Disruption of Smooth Pursuit Eye Movements in Cirrhosis: Relationship to Hepatic Encephalopathy and its Treatment

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Keywords: electroencephalography; electro-oculography; healthy volunteers; psychometry

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List of Abbreviations:

SPEM: smooth pursuit eye movements; CFF: critical flicker frequency; HMST: Hodkinson mental state test; MMST: Mini-mental state' test; NCT-A: Number Connection Test A, NCT-B: Number Connection Test B; DS: digit symbol test; DC: digit copying test; EEG: electroencephalogram; TRMS: total root mean square; RMS: root mean square; SRMS: SPEM root mean square; HE: hepatic encephalopathy.

Financial Support: none

Smooth pursuit eye movements (SPEM) are the conjugate movements used to track the smooth trajectory of small dots. Jerky or 'saccadic' ocular pursuit has been reported in patients with cirrhosis, but no formal assessment of SPEM has ever been undertaken. The aim of this study was to evaluate SPEM in patients with cirrhosis and varying degrees of hepatic encephalopathy. The patient population comprised 56 individuals (31 men: 25 women) of mean (range) age 51.1 (25-70) years, with biopsy-proven cirrhosis, classified, using clinical, electroencephalographic and psychometric variables, as either neuropsychiatrically unimpaired or as having minimal or overt hepatic encephalopathy; patients were further categorized in relation to their treatment status. The reference population comprised 28 healthy volunteers (12 men: 16 women) of mean (range) age 47.3 (26-65) years. SPEM was assessed using an electro-oculographic technique. Visual inspection of the SPEM recordings showed clear disruption of smooth pursuit in the patients with minimal hepatic encephalopathy, and more pronounced disruption, if not complete loss of smooth pursuit, in patients with overt hepatic encephalopathy. The differences observed in quantifiable SPEM indices between the healthy volunteers/unimpaired patients and those with overt hepatic encephalopathy were significant ($p < 0.05$). In conclusion, SPEM performance is impaired in patients with hepatic encephalopathy in parallel with the degree of neuropsychiatric disturbance: the pathophysiology of these changes in unknown but retinal, extrapyramidal and attentional abnormalities are likely to play a role. Treatment status confounds the classification of neuropsychiatric status and should be taken into account when categorizing these patients.

Hepatic encephalopathy is characterized by deficits in cerebral neurotransmission primarily of the glutamatergic, GABAergic and endogenous opioid systems (1). Low-grade astrocyte swelling, which results in alterations in glio-neuronal communication, is also thought to play a role in the genesis of this syndrome (2). Similar low-grade swelling occurs in the retinal glial (Müller) cells, resulting in the development of morphological changes that mirror those of the cerebral astrocytes. The term 'hepatic retinopathy' has been coined to describe these histopathological alterations (3). The presence of hepatic retinopathy is associated with a number of functional abnormalities (4), including an alteration in critical flicker frequency (CFF), which is defined as the highest frequency at which the flicker of a flickering light source can be detected (5). The exact relationship between the changes in the retinal and cerebral glial cells has not been defined but it has been suggested that alteration in the CFF threshold may serve as a diagnostic marker for hepatic encephalopathy (5).

One of the key factors determining CFF integrity is the initial perception of velocity, or movement, across the retina (6). This facility is also key to the execution of smooth pursuit eye movements (SPEM), which are the conjugate movements used to track, or pursue, the smooth trajectory of small dots. Impaired pursuit occurs when individuals cannot track the dot trajectory accurately. In these instances, the trajectory of the eye is no longer smooth but interspersed with anticipatory and corrective catch-up saccades resulting in a pattern of jerky or cogwheel pursuit (7). Unilateral or bilateral pursuit abnormalities can be observed in the presence of structural abnormalities of the pursuit pathways in the cerebral cortex, pons and cerebellum (7) and in situations characterized by disruption in cerebral neurotransmission, for example, in Parkinsonism (8) and schizophrenia (9) and during medication with various neuroactive drugs (7). Although 'saccadic' ocular pursuit has been observed in patients with cirrhosis, particularly in those with hepatic encephalopathy (10), no formal assessment of SPEM has been undertaken in this patient population.

Difficulties arise in delineating relationships between variables such as SPEM and the neuropsychiatric abnormalities observed in patients with chronic liver disease, particularly in determining the causality of any identified association. This reflects, at least in part, the fact that there is no reference or 'gold' standard for the diagnosis of hepatic encephalopathy (11) but also the fact that no guidance is available on the classification of patients on long–term maintenance treatment (11). Previous workers have either tended to exclude treated patients from their studies (5) or else to classify them as having overt hepatic encephalopathy irrespective of their status on the day of study (12). Thus, there is an obvious need to obtain a consensus on whether long-term maintenance treatment should be taken into account as a separate variable for classification purposes.

