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ELECTROPHYSIOLOGICAL CORRELATES OF ATTENTIONAL PROCESSES IN PATIENTS WITH LIVER CIRRHOSIS WITHOUT MINIMAL OR CLINICALLY-OVERT HEPATIC ENCEPHALOPATHY

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Liver cirrhosis is often accompanied by a spectrum of cognitive deficits, labelled hepatic encephalopathy (HE). The precise specification of cognitive impairment associated with HE has not been yet elucidated. The aim of this study was an attempt to examine cortical function in cirrhotic patients using EEG event-related potentials during a demanding task involving selective attention. We compared group of 30 patients with liver cirrhosis without minimal or overt HE with education-, age- and sex-matched 29 non-cirrhotic controls. Both groups performed an attentional blink (AB) task, which requires detecting and identifying two target characters in a longer series of rapidly and sequentially presented characters. EEG signals from 32 electrodes were measured and then analyzed in the paradigm of event-related potentials (ERP). Though the groups did not differ in the detection rate of the target stimuli, ERP waveforms revealed two group differences of component amplitudes. The first difference was related to the waveform amplitude within the 200-400 ms after first target in the right frontal region (frontocentral N2 component). Moreover, in patient group this amplitude positively correlated with the blood plasma level of alkaline phosphatase and gamma-glutamyl transpeptidase. The second amplitude difference was observed in the midline parieto-occipital regions within the 400-600 ms after the first target (P3b component). The AB task and ERP analysis allowed to find differences in cortical functioning in cirrhotic patients even without overt cognitive deficits. Our finding demonstrates that liver dysfunction can influence cortical processing associated with detecting and categorizing stimulus change.

Key words: *attentional blink, cognitive functions, electroencephalography, event-related potentials, hepatic encephalopathy, liver cirrhosis*

INTRODUCTION

Liver cirrhosis is regarded as a terminal stage of chronic liver diseases of various etiology. The most common alcoholic disease, hepatitis B and C viruses, autoimmune hepatitis, toxins and pharmaceuticals, nonalcoholic steatohepatitis (NASH), or metabolic diseases such as hematochromatosis or Wilson's disease, or more rarely, diseases of the bile duct. Irrespective of etiology, liver cirrhosis can lead to major complications such as portal hypertension and hepatic encephalopathy (HE) (1). Spectrum of HE related disorders ranges from subtle attentional or orientation deficits mixed with other cognitive symptoms is associated with minimal hepatic encephalopathy (MHE), through clinically overt HE up to the deep coma or brain damage (2). MHE is defined as the presence of deficits of cognitive functions measurable with psychological tests in patients with liver disease or patients with portosystemic shunt, without neurological deficits or after exclusion of other possible causes of these deficits (3). Depending on the test used, MHE is observed in up to 75% of patients with liver cirrhosis (4). Apart from psychological tests, such as Rey auditory verbal learning test (AVLT), verbal fluency test (VFT), trail making test (TMT) - A and B-versions , digit symbol test (DST), block design test (BDT), mental rotation test (MRT), also electrophysiological techniques are used in the diagnosis of MHE. One of the most commonly used tests are the cognitive event-related potentials, and in the focus of research is the P300 component, usually elicited with the use of the auditory odd-ball procedure (5, 6).

The procedure involves a random interleaved presentation of two types of short tones: frequent standards (85% probability) and rarer deviants (15% probability). Inter-trial interval is also random and changes within range of 900-1100 ms. The P300 component usually takes form of a positive deflection of the event-related response after deviant stimuli which appears 250-450 ms after stimulus onset. Its appearance reflects cognitive evaluation of the stimulus (7). The main

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parameters of this component are the amplitude relative to pre-stimulus baseline and the latency of the peak amplitude from the onset of the stimulus. Cognitive event-related potentials technique is a relatively simple and easy to implement method. The high temporal resolution of this method makes it possible to study neuronal correlates of transient cognitive processes. HE spectrum patients reveal longer latency and decreased amplitude of P300. However, the P300 component is observed at many various cognitive tasks, which makes its interpretation in clinical studies difficult (8, 9).

A more specific cognitive task could point at the stage of information processing which is sensitive to the influence of liver dysfunction on the brain. This was the rationale of using the attentional blink task in this study (8). This task requires subjects to view a series of rapidly presented visual stimuli, for example single digits, called distractors, among which two target stimuli are presented. Subjects are required to recognize and remember both target stimuli (*Fig. 1*). If the interval between target stimuli falls between 200-500 ms a marked decrease in recognition of the second stimulus is observed. This phenomenon is called an 'attentional blink' (*Fig. 1B*). This effect is observed in almost all subjects and it is widely considered as an evidence for the limits of attentional system of the brain. More specifically, the attentional blink occurs at the stage of the transfer of information between the parallel stage of early attentional processing and the later stage, probably functioning in a serial fashion, when information enters working memory (11).

The aim of this study was to identify the aspects of higher-level cortical processing that are affected by physiological effects of liver cirrhosis even without any measurable presence of cognitive deficits. To do this, we chose a demanding attentional task to amplify differences in brain activity between patients and non-cirrhotic controls and then compared the event-related potentials evoked by experimental stimuli in both groups, and correlated these results with physiological markers of liver dysfunction.

