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A Possible Trait and Status Marker in Bipolar Disorder: The Electroretinogram-Pattern

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ABSTRACT

Background. The similarity between retinal cells and neurons of the central nervous system allows non-invasive methods to study retinal function, such as the Electroretinogram-Pattern (PERG) to be postulated as possible biomarkers, useful and safe in the study of psychiatric pathologies such as Bipolar Disorder (BD). The objective of the present study is to characterize the differences in the results in the PERG of patients with BD and healthy subjects, as well as to evaluate a possible correlation between these results and the affective decompensations of the manic pole in the group of bipolar patients.

Material and methods. A cross-sectional study was carried out in a sample of 34 bipolar patients in different clinical states and 36 healthy controls. The independent variables were collected: sex, age, drugs and clinical status, measured using validated scales and later the PERG was performed, obtaining the dependent variable of interest, the mean amplitude of the P50 wave. Results. There is a statistically significant difference in the PERG results between BD patients and controls, and also between the various clinical states of BD patients. Likewise, we found a negative correlation between the severity of the mania and the mean amplitude of the P50 wave. Conclusions. The differences found, both between healthy subjects and bipolar patients, and between affective states within BD, suggest that alterations in retinal function, measured by PERG, may be a promising biomarker of trait and status in BD.

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Key words. Bipolar Disorder; Pattern electroretinogram; retina biomarker; mania

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UN POSIBLE MARCADOR DE RASGO Y ESTADO EN EL TRASTORNO BIPOLAR: EL ELECTRORRETINOGRAMA-PATRÓN

RESUMEN

Introducción. La similitud entre las células retinianas y las neuronas del sistema nervioso central permite que métodos no invasivos de estudio de la función retiniana, como el Electrorretinograma-Patrón (PERG) se postulen como posibles biomarcadores, útiles y seguros en el estudio de patologías psiquiátricas como el Trastorno Bipolar (TB). El objetivo del presente estudio es caracterizar las diferencias en los resultados en el PERG de pacientes con TB y sujetos sanos, así como evaluar una posible correlación entre estos resultados y las descompensaciones afectivas del polo maniaco en el grupo de pacientes bipolares.

Material y métodos. Se realizó un estudio transversal en una muestra de 34 pacientes bipolares en diferentes estados clínicos y 36 controles sanos. Se recogieron las variables independientes: sexo, edad, fármacos y estado clínico, medidas mediante escalas validadas y posteriormente se realizó el PERG obteniendo la variable dependiente de interés, la amplitud media de la onda P50.

Resultados. Existe una diferencia estadísticamente significativa en los resultados del PERG entre pacientes con TB

y controles, y también entre los diversos estados clínicos de los pacientes con TB. Asimismo, encontramos una correlación negativa entre la gravedad de la manía, y la amplitud media de la onda P50.

Conclusiones. Las diferencias encontradas, tanto entre sujetos sanos y pacientes bipolares, como entre los estados afectivos dentro del TB, sugieren que las alteraciones en la función retiniana, medidas mediante PERG, pueden ser un prometedor biomarcador de rasgo y de estado en TB.

Palabras clave. Trastorno Bipolar, Electrorretinograma-Patrón, retina, biomarcador, manía.

INTRODUCTION

Bipolar disorder (BD) is a serious mental illness that affects more than 1% of the world's population[1]. It is characterized mainly by mood fluctuations that are often associated with functional and cognitive impairment and a significant reduction in the quality of life[2]. Both BD diagnosis and affective episodes are based primarily on the assessment by a psychiatrist following the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)[3], or the International Classification of Diseases, 10th Revision (ICD-10)[4]. Therefore, the influence of the clinician's subjectivity adds to the diagnostic difficulties caused by intrinsic factors in psychiatry, such as symptom overlap or phenotypic heterogeneity.

Therefore, current research has focused on the study of biomarkers that allow a diagnosis based on biological findings. Biomarkers can also serve to identify or quantify the risk of relapse of mental illnesses[5,6]. However, in psychiatry, a fundamental limitation is the difficulty in accessing the living human brain[6]. The brain and retina are derived from the same embryonic tissue. This motivates the postulation of functional and structural study techniques of the retina as minimally invasive techniques, which are increasingly attracting attention as promising tools in the study of psychiatric disorders. The growing interest has been evidenced by recent publications in high impact journals[7]. In fact, some experts have pointed to the vision as the next frontier in psychiatry[8].