The aim of the present study was, therefore, to determine the integrity of SPEM in patients with cirrhosis with varying degrees of neuropsychiatric impairment controlling for the possible confounding effect of long-term maintenance treatment for hepatic encephalopathy.

Patients and Methods

Study Populations. The patient population comprised 56 individuals (31 men: 25 women) of mean (range) age 51.1 (25-70) years, with biopsy-proven cirrhosis. The aetiology of the liver lesion was determined on the basis of clinical, laboratory and histological variables. The functional severity of the liver injury was assessed using Pugh's modification of the Child's grading system (13).

Patients were excluded from the study if they were under 16 or over 70 years of age, could not speak English or obey spoken commands, had misused alcohol in the preceding 3 months, had a history of insulin-dependent diabetes mellitus, significant head injury, cerebro-vascular disease or arterial hypertension, or had impaired eye muscle function or visual acuity of less that 6/6, in either eye, with corrective lenses, or were taking neuroactive drugs.

The reference population comprised 28 healthy volunteers (12 men: 16 women) of mean (range) age 47.3 (26-65) years. None had a history, clinical or laboratory evidence of alcohol misuse or chronic liver disease; none drank alcohol in excess of 20 g/day, was on long-term medication, had defective eye muscle function or impaired visual acuity.

Neuropsychiatric Assessment. All patients were clinically stable at the time of the study. Details of their neuropsychiatric history were recorded and confirmed by reference to a third party, usually a relative, in every case. Patients were examined and their mental state assessed using the West Haven criteria (14), the Hodkinson mental state test (HMST) (15) and a modified version of the 'Mini-mental state' test (MMST) (16). Psychometric performance was assessed, under standardized conditions, by the same observer, using Number Connection Tests A (NCT-A) and B (NCT-B) (14), the digit symbol (DS) subtest of the Wechsler Adult Intelligence Scale (17) and the digit copying (DC) subtest of the Kendrick battery (18). Electroencephalograms (EEGs) were recorded, eyes closed, in a condition of relaxed wakefulness, using silver-silver chloride electrodes placed according to the International

10-20 system; the traces were analysed visually by a single observer blinded to the subjects' clinical status.

SPEM Assessment. Assessments were carried out, in a darkened room, by an operator who was blinded to the clinical status of the subject. An EEG electrode was placed at both the inner and outer canthus of each eye to record eye movements (19). Subjects were asked to sit comfortably with their eyes at approximately 30 cm from the computer monitor, and to eye-track the progress of a computer generated, 1 cm diameter, white dot across the screen, without moving their head. The dot moved in a horizontal, pseudo-random, sinusoidal fashion at frequencies increasing from 0.2 Hz to 0.5 Hz at 0.1 Hz intervals, with interspersed pauses between frequency changes. Two complete sinusoids were randomly embedded within each set of dot movements for purposes of analysis (Figure 1). The tracking positions of each eye were recorded and then superimposed on the digitally filtered trace of the dot (Figure 1).

If the eye voltages exceeded the range of the analogue-to-digital converter no analysable data could be obtained; recordings containing less than 90% of analysable trace were excluded. SPEM can be differentiated from saccades and other fast eye movements on the basis of velocity; for purposes of this study, eye movements were qualified as SPEM if their velocity was below five times the maximum dot velocity.

The following indices were calculated, over the period of the two full sinusoids, separately for left and right eye and then averaged for each dot velocity:

- *SPEM time*: the fraction of SPEM in the tracing, which ranges from 0 (none of the tracing qualified as SPEM) to 1 (all of the tracing qualified as SPEM). This index is a measure of tracking ability or compliance with the task as it represents the amount of time spent in appropriate tracking of the dot as opposed to fast eye movements such as saccades.

- *Total root mean square (TRMS):* root mean square (RMS) of the error in each eye position compared to the dot position. TRMS was normalized to the RMS of the dot position for each sample used:

$$TRMS = [\Sigma (\text{eye position} - \text{dot position})^2] / [\Sigma (\text{dot position})^2]$$

This index is a measure of the error between the positions of the eye and dot both during smooth pursuit movement and faster eye movements; it thus provides a measure of both tracking ability and tracking accuracy.

- *SPEM root mean square (SRMS)*: RMS of the error in each eye position compared to the dot position on the sections of the tracing qualified as SPEM. SRMS was normalized to the RMS of the dot position for each sample used:

$$SRMS = [\Sigma (\text{eye position} - \text{dot position})^2] / [\Sigma (\text{dot position})^2]$$

This index is a measure of the error between the position of the eye and the dot in the sections of the tracing qualified as SPEM; it thus provides a measure of tracking accuracy.

