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Detection of minimal hepatic encephalopathy: Normalization and optimization of the Psychometric Hepatic Encephalopathy Score. A neuropsychological and quantified EEG study☆

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Background/Aims: Psychometric Hepatic Encephalopathy Score (PHES) and EEG are used to detect minimal hepatic encephalopathy (MHE). We aimed at standardizing PHES in Italy and comparing Italian, German and Spanish norms in EEG characterized cirrhotic patients.

Methods: PHES was standardized on 228 normal individuals. Repeatability was studied in 128 individuals. One hundred patients with liver cirrhosis underwent EEG and PHES which was computed on the Spanish, German and the Italian norms.

Results: Age and education levels were predictors of psychometric tests; therefore, adjusted Z scores were calculated. Practice effect ($p < 0.01$) was detected. In the patients, the Italian norms were closer to the Spanish norms (difference -0.14 ± 1.32, $p = 0.29$) than to the Germans ones (difference 1.97 ± 2.07, $p < 0.001$). The PHES calculated on the Italian norms was correlated with the EEG mean dominant frequency more closely than the ones calculated on the German and Spanish norms ($r = 0.38$, $r = 0.31$, $r = 0.33$, respectively – $p < 0.01$). The detection of MHE on the basis of PHES and EEG showed limited agreement (73%, Cohen's $K = 0.32$).

Conclusions: (i) Valid norms for PHES were produced, (ii) clues for the use of common norms in Latin Countries were found, (iii) different findings between PHES and EEG possibly reflect various features of MHE.

Keywords: Minimal hepatic encephalopathy; Mild cognitive impairment; Psychometric tests; Spectral EEG; Liver cirrhosis

1. Introduction

There is increasing interest in the detection of the first, sometimes apparently negligible, or subclinical signs of hepatic encephalopathy, since this condition, called minimal hepatic encephalopathy (MHE) [1,2], has been proven to be associated with the risk of overt hepatic encephalopathy (HE) and death and to damage activities such as driving [3–6]. In addition, some data may suggest a relationship with the quality of life [7,8].

Neuropsychological examination, which per se highlights a form of mild cognitive impairment mainly involving the anterior attention system and psychomotor speed [3,9–14], is the cheapest and simplest way of

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Abbreviations: PHES, psychometric hepatic encephalopathy score; EEG, electroencephalogram; MHE, minimal hepatic encephalopathy; LTT, line trait test; DST, digit symbol test; TMT-A, trial making test, subtype A; TMT-B, trial making test, subtype B; SDT, serial dotting test; MDF, mean dominant frequency; MZPS, mean Z psychometric score; ROC, receiving operating characteristic curve; HE, hepatic encephalopathy.

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detecting the adverse effect of liver dysfunction or shunting on brain functioning.

The search for an efficient paper and pencil psychometric tool to discern mild cognitive impairment, which is related to liver cirrhosis, prompted Schomerus and Hamster [15] to devise a psychometric battery comprising the Digit Symbol Test (DST), the Trail Making Test A (TMT-A), the Trail Making Test B (TMT-B), the Serial Dotting Test (SDT) and the Line Tracing Test (LTT). Such a selection was based both on a discriminant analysis and clinical practice. This battery of tests generates a synthetic score that was called Psychometric Hepatic Encephalopathy Score (PHES) by Weissenborn et al. [16]. The use of PHES was suggested tout court as one of the preferable tools to detect MHE by an international group of experts [17]. Subsequently, PHES was found to be able to identify patients with liver cirrhosis with reduced brain glucose oxidation [18] and individuals with reduced tolerance to an oral load of amino acids mimicking hemoglobin [19].

However, this battery was standardized only in Germany [15,16] and, recently, in Spain [20,21] where it was proven to detect patients with reduced survival expectancy [21].

In contrast with the German standardization [16], the Spanish standardization of PHES summarizes the errors and the time needed to perform the LTT to produce a single output for this test [20]. In fact, it had been already shown that the errors and the time needed to perform the LTT are inversely related variables [22].