Among the techniques used to study retinal function is the pattern electroretinogram (PERG), a type of electroretinogram (ERG) that uses an alternating or checkerboard stimulus to measure the electrical response of retinal ganglion cells to contrast. This response is represented graphically by a positive wave (P50) and a negative wave (N95), with amplitude and latency being the main parameters to be measured[9].

The study of ganglion cells in psychiatry relies on the fact that these cells, whose axons form the optic nerve, constitute the last retinal relay before the transmission of visual information to the cerebral cortex and share anatomical and functional characteristics with thalamic and cortical neurons, thus being able to provide fundamental information on brain function[10]. In this sense, their important role in mood modulation and in the synchronization of circadian rhythms has been demonstrated in relation to the release of melatonin by the pineal gland[11].

Likewise, among the neurotransmitters that mediate the processing and transmission of visual information, the main one is dopamine[12] which plays a fundamental role in the adaptation to light[13]. The role of dopamine has been widely demonstrated in the pathophysiology of mental illness and can support the usefulness of electroretinography in psychiatry[14,15]. In fact, abnormal retinal function has been documented in schizophrenia, drug abuse and attention deficit hyperactivity disorder[16-18].

Most research studies using electrophysiological techniques have focused on depression[19-21], reporting lower retinal contrast gain in medicated and unmedicated depressed patients compared to those in healthy controls, in addition to a positive correlation between severity of depression and contrast gain[22]. Besides, most studies have found ERG abnormalities in patients with seasonal affective disorder (SAD)[24,25], describing abnormal sensitivity of rods (photoreceptors responsible for vision in low light conditions) in the same[24,26], with the exception of Oren et al[23].

With respect to BD, its association with visual processing deficits[27], as well as with visual hyperesthesia in manic episodes, has been demonstrated[28]. This indicates that the pathophysiology of BD could involve sensory pathways and that abnormal ganglion cell function may be a consequence of brain dysfunction[29]. However, although it has been suggested that these deficits could be a feature of BD,[30,31] there are few studies about this issue. It should be mentioned the recent publication by Hébert et al.[32] characterized and compared the ERG scores of patients with schizophrenia and BD and healthy controls. The authors defended the ERG is a reliable tool in the categorical discrimination between BD and schizophrenia, as well as between both groups and controls. Their conclusions include the need for analysing the differences in PERG according to the affective state of BD to study it as a possible marker of state and not only of diagnosis[32].

Specifically in BD, it has been suggested that this type of technique for studying ganglion cells through electroretinography could be a particularly interesting approach both for diagnosis and for the follow-up and prevention of relapses[15]. However, despite being an emerging

field in psychiatric research[29,33,34], to our knowledge, this is the first study that analysed retinal functionality using the PERG technique as a possible biomarker for patients with BD.

The aim of our study is to evaluate PERG recordings in patients with BD and to explore how different affective states may affect electroretinography patterns. Based on previous studies on affective disorders, we expect patients with BD to show a significant reduction in retinal contrast compared to healthy controls. Second, we hypothesize that clinical status has an effect on PERG recordings. Third, based on previous studies that found a correlation between PERG amplitude and severity of manic symptoms, we expect a negative correlation between severity of mania and magnitude of P50[19,21].

MATERIALS AND METHODS

Participants

The sample comprised 34 patients diagnosed with BD (27 with BD type 1, three with BD type 2, and four with schizoaffective disorder). Among all samples, 25 were patients which were consecutively admitted to the psychiatric inpatient ward of the La Fe University and Polytechnic Hospital of Valencia, and nine were outpatients at the BD Reference Unit of the same centre. Five additional patients were excluded since their clinical condition made it impossible to perform PERG correctly.

The control group comprised a total of 36 subjects, matched by age and sex with the group of patients, and whose recruitment was randomized from health personnel and their relatives. Prior to inclusion, the Global Health Questionnaire (GHQ-12)[35] was administered to identify minor psychiatric disorders in the general population and community clinical settings.