- *Gain*: the sum of the ratios of the eye and dot velocities when the dot velocity exceeds a threshold of 0.25 times its maximum in the sections of the tracing qualified as SPEM. The instantaneous Gain was normalized for dot velocity for each sample used; the sum of the instantaneous Gains was re-normalized by dividing by the number of samples used:

$$Gain = \Sigma [(\text{eye velocity}) / (\text{dot velocity})] / (\text{Count of samples})$$

This index is a measure of the eye/dot velocity match and hence of tracking accuracy (20). Tracking would be qualified as abnormal both if Gain <1 - slow eye movement; the eye lags behind the dot - and if Gain >1 - fast eye movement; the eye anticipates dot motion. In order to facilitate correlation analysis, an additional parameter, Gain2, ranging from zero to 1, which qualified abnormal performance in one direction only, was defined:

$$Gain2=(1-Gain)^2$$

Repeat studies were undertaken in 15 patients to monitor progress over time and/or the response to treatment with a non-absorbable disaccharide.

Patient Classification. Age-and education-adjusted normative data for the psychometric tests used in this study are not available for the British population. NCT-A and NCT-B results were, therefore, scored in relation to age- and education-adjusted reference values obtained from a healthy Italian population (21) and age-adjusted reference values obtained from a healthy German population (22); the DS was scored with reference to age-adjusted values obtained from a healthy German population (22). The adjusted test results were considered abnormal if they exceeded two standard deviations from the mean. The DC was defined as abnormal below a fixed score threshold of 124, corresponding to the completion of ≤ 100 copies in 120 seconds (18). Overall psychometric performance was classified as impaired if two or more of the individual tests were abnormal. The EEG was considered abnormal if the central-posterior mean frequency was < 9 Hz and/or there were significant bursts of slow activity in the theta/delta range.

Neuropsychiatric status on the day of the study was classified as (i) *unimpaired*: individuals who had no history or clinical evidence of hepatic encephalopathy and no defining EEG or psychometric test abnormalities; (ii) *minimal hepatic encephalopathy*: individuals who showed no clinical evidence of hepatic encephalopathy but had an abnormal EEG and/or impaired psychometric performance; (iii) *overt hepatic encephalopathy*: individuals with clinically evident neuropsychiatric disturbances (14); these patients invariably demonstrated EEG and/or psychometric abnormalities. Patients were further classified, on the basis of long-term treatment with a non-absorbable disaccharide, as either *treated* or *untreated*.

Statistical Analysis. The distributions of the neuropsychiatric variables, the laboratory parameters and the SPEM indices were tested for normality using the Shapiro-Wilk's W test. Variables that were not normally distributed were Ln transformed or 1/Ln transformed and re-

tested for normality. Ln NCT-A, 1/Ln NCT-B, DS, Ln SRMS, Ln TRMS, and Ln Gain2 were normally distributed at all dot frequencies. Differences between normally distributed group variables were examined by one-way ANOVA/ANCOVA which included an age-adjustment; subsequent between groups comparisons were performed, where appropriate, using the Scheffé test. The results were represented as means and 95% confidence intervals (bars). Differences between non-normally distributed group variables were examined using the Kruskal-Wallis test; subsequent between groups comparisons were performed, were appropriate, using the Mann-Whitney U test and applying the Bonferroni correction for multiple comparisons. The results were represented as Box and Whisker plots (mean and standard error [box] and standard deviation [whisker]). Correlations between SPEM indices and the other variables were tested using the Pearson r.

Ethics. The study was conducted according to the Declaration of Helsinki (Hong Kong Amendment) and Good Clinical Practice (European guidelines). The protocol and amendments were submitted to, and approved by, the Royal Free Hospital Ethics Committee. All participating subjects provided written, informed consent.

Results

The aetiology of the cirrhosis was alcohol in forty-six (82%) of the 56 patients, hepatitis C in five (9%), cryptogenic in three (5.4%) and biliary in two (3.6%). Functionally, 32 (57.1%) were Child's Grade A, 21 (37.5%) Child's Grade B, and three (5.4%) Child's Grade C.

On the day of study, 11 (19.6%) of the 56 patients were classified as neuropsychiatrically unimpaired, 20 (35.7%) as having minimal hepatic encephalopathy and 25 (44.6%) as having overt hepatic encephalopathy; nine of the individuals classified as having minimal and eight classified as having overt hepatic encephalopathy had experienced one or more episodes of overt hepatic encephalopathy and were on long-term maintenance treatment with a non-absorbable disaccharide (Table 1).

Demographic and Neuropsychiatric Variables. The patients and healthy volunteers were of comparable age overall (Table 1).