MATERIAL AND METHODS

Subjects

The patients participating in this study where recruited from the patients with liver cirrhosis admitted between October 2008 and March 2011 to our outpatient clinic in Department of Gastroenterology, Hepatology and Infectious Diseases in Cracow. The study wasapproved by the Local Ethics Committee and performed in accordance with the Helsinki Declaration. Initially the whole study included 106 subjects: 57 patients with liver cirrhosis and 49 controls The control group consisted of patients with functional gastrointestinal disorders, mainly irritable bowel syndrome (IBS). Groups were matched according to age, sex and education. Liver cirrhosis was diagnosed on the basis of laboratory test results, USG (abdominal ultrasound exam), CT (computed tomography), MR (magnetic resonance) and in a few patients a liver biopsy. Prior to the study all subjects have read and signed an informed consent. Biochemical markers analysis and neuropsychological examination was performed in all participants. The neuropsychological assessment included trail making test (TMT) part A and B, digit symbol test (DST) and block design test (BDT) from Wechsler adult intelligence scale revised. The data analysis was preceded with a two-stage screening procedure. The first post-hoc screening stage was based on the results of the four neuropsychological tests that have been administered to all subjects: trail making test A, trail making test B (12) as well block design and digit symbol from the Polish adaptation of Wechsler adult intelligence scale-revised (WAIS-R) (13). The patients whose scores in more than two tests were beyond two standard deviations of the control group means were regarded as patients with minimal hepatic encephalopathy (14).

The second stage was based on the results of the experimental procedure. Only subjects that obtained at least 15 correct trials and had d' value greater than zero in each experimental condition have been analyzed. After applying these

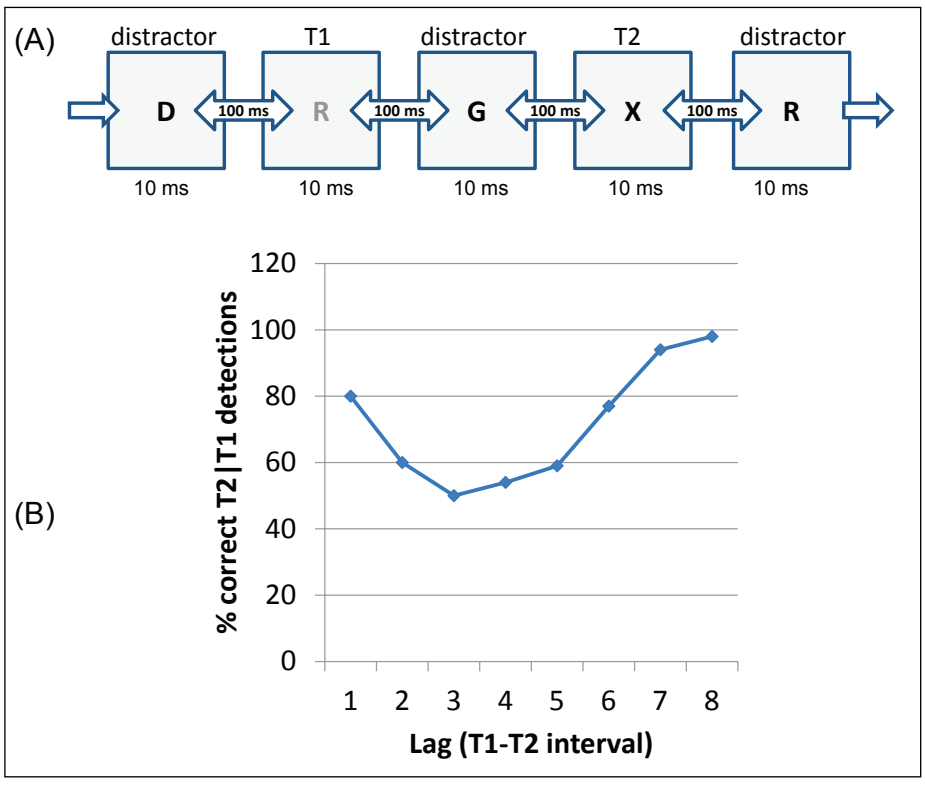

Fig. 1. (A) The attentional blink paradigm. Timing parameters are the actual values used in the study. T1-the first target stimulus. T2-the second target stimulus. (B) Typical accuracy for T2 detection at different values of T1-T2 interval only for trials with correct T1 recognition. Note the marked decrease of T2 visibility between 2-6 T1-T2 lag interval range.

Table 1. Demographic, laboratory and neuropsychological descriptive statistics of patients with liver cirrhosis and non-cirrhotic control group. The last column denotes the significance level of statistical test of group differences.