Prior to PERG, patients gave their informed consent. The study was approved by the Ethics Committee of the La Fe University and Polytechnic Hospital of Valencia. The authors of this study and the ethics committee concluded that there was no justification for the interruption or modification of treatment during the study, given that a large number of patients were in a serious clinical condition, which could constitute a significant risk.

Inclusion criteria

Patients who met the described inclusion criteria and the DSM-IV-TR criteria for BD[36] (in force when recruitment began) and agreed to participate underwent a semi-structured interview independently by two psychiatrists. Only patients whose clinical diagnoses were agreed upon by the two psychiatrists were finally included in the study.

For outpatients, the psychiatrist performed the assessment using the Clinical Global Impression scale for BD (CGI-BD)[37] with scores of CGI-M = 1, CGI-D = 1 and CGI-G <3; the Spanish version of the Chinese Polarity Inventory (CPI)[38] with depression score <20 and mania score <15; the numerical evaluation scale (NES)[39] with a score of 50; the Montgomery-Asberg Depression Scale (MADRS)[40] with a score <7; and the Young Mania Rating Scale (YMRS)[41] a with score <6. Of these patients, seven had been stable in the last three months.

Exclusion criteria for both groups were existence of another psychiatric or neurological disorder, ophthalmologic or visual pathology and active use of psychoactive substances. In the case of healthy controls, an additional exclusion criterion was a GHQ-12 score of more than 5[35].

The study followed a naturalistic design with no restrictions regarding pharmacological or psychotherapeutic treatment.

Procedure

The YMRS[41] scale was administered to the patients admitted prior to PERG. However, the neurophysiologist who performed the test was blinded to the results. A total of 25 patients with BD met the criteria for manic episodes (YMRS > 20).

Instruments

PERG

PERG was performed using the Medelec Synergy version 11.1 device (Oxford Instruments Medical). The following settings were used: low filters of 1 Hz and high filters of 100 Hz, acquisition time of 200 ms, sensitivity of 2 mV and sweep limit of 100. Specifically, transient type PERG was used since the stimulus alternation frequency was less than 8 cycles per second and continuous amplitude variation was used.

The standard pattern established by the International Society for Clinical Electrophysiology of Vision (ISCEV) for PERG recordings was followed: performing the test binocularly, without mydriasis, with the patient facing the stimulus screen at a distance of 1 m, and placing two recording electrodes on the cornea or inferior bulbar conjunctiva without interfering with the visual axis, two reference electrodes on the outer edge of each eye and one reference electrode on the forehead. Following recommendations, between 150 and 200 responses were obtained to increase the signal-to-noise ratio, and the total test time was approximately 30 min.

In the present study, we preferred the P50 wave over the N95 since the former provides information on the macular and photoreceptor response. In addition, the N95 is a long

wave with a less well-defined and less sharp peak than the P50, which makes it more difficult to interpret[4]. Based on the literature, a P50 wave amplitude greater than or equal to 4.5 μV is considered normal. Given that the aim of the study is not the specific result of each eye, but the study relies on the evaluation of the Central Nervous System through the retina, we created a new measurement variable: the mean of the amplitude of both eyes. The mean amplitude, although not included in the standard procedure, was adopted in our investigation.

It should be noted that prior to PERG, all subjects were evaluated with visual evoked potentials (VEPs) to verify the integrity of the optical pathway. No patient was eliminated from the study for this reason.

Statistical analysis

All analyses were performed with SPSS v.23.0. For categorical variables, a $\chi 2$ test with Fisher's exact test was applied. For continuous variables, a Student's t-test or ANOVA with the Games–Howell post hoc test was used since the variances were not equal in any of the tests performed. A correlation analysis was also performed between the YMRS results and the amplitude of the P50 collected by PERG.

RESULTS

Sample description

Four patients in the control group had scores above 5 on the GHQ-12 scale and were therefore not included in the analysis. Finally, the sample comprised 36 controls and 34 patients. There were no statistically significant differences between groups with respect to sex, with the percentage of women being 69.4% in the control group and 52.9% in the experimental group ($\chi 2 = 2.01$; $p = 0.22$). Likewise, the age distribution was similar in both groups ($t = 0.05$; $p = 0.96$), the ages of the control and patient groups were 44.9 ± 13.9 control group and 44.7 ± 10.8 (mean ± SD), respectively.