There were no significant differences in psychometric and EEG performance between the healthy volunteers and the cirrhotic patients classified as neuropsychiatrically unimpaired (Table 1). Patients with minimal hepatic encephalopathy performed significantly less well than the healthy volunteers and the unimpaired cirrhotic patients on a number of individual tests but significantly better than patients with overt hepatic encephalopathy ($p<0.05$; Table 1). Patients with overt hepatic encephalopathy performed significantly less well than healthy volunteers and unimpaired cirrhotic patients on most individual tests ($p<0.05$; Table 1). In general treated patients showed less psychometric/neurophysiological impairment than their untreated counterparts (Table 1; Figure 2).

SPEM Recording and Analysis. Overall, 299 (89%) of the 336 initial individual frequency recordings were suitable for analysis. Only the data recorded at 0.4 and 0.5 Hz are presented. No perceptible differences were observed, on visual inspection, between the SPEM recordings obtained from patients who were neuropsychiatrically unimpaired and the healthy volunteers

(Figures 3a & b). However, obvious impairment in pursuit movement was observed in the recordings obtained from the patients with both minimal and overt hepatic encephalopathy (Figures 3c & d).

Significant differences were observed in measured SPEM indices between the healthy volunteers and the patients with cirrhosis both in relation to their neuropsychiatric and treatment status.

In the total patient population of 56 individuals, progressive impairment in neuropsychiatric performance was associated with a parallel deterioration in SPEM performance evidenced by increases in TRMS and SRMS together with decreases in Gain, Gain2 and SPEM time (Table 2; Figure 4a). The patients with overt hepatic encephalopathy performed significantly less well that both the healthy volunteers and the unimpaired cirrhotic patients (Table 2: Figure 4a).

Seventeen of the 56 patients had a history of overt hepatic encephalopathy and were on maintenance treatment with a non-absorbable disaccharide; of these nine were categorized as having minimal and eight as having overt hepatic encephalopathy, based on their current status. Subcategorization in relation to treatment status produced a much more complex picture of the relationship between SPEM performance and neuropsychiatric status (Table 2; Figure 4b). Thus significant differences were observed in SPEM variables between the *untreated* patients with overt HE and both the healthy volunteers and the unimpaired cirrhotic patients. However, there were no significant difference between SPEM variables in the *treated* patients with overt HE and the other patient groups (Table 2; Figure 4b). In contrast the patients with minimal hepatic encephalopathy on treatment performed less well than their untreated counterparts although the intergroup difference were not significant (Table 2; Figure 4b).

Significant correlations were observed between SPEM variables and the mental state test scores and psychometric test results, but not with the Pugh score or the EEG mean frequency (Table 3). There were no significant differences in neuropsychiatric and SPEM variables in relation to the aetiology of the liver injury.

Changes were observed in pursuit behaviour in the 15 patients studied over time/in response to initiation of treatment, which mirrored the changes in clinical state and neuropsychometric performance although, in general, the changes in SPEM variables occurred earlier (Table 4; Figure 5).

Discussion

Abnormalities in smooth pursuit were observed in patients with hepatic encephalopathy reflecting impairment of both tracking ability and accuracy. The degree of SPEM impairment paralleled the changes in neuropsychiatric status suggesting a common pathophysiology. Treatment status had a confounding effect on the classification of neuropsychiatric status.

SPEM and the Degree of Hepatic Encephalopathy. There is no 'gold standard' for the diagnosis of hepatic encephalopathy. This creates significant difficulties in the evaluation of abnormalities such as those observed in SPEM, which are clearly related to the presence of neuropsychiatric dysfunction and may have diagnostic utility. Visual inspection of the SPEM recordings showed clear disruption of smooth pursuit in the patients with minimal hepatic encephalopathy, with interspersion of both corrective catch-up and anticipatory saccades, and more pronounced disruption, if not complete loss of smooth pursuit, in patients with overt hepatic encephalopathy. However, use of more objective performance measures did not provide the same degree of differentiation and grading thresholds for SPEM performance, in relation to the degree of neuropsychiatric impairment, could not be defined.

There are a number of possible explanations for the lack of quantifiable differences in SPEM performance between the population subgroups despite the obvious visual differences. The most obvious of which is that the eye detects differences in the traces, which are not captured by the numerical analysis. The system for quantifying the SPEM traces assessed the most obvious measurement variables but clearly there is more to be gained from the numerical analysis. Other factors, which might help explain the lack of quantitative distinction between population subgroups, include the rigor of the statistical analysis; the intrinsic limitations of the system used to assess neuropsychiatric status in this patient population and the fact that abnormalities of the defining variables arise at differing stages of disease progression on an individual basis.