To improve the insight into PHES and its applicability, we performed a study aimed at (1) standardizing PHES, (2) evaluating its repeatability, (3) comparing the results of PHES standardizations with objective neurophysiological findings obtained by quantified EEG in a group of patients with liver cirrhosis.

2. Material and methods

Two samples were considered:

A sample of healthy Italian individuals to standardize PHES.

A sample of consecutive patients with liver cirrhosis to compare (i) Italian, German and Spanish PHES standardizations and (ii) PHES with EEG findings.

PHES standardization sample. A convenience sample of 228 healthy individuals (108 males) from several areas of Italy (102 subjects from urban areas and 126 from rural villages) was selected. The sample was stratified according to gender and age in order to have participants for each of the following age classes: 18–30 years, 30–40 years, 40–50 years, 50–60 years, 60–70 years, and 70–85 years. Depending on their occupation, they were classified as 'Blue collars' and 'White collars' workers. 'Blue collars' were craftsmen, farmers, housewives, nurses and hospital technical staff. 'White collars' were clerks, students, technical assistants, tradesmen, secretaries and university graduates. Four educational levels were considered: at least 5 years; at least 8 years; at least 13 years; and university degree ($\geqslant$17 years). All subjects were required to have a fair knowledge of numbers and of the Italian alphabetical sequence. An interview and a questionnaire were completed to exclude alcohol misuse (>50 g/day for males and 20 g/day for females), consumption of psychotropic drugs, insulin-dependent diabetes, or diseases that can damage cognitive functions. Following their informed consent, each individual underwent the five tests in a random sequence.

To assess the repeatability of the tests, they were repeated in a subgroup of 128 of the above individuals (after a median time of 779 days: interquartile interval 666–844).

Patient sample. A convenience sample of 100 patients with liver cirrhosis (71 males) was studied. All patients underwent neuropsychological and neurophysiological assessment the same day. Patients with diseases which influence mental function and those with overt hepatic encephalopathy were excluded from the study. Their clinical and biochemical findings are shown in Table 1.

Informed consent was obtained from all participants, according to the Declaration of Helsinki and standards established by the Responsible Authority which approved the study.

2.1. Neuropsychological evaluation

The PHES battery comprised the DST, the TMT-A, the TMT-B, the SDT and the LTT. We used the forms for the PHES battery that had been kindly provided by Prof. Karin Weissenborn for DST, SDT and LTT. We used our previously developed forms for TMT-A and TMT-B [22], because of the differences between the

Table 1
Demographic, clinical and biochemical data of cirrhotic patients and demographic data of controls

Cirrhotic patients			
Age (mean ± SD)	56 ± 11 years	Previous alcohol abuse	49%[a]
Males	71%	Child A	18 (54%[a])
		Child B	49 (47%[a])
Education		Child C	33 (50%[a])
5 years	35%	Albumin (g/L)	32 ± 7
8 years	40%	INR	1.52 ± 0.36
13 years	12%	MELD	9.0 ± 6.9
University degree	12%		
PHES standardization sample			
Age 18–30, $n = 46$, males (%) 46, educ. lev. % (1st/2nd/3rd/4th): 0/35/39/26			
Age 30–40, $n = 42$, males (%) 48, educ. lev. % (1st/2nd/3rd/4th): 7/50/29/14			
Age 40–50, $n = 42$, males (%) 41, educ. lev. % (1st/2nd/3rd/4th): 12/57/24/7			
Age 50–60, $n = 46$, males (%) 46, educ. lev. % (1st/2nd/3rd/4th): 24/50/15/11			
Age 60–70, $n = 31$, males (%) 55, educ. lev. % (1st/2nd/3rd/4th): 45/26/23/6			
Age 70–85, $n = 21$, males (%) 50, educ. lev. % (1st/2nd/3rd/4th): 61/10/19/10			

[a] Reported alcohol abuse either isolated or associated with HCV/HBV hepatits.

