION

All patients underwent a comprehensive standardised psychiatric examination supplemented by procedures developed specifically to assess personality and behavioural characteristics of patients with epilepsy.⁴ All patients underwent a semistructured psychiatric interview (with DB) and a next of kin was interviewed to verify the completeness and accuracy of the information. Patients and next of kin jointly completed the epilepsy questionnaire and, separately, a modified form of the neurobehavioural inventory.²² The epilepsy questionnaire focused on mood and mood lability, energy, sleep disturbances, atypical pain, irritability, anxiety, specific fears, paranoid ideation, hallucinatory experiences, confusional episodes in the absence of seizures, and various personality characteristics (for example, viscosity, good heartedness, religiosity). In addition, to assess the severity of self rated depressed mood patients were administered the Beck depression inventory (BDI),²³ the Centre for Epidemiological Studies depression scale,²⁴ and the Minnesota multiphasic personality inventory (MMPI).²⁵ These data were not used by the psychiatrist in his determination of mood state.

NEUROPSYCHOLOGICAL EXAMINATION

All patients underwent a comprehensive neuropsychological evaluation that included measures of psychometric intelligence (WAIS-R verbal, performance, and full scale IQ²⁶), language function (WRAT-R reading,²⁷ MAE visual naming²⁸—number correct, and token test²⁹—number correct); visuo-perceptual and visuospatial abilities (judgement of line orientation³⁰—number correct, facial recognition test³⁰—number correct); verbal memory (WMS logical memory³¹—number of units on immediate recall and % retained after 30 minutes, Warrington word recognition³²—number correct); visual memory (WMS visual reproduction³¹—number of units on immediate recall and % retained after 30 minutes, Warrington face recognition³²—number correct); executive functions (trail making test (B)³³—time completed, Wisconsin card sort³⁴—perseverative responses, controlled oral word association³⁵—number of words); and psychomotor/attention (trail making test -A³³—time completed). No subjects were on antidepressant medication at the time of neuropsychological testing.

NEUROPATHOLOGY

Surgical specimens were obtained according to methods described elsewhere.³⁶ Pathology was graded according to a standardised system providing ratings of the degree of hippocampal sclerosis from none or mild (grade 0) to marked (grade 4).^{21 36}

STATISTICAL ANALYSIS

Continuous variables were analyzed using t tests, analysis of variance (ANOVA), and analysis of covariance (ANCOVA). Discrete variables were analyzed using likelihood ratio and Wald χ^2 tests. Given the number of experiment-wise comparisons the α level was set at 0.05 despite the directional hypothesis of the investigation (depressed patients expected to show poorer cognitive performance).

Results

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Semistructured psychiatric interview showed that 24 (34%) patients exhibited depressed mood and 46 (66%) did not. Demographic and clinical characteristics of depressed and non-depressed patients are shown in table 1. Female patients exhibited a twofold increase in depressed mood compared with male patients (female 66.7% *v* male 33.3%) but this difference failed to reach statistical significance (likelihood ratio $\chi^2(1)=2.83$, $p<0.10$).

There were no significant differences between the depressed and non-depressed patients in chronological age, education, handedness, patient's age at seizure onset, and laterality of temporal lobe seizure onset (table 1). There was no significant relation between depression and antiepileptic drug monotherapy versus polytherapy (likelihood ratio $\chi^2(1)=3.56$, $p>0.1$).

Seizure frequency was higher in depressed than in non-depressed patients (table 1). Seizure frequency in the left temporal lobe epi-

Table 2 Symptoms accompanying depressive mood

	Depressed	Non-depressed
Anergia	17 (70.8)***	9 (19.5)
Sleep disturbances	10 (41.6)**	4 (8.7)
Pain	12 (50.0)*	8 (17.3)
Euphoria	7 (29.1)	7 (15.2)
Irritability	16 (66.6)**	12 (26.0)
Anxiety	14 (58.3)***	3 (6.52)
Specific phobias	8 (25)**	0

Values are No (%) of patients with positive symptoms, * $p < 0.005$; ** $p \leq 0.001$; *** $p < 0.00001$.

lepsy group did not differ significantly between the depressed and non-depressed patients ($p > 0.1$) whereas in the right temporal lobe epilepsy group the depressed patients exhibited significantly poorer seizure frequency compared with non-depressed patients ($p < 0.05$).