		Group								
		Liver cirrhosis				Control				
		Mean	Standard Deviation	Count	Column Valid N %	Mean	Standard Deviation	Count	Column Valid N %	p value
Age		38.2	10.6			41.3	13.7			.363
Sex	Male			15				16		.691
	Female			15				13		
Education years		14.20	2.27			15.17	2.30			.102
Aetiology of cirrhosis	Autoimmune hepatitis			11	36.7%					
	Haemochromatosis			1	3.3%					
	PSC			1	3.3%					
	Non-alcoholic steatohepatitis			1	3.3%					
	Toxic			4	13.3%					
	Viral hepatitis B			8	26.7%					
	Viral hepatitis C			4	13.3%					
Child-Pugh class										
	A			19	63.3%					
	B			11	36.7%					
Bilirubin (mg/dL)		20.19	17.71			13.21	7.63			.034
Aspartate aminotransferase (U/L)		59.53	53.26			29.31	14.81			.003
Alanine transaminase (U/L)		106.10	140.84			37.96	23.81			.002
Gamma-glutamyl transpeptidase (U/L)		173.62	284.60			45.76	55.53			.000
Cholinesterase (U/L)		9056.60	2594.31			9458.07	2115.17			.400
Alkaline phosphatase (U/L)		208.20	143.26			158.38	102.03			.083
Albumin (g/L)		46.03	3.59			46.45	3.32			.703
Ammonia (µg/dL)		41.32	34.88			21.86	7.36			.001
Prothrombin (INR)		1.05	.09			1.01	.09			.009
Urea (mg/dL)		5.00	1.34			5.17	1.51			.383
Platelets (/µL x 10^3)		200.07	83.08			229.90	66.79			.383
TMT A (sec)		25.6	8.1			26.7	8.5			.788
TMT B (sec)		56.0	20.2			70.2	40.1			.932
WAIS-R BDT score		12.9	2.6			12.9	2.7			.461
WAIS-R DST score		12.1	2.1			12.7	2.6			.097

PSC - primary sclerosing cholangitis. TMT: trail making test. DST: digit symbol test. BDT: block design test.

criteria 29 controls and 30 cirrhotic patients were included in the final behavioral and ERP analysis. Demographic and clinical data of these patients are shown in *Table 1*. The significance of differences between demographic and laboratory parameters was verified using the independent samples Mann-Whitney U test or Pearson χ^2 where applicable.

Table 2. Examples of stimuli series for all conditions.

Lag1	D O P A **T** X O A E R N H G A M E G E V L E
Lag2	L M J D **R** G X R M N T H T S Y W B G O T W
Lag7	L M Y N B **O** S B W G M U X P H D C Y U L O
No_T2	C A S M V **T** Y J Y D S H M V P V Y P B L O

Experimental procedure

Target stimuli and distractors were presented in the middle of the computer screen with frequency of 10 Hz (cf. *Fig. 1A*). The set of distractors and T1 targets contained capital letters: B, C, D, G, H, J, M, N, P, R, S, W, A, E, O, U, Y. One experimental trial consisted of 21 characters randomly selected from the set. The distractors were presented in black font. T1 target stimuli were presented in the green font (half of occurrences of T1 stimuli were vowels) at positions 5 to 8 within the series. T2 target stimuli were in 75% occurrences the black letters X, presented either right after the T1 target stimulus (Lag1 condition), two places later (Lag2 condition) or 7 places later (Lag7 condition). In 25% trials the T2 target stimuli was not presented at all (the no T2 condition). *Table 2* shows the examples of trials for all conditions.

After each experimental trial subjects were asked to indicate the green letter which was shown previously by pressing the appropriate key on the keyboard, and then to give a 'yes/no' response to question about the occurrence of the letter X in the preceding series. In total each subject was shown 288 trials in four blocks separated by three short breaks for rest.

Data acquisition

The electroencephalogram (EEG) was recorded by Biosemi Active Two System (Biosemi B.V., Amsterdam, The Netherlands) from 32 Ag-ACl electrodes held on the scalp by an elastic cap (Electrocap International, Eaton, OH), accompanied with electrodes positioned at left and right mastoid sites, horizontal electrooculogram (HEOG) sites at the outer right and left canthi, and vertical electrooculogram (VEOG) sites above and below the right eye. EEG data were sampled at 256 Hz with 24-bit resolution and stored on the computer hard disk. Then they were high-pass and low-pass filtered offline using a zero phase-shift Butterworth filter with 0.01 Hz and 30 Hz cut-off fregnencies, respectively, and re-referenced to the average of the left and right mastoids.

Behavioral data analysis

Correct responses to T2 stimuli were analyzed and parameterized into d' index (15). Its value is based on correct responses (hits) and incorrect positive responses when no T2 stimulus was present (false alarms). D' is an estimate of the individual sensitivity to T2 stimuli and can be used to reject subjects who gave random responses (in such cases d' falls below zero). The individual d' values were analyzed with a two-way ANOVA with a between-subject factor of Group (controls *vs*. patients with liver cirrhosis) and within-subjects Lag factor of experimental condition (three levels corresponding to the three T1-T2 intervals). Also multinomial contrasts were applied to study planned comparisons.