SPEM Performance in Relation to Treatment Status. There are no guidelines for classifying neuropsychiatric status in patients on long-term maintenance treatment for hepatic encephalopathy. At any given time these individuals, if tested, may still show evidence of overt hepatic encephalopathy, may appear clinically normal but with impaired psychometric and electrophysiological performance, thereby fulfilling the diagnostic criteria for minimal hepatic encephalopathy, or may even appear neuropsychiatrically unimpaired with no discernable clinical, psychometric or electrophysiological abnormalities. Significant difficulties therefore arise in determining how these patients should be categorised, particularly in studies designed to test the potential diagnostic utility of established or novel test systems.

In the best of previous studies workers have tended to determined status 'on the day of study' using a combination of clinical, psychometric and/or electrophysiological variables choosing to either exclude all treated patients (5) or else to classify them as having *overt* hepatic encephalopathy irrespective of their current status (12). Both these approaches are pragmatic and have merit but do not provide data that are applicable to the mixed population of treated and untreated patients encountered in a clinical setting.

In the present study account was taken of the potential confounding effect of maintenance treatment on the classification of neuropsychiatric status and evidence obtained that the distinction between the treated and untreated patients clearly had significant implication for classification purposes. Treatment status should, therefore, be included as a separate variable when classifying neuropsychiatric status in this patent population

There was also evidence in the present study that the various changes in cerebral function observed in patients with hepatic encephalopathy may not occur synchronously and may improve at differing rates following treatment. Thus, the untreated patients with minimal hepatic showed *greater* impairment of psychometric performance but *less* disruption of SPEM

performance than their treated counterparts while in the serial studies SPEM parameters seemed to improve earlier than other neuropsychiatric variables in response to treatment.

SPEM and Hepatic Encephalopathy: Pathophysiology. SPEM abnormalities were observed in patients with hepatic encephalopathy reflecting impairment of both tracking ability and accuracy. The functional correlates of the abnormalities observed in SPEM performance and the relative utility of the indices used to qualify smooth pursuit remain generally unclear (23). Nevertheless, there are number of possible explanations for the pursuit abnormalities observed in patients with cirrhosis exhibiting neuropsychiatric change:

i) ***Impairment in the motor control of eye movements***. In 1976 Plum and Hindfelt (24) referred to 'abnormal ocular motor and skeletal muscle movement control' as features typical of chronic hepatic encephalopathy. In 1996 Krieger and colleagues (10) identified abnormalities of saccadic ocular pursuit in 26 (51%) of 51 consecutive patients with cirrhosis with no clinical evidence of hepatic encephalopathy; the abnormalities were more common in those with a past history of overt hepatic encephalopathy. Principle component analysis classified the ocular pursuit abnormalities, together with incoordination, alterations of muscle tone and tremor, into a category of subcortical motor performance, which the authors claimed expressed the functioning of the striatopallidonigral and cerebellar systems controlling movement and posture (10). The neurological abnormalities Kreiger and his colleagues (10) observed were assessed as dichotomised variables and no further information on the eye movement abnormalities, in particular no formal assessment of ocular motor function, was included

None of the patients in the present study had clinical evidence of oculomotor paresis or dysfunction. However, the changes observed in smooth pursuit might reflect more subtle abnormalities of motor control. Joebges and coworkers (25) have, for example, recently shown that the abnormalities observed in patients with hepatic encephalopathy in the

execution of diadochokinetic limb movements are due to a delay in movement initiation rather than a reduction in movement velocity. A deficit in movement initiation, perhaps reflecting dysfunction in the neural loops connecting the prefrontal cortex and the basal ganglia, would prolong the latency of the onset of tracking and could be a determinant in the generation of early corrective catch-up saccades.

ii) ***Hepatic retinopathy***. Pursuit eye movements allow maintenance of the image of a moving object on the fovea and are controlled by visual feedback (26). Very little information is available currently on the functional correlates of the post-mortem and electro-retinographic abnormalities described in the retinas of individuals with cirrhosis (3,4). Significant lowering in the CFF threshold has been observed in patients with minimal hepatic encephalopathy and attributed to the presence of hepatic retinopathy (5). However, retinal function was not examined directly in this study (5) and although CFF undoubtedly reflects the efficacy of the visual apparatus it also reflects the functional state of the cerebral cortex. None of the patients included in the present study had defective vision on routine testing. Nevertheless the presence of subtle defects in visual feedback relating to the presence of hepatic retinopathy cannot be excluded. Studies combining assessments of retinal function, SPEM and CFF are clearly needed.

iii) ***An attentional deficit***. Abnormalities in smooth pursuit are commonly found in patients with schizophrenia and are attributed, by some workers, to the presence of global attentional and inhibitory dysfunction (23, 27, 28). This attribution is supported by the observation that SPEM abnormalities can be reversed in schizophrenic patients, to a degree, by attention enhancing techniques, and by the fact that at least one of the pathological components of SPEM performance, task-inappropriate intrusion of anticipatory saccades, has been conceptualised as a failure of inhibitory control (29, 30). However, the role of attentional and

inhibitory dysfunction in the genesis of smooth pursuit abnormalities has been questioned, as adults with attention-deficit/hyperactivity syndrome do not exhibit pursuit abnormalities (30).

