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Impairment of Response Inhibition Precedes Motor Alteration in the Early Stage of Liver Cirrhosis: A Behavioral and Electrophysiological Study

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Abnormality in movement initiation may partially explain psychomotor delay of cirrhotic patients, even in the absence of overt hepatic encephalopathy (HE). Therefore, the aim of this study was to determine the mechanisms of psychomotor delay observed in patients with cirrhosis in the absence of overt HE. Fourteen patients with nonalcoholic cirrhosis and 12 healthy matched control subjects underwent the lateralized readiness potential (LRP) measurement elicited by a visuospatial compatibility task (Simon task). Stimulus-triggered LRP onset reflects the time in which response is selected, while response-triggered LRP onset reflects motor execution. Cirrhotic patients showed delayed reaction times (RTs) compared to controls, particularly those with trial-making test A (TMT-A) or electroencephalogram (EEG) alterations. Stimulus-triggered LRP onset was found to be delayed in cirrhotic patients compared to controls, with a significant Group-versus-Condition interaction, showing a reduced cognitive ability to cope with interfering codes, even in patients without minimal HE (MHE). Response-triggered LRP was found to be delayed only in the patients with TMT-A or EEG alterations. In conclusion, cirrhotic patients without overt HE display a psychomotor slowing, depending firstly on response inhibition and only later accompanied by impaired motor execution.

Key words: Minimal hepatic encephalopathy; lateralized readiness potential; evoked potentials; hepatic encephalopathy; Simon task; trial making test; EEG.

INTRODUCTION

Hepatic encephalopathy (HE) is a neuropsychiatric syndrome that develops in patients with severe liver disease and/or portal-systemic shunting (Butterworth, 2000; Ferenci *et al*., 2002). It is characterized by a wide spectrum of clinical manifestations, ranging from alterations of psychometric performance to stupor and coma (Ferenci *et al*., 2002). One of

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Abbreviation used: EEG, electroencephalogram; ERP, Event Related Potential; HE, hepatic encephalopathy; MHE, minimal hepatic encephalopathy; LRP, Lateralized Readiness Potential; RTs; reaction times; TMT-A, Trial Making Test A.

the earliest symptoms of HE is bradykinesia, which manifests as a delay in the performance of voluntary movements, similar to that observed in patients with Parkinson's disease (Sherlock *et al*., 1954). However, movement features were proved to be different in these two conditions. Patients with minimal and grade1 HE have delayed movement initiation, whereas those with Parkinson's disease have decreased movement velocity (Joebges *et al*., 2003).

Motor behavior can be divided in different stages: (i) premotor selection or preparation of the sequence of acts to be executed, (ii) programing of the neural pattern that is necessary to produce muscular contraction, and (iii) execution of motor command. An additional inhibitory stage is necessary if an automatic wrong response is partially prepared (Coles, 1989; Kutas and Donchin, 1980).

Therefore, the aim of the present study was to further delineate the nature of psychomotor delay in patients without overt HE, using a technique particularly suited for this purpose—the recording of the lateral readiness potential (LRP) (Coles, 1989) during the execution of a visuomotor compatibility task, the Simon task (Simon and Rudell, 1967).

PATIENTS AND METHODS

Patients

The population study consisted of 14 patients with nonalcoholic cirrhosis who had no evidence of overt HE and 12 healthy aged-matched control subjects with a similar education level ($p = 1.15$) (Table 1).

Table 1. Demographic, Clinical, and Biochemical Data of Cirrhotic Patients and Demographic Data of Controls

	Cirrhotic patients	Controls
Age[a]		
Males	49 (11) years 85%	50 (13) years 75%
Education[a]	8 (5)	13 (7)
Aetiology (No.):		
HBV	3	
HCV	8	
Other	3	
Child-Pugh Class (No.):		
A	3	
B	8	
C	3	
Biochemical data[a]:		
Albumin (g/L)	32 (14)	
Prothrombin activity (%)	62 (12)	
Total bilirubin (mmol/L)	31 (24)	
Aspartate Amino Transferase (UI)	76 (84)	

Note. No. of cirrhotic patients with minimal hepatic encephalopathy (TMT-A or EEG alteration): 4/14.
[a]Median (interquartile interval).