Electroencephalogram data analysis

In the first step of analysis data were divided into 1150 ms long segments, with 150 ms pre-stimulus period. Segments containing large artifacts were rejected using visual inspection. Eye movements and eye blink artifacts have been corrected using an ICA algorithm (16). Further rejection of artifacts was based on the ±30 μV amplitude threshold. Trials in which subject did not recognized T1 stimulus correctly were also rejected.

ERP responses for each group were grand averaged and compared. After visual inspection of grand averange waveforms, the ERP fragments with biggest between-group differences in most conditions were identified. For these fragments a mean amplitude for the given time-period was calculated, for each electrode separately.

Amplitude data from all electrodes were collapsed into 9 regions - six regions covering left and right lateral surface of the scalp, and three placed along the midline (*Fig. 2*).

The averaged amplitudes of the selected ERP fragments have been subjected to a two-way ANOVA. Outliers with amplitude values larger than two standard deviations from the group mean were excluded from the analysis. The factors used were the same as in the behavioral data analysis (*i.e.* between-subjects factor of Group and within-subject factor of Lag). ANOVA was computed for each region separately.

Spearman's rank correlation test was used to measure correlation between biochemical markers and the amplitudes of the event-related components in regions where a significant group difference was found. The correlation analyses were done exclusively in the liver cirrhosis group. We report only correlations between biochemical marker level and ERP amplitude which were $p<0.05$ significant in all three experimental conditions.

RESULTS

Behavioral results

ANOVA did not reveal any group difference - either the main effect of Group ($F(1,59)<1$), nor the interaction effect between Group and Lag factors ($F(2,118)<1$). There was however a significant main effect of Lag factor ($F(1,40)=20.46$, $p<0.001$). The quadratic trend for this factor revealed strong effect $F(1,59)=55.32$, $p<001$, thus showing the expected highest decrease of T2 stimulus visibility for the Lag2 condition (*Fig. 3*).

Event-related potentials results

The visual inspection of grand averaged event-related responses revealed two fragments showing the most pronounced

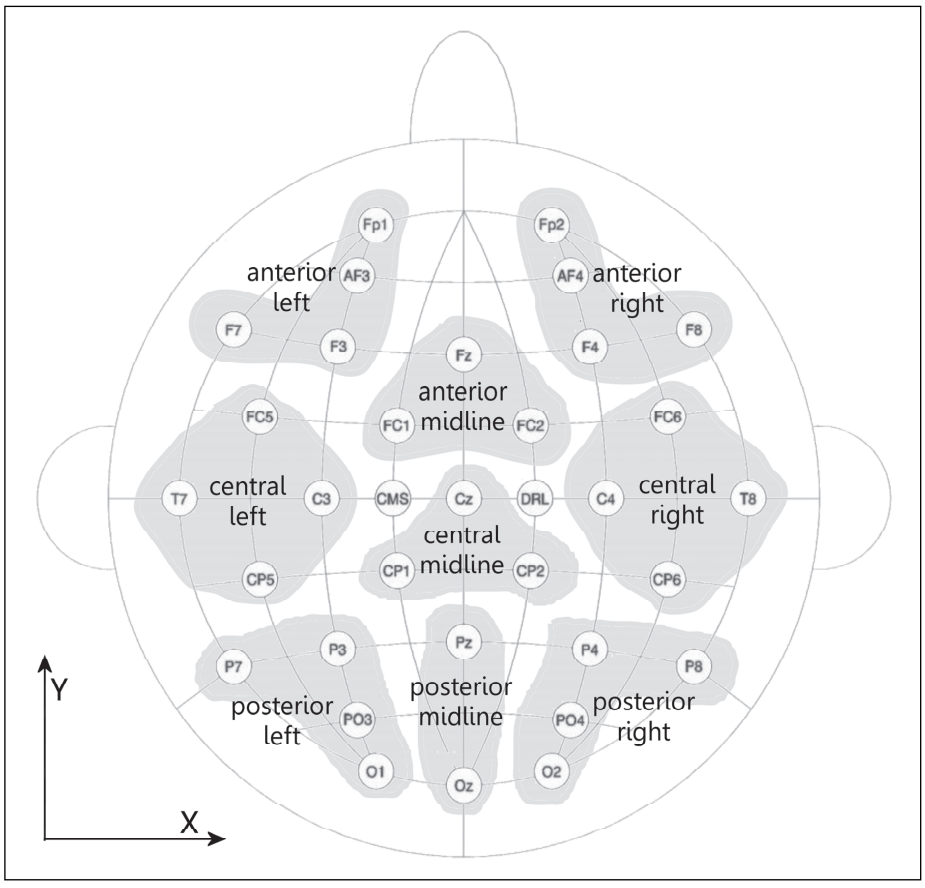

Fig. 2. Location of electrode groups (regions) used in the study. Electrode names are inside white circles.