Italian and German alphabet sequences. In a group of 30 subjects the two kinds of forms (which also differ for the dimension of circles and letters) were randomly presented and their interchangeability was verified (comparable mean values with a random error <5% and <7%, respectively).

The psychometric battery was administered to the controls at their homes by a trained neuropsychologist (SO) and by a medical student who had had specific neuropsychological training (FC). In the patients with liver cirrhosis, the battery was administered in a quiet, well-lit room by a trained neuropsychologist. The sequence of test presentation was randomized. A practice run was administered for all tests.

The PHES[1] was calculated according to: (1) the Italian norms derived from our standardization sample, (2) the Spanish norms (the automatic procedure is freely available on the web site http://www.redeh.org) and (3) the German norms (via the predictive equations obtained by the German normative tables kindly provided to us by Prof. Karin Weissenborn and then verified for each patient on the tables themselves).

2.2. Neurophysiological evaluation

Each patient underwent digital electroencephalographic recording. Spontaneous closed-eyes activity was recorded by digital EEG equipment (Brainquick 3200, Micromed, Italy) in the morning. A standard 21-channel cap (Micromed, Italy) was used, and the electrodes placed according to the 10–20 International System [23]. The EEG tracing was assessed by spectral analysis after visual inspection to exclude artefacts. Spectral analysis was carried out on the derivation P3-P4 in the frequency range of 1–25.5 Hz [14]. The EEG alterations were classified into three grades according to mean dominant frequency MDF (i.e. the mean frequency weighted by the power of each frequency band) and to the relative power of the theta and delta bands as follows: grade 1 – MDF > 6.8 Hz and theta relative power ⩾ 35% –, grade 2 – MDF ⩽6.8 Hz and delta relative power < 49% –, grade 3 – MDF ⩽ 6.8 Hz and delta relative power ⩾ 49%, as previously described [24].

2.3. Statistics

Results are expressed as means ± SD, unless otherwise specified. The fitting of the data to normal distribution was ascertained by the Shapiro–Wilk test. The raw data of DST were normally distributed. The results of the other psychometric tests were log transformed to fit the Gaussian distribution, or, at least, to reduce their positive skew (TMT-B and SDT had massive positive skew which was not completely eliminated by log transformation).

The study of the effect of factorial variables on psychometric tests was assessed by ANCOVA, adjusting for age. The Tukey test was used for post hoc comparisons.

Univariate regression analysis was performed by the Pearson's r or the Spearman's R, as needed. Multivariate regression was performed using both factorial and continuous predictors by a general regression modeling procedure. The Bland and Altman technique were used to compare different estimates [25].

The agreement between classifications was performed by the Cohen's K.

Receiver operating characteristic (ROC) curves analysis was performed to ensure classification efficacy.

Statistical analysis was performed using the packages 'Statistica 6.0' (StatSoft Inc., Tulsa, OK, USA) and SPSS 15.0.1 (SPSS Inc., Chicago, IL, USA).

[1] The PHES is the sum of the integer scores of each test computed from the adjusted Z values as follows: score = −3 for $Z \leqslant 3$, score = −2 for $-3 < Z \leqslant -2$, score = −1 for $-2 < Z \leqslant -1$, score = 0 for $-1 < Z < 1$, score = 1 for $Z \geqslant 1$.

Table 2
Unvaried predictors of psychometric tests

Test	Age	Education level	Job	Gender
DST	$r = -0.68^*$	$F_{3,223} = 27^*$	$F_{2,223} = 15.0^*$	$F_{1,223} = 2.0$
TMT-A	$r = 0.46^*$	$F_{3,223} = 10^*$	$F_{2,223} = 0.7$	$F_{1,223} = 0.3$
TMT-B	$r = 0.50^*$	$F_{3,223} = 26^*$	$F_{2,223} = 5.7^{\circ}$	$F_{1,223} = 1.4$
SDT	$r = 0.42^*$	$F_{3,223} = 4^{\circ}$	$F_{2,223} = 8.2^*$	$F_{1,223} = 1.4$
LTT-wt	$r = 0.35^*$	$F_{3,223} = 5^{\circ}$	$F_{2,223} = 0.9$	$F_{1,223} = 0.0$

Age was assessed by regression analysis. Categorical measures (education level, job, gender) were assessed by ANCOVA, using age as covariate; $^*p < 0.001$; $^{\circ}p < 0.01$.