The diagnosis of cirrhosis was made on the basis of historical, clinical, laboratory, endoscopic, and radiological findings; histological confirmation was obtained in 10 of the patients. With one exception, none of the patients had ever manifested overt features of HE and none were on maintenance treatment for this condition. None had evidence of overt HE at the time of the study. In detail, mental state evaluation did not show abnormal orientation (personal identity, present situation, place, and time), patients were self-governing and carried out their normal occupations, they did not have neurological abnormalities on routine neurological examination (however, two patients had mild tremors).

None of the study subjects had a history of past or current alcohol misuse; none had a history or had current evidence of neurological disease or impairment, for example, Transitory Ischemic Attack (TIA), stroke, head trauma, or epilepsy; none had systemic disease likely to affect cerebral functioning, for example, diabetes, cardiovascular, respiratory, or renal insufficiency, neuropsychiatric disorders or dementia; none used psychotropic mediations and none had uncorrectable impairment of visual acuity or were color blind.

The presence of visuopractic alterations was assessed in all patients on the basis of their performance on the trial-making test A (TMT-A). The TMT-A was evaluated using an age- and education-level-adjusted Z score; values >2 were considered to be abnormal (Amodio *et al*., 2001). Spectral analysis of digitalized electroencephalogram (EEG) was also considered for patient characterization (Quero *et al*., 1996). Details on EEG analysis have been reported previously (Amodio *et al*., 1999a, 2001). In brief, the EEG was considered to be abnormal if the mean dominant frequency was $\leq$7.3 Hz or the theta relative power $\geq$35% (Amodio *et al*., 1999b). Patients having abnormal TMT-A or EEG were considered to have minimal HE (MHE) (Quero *et al*., 1996).

The study was conducted according to the Helsinki criteria and approved by the local ethical committee. Informed consent was obtained by each patient before the beginning of the experimental session.

The Stimulation Paradigm

A visual version of the Simon task was used as a stimulation paradigm (Simon and Rudell, 1967). In this paradigm, two different visual stimuli are presented on either the left or the right side of a computer screen (Fig. 1). The task of the subject is to respond as fast as possible to the appearance of the stimuli, by pressing either left- or right-side keys in response to specific predetermined instructions.

The "Simon effect" is defined as the slowing of reaction times (RTs) and a trend for a reduction of accuracy observed when the position of the target stimulus on the screen does not correspond spatially with the position of the response key ("non-corresponding condition"), whereas, if the stimulus and the response correspond spatially, RTs are reduced and accuracy increased ("corresponding condition"). Irrelevant stimulus position produces an automatic activation of the ipsilateral response. The additional time required to inhibit the tendency to activate the wrong response in the non-corresponding condition produces the cost of the Simon effect (Vallesi *et al*., 2005; Wascher *et al*., 2001; Wascher and Wauschkuhn, 1996).

In the present experiment, participants were seated in front of a computer screen with their head positioned in an adjustable head-and-chin rest. The distance between the eyes

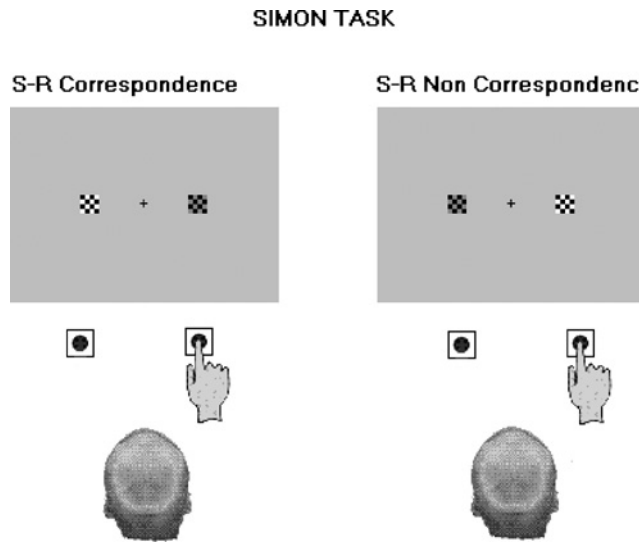

Figure 1. Schema of the Simon task. On the left side of the figure an example of right hand corresponding condition (the relative position of the stimulus on the screen corresponds with the relative position of the responding hand). On the right side of the figure an example of the right hand non-corresponding condition (the relative position of the stimulus on the screen does not correspond with the relative position of the responding hand). The Simon effect consists of slower reaction times (RTs) for the non-corresponding condition, compared to the corresponding one.