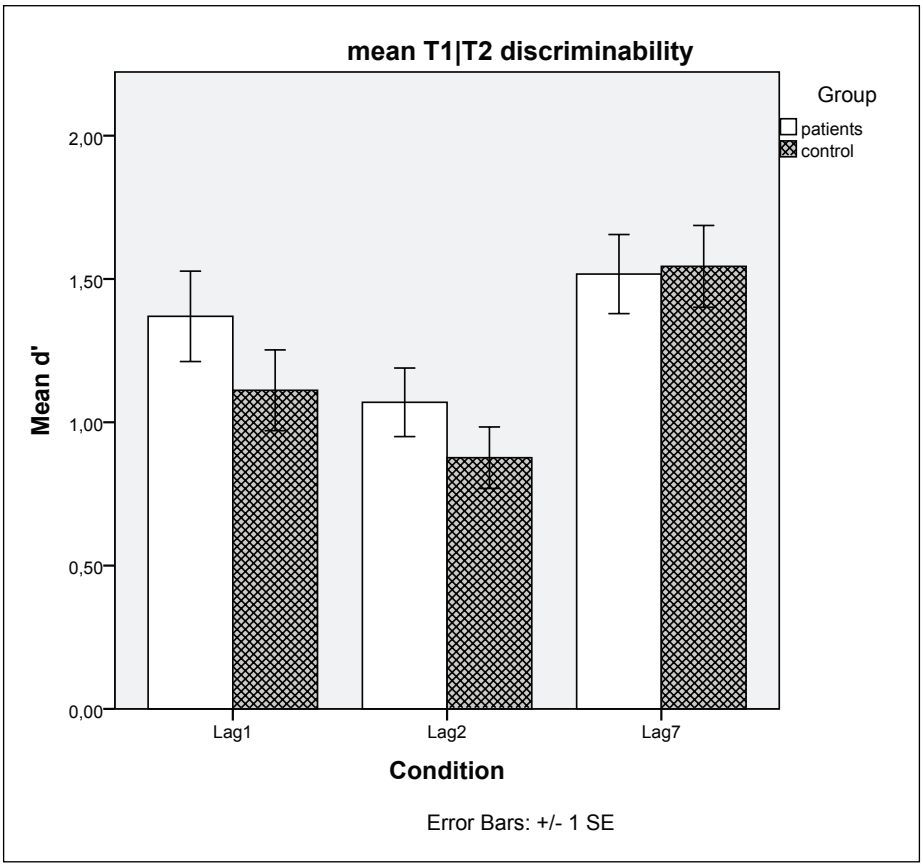

Fig. 3. Mean d' values for both groups across experimental conditions. Whiskers depict standard error of the mean.