SEVERITY OF DEPRESSION

Patients with clinically assessed and determined depressed mood exhibited significantly worse self reported depressive symptoms on the CES-D, BDI, and MMPI depression scale (table 1). Two factor ANOVAs (depressed/non-depressed mood and left/right temporal lobe seizure onset) were computed for the CES-D, BDI, and MMPI-D. Results yielded significant main effects of depression across all measures (CES-D $F(1, 63) = 8.8$, $p < 0.005$; BDI $F(1, 61) = 5.5$, $p < 0.025$; MMPI-D $F(1, 62) = 9.3$, $p < 0.004$) and no significant side or interaction effects (all $p > 0.2$). There were no significant laterality effects for the CES-D (left temporal = 12.8 (9.4), right temporal = 13.9 (10.1), $t(61) = 0.43$, $p > 0.5$), BDI (left = 6.73 (6.2), right = 9.17 (8.5), $t(59) = 1.28$, $p > 0.2$), or MMPI-D scale (left = 64.2 (14.3), right = 65.8 (16.9), $t(60) = 0.4$, $p > 0.7$). Patients with clinically determined depressed mood exhibited significantly rates of lack of energy, poor sleep, pain, irritability, anxiety, and phobias (table 2). All patients had been followed up by their referring physicians for treatment of chronic epilepsy, but depression had not been recog-

nised or treated as reflected by lack of antidepressant medication therapy. At the end of the monitoring period, 20 of the 24 patients with depressed mood (83.3%) required and were treated with antidepressant medication.

NEUROPATHOLOGY

A surgical specimen adequate for grading of hippocampal pathology was obtained from 63 patients. There was no significant relation between degree of mesial temporal lobe sclerosis and depressed mood (Wald $\chi^2(4) = 0.5$, $p > 0.7$), side of focus (Wald $\chi^2(4) = 2.2$, $p > 0.9$), or their interaction (Wald $\chi^2(4) = 2.6$, $p > 0.6$).

NEUROPSYCHOLOGICAL ASSESSMENT

Comparisons between depressed/non-depressed patients across the neuropsychological battery are shown in table 3. ANCOVA (with seizure frequency as a covariate) showed that depressed patients exhibited significantly lower performance on the summary IQ measures (WAIS-R FSIQ ($p < 0.006$), VIQ ($p < 0.03$), PIQ ($p < 0.004$)), language function (visual naming ($p < 0.006$), token test ($p < 0.009$)), visuooperceptual ability (judgement of line orientation ($p < 0.03$)), memory function (visual reproduction, % retained ($p < 0.001$)), and psychomotor speed/alternation (trails A ($p = 0.05$), trails B ($p < 0.03$)). Similar trends were evident for additional measures of memory, language, and visuooperceptual ability (logical memory, % retained ($p < 0.10$)), verbal fluency ($p < 0.06$), facial recognition test ($p < 0.06$)), but these differences did not reach statistical significance.

Additional analyses were performed to compensate for possible data deviation from linearity. Comparisons between depressed/non-depressed patients were performed after subjects were equated for seizure frequency. Non-depressed patients with less than five seizures/month and three patients with seizure frequency greater than 270/month (outlier Mahalanobis distance > 5) were excluded. These selection criteria yielded 22 depressed (mean seizure frequency 31.9 (SD 55.0)) and 24 non-depressed patients (19.0 (SD 19.8)) ($t(42) = -1.0$, $p > 0.3$). Results (available in detail from the authors) showed that depressed patients had significantly poorer performance across measures of verbal and non-verbal psychometric intelligence, language, visual memory, and executive abilities, consistent with the prior results.