3. Results

3.1. PHES standardization sample

Males and females were homogeneously distributed throughout the age classes ($\chi^2 = 1.76$, $p = 0.88$); in contrast, an inverse association between age and education levels ($\chi^2 = 68$, $p < 0{,}001$) was detected, according to expectations, as no young individual had an education level lower than 5 years.

The LTT-t and the LTT-e were confirmed to be related to one another: an inverse hyperbolic-shaped relationship was likely ($p < 0.001$). Therefore, LTT performance was measured by error-weighted time, as follows: w-LTT = LTT-t * (1 + LTT-e/100) [22].

Age as well as 'educational level' (four levels) were predictors of all tests; 'job' (two levels) was a predictor for DST, TMT-B and SDT; in contrast, gender did not have any role on test performance (Table 2).

In the multivariate analysis, age and of education level were confirmed to be independent predictors for all tests except SDT and LTT-wt. In contrast, the job was irrelevant for all tests (Table 3).

Adjusting for age, a ceiling effect after 13 years of education was detected for DST, TMT-A and TMT-B, and a ceiling effect after 5 years of education was detected for SDT and w-LTT.

The predictive equations were parameterized on the relevant factors and used to compute the Z score, according to the formula: Z score = (measured value − expected value)/standard deviation of the residuals, after having verified the normal distribution of the residuals (Table 4).

Table 3
Predictors of psychometric tests on multivariate analysis

Test	Age	Education level	Job
DS	79.1*	16.8*	1.7
TMT-A	33.0*	9.7°	–
TMT-B	12.9*	9.8°	2.7
SD	31.7*	2.0	0.5
w-LTT	24.9*	4.9	–

F values on multivariate analysis $^*p < 0.001$; $^{\circ}p < 0.01$.

Table 4
Parameters of the predictive equations for the psychometric tests

Test	Intercept	Age (years)	Education 5 years	Education years	Education 13 years	Education ⩾ 17 years	SD
DST	56.57	−0.343	−7.710	−0.036	0	0	8.311
TMT-A	3.194	0.009	0.208	−0.0214[a]	0	0	0.363
TMT-B	4.035	0.009	0.368	−0.0249[a]	0	0	0.399
SDT	3.654	0.006	0.054	0	0	0	0.263
w-LTT	4.090	0.005	0.073	0	0	0	0.236

[a] *Note:* not significant.