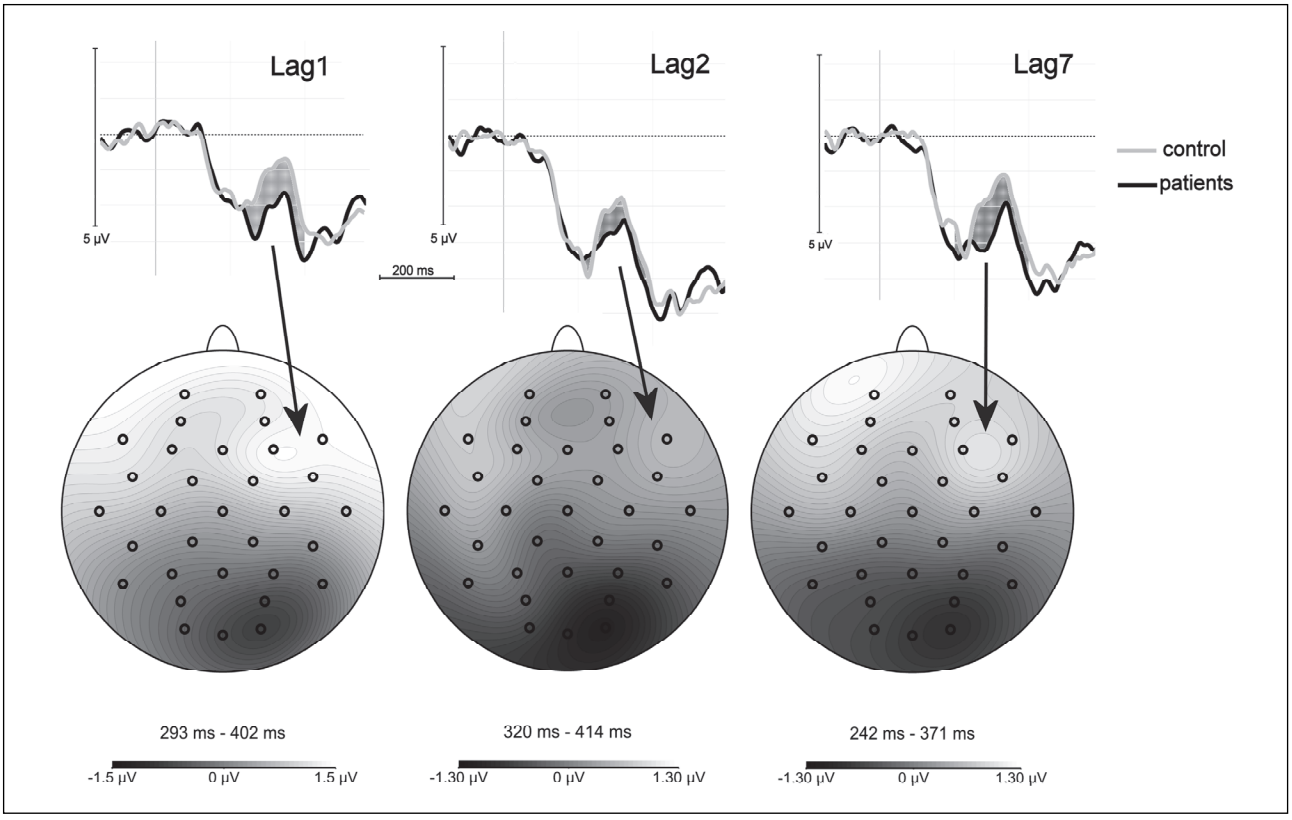

Fig. 4. The AB1/N2 component. The upper panel depicts event-related potentials obtained from the anterior-right region for each condition. Spatial maps on the lower panel represent spatial distribution of the ERP amplitude differences observed within the 200-400 ms time-window (represented by the shadowed area between the waveforms in the upper panel and the time). The time ranges below maps represent the specific time ranges on which the computed difference image was based. Black arrows point at the locations from which the waveforms were computed. Black circles on the spatial maps denote electrode sites.

differences between controls and patients. They will be referred as to AB1 and AB2 components henceforth. In the Discussion section they will be interpreted in terms of known ERP components.

The AB1 component was observed over right frontal and central electrodes within the 200-400 ms time-window after T1 stimulus onset. In this case, the difference depended on the decreased amplitude of the negative deflection within 200-400 ms in the patients group (*Fig. 4*).

ANOVA on averaged amplitudes for this component revealed Group × Lag interaction effect in the anterior-right region ($F(2,110)=3.57$, $p<0.05$). The simple main effects analysis revealed a significant difference at Lag1 condition ($F(1,55)=6.24$, $p<0.05$). Moreover, Group × Lag interaction approached significance in the central-right region ($F(2,110)=3.01$, $p<0.06$), and simple main effect approaching significance at Lag1 condition was observed ($F(1,55)=3.49$, $p<0.07$).

In the patient group we observed a positive correlation between AB1 amplitude in the anterior-right region and alkaline phosphatase (AP) and gamma-glutamyl transpeptidase (GGTP) levels in all three conditions. The respective correlations are given in *Table 3*.

The AB2 component was observed over the central and posterior regions within the 400-600 ms time-window after T1 stimulus onset. This difference appears to be dependent on the increased amplitude of positive deflection in the controls group against the patients.

Interaction effects Lag × Group factor were observed in three regions: the central-midline region ($F(2,112)=3.61$, $p<0.05$), the posterior-midline region ($F(2,112)=3.58$, $p<0.05$), and the posterior-left region ($F(2,112)=3.31$, $p<0.05$). The simple main effects analysis for the central-midline region did not reveal any significant effects. However, the analysis of means suggests that in both groups there occurred a gradual decrease of amplitude, which was more pronounced in the patient group with liver cirrhosis . In the posterior-midline region the simple main effects analysis revealed the significant difference between groups in the Lag7 condition ($F(1,56)=6.77$, $p<0.05$). Again however, overall inspection of means suggest that amplitudes in the control group remained stable, while in the patient group with liver cirrhosis they gradually ecreas. The same pattern of changes of means was observed in the posterior-left region.

No significant correlations between the AB2 component mean amplitude and the biochemical markers were found that would have spanned across all three experimental conditions in any of these regions.

Table 3. Correlation coefficients between the biochemical markers and AB1 the component amplitude in the patient group (N=29).

Biochemical marker	Anterior-Right region Lag1	Anterior-Right region Lag2	Anterior-Right region Lag7
Alkaline Phosphatase	.434*	.498**	.517**
Gamma-glutamyl transpeptidase	.493**	.483**	.587**

Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).