Neuropsychological performance was then examined within the left and right temporal lobe groups (table 4). When seizure frequency was subjected to covariance analysis, in the left temporal lobe epilepsy group, depressed patients, compared with non-depressed patients, exhibited significantly lower WAIS-R FSIQ, PIQ ($p < 0.004$), and VIQ ($p < 0.015$) scores, language scores (token test ($p < 0.001$), visual naming ($p < 0.006$)), visuooperceptual and spatial performance (judgement of line orientation, facial recognition (both p values < 0.03)), complex psychomotor processing (trails B ($p < 0.03$)), visual memory (visual reproduction-immediate ($p < 0.015$)), and

Table 3 Neuropsychological status in depressed and non-depressed groups

Domains	Depressed (n=24)	Non-depressed (n=46)
Psychometric intelligence:		
Full Scale IQ	82.2 (9.2)*	89.4 (11.8)
Verbal IQ	84.0 (9.8)†	90.1 (12.5)
Performance IQ	82.6 (10.4)‡	90.5 (12.8)
Language:		
WRAT-R Word reading	82.7 (15.7)	86.9 (15.1)
Token test	39.8 (3.8)§	41.9 (2.4)
Visual naming	43.0 (8.8)¶	48.4 (7.6)
Visuospatial		
Judgement of line orientation	21.7 (5.3)**	24.0 (4.7)
Facial recognition	44.1 (5.6)	45.6 (3.8)
Memory/learning:		
WMS Logical memory (immediate)	10.0 (6.5)	11.5 (6.3)
M	47.7 (31.5)††	62.7 (27.4)
RMT Word recognition	39.5 (6.1)	40.4 (5.8)
WMS Visual reproduction (immediate)	5.2 (2.4)‡‡	7.2 (2.5)
WMS Visual reproduction (% retained)	66.8 (32.8)	75.9 (24.7)
RMT Face recognition	36.8 (6.3)	38.7 (4.8)
Psychomotor/attention:		
Trail making test (A)	40.2 (15.7)	35.5 (11.8)
Executive function:		
Controlled oral word association	27.8 (5.9)§§	32.7 (9.7)
Trail making test (B)	91.8 (43.2)¶¶	75.7 (28.3)
Wisconsin card sort test (perseverative responses)	22.1 (17.2)	18.5 (21.7)

Values are means (SD) scores. * $t(68) = 2.57$, $p < 0.01$; † $t(68) = 2.08$, $p < 0.05$; ‡ $t(68) = 2.59$, $p < 0.01$; § $t(68) = 2.71$, $p < 0.009$; ¶ $t(68) = 2.65$, $p < 0.01$; ** $t(68) = 1.83$, $p < 0.08$; †† $t(68) = 2.05$, $p < 0.05$; ‡‡ $t(68) = 3.15$, $p < 0.003$; §§ $t(68) = 2.23$, $p < 0.04$; ¶¶ $t(68) = 1.87$, $p < 0.07$.

Table 4 Neuropsychological status in depressed and non-depressed left and right temporal lobe groups