and the screen was fixed at 80–85 cm. The target stimuli were 4 × 4 red-and-black or green-and-black chessboards subtending a visual angle of 1.4°. The stimuli were presented one at a time and in a random sequence 3.3° to the right or left of a central fixation cross on a constantly white background. A 4 × 4 black-and-white chessboard was used as contralateral filler to avoid exogenous perceptual asymmetries (Valle-Inclán, 1996). The stimulus was displayed for 176 ms. The maximal response time allowed was 1200 ms.

Participants were encouraged to maintain fixation on the central cross in the center of the screen, to react as quickly and accurately as possible. One half of the participants (randomly selected) were instructed to press the left button (the letter "Z" of the keyboard) with their left index finger if the displayed chessboard was red-and-black, and the right button (the letter "M" of the keyboard) with their right index finger if it was green-and-black, independently of its spatial position. The remaining patients were given opposite instructions. A practice run of 40 trials was allowed and then each color × position combination was presented 75 times in a randomized sequence, for a total of 300 experimental trials. The inter-trial interval ranged from 800 to 1200 ms in random manner. RTs and accuracy were recorded for each trial.

EEG Recording System

The EEG was continuously recorded with Ag/AgCl electrodes from 29 standard locations, according to the international 10/20 system (American Electroencephalographic

Society, 1994), using a precabled elastic cup. The ground was Fpz; the reference was provided by the earlobe electrodes shorted together. Two electrodes were placed on the outer cantus and under the left eye, respectively, to record eye movements (horizontal and vertical electro-oculogram (EOG)). Impedance was kept lower than 5 kΩ. Each channel had its own analogical-to-digital converter (ADC); signals were digitally filtered in the 0.03–70 Hz range. The EEG signals were digitalized online; the sampling frequency was 512 Hz and the conversion resolution was 0.19 μV/digit.

Trials with erroneous or anticipated responses (RT $<$150 ms), trials without response, and those with artefacts (e.g., EOG variations exceeding $\pm$50 μV, or variations of any scalp electrode exceeding $\pm$100 μV) were automatically excluded from further analyses.

Computation and Analysis of the Lateralized Readiness Potential

The LRP is the lateralized part of the readiness potential, or "*Bereithschaftspotential*" and, in general terms, its onset provides a measure of response selection or preparation.

LRP is a negative-going event-related potential (ERP) that precedes voluntary movements and is maximal in the derivations C3 and C4, i.e., in the scalp area corresponding to the motor cortex contralateral to the responding hand (De Jong *et al*., 1988; Gratton *et al*., 1988). The LRP is generated by the activation of motor cortex contralateral to the hand that has to be moved. Therefore its beginning—i.e., the wave onset—reflects the point in time at which the response side (left hand vs. right hand) is determined (Coles, 1989; Kutas and Donchin, 1980).

To obtain the LRP, the ERP recorded from C4 is subtracted from that recorded from C3 when right hand responses are required, and vice versa (C4$-$C3) when left hand responses are required. The typical LRP waveform is obtainable by computing the average of above described subtractions, according to the following formula (Coles, 1989):

$$\mathrm{LRP} = [(\mathrm{C3} - \mathrm{C4})_{\text{Right hand}} + (\mathrm{C4} - \mathrm{C3})_{\text{Left hand}}]/2.$$

If a subject responds to the stimulus with the correct hand, the wave obtained is a negative one. In contrast, if the subject responds to the stimulus with the incorrect hand, the wave obtained is a positive one. In a classical Simon task, the early LRP deflection is often in the direction of the response ipsilateral to the stimulus, i.e., it is in the correct sense for corresponding trials and in the incorrect sense for the non-corresponding trials. In the latter case, the deflection will then change its polarity in the direction of the instructed response (Praamstra and Oostenveld, 2003; Vallesi *et al*., 2005; Wascher and Wauschkuhn, 1996).