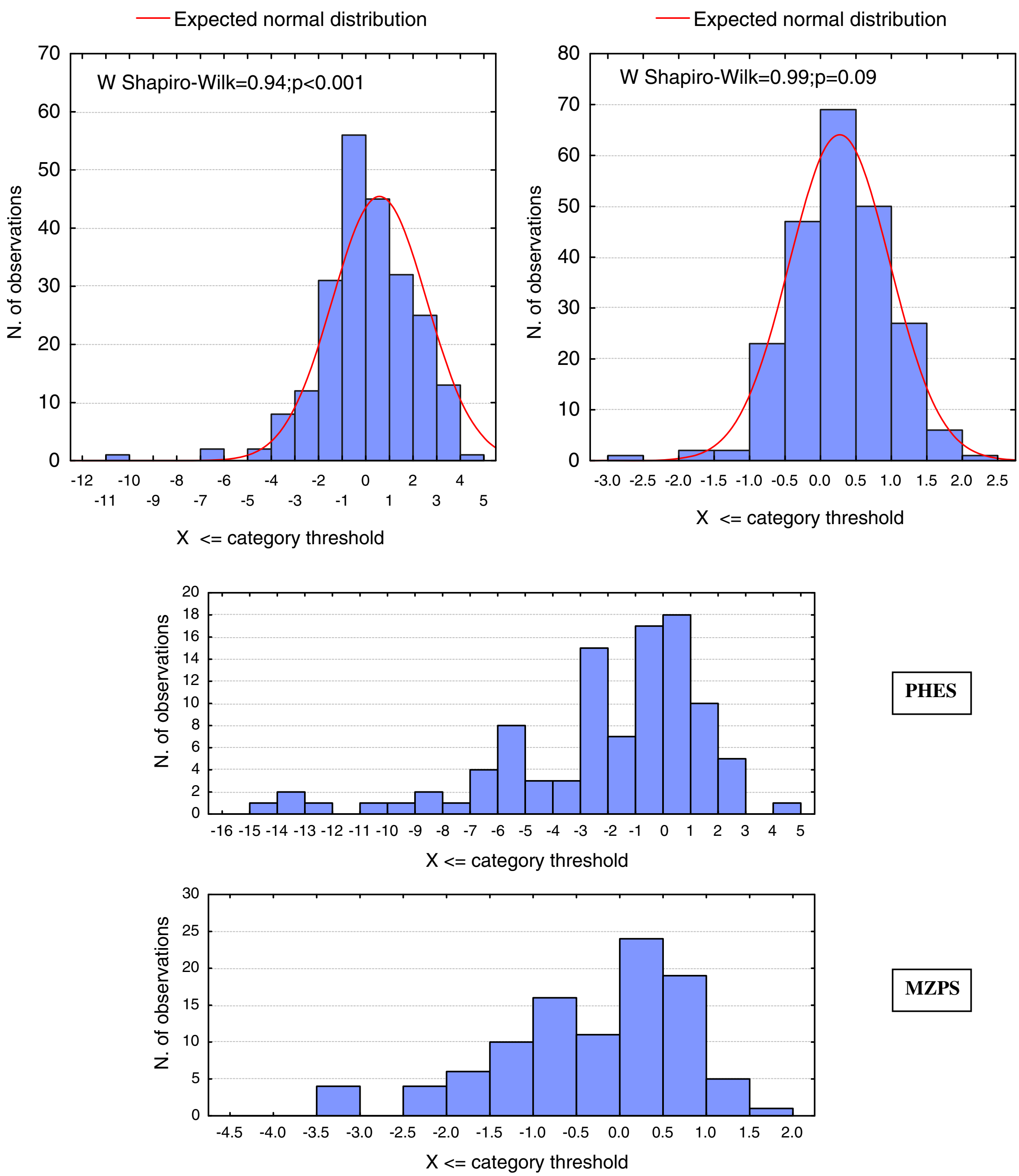

Fig. 1. Distributions of PHES and MPZS in normal individuals and in cirrhotic patients.

From the Z scores, both the PHES and the mean Z scores of the psychometric tests (MPZS) were calculated. Less than 2.5% of normal subjects had a PHES score $\leqslant -4$ or a MPZS $\leqslant -1$ (Fig. 1). These outliers lived in non-urban areas.

The repeatability of the tests was found to be limited (Table 5).

3.2. Patients with liver cirrhosis

A relevant number of patients with liver cirrhosis had low PHES scores (and MPZS) (Fig. 1). The PHES calculated on Italian norms was close to that calculated on the Spanish norms (Fig. 2). The score on the Germans norms was lower than that found on the Spanish and Italian norms (Table 6) and a reasonable cut-off for the PHES was found to be $\leqslant -4$ for our standardization. With this cut-off, the patients with low PHES amounted to 25. They were those with MPZS $\leqslant -1$.