Electrophysiological results

There was no association between PERG results and sex ($t = 1.91$, $p = 0.06$). There was an inverse correlation between age and P50 amplitude of the participants (Pearson correlation coefficient = -0.28; $p = 0.02$). Since, as we have previously shown, there was no difference in age between the two groups, this decrease in P50 amplitude with age did not bias our results.

As shown in Table 1, there was a significant difference in P50 wave amplitude between controls and patients diagnosed with TB (controls 9.43 ± 3.82 and patients 6.4± 1.39, $p = 0.000$). Regarding clinical status, the P50 amplitude was higher in patients with euthymia than in those with mania/hypomania (euthymia 5.91±1.35 and mania/hypomania 4.33±1.21, $p = 0.001$).

As shown in Figure 1, the amplitude of the P50 wave was higher for healthy participants than that for patients, with values within the normal range (well above 4.5 μV). It was also higher in patients with euthymia than in patients with mania/hypomania. In the latter, the P50 amplitude was below the normal threshold, reaching pathological values in most patients with TB.

Table 1 Mean amplitude of the P50 wave

Subjects		Participants (N)	YMRS	P50 mean amplitude	Significance
Controls		36		9.43 ± 3.82	
Patients		34	32.24 ± 17.19	4.64 ± 1.39	0.000[a]
Clinical status	Controls	36		9.43 ± 3.82	
	Mania / hypomania	25	41.44 ± 8.02	4.33 ± 1.21	0.000[b]
	Euthymia	7	4.14 ± 1.07	5.91 ± 1.35	0.001[b]

a Average amplitude of both eyes Student's t.
b Average width of both eyes ANOVA with Games-Howell post hoc test.
YMRS: Young Mania Rating Scale

Effects of medication

Since psychopharmacological treatments were not withdrawn, a crucial point in this study was the analysis of the possible influence exerted by different types of psychotropic drugs on the PERG results in TB. As shown in Table 2, there was no significant difference between the different groups.

Severity of mania

To verify the relationship between severity of mania measured by YMRS and the mean P50 wave amplitude, we performed a correlation analysis between both variables that included only patients to avoid overemphasis on the correlation coefficient. As expected, the correlation was high and negative (Pearson correlation coefficient = -0.41; p = 0.015) and indicated that the P50 wave amplitude decreases with clinical severity of mania as measured by the YMRS. These results are shown in the scatterplot depicted in Figure 2.