There is now considerable evidence that patients with cirrhosis, particularly those with evidence of hepatic encephalopathy, exhibit attentional dysfunction, more specifically, deficits of complex attentional skills (31-35). Their inability to disengage previously focused attention (35) may play a role in their inability to track small moving objects.

It is highly likely that the abnormalities observed in smooth pursuit in patients with hepatic encephalopathy are multifactorial in origin and that the relative importance of each factor may vary in a given individual at different stages of their disease.

Conclusions. Quantifiable abnormalities are observed in smooth pursuit movement in patients with cirrhosis, which parallel the changes observed in neuropsychiatric status. The pathophysiology of the abnormalities in SPEM is unknown but impairment of the motor control of eye movements, functional abnormalities associated with the development of hepatic retinopathy and attentional dysfunction are all likely to play a role. Classification of the neuropsychiatric status of patients with cirrhosis, which is key to the assessment of the diagnostic utility of variables such as smooth pursuit, should take account of the patients' treatment status, a taxonomic category that has, to date, received little, if any, attention.

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Table 1. Demographic and Assessment Variables in the Reference Population and in the Various Patient Populations

Study population (n)		*Age (yr)	Gender (% Male)	Pugh's score (13) (5-15)	Mental state (14) (0-IV)	HMST (0-10)	MMST (0-38)	*NCT-A (sec)	NCT-A abnormal (n;%)	*NCT-B (sec)	NCT-B abnormal (n;%)	*DS (n correct)	DS abnormal (n;%)	DC (score)	DC abnormal (n;%)	EEG (Hz)	EEG abnormal (n;%)
Healthy volunteers (28)		47.3 (26-65)	43	-	0	9.7 (8-10)	36.3 (32-38)	33.6 (18-60)	0 (0%)	71.8 (30-120)	0 (0%)	61.4 (35-90)	0 (0%)	168.5 (60-208)	3 (11%)	^^10.0 (8.5-12.0)	1 (3.5%)
Cirrhosis: unimpaired (11)		47.6 (36-65)	73	5.4 (5-7)	0	9.8 (9-10)	35.6 (33-38)	24.5 (19-28)	0 (0%)	69.8 (47-140)	0 (0%)	57.9 (40-78)	0 (0%)	174.3 (133-208)	0 (0%)	9.9 (9-12)	0 (0%)
Cirrhosis: Minimal HE	Minimal HE All (20)	49.0 (25-69)	50	6 (5-8)	0	9.2 (7-10)	34.3^{+} (26-38)	34.6 (15-70)	0 (0%)	112.6^{+} (35-300)	2 (10%)	49.2^{++} (27-77)	0 (0%)	144.6 (97-208)	6 (30%)	$8.9^{++,\#}$ (6.5-11)	13 (65%)
	Minimal HE Untreated (11)	42.2 (25-66)	55	6.3 (5-8)	0	9 (7-10)	33.5 (26-37)	37.4 (15-70)	0 (0%)	114.2 (35-300)	2 (10%)	48.6 (34-77)	0 (0%)	141.8 (97-208)	4 (36%)	8.7^{++} (6.5-11)	7 (63%)
	Minimal HE Treated (9)	57.4 (41-69)	44	5.7 (5-7)	0	9.4 (8-10)	35.2 (33-38)	31.2 (19-42)	0 (0%)	110.6 (57-178)	0 (0%)	49.9 (27-64)	0 (0%)	148.1 (106-208)	2 (22%)	9.1 (7.5-10.5)	6 (67%)
Cirrhosis: Overt HE	Overt HE All (25)	54.3 (32-70)	52	7.3 (5-13)	0-II	$8.7^{++,\#\#}$ (6.5-10)	$30.7^{++,\#\#,\lozenge\lozenge}$ (17-37)	$55.2^{++,\#\#,\lozenge\lozenge}$ (30-115)	7 (28%)	$176^{++,\#\#,\lozenge\lozenge}$ (68-300)	10 (42%)	$33.9^{++,\#\#,\lozenge\lozenge}$ (8-58)	12 (50%)	$105.2^{++,\#\#,\lozenge\lozenge}$ (60-208)	20 (80%)	$8.5^{++,\#\#}$ (5.5-12)	13 (54%)
	Overt HE Untreated (17)	51.9 (32-70)	59	7.6 (5-13)	0-II	8.7^{+} (6.5-10)	$30.3^{++,\#}$ (17-37)	$56.9^{++,\#\#,\ddagger,\bullet}$ (30-115)	6 (35%)	$^197.4^{++,\#\#,\ddagger}$ (75-300)	9 (56%)	$33.8^{++,\#\#}$ (8-58)	9 (52%)	$100.6^{++,\#\#,\bullet}$ (61-135)	14 (56%)	$8.4^{++,\#\#}$ (5.5-10.5)	9 (53%)
	Overt HE Treated (8)	59.5^{Δ} (45-70)	38	6.6 (5-8)	0-II	$8.7^{++\#\#}$ (8-9)	$31.4^{++,\#\#}$ (28-35)	$51.5^{++,\#\#,\square}$ (30-77)	1 (12.5%)	$133.7^{++,\#}$ (68-300)	1 (12.5)	$34.2^{++,\#\#}$ (13-54)	3 (37.5)	115^{+} (60-208)	6 (75%)	8.9 (6.5-12)	4 (50%)