Quantitative EEG was found to be altered in 31 subjects. Considering these patients as those having objective evidence of encephalopathy, ROC analysis supported the selection of a cut-off $\leqslant -4$ on the Italian norms that roughly corresponded to the cut-off of $\leqslant -5$ on the German norms (Table 7), thereby providing an independent criterion of evidence supporting the use of the cut-off $\leqslant -4$.

Further evidence of the validity of PHES Italian norms was provided by their tighter correlation with the EEG mean dominant frequency (assumed to be an overall measure of EEG activity) than the other norms (Table 8). As expected, psychometrical and EEG measures were related to the severity of liver failure (Table 9).

The diagnosis of MHE based on PHES alteration and the one based on EEG alteration were found to be associated one another ($\chi^2 = 10.7$ $p < 0.01$); however, their agreement was rather limited (73% Cohen's $K = 0.32$): 14 patients had both abnormal PHES and EEG, 59 had both normal PHES and EEG, 17 had abnormal EEG only, and 10 had abnormal PHES only.

Table 5
Repeatability of psychometric tests

Test	First measure	Second measure	DS of the paired differences
DS	43 ± 1.2[a]	45 ± 1.3[b]	8
TMT-A	39 ± 1.6	32 ± 1.3[b]	13
TMT-B	94 ± 5.8	71 ± 4.0[b]	50
SD	58 ± 1.5	53 ± 1.2[b]	8
w-LTT	76 ± 1.7	64 ± 1.7[b]	18
PHES	0.3 ± 0.2	1.2 ± 0.1[b]	1.5
MZS	0.16 ± 0.06	0.54 ± 0.06[b]	0.49

[a] Mean ± SEM.
[b] $p < 0.01$.

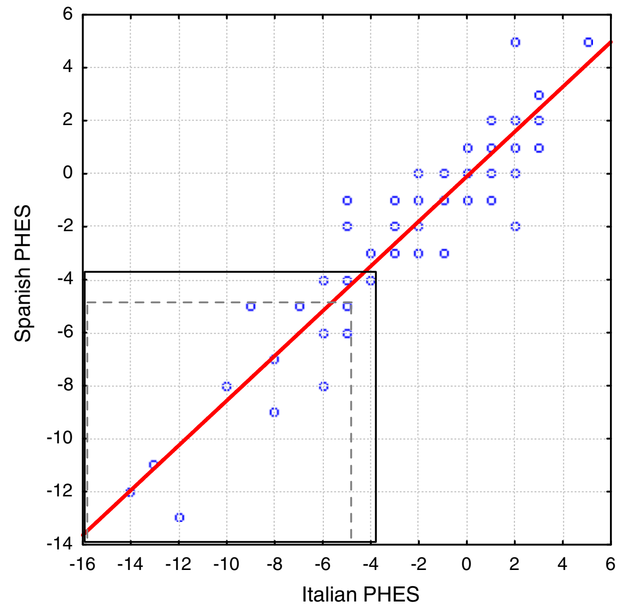

Fig. 2. Relationship between PHES calculated by Spanish and by Italian norms.

The patients with isolated PHES alteration, compared to those with isolated EEG alteration, had lower education level (7.9 ± 1.4 vs. 11.7 ± 1.2 years, $p < 0.05$), a trend towards a higher prevalence of alcohol misuse (67%, CI95% = 30–93% vs. 44%, CI95% = 20–70%, p: n.s.), while their age and liver function were similar (58 ± 4 vs. 58 ± 2 years and INR = 1.7 ± 0.2 vs. 1.7 ± 0.2, respectively).

The diagnosis of MHE on the basis of PHES classification showed good agreement with the alternative criterion of at least two out of TMT-A, TMT-B or DST [17] (Cohen's kappa = 0.65). A mean Z values of TMT-A, TMT-B, DST $\leqslant -1$ had sensitivity of 79% and specificity of 93% with respect to PHES classification (Cohen' $K = 0.70$ area under ROC = 0.995).