Domains	Left temporal		Right temporal	
	Depressed (n=15)	Non-depressed (n=32)	Depressed (n=9)	Non-depressed (n=14)
Psychometric intelligence:				
Full scale IQ	79.2 (7.1)*	89.0 (10.7)	87.2 (10.7)	90.2 (14.5)
Verbal IQ	80.8 (8.5)†	89.2 (10.6)	89.3 (9.8)	92.1 (16.5)
Performance IQ	80.2 (8.6)‡	91.0 (12.1)	86.6 (12.5)	89.5 (14.7)
Language:				
WRAT-R Word reading	80.7 (15.7)	86.4 (15.0)	86.1 (16.0)	88.2 (16.1)
Naming	41.2 (8.5)§	47.3 (7.6)	46.2 (8.8)	51.1 (7.2)
Token test	38.8 (4.1)¶	41.9 (2.3)	41.5 (2.7)	41.7 (2.6)
Visuospatial:				
Judgment of line orientation	21.6 (5.3)**	24.0 (3.7)	21.8 (5.7)	24.0 (6.5)
Facial recognition	43.0 (5.9)††	45.7 (4.2)	46.0 (4.6)	45.4 (2.9)
Memory/learning:				
WMS Logical memory (immediate)	8.0 (5.8)	10.2 (5.7)	13.3 (6.6)	14.3 (6.9)
WMS Logical memory (% retained)	48.4 (32.9)	56.0 (28.8)	46.6 (31.1)†††	78.0 (15.9)
RMT Word recognition	38.9 (5.6)	40.5 (4.9)	40.5 (7.1)	40.3 (7.8)
WMS Visual reproduction (immediate)	5.4 (2.4)‡‡	7.3 (2.3)	4.7 (2.5)	6.8 (3.0)
WMS Visual reproduction (% retained)	73.0 (33.5)	78.4 (22.8)	56.6 (30.8)	70.1 (28.7)
RMT Face recognition	37.0 (4.9)	39.1 (4.7)	36.4 (8.5)	37.7 (5.2)
Psychomotor/attention:				
Trail making test (A)	37.8 (15.0)	34.2 (12.7)	44.2 (16.2)	38.3 (9.36)
Executive abilities:				
Controlled oral word association	27.6 (4.23)§§	32.2 (9.9)	28.2 (8.2)	33.8 (9.5)
Trail making test (B)	95.8 (52.2)¶¶	73.3 (25.7)	85.1 (22.5)	81.0 (33.8)
Wisconsin card sort test (perseverative responses)	26.5 (17.1)***	15.9 (13.3)	14.8 (15.6)	24.5 (34.1)

Values are means (SD). Intralobe *t* tests: Left: **t* (45)=3.20, *p*<0.003; †*t* (45)=2.69, *p*<0.01; ‡*t* (45)=3.08, *p*<0.004; §*t* (45)=3.28, *p*<0.003; ¶*t* (45)=2.45, *p*<0.01; ***t* (45)=1.76, *p*<0.09; ††*t* (45)=1.81, *p*<0.08; ‡‡*t* (45)=2.55, *p*<0.01; §§*t* (45)=1.70, *p*<0.1; ¶¶*t* (45)=1.98, *p*<0.05; ****t* (45)=2.31, *p*<0.03. Right: †††*t* (21)=3.19, *p*<0.004.

problem solving (WCST perseverative responses (*p*<0.007)). Compared with non-depressed patients with right temporal lobe epilepsy, depressed patients in the same group showed fewer differences with lower memory scores (WMS logical memory, % retained (*p*<0.015), and a trend for poorer visual reproduction, % retained (*p*<0.06)). As neurocognitive data were analyzed across groups of differing sizes, we also examined side by side depressed mood interactions controlling for seizure frequency. The measures that reached statistical significance for the interaction were the token test (*F*(1, 61)=6.77, *p*<0.012) and Wisconsin card sort perseverative responses (*F*(1, 61)=4.32, *p*<0.05). Facial recognition showed a non-significant trend (*F*(1, 61)=3.85, *p*<0.097). Using samples equated for seizure frequency yielded essentially the same results.

Discussion

The present study examined the effects of depressed mood on cognition among patients with lateralised temporal lobe epilepsy. The following are the salient findings.