The onset of the LRP wave was detected by an automatic procedure that was implemented with the software Matlab (The MathWorks, Software Inc.). The procedure was based on the criterion that the onset was considered to be the first sampling point of a series of values exceeding, for at least 50 ms, 35% of the most negative peak amplitude.

The LRP can be computed in two ways:

a) from the time of the stimulus—in this case it will be a stimulus-locked phenomenon (s-LRP);
b) backwards from the time of the motor response—in this case it will be a response-locked phenomenon (r-LRP).

All of the LRP-related measures are useful chronometric markers of different cognitive operations from premotor to motor processing. The LRP onset is used as a temporal marker to bisect the experimental effects on RTs (Osman *et al*., 1995). Any impairment in the processes preceding response selection, for example, the perceptual-to-motor transmission or the inhibition of conflicts occurring during the transmission, will influence the interval between stimulus and s-LRP onset. In contrast, the interval between r-LRP onset and RTs reflects pure motor execution from the beginning of motor command in M1 area to the overt response by the peripheral limb (van der Lubbe and Verleger, 2002). That is, all these LRP-related measures are useful chronometrical markers of different ongoing cognitive operations, from premotor selection to motor execution (Osman *et al*., 1995; van der Lubbe and Verleger, 2002).

Data Processing

To detect the LRP, the EEG recorded during Simon task execution was averaged separately for each of the four experimental combinations of stimulus positions (left vs. right) and response positions (left vs. right). The s-LRP was calculated averaging 1000 ms epochs, from 100 ms before the stimulus to 900 ms after the stimulus, with a baseline correction consisting in subtracting the 100 ms prestimulus mean amplitude from every sampling point. The r-LRP was calculated averaging 1000 ms epochs, from 600 ms before the RT to 400 ms after the RT, with a baseline correction consisting in subtracting the signal mean amplitude from 600 to 500 ms before RT from every sampling point.

Statistics

Each variable was checked by Kolmogorov–Smirnov test to evaluate its fit to the Gaussian distribution. The Gaussian-distributed variables are expressed as mean ± standard error; the non-Gaussian distributed ones are expressed as median and interquartile interval.

Repeated measures were compared by the paired Student's *t* test for Gaussian distributed variables, and by the Wilcoxon test for non-Gaussian distributed variables.

Repeated measures analysis of variance (ANOVA) was used to assess the effect of group factor (between cirrhotics and controls) and that of the condition factor in the Simon task (within corresponding vs. non-corresponding condition). Post hoc analysis was carried on by the Tukey test.

RESULTS

Ten of the 14 patients with cirrhosis had neither TMT-A nor EEG alterations, whereas the four remaining had signs of MHE according to Quero's criteria (Quero *et al*., 1996).

Behavioral Data

The Simon effect was observed in both healthy controls and in cirrhotic patients. Non-corresponding trials were performed more slowly than corresponding ones. Accuracy in non-corresponding trials was marginally reduced (Table 2). In cirrhotic patients, the RTs for

Table 2. Reaction Times and Accuracy for Each Group and Each Simon Task Condition

Group (n)	Corresponding condition		Non-corresponding condition	
	RT (ms) (mean ± SE)	Accuracy (%) median (interq. interval)	RT (ms) (mean ± SE)	Accuracy (%) median (interq. interval)
Controls (12)	473 ± 20	97.1 (3)	492 ± 20*	95.75 (3)
Cirrhotic patients (14)	594 ± 38†	91.75 (7)	624 ± 37*,†	89.45 (8)*
Cirrhotics without MHE (10)	528 ± 30	95.8 (4)	561 ± 30*	93.9 (7)
Cirrhotics with MHE (4)	758 ± 52†	87.75 (14.5)	781 ± 57*,†,‡	85.0 (14)†,‡

$^{*}p < 0.05$ versus corresponding condition;$^{\dagger}p < 0.05$ versus controls; $^{\ddagger}p < 0.05$ versus cirrhotic patients without MHE.

both the corresponding and the non-corresponding conditions were significantly delayed compared to the healthy controls (ANOVA: $F(1, 24) = 8$, $p < 0.01$) whereas the accuracy was significantly reduced for the non-corresponding condition only (post hoc test: $p < 0.05$). A trend for a higher cost of the Simon task in cirrhotic patients than in controls was detectable, even if it did not reach statistical significance (30 ± 6 vs. 19 ± 6 ms, $p = 0.22$).