4. Discussion

The PHES was recommended as a preferential psychometric battery score to detect the peculiar mild cognitive impairment reflecting the condition of MHE [17]. However, (i) the battery was standardized only in Germany and Spain [16,20], (ii) different procedures were used to calculate the PHES, (iii) its repeatability was never tested and (iv) its comparison with an objective neurophysiological tool independent of patients' cooperation was never performed. This study reports the accurate procedure used to define PHES norms in Italy and provides data on PHES repeatability. The comparison of the Italian, Spanish and German PHES norms in a group of patients with liver cirrhosis proved the valid-

Table 6
Relationship between the PHES score calculated on the Italian norms and those calculated on the Spanish and Germans norms in 100 patients with liver cirrhosis

	Mean score ± SD	Pearson's r	Spearman's R	Difference of the scores	SD of the differences between the scores
Spanish PHES	−1.44 ± 3.40	0.94	0.89	−0.14, $p = 0.29$	1.32
German PHES	−3.55 ± 4.73	0.91	0.88	1.97, $p < 0.001$	2.07
Italian PHES	−1.58 ± 3.76	/	/	/	/

ity of the Italian standardization on the basis of the relationship with objective neurophysiologic findings.

The standardization group in this study comprised a convenience sample of subjects that had been stratified by age and gender. It was selected among individuals living in the community, both in rural and urban areas, and was tested at home by trained personnel. This way, it is reasonable to assume that it is at least as representative as the samples selected in Germany and Spain, even if the number of subjects that had been tested was lower than that tested in Germany and Spain, where control for such potential confounders had not been considered nor reported.

We confirmed the presence of a positive skew in test distribution that was already found in a previous study of our group [22] and in Germany. Therefore, log transform was used in accordance with the German study, but at odds with the Spanish one.

In accordance with the Spanish authors [20], we synthesized the information provided by time and errors of LTT, since these two measures were confirmed to be related to one another [22]. The Spanish approach consisted in summarizing time and errors, but this produces a rather arbitrary measure. Due to the nearly-inversely hyperbolic relationship between LTT time and errors, we preferred to weight time by errors by multiplying these two variables. Further study, however, is needed to have full insight into proper modeling of the relationship between errors and test performance time of LTT.

Age, education level and, for some tests, job were confirmed to be predictors of psychometric performance at univariate analysis [22,27]. At any rate, the multivariate approach reduced the number of significant predictors to age and education level, both in our study and in the Spanish and German ones [20,21,27]. In the German study, however, education was later excluded, both for the sake of simplicity and due to its negligible effect [27]. This approach might have been justified in Germany, but has poor applicability in countries where some population groups have low levels of education.

Our data proved that 'education' behaves as a factorial variable with a ceiling effect and the greater effect concerned the group who had had only five years of formal education [22].

The MPZS was found to have a normal distribution in the reference population; whereas the PHES was left-skewed because of the ceiling effect towards positive values that characterizes PHES computation. The consequences of this ceiling effect should be considered when PHES is used to evaluate interventional trial.

A rather surprising finding was the detection of a few normal subjects with abnormal low PHES. This finding did not correspond to the Spanish experience with a normal sample, yet larger than the one we had. This difference can be due to the fact that our sample was collected even in peripheral areas of the country, where the attitude or the cooperation to psychometric testing might have been lower than in the cities. In fact, the normal individuals with low PHES values actually came from these peripheral rural areas.

The repeatability of the tests comprising the PHES, and of the PHES itself was found to be limited, especially when considering our previous observation on some of these tests [22]. What appeared rather surprising was the detection of an improved performance on retesting, even if retesting was performed after a long time from the first measuring. Such a finding proves that a control group is necessarily required in any clinical trial using PHES as an outcome, and possibly any psychometric index.