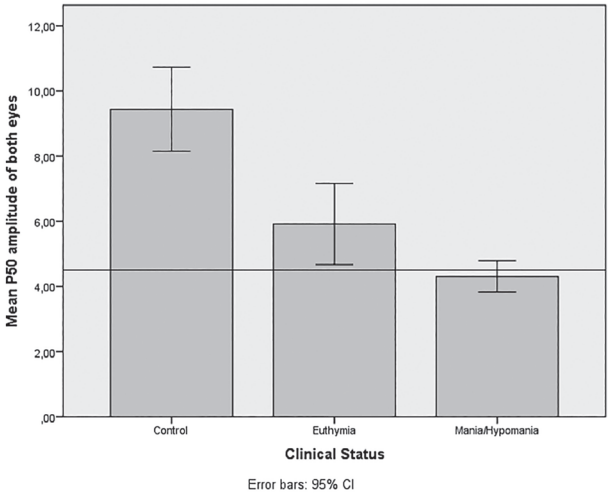

Figure 1 Graph of clinical state and wave amplitude P_{50} in PERG

Table 2 Amplitude of the P50 wave according to group of psychotropic drugs

Drug	Prescription	N	Mean amplitude of the P wave 50	Significance*
Lithium	No	10	4.09± 0.71	
	Yes	24	4.87 ± 1.54	0.137
Valproate	No	24	4.77 ± 1.61	
	Yes	10	4.30 ± 0.51	0.202
Lamotrigine	No	27	4.69 ± 1.43	
	Yes	7	4.44 ± 1.27	0.685
Gabapentin	No	32	4.52 ± 1.34	
	Yes	3	6.47 ± 0.67	0.520
APS 1ºG	No	27	4.70 ± 1.48	
	Yes	7	4.37 ± 0.95	0.578
Aripiprazole	No	23	4.84 ± 1.57	
	Yes	11	4.21 ± 0.79	0.224
Olanzapine	No	31	4.64 ± 1.45	
	Yes	3	4.53 ± 0.35	0.895
Quetiapine	No	19	4.88 ± 1.47	
	Yes	14	4.32 ± 1.24	0.243
Risperidone	No	30	4.55 ± 1.24	
	Yes	4	5.31 ± 2.36	0.307
Paliperidone	No	27	4.69 ± 1.50	
	Yes	7	4.45 ± 0.90	0.696
Amisulpiride	No	25	4.82 ± 1.39	
	Yes	5	3.57 ± 0.78	0.062
Antidepressant	No	31	4.66 ± 1.44	
	Yes	3	4.33 ± 0.71	0.698
Benzodiazepine	No	2	4.93 ± 1.03	
	Yes	2	4.62 ± 1.42	0.767

* Student's t test

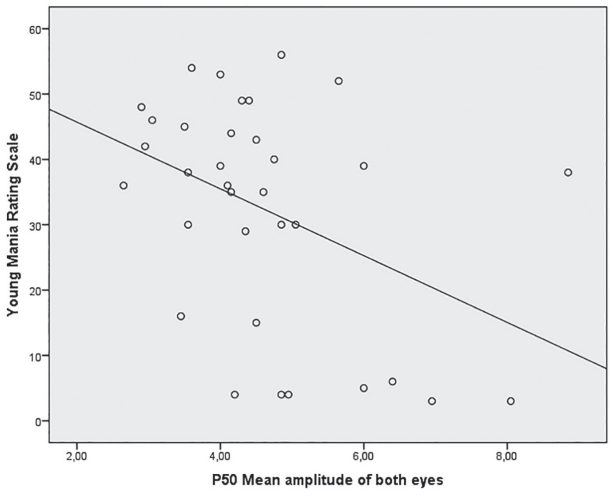

Figure 2 Scatterplot of the YMRS and the P50 Mean amplitude of both eyes

DISCUSSION

In the present study, we found that TB patients show changes in contrast processing measured by PERG, with a significant reduction in the P50 wave amplitude compared to healthy controls. We also found that the P50 amplitude differs between the three disease states (euthymia, hypomania and mania) and that there is a negative correlation between YMRS scores and the maximum P50 amplitude, i.e. a greater decrease in amplitude with greater clinical severity.

The differences found between patients and controls were consistent with previous research[15,19,21]. One example is the study by Schwitzer et al., in which a significant reduction in retinal contrast gain was observed in unmedicated and medicated patients with major depressive disorder compared to age- and sex-matched controls[45]. Similarly, a study testing the effect of light therapy on SAD patients during winter found that prior to light therapy, patients had significantly lower ERG peak amplitudes compared to controls. However, in summer and after 4 weeks of light therapy, these changes disappeared[25], so the hypothesis was that dysregulation of brain neurotransmitters could be the origin of both mood disorders and changes in retinal sensitivity[24]. These results are in contrast to those of the study by Oren et al, in which no differences were found between patients with SAD and controls[23], although the small sample size was noteworthy.

In our study, we found that it was impossible to withdraw patients from treatment, so the possible influence of treatment is a crucial point in the evaluation of the results. However, analyses show that there is no difference between patients taking and not taking certain drugs. The results obtained in our study regarding the influence of pharmacological therapy show that they are independent of it, which is consistent with the results of other studies regarding antidepressants[19,20,45]. Regarding the influence of sex, in our study, we found no significant differences, in contrast to previous studies which do describe greater variability in the ERG waveform in men, mainly those diagnosed with schizophrenia, with greater homogeneity being observed in the results of women, whether controls or patients[34].

Based on what has been described, affective disorders and vision seem to share a physiological link[14,15,32,46]. Our study, supported by the available literature, indicates that visual processing deficits are present in euthymic periods and that the pathophysiology of BD affects visual pathways, supporting the idea that visual processing deficits may be a feature of BD[30].