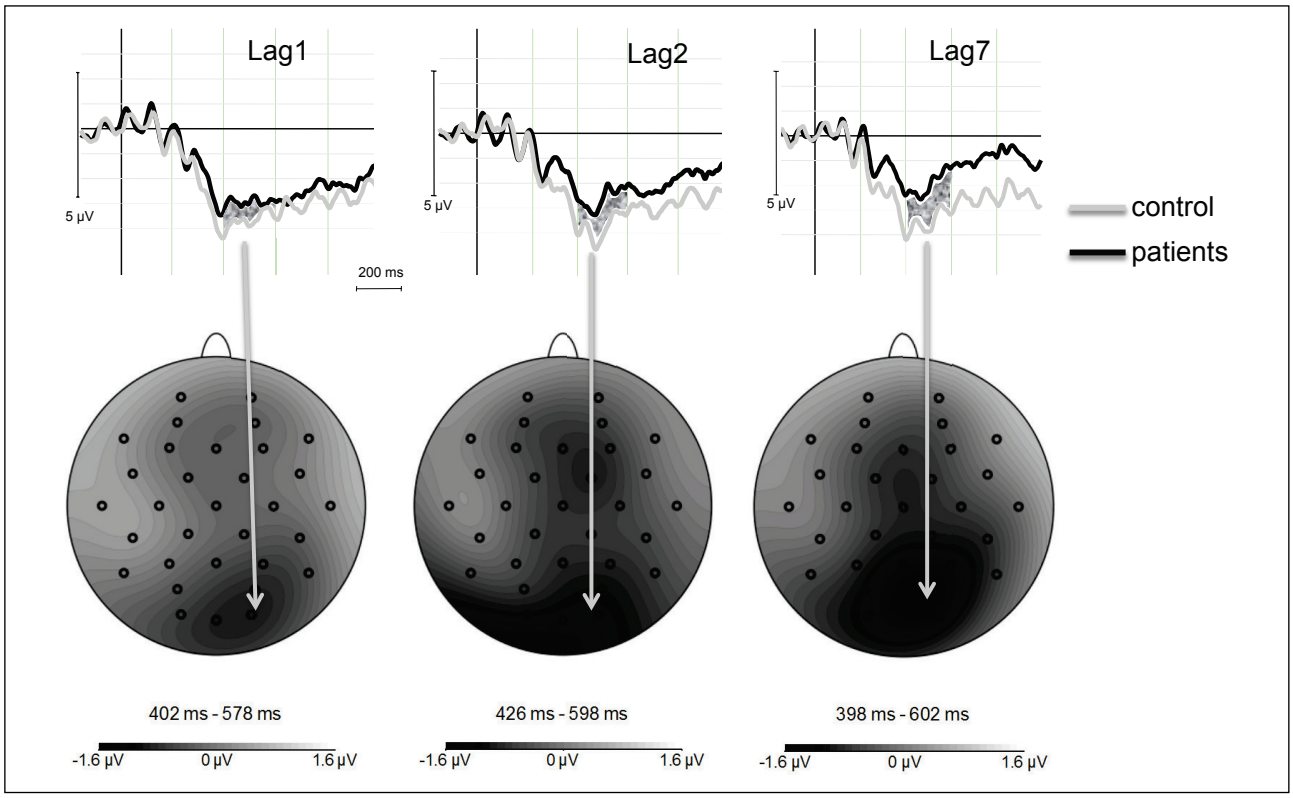

Fig. 5. The AB2/P3b component. The upper panel depicts event-related potentials obtained from the posterior-midline region for each condition. The spatial maps on the lower panel represent distribution of the ERP amplitude differences in the 400-600 ms time window (represented by the shadowed area between the waveforms in the upper panel). The time ranges below maps represent the specific time ranges on which the computed difference image was based. Black arrows point at the locations from which the waveforms were computed. Black circles on the spatial maps denote electrode sites.

DISCUSSION

Liver cirrhosis, regardless of its etiology may lead to serious complications such as portal hypertension, ascites, hepatic encephalopathy HE (1). In this study we examined event-related potentials during demanding attention cognitive task in patients with liver cirrhosis (without overt or minimal hepatic encephalopathy) and compared them with the results obtained in the matched control group. Since there were no significant differences in behavioral performance between groups, the observed differences in ERP waveforms can be attributed to different physiological condition of controls and liver cirrhosis patients. Notable differences in the ERP waveforms were observed in two time-windows, or components. In the first time-window the difference was a result of the decrease of the amplitude of negative deflection with the latency 200-400 ms in the group of patients with liver cirrhosis. Anatomically, this difference was located in the right frontal region. The second difference between the ERP waveforms was observed within the 400-600 ms time-window after T1 stimulus onset. The group of patients with liver cirrhosis displayed the decreased amplitude of the positive deflection in comparison to the control group.

The AB1 component can be related to the so called frontocentral N2 complex. The frontocentral N2 component is often observed when subjects detect the rare stimuli that deviate from the previous sequential stimulus stream (17), thus being sensitive to mismatch between expectation and the stimulus (18). In this study the component can be interpreted in terms of the detection and categorization of the first target stimulus from the stream of distractors. The amplitude of this component was reduced in the patient group, and this effect was corroborated by the correlation between the amplitude and the level of two liver cirrhosis biomarkers (AP and GGTP) The higher were the levels of these biomarkers the shallower was the negative deflection in the 200-400 ms time window which we identify as the amplitude of AB1/N2. Animal studies evidence that serum concentration of liver damage biomarkers can be a direct correlate of the structural and functional symptoms of brain damage (2). We speculate this difference could be associated with slightly decreased efficiency of the neural network associated with novel stimulus categorization. Though in our study did not affect behavioral responses, one can assume that it would be more evident if subjects with more severe forms of encephalopathy were included.

The polarity and latency of the AB2 component suggest that this ERP fragment can be related to the P3b component. We link this difference with the previous N2 component, thus forming a complex cortical response reflecting detection and categorization of change in the stimulus stream.