The use of the PHES in the cirrhotic population corroborated the opinion that a value $\leqslant -4$ is the proper cut off for the detection of the 'mild cognitive impairment' reflecting MHE. Such a value was found (i) to include normal individuals only exceptionally and (ii) to provide a discrimination between a cirrhotic patient with or without EEG abnormalities (an external criterion of brain dysfunction) roughly comparable to the cut-off $\leqslant -5$ of the PHES computed with the German norms. This can be due to (i) the way in which the LTT is computed (one variable Z score in Spain and Italy, two

Table 7
Area under ROC curves, sensitivity and specificity depending on PHES cut-off and different PHES norms

	PHES German norms	PHES Spanish norms	PHES Italian norms
AUC	0.72 ± 0.052	0.76 ± 0.048	0.76 ± 0.048
Score $\leqslant -4$ sensitivity/ specificity	58/66	39/88	45/85
Score $\leqslant -5$ sensitivity/ specificity	48/76	35/91	42/88

The MPZS provided an AUC of 0.78 ± 0.047; its sensitivity/specificity were 45 and 85, respectively, for the cut-off $\leqslant -1$.

Table 8
Matrix of correlations across the EEG mean dominant frequency, the PHES calculated according various norms and the psychometric tests comprising the PHES

PHES (Italian norms)	0.37 $p < 0.0001$	DST Z score	0.22 $p = 0.025$
MPZS (Italian norms)	0.37 $p < 0.0001$	TMT-A Z score	0.33 $p = 0.001$
PHES (Spanish norms)	0.33 $p = 0.001$	TMT-B Z score	0.23 $p = 0.021$
PHES (German norms)	0.31 $p = 0.002$	SDT Z score w-LTT Z score	0.33 $p = 0.001$ 0.34 $p = 0.001$

Significant also after Bonferroni's adjustment for multiple comparisons.

variables Z score in Germany), (ii) to the different way of managing the educational level (education-adjusted values in Italy and Spain vs. non-educated adjusted values in Germany), (iii) different schooling in Germany.

The agreement between Spanish and Italian norms is a clue supporting the validity of both of them, since they refer to two countries that share similar cultural and social features. In addition, the relationship of PHES and its composing psychometric tests with quantified EEG findings provided external evidence of their validity.

The agreement between psychometric investigation and EEG findings was, however, incomplete. Such a well-known fact [26,28] might depend on: (1) the maintenance of cognitive competence, despite mild organic neuronal dysfunction in well-trained intelligent individuals, (2) the relative insensitivity of the EEG to subcortical dysfunction (*per se* the EEG reflects only cortical neuronal activity). In line with this interpretation, the disagreement between cognitive and neurophysiologic findings concerned mainly the two extremes of low-educated alcoholic misusers (who had a higher probability of low cognitive performance) and highly educated abstinent people (who had a higher probability of maintaining cognitive performance even when the EEG slowed).

Table 9
Relationship of psychometric and neurophysiologic variables with liver function

	Child	Meld
PHES (Italian norms)	$R = -0.31$	$R = -0.30$
MPZS (Italian norms)	$R = -0.34$	$R = -0.27$
DS Z score	$R = -0.33$	R = −0.21
TMT-A Z score	$R = -0.31$	$R = -0.26$
TMT-B Z score	$R = -0.22$	$R = -0.30$
SD Z score	$R = -0.12$	$R = -0.12$
w-LTT Z score	$R = -0.36$	$R = -0.22$
MDF	$R = -0.37$	$R = -0.36$

Using Bonferroni adjustment for multiple comparisons, only MDF and w-LTT vs. Child were significant. The use of adjustment for multiple comparison can be inadequate since the variables are not independent of each other.
Plain comparison without adjustment gave significant values for all tests except SDT, DST vs. Meld and TMT-B vs. Child.

The finding that both psychometric and neurophysiologic investigation were confirmed to be related with liver dysfunction [4,21], is in line with the well established knowledge that both are the expression of hepatic encephalopathy, i.e. brain dysfunction due to liver failure and/or shunt.

Finally, the recognition that TMT-A, TMT-B or DST alterations are good predictors of the overall PHES alteration supports the use of at least two of the above tests in simplified settings [17].

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