In our research, we further showed that the amplitude is different between the three disease states, which is in apparent contrast with the results of Balogh et al., in whose study of patients with schizophrenia or type I BD, only the first group had a pathological ERG[47]. This apparent discordance in findings may be explained by the fact that the electrophysiological test used was the flash electroretinogram, whose target of study, unlike the PERG, are photoreceptors and non-neuronal cells of the retina.

Our results show a negative correlation between the P50 wave amplitude and BD severity, such that the maximum P50 amplitude decreases with severity of mania. Also, Bubl et al. found a reduced contrast gain in patients with major depression, which was correlated with clinical severity[21], and similar results have been described for Parkinson's disease[48].

As mentioned above, dopamine is the main neurotransmitter for the processing and transmission of visual information[12], so one theory that could explain our results is that of impaired dopaminergic transmission. This hypothesis proposes that an intrinsic dysregulation in the homeostatic regulation of dopaminergic function would lead to cyclical changes resulting in depressive and manic phases. Thus, manic phases would underlie a state of hyperdopaminergia due to an increase in D2/D3 receptor levels, while increased levels of dopamine transport could underlie depressive episodes[49]. In this sense, basal dopamine activity would exhibit an inverted U-function, whereby high basal levels of it would lead to reduced neuronal activity after stimulation, resulting in decreased amplitude, and low levels would result in a higher level of activity. Our results support this hypothesis and agree with those obtained by Bubl et al., who found a reduction in VEP and PERG according to the severity of depression[20,21]. It is noteworthy that different phases of the condition lead to

similar alterations in the PERG, and, therefore, this method does not allow us to distinguish the sign of the phase (depressive or manic/hypomanic) and thus mixed states.

STRENGTHS AND LIMITATIONS OF THE STUDY

One of the main strengths of our study is the diagnostic reliability obtained by means of the independent examination carried out by two psychiatrists, both in patients belonging to the Specialised Bipolar Disorder Unit and in hospital inpatients. Likewise, the GHQ-12 was administered to the controls to ensure that there were no other clinical entities that went unnoticed and could influence the results. It is also worth highlighting the use of PERG as the technique of choice as it is a faster, simpler and non-invasive type of ERG, requiring no pupillary dilation or adaptation period[45]. However, its main advantage over other techniques lies in the fact that its measurements are not altered by variations in the attentional state, thus overcoming what could have been an important limitation in patients in a manic or hypomanic state.

As limitations, the sample size was small, especially with respect to the hypomanic state, resulting in a heterogeneous sample of patients. This lack of parity between the different groups of patients with BD is because this is the first study carried out on BD using this technique, which was largely exploratory and interested in obtaining a population with different degrees of illness. Nevertheless, the results were statistically significant, with a strong correlation between the YMRS score and PERG alterations. The impossibility of ruling out specific effects of psychotropic drugs should also be considered, despite the fact that in previous research, results did not differ according to pharmacological therapy[19,20]. Regarding the methodology, it should be noted that the neurophysiologist who conducted PERG was unaware of the diagnosis and the results of the psychometric assessments of all participants, although given the characteristics of the test, direct contact could not be avoided. However, the calibration of the apparatus was standard and was not changed at any time during the study.

CONCLUSIONS

Our results are consistent with the available literature, and differences were observed between healthy participants and those diagnosed with BD regardless of whether they were in mania or euthymia. This supports the hypothesis that alterations in retinal functionality could be a biomarker of BD. Thus, PERG could be postulated as an objective technique, complementary to clinical assessment, for the diagnosis of BD.

We also found that visual information processing is impaired during the affective states of BD, with a negative correlation between the severity of mania and the mean P50 wave amplitude. This suggests that PERG monitoring of retinal functionality could be used as a biomarker of mood fluctuations in BD.

However, our results, although positive, are preliminary and need to be replicated. It is particularly important to be able to carry out longitudinal studies that allow us to compare the results in the same patient in different affective phases. In the same way, studies that analyse, in depth, the effects of medication on retinal function would allow us to distinguish the effects of the mental disorder itself from those derived from psychotropic drugs. In short, it is necessary to deepen this line of research to check whether PERG can definitively postulate itself as a technique with a promising future in the study of mental illnesses.

Conflict of interest

The authors declare that they have no conflict of interest related to this publication.

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