Data are crude – non Ln transformed – and are expressed as mean (range) or absolute number (%); *normal or normalized variables; ^n = 16; ^^n = 27

Significance of the differences between healthy volunteers and patients with minimal / overt HE: $^{+}p<0.05$; $^{++}p<0.02$
Significance of the differences between unimpaired patients and patients with minimal / overt HE: $^{\#}p<0.05$; $^{\#\#}p<0.02$
Significance of the differences between patients with minimal and overt HE: $^{\lozenge}p<0.05$; $^{\lozenge\lozenge}p<0.02$
Significance of the differences between patients with untreated minimal HE and untreated overt HE: $^{\ddagger}p<0.02$
Significance of the differences between patients with untreated minimal HE and treated overt HE: $^{\Delta}p<0.02$
Significance of the differences between patients with treated minimal HE and untreated overt HE: $^{\bullet}p<0.02$
Significance of the differences between patients with treated minimal HE and treated overt HE: $^{\square}p<0.05$

Table 2. SPEM Indices in Healthy Volunteers and in Cirrhotic Patients, by Degree of Current Neuropsychiatric and Treatment Status

SPEM variables	Healthy volunteers (n = 26 at 0.4; 25 at 0.5)	Cirrhotic patients						
		Unimpaired (n = 11)	Minimal HE All (n = 16)	Minimal HE Untreated (n = 8)	Minimal HE Treated (n = 8)	Overt HE All (n = 22 at 0.4 25 at 0.5)	Overt HE Untreated (n = 14 at 0.4; 17 at 0.5)	Overt HE Treated (n=8)
0.4 SPEM time	0.99±0.015	0.99±0.01	0.98±0.02	0.98±0.02	0.98±0.02	0.98±0.01$^{\Delta\Delta,+}$	0.98±0.02^^	0.99±0.01
*0.4 TRMS	0.06±0.07	0.05±0.04	0.11±0.10	0.10±0.12	0.13±0.09	0.12±0.07$^{\Delta,+}$	0.14±0.08$^{\wedge,\ddagger}$	0.08±0.04
*0.4 SRMS	0.06±0.06	0.05±0.04	0.10±0.09	0.08±0.10	0.12±0.09	0.11±0.07$^{\Delta,+}$	0.14±0.08$^{\wedge,\ddagger}$	0.07±0.04
0.4 Gain	0.95±0.12	0.99±0.04	0.83±0.23	0.91±0.20	0.75±0.23	0.85±0.20	0.80±0.22	0.92±0.11
*0.4 Gain2	0.10±0.09	0.04±0.04	0.19±0.21	0.11±0.19	0.27±0.21$^{\square}$	0.18±0.18^{++}	0.23±0.21‡‡	0.10±0.09
0.5 SPEM time	0.99±0.01	0.99±0.01	0.99±0.01	0.99±0.01	0.99±0.01	0.98±0.02	0.97±0.02	0.99±0.02
*0.5 TRMS	0.09±0.11	0.06±0.06	0.09±0.09	0.06±0.03	0.12±0.12	0.13±0.11	0.14±0.12	0.10±0.09
*0.5 SRMS	0.08±0.09	0.06±0.06	0.09±0.08	0.06±0.03	0.12±0.11	0.12±0.09	0.13±0.10	0.10±0.08
0.5 Gain	0.98±0.10	0.99±0.08	0.90±0.15	0.95±0.13	0.86±0.16	0.77±0.25$^{\Delta\Delta\Delta,+}$	0.71±0.27^^^,‡	0.89±0.17
*0.5 Gain2	0.08±0.07	0.06±0.04	0.13±0.12	0.10±0.09	0.15±0.15	0.25±0.23$^{\Delta}$	0.30±0.25^	0.14±0.14

Data are crude (non Ln-transformed) and expressed as mean ± 1SD; *normal or normalized variables