Firstly, depressed mood was associated with significant adverse effects across a wide range of neuropsychological domains including general intelligence, language, visuoperceptual abilities, memory, and executive functioning. There was a significant difference in seizure frequency between the depressed versus non-depressed patients in the right but not left temporal lobe epilepsy group, and when seizure frequency was accounted for with the use of two differing statistical approaches, the adverse effects of depressed mood on cognition remained evident. Thus, consistent with the more general neuropsychological and neuropsychiatry literature, depression seems to be associated with decreased efficiency of cognitive functioning among patients with unilateral temporal lobe epilepsy. To our knowledge, this

is the first report to demonstrate that comorbid depression is associated with poorer neuropsychological status in temporal lobe epilepsy. Whether this relation between mood state and cognition influences the lateralising ability of the neuropsychological examination remains to be determined. The degree to which comorbid psychiatric disorder affects the specificity and sensitivity of neuropsychological procedures to lateralised temporal lobe lesions is an issue of clinical relevance.

Secondly, whereas there was no difference in the frequency of depression in left versus right temporal lobe epilepsy groups, the effects of depression on neuropsychological status seemed to be somewhat accentuated in patients with left compared with those with right temporal lobe epilepsy. These findings need to be interpreted with caution due to differing group sizes in our sample. Studies with larger sample sizes are needed to determine whether depressed compared with non-depressed left temporal lobe patients exhibit greater impairment in cognition (for example, general intelligence, executive, language, visuoperceptual functions, and visual memory) compared with patients with right temporal lobe epilepsy.

Thirdly, consistent with previous reports,³⁻⁵ a significant proportion (34%) of the patients with epilepsy studied here were depressed. Surprisingly, none of these patients with chronic and intractable epilepsy and comorbid depression had been treated with antidepressant medications on presentation to the monitoring unit. On discharge, 85% of the depressed patients were started on antidepressant drugs. Undertreatment of depression is recognised to be a common problem in the general population as well as in primary medical care populations, but less is known about the extent of undertreatment in neurological populations, including epilepsy. However, very recent evidence has suggested that underrecognition and

undertreatment of comorbid interictal depression in chronic epilepsy is not uncommon,^{5 37 38} and the current findings reinforce that point. More attention to the degree to which comorbid psychiatric disorder is underrecognised and undertreated among patients with chronic epilepsy is needed, along with empirical study of the efficacy of subsequent treatment and impact on cognitive status.

Finally, longitudinal investigation is required to conclusively demonstrate that depression is causally associated with additional neuropsychological morbidity among patients with chronic temporal lobe epilepsy. It might be speculated that, at least in the population studied here, one possible factor linking depressed mood with impaired cognition was seizure frequency. Neuropsychological performance is affected by seizure frequency,^{39 40} but in the present study the adverse effects of depression on cognition remained when seizure frequency was controlled. Among the patients with left temporal lobe epilepsy there was no difference in seizure frequency with the differences in cognition between depressed and non-depressed patients evident. Alternatively, it could be speculated that more impaired cognition predisposed patients to depressed mood. These potential confounding issues can be clarified most directly in a prospective investigation, and the current results suggest that such an inquiry is indicated.

The neuropathological status of the mesial temporal lobe was comparable across depressed and non-depressed patients with left and right foci and it would seem that lateralised hippocampal pathology is not the neuropathological substrate of combined depressed mood and cognitive impairment in temporal lobe epilepsy. Other regions of the limbic system (for example, the amygdala) are possible candidates.^{6 41} The brain dysfunction underlying the identified cognitive impairment associated with depression may be at a functional (blood flow or metabolism) rather than a structural anatomical level.

In conclusion, among patients with chronic temporal lobe epilepsy, adequacy of neuropsychological functioning seems to be adversely affected by comorbid interictal depression. Although there is no greater incidence of depression in left compared with right temporal lobe epilepsy, the hypothesis is raised that neuropsychological performance may be more adversely affected in patients with left temporal lobe epilepsy. Depression in epilepsy seems to be underrecognised, or at least undertreated, and greater attention should be directed to early recognition and treatment of depression given its adverse effects on quality of life.

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