We have not find any ERP study addressing the critical fusion frequency using ERP paradigm, but one fMRI study showed that detection of discontinuity in flicker streams also evoked activity in the frontal and parietal cortices (19). As the critical fusion frequency threshold is a very sensitive estimate of hepatic encephalopathy (20, 21), our results can pinpoint at the possible aspects of cortical functioning which are related to this task, *i.e.* detection and categorization of change in visual patterns. Of course further research is needed to confirm this hypothesis. The attentional blink procedure employed in this study revealed that patients with liver cirrhosis differ from controls in the aspects of attentional processing associated with visual change detection and categorization. This observation proves that EEG event-related potentials can be a sensitive measure to detect functional brain abnormalities accompanying liver cirrhosis, even without any overt cognitive deficits.

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REFERENCES

1. Cichoz-Lach H, Celinski K, Slomka M, Kasztelan-Szczerbinska B. Pathophysiology of portal hypertension. *J Physiol Pharmacol* 2008; 61: 231-238.
2. Ilic S, Drmic D, Zarkovic K, *et al*. High hepatotoxic dose of paracetamol produces generalized convulsions and brain damage in rats. A counteraction with the stable gastric pentadecapeptide BPC 157 (PL 14736). *J Physiol Pharmacol* 2010; 61: 241-250.
3. Dhiman RK, Saraswat VA, Sharma BK, *et al*. Minimal hepatic encephalopathy: consensus statement of a working party of the Indian National Association for Study of the Liver. *J Gastroenterol Hepatol* 2010; 25: 1029-1041.
4. Sood GK, Sarin SK, Mahaptra J, Broor SL. Comparative efficacy of psychometric tests in detection of subclinical hepatic encephalopathy in nonalcoholic cirrhotics: search for a rational approach. *Am J Gastroenterol* 1989; 84: 156-159.
5. Saxena N, Bhatia M, Joshi YK, Garg PK, Dwivedi SN, Tandon RK. Electrophysiological and neuropsychological tests for the diagnosis of subclinical hepatic encephalopathy and prediction of overt encephalopathy. *Liver* 2002; 22: 190-197.
6. Saxena N, Bhatia M, Joshi YK, Garg PK, Tandon RK. Auditory P300 event-related potentials and number connection test for evaluation of subclinical hepatic encephalopathy in patients with cirrhosis of the liver: a follow-up study. *J Gastroenterol Hepatol* 2001; 16: 322-327.
7. Polich J. Updating P300: an integrative theory of P3a and P3b. *Clin Neurophysiol* 2007; 118: 2128-2148.
8. Donchin E, Coles MGH. Is the P300 component a manifestation of context updating? *Behav Brain Sci* 1988; 11: 357-374.
9. Hansenne M. The p300 cognitive event-related potential. I. Theoretical and psychobiologic perspectives. *Neurophysiol Clin* 2000; 30: 191-210.
10. Martens S, Wyble B. The attentional blink: past, present, and future of a blind spot in perceptual awareness. *Neurosci Biobehav Rev* 2010; 34: 947-957.
11. Chun MM, Potter MC. A two-stage model for multiple target detection in rapid serial visual presentation. *J Exp Psychol Hum Percep Perform* 1995; 21:109-127.
12. Strauss E, Sherman EMS, Spreen O. A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary. Oxford, New York, Oxford University Press, 2006.
13. Brzezinski J, Gaul M, Hornowska E, Jaworowska A, Machowski A, Zakrzewska M. Skala inteligencji Wechslera dla doroslych. Wersja zrewidowana - renormalizacja. Polska adaptacja WAIS-R (PL). Warszawa: Pracownia Testow Psychologicznych Polskiego Towarzystwa Psychologicznego, 2004.
14. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy - definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology. *Hepatology* 2002; 35: 716-721.
15. McNicol D. A Primer of Signal Detection Theory. Mahwah, NJ, USA, Lawrence Erlbaum Associates Publishers, 2005.
16. Makeig S, Jung TP, Bell AJ, Ghahremani D, Sejnowski TJ. Blind separation of auditory event-related brain responses

into independent components. *Proc Natl Acad Sci USA* 1997; 94: 10979-10984.
17. Folstein JR, Van Petten C. Influence of cognitive control and mismatch on the N2 component of the ERP: a review. *Psychophysiology* 2008; 45: 152-170.
18. Luck SJ. Event-related potentials. In: APA Handbook of Research Methods in Psychology, Cooper H, Camic PM, Long DL, *et al*. (eds). Vol 1: Foundations, Planning, Measures, and Psychometrics. Washington, DC USA, American Psychological Association, 2012, pp. 523-546.
19. Carmel D, Lavie N, Rees G. Conscious awareness of flicker in humans involves frontal and parietal cortex. *Curr Biol* 2006; 16: 907-911.
20. Sharma P, Sharma BC, Puri V, Sarin SK. Critical flicker frequency: diagnostic tool for minimal hepatic encephalopathy. *J Hepatol* 2007; 47: 67-73.
21. Sharma P, Sharma BC, Sarin SK. Critical flicker frequency for diagnosis and assessment of recovery from minimal hepatic encephalopathy in patients with cirrhosis. *Hepatobiliary Pancreat Dis Int* 2010; 9: 27-32.

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