Significance of the difference between healthy volunteers and patients with overt HE: $^{\Delta}$ $p < 0.05$; $^{\Delta\Delta}$ $p < 0.005$; $^{\Delta\Delta\Delta}$ $p < 0.002$
Significance of the difference between unimpaired cirrhotic patients and patients with overt HE: $^{+}$ $p < 0.05$; $^{++}$ $p < 0.02$
Significance of the difference between healthy volunteers and untreated patients with overt HE: ^ $p < 0.05$; ^^ $p < 0.01$; ^^^ $p < 0.002$
Significance of the difference between unimpaired cirrhotic patients and treated patients with minimal HE: $^{\square}$ $p < 0.02$
Significance of the difference between unimpaired cirrhotic patients and untreated patients with overt HE: ‡ $p < 0.05$; ‡‡ $p < 0.02$

Table 3. Correlations Matrix between SPEM and Demographic/Neuropsychiatric Variables in the Healthy Volunteers and the Patients with Cirrhosis.

SPEM variables	*Age	**Pugh score (13)	HMTS	MMST	*NCT-A	*NCT-B	*DS	DC	EEG
0.4 Hz, SPEM time	-0.21	-0.11	0.14	**0.31**	-0.11	0.21	**0.30**	0.18	0.15
*0.4 Hz, TRMS	**0.28**	0.19	**-0.27**	**-0.39**	**0.29**	**-0.34**	**-0.38**	**-0.32**	-0.14
*0.4 Hz, SRMS	**0.29**	0.20	**-0.28**	**-0.40**	**0.31**	**-0.35**	**-0.38**	**-0.33**	-0.13
*0.4 Hz, Gain2	**0.25**	0.17	-0.20	-0.22	0.20	**-0.26**	**-0.29**	-0.22	-0.02
0.5 Hz, SPEM time	**-0.23**	0.04	**0.34**	**0.47**	**-0.30**	**0.33**	**0.41**	**0.26**	0.08
*0.5 Hz, TRMS	**0.24**	0.02	**-0.40**	**-0.43**	**0.26**	**-0.30**	**-0.35**	-0.18	-0.03
*0.5 Hz, SRMS	**0.25**	0.02	**-0.40**	**-0.43**	**0.26**	**-0.30**	**-0.35**	-0.18	-0.02
*0.5 Hz, Gain2	0.15	0.05	**-0.30**	**-0.32**	**0.24**	-0.20	**-0.33**	**-0.30**	-0.13

*Normal or normalized variables **Patients with cirrhosis only

Values in bold typeface are significant with $p < 0.05$

Table 4. Effect of Treatment on Assessment Variables in a Patient with Overt Hepatic Encephalopathy Before and During Treatment with Lactulose

Status	Mental state (14) (0-IV)	NCT-A (sec)	NCT B (sec)	DS (n correct)	DC (score)	EEG (Hz)	0.5 Hz SPEM time	0.5 Hz TRMS	0.5 Hz SRMS	0.5 Hz Gain
Untreated	I-II	45	94	40	125	8.0	0.97	0.05	0.05	0.84
Treated: 2 months	0-I	51	90	42	125	9.0	0.99	0.03	0.03	0.85
Treated: 4 months	0-I	41	135	40	152	8.5	1	0.02	0.02	0.88

Legends to Figures

Figure 1: Overlaid dot (light grey) and subject's eye positions (dark grey). The arrows indicate the beginning and end of the two full sinusoids used for analysis.

Figure 2: Age-adjusted Digit Symbol Test results expressed as mean and 95% confidence interval in healthy volunteers and in patients with cirrhosis:

Panel A: Patients categorized by their neuropsychiatric status on the day of study, irrespective of treatment status.

Panel B: Patients categorized by their neuropsychiatric status on the day of study and their treatment status.

Figure 3: Smooth pursuit eye movements in a healthy volunteer and in three individual patients with cirrhosis, by degree of neuropsychiatric impairment. The dot position is denoted in light grey and the eye position in dark grey.

- In the healthy volunteers and in the unimpaired patients with cirrhosis pursuit is smooth
- In the patients with minimal hepatic encephalopathy pursuit is smooth but interspersed with corrective catch-up saccades
- In the patients with overt hepatic encephalopathy pursuit is no longer smooth but accomplishes by a series of corrective catch-up saccades producing a jerky or cogwheel pattern.

Figure 4: Gain at 0.5 Hz in healthy volunteers and in the patients with cirrhosis, represented as the mean, standard error [box] and standard deviation [whisker]:

Panel A: Patients categorized by their neuropsychiatric status on the day of study irrespective of treatment status.

Panel B: Patients categorized by their neuropsychiatric status on the day of study and their treatment status.

Figure 5: SPEM recordings in a patient with overt HE at baseline and after 2 and 4 months of treatment with a non-absorbable disaccharide. Dot velocity 0.5 Hz; dot position in light grey; patient's eye positions in dark grey.