The RT delay was significantly greater, for both conditions, in patients with MHE than in the other groups (ANOVA: $F(2, 23) = 17.3$, $p < 0.001$; post hoc test: MHE vs. non-MHE, and MHE vs. controls: $p < 0.001$) (Table 2). Moreover, patients with MHE performed the task with less accuracy compared to both controls and patients without MHE (ANOVA: $F(2, 23) = 5.0$, $p < 0.02$; post hoc test: MHE vs. controls, and MHE vs. non-MHE: $p < 0.05$).

The eight patients with hepatitis C virus (HCV)-related cirrhosis did not present any behavioral features different from the six without HCV-related cirrhosis.

Electrophysiological Correlates of the Simon Task

s-LRP Onset Latency

S-LRP onset latency was significantly prolonged in non-corresponding trials compared to corresponding ones, both in healthy controls and in cirrhotic patients (Table 3).

S-LRP onset latency was delayed in cirrhotic patients in comparison to healthy controls both for the group as a whole (ANOVA: $F(1, 24) = 5.6$, $p < 0.05$) and for the population

Table 3. LRP for Each Group and Each Simon Task Condition (Mean ± SE)

	Corresponding condition		Non-corresponding condition	
	s-LRP	r-LRP	s-LRP	r-LRP
Controls (12)	231 ± 10	−181±15	307 ± 20*	−166±10
Cirrhotic patients (14)	246 ± 23†	−235 ± 22	401 ± 25*,†	−187 ± 23
Cirrhotics without MHE (10)	229 ± 20	−204 ± 23	385 ± 23*,†	−169 ± 17
Cirrhotics with MHE (4)	288 ± 65†	−313 ± 28†,‡	440 ± 67*,†	−233 ± 67†,‡

$^{*}p < 0.05$ versus correspondent condition; $^{\dagger}p < 0.05$ versus controls; $^{\ddagger}p < 0.05$ versus cirrhotics without MHE.

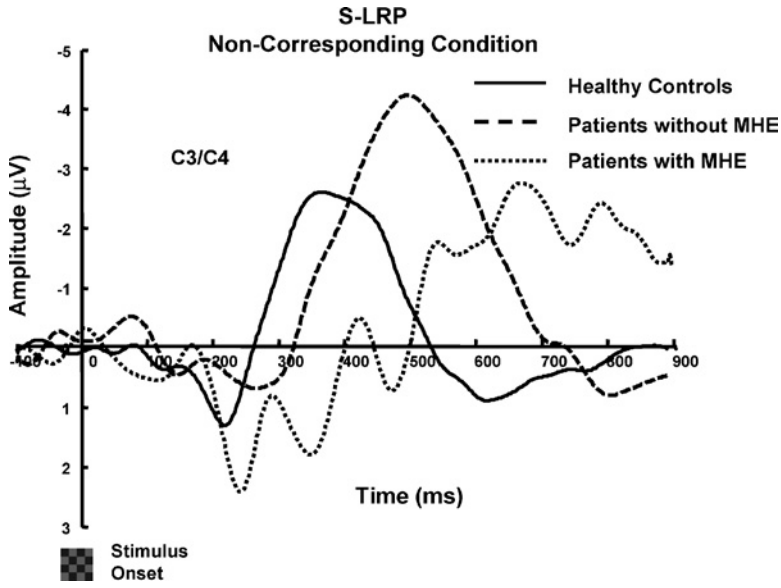

Figure 2. Grand mean of s-LRP in controls, cirrhotic patients without minimal hepatic encephalopathy (MHE), and with MHE elicited by the non-corresponding trials of the Simon task. The delay of s-LRP shows the impairment of response selection in cirrhotics.

subgroups viz. patients with MHE (ANOVA: $F_{1,14} = 7.1,\ p < 0.02$) and without MHE ($F_{1,20} = 4.7,\ p < 0.05$).

In addition, s-LRP latency in non-corresponding condition was significantly much prolonged in cirrhotic patients (ANOVA Group $\times$ Condition interaction: $F(1, 23) = 4.7$, $p < 0.05$). On closer inspection, the Group $\times$ Condition interaction was present also in the group of patients without MHE, showing an initial impairment in coping with interference (Table 3 and Fig. 2).

r-LRP Onset Latency

The onset latency of r-LRP was comparable in corresponding and non-corresponding trials and between healthy controls and cirrhotic patients (Table 3). However, in cirrhotic patients with MHE the r-LRP onset latency was significantly prolonged (ANOVA: $F(2, 24) = 5.6,\ p = 0.01$; post hoc MHE vs. non-MHE: $p = 0.03$, MHE vs. controls: $p = 0.008$, without Group $\times$ Condition interaction) (Fig. 3).

The eight patients with HCV-related cirrhosis did not present any LRP features different from the six without HCV-related cirrhosis.

DISCUSSION

In this study we have shown that, on the whole, cirrhotic patients without overt HE showed delayed RTs compared to controls, particularly those with TMT-A or EEG

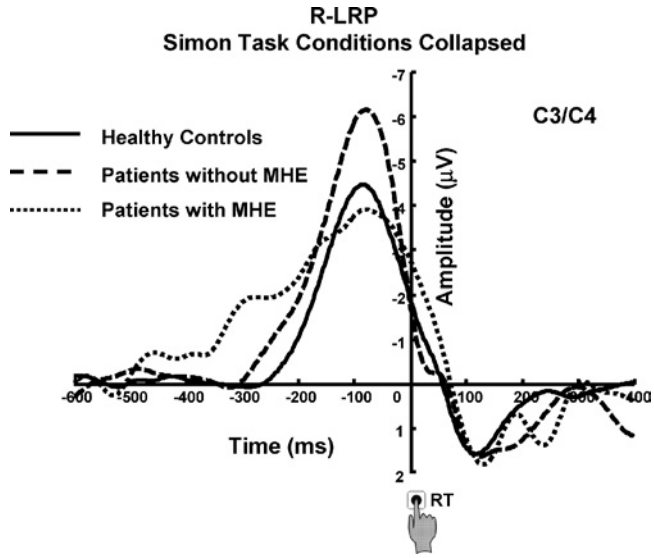

Figure 3. Grand mean of r-LRP in controls, cirrhotic patients without MHE, and with MHE elicited by the Simon task (the responses for corresponding and non-corresponding condition were pooled together, since there was not a significant difference). The higher delay between the r-LRP onset and the response evidences the delay of motor execution in patients with MHE.

alterations. Response selection in the non-corresponding condition of the Simon task was delayed in cirrhotic patients compared to controls, with a significant Group-versus-Condition interaction showing a reduced cognitive ability to cope with interfering codes. Response execution time was found to be delayed only in a small subgroup of individuals with TMT-A or EEG alterations.

Psychomotor delay is a well-recognized feature that may occur in cirrhotic patients, even in those without overt HE (Amodio *et al*., 1998, 2005; Schomerus and Hamster, 1998). The delay may reflect a cognitive dysfunction preceding the activation of motor cortex or may reflect, at least in part, the presence of bradykinesia (Joebges *et al*., 2003; Jover *et al*., 2003), or even a reduction in motor ability associated with the muscle wasting (Tarter *et al*., 1997) that is commonly observed in patients with liver cirrhosis (Caregaro *et al*., 1996).

In this study we have explored the mechanisms at the basis of psychomotor slowing by studying the LRP recorded during the execution of the Simon task. The LRP provides information on the central covert premotor and motor processes, preceding the overt response execution (Osman *et al*., 1995). LRP is particularly useful if applied during the execution of the Simon task because this requires a one-hand response choice, which is characterized by subprocesses such as selection, programing, and execution, and of an additional stage of inhibition of early automatic tendencies to respond towards stimulus side in the non-corresponding condition (Gratton *et al*., 1988).

Besides the generic confirmation of the existence of psychomotor slowing, the other behavioral finding of our study was that task interference, which in the Simon task is visuospatial in nature, presented a trend for a higher cost in cirrhotic patients than in controls.

Actually, in the present study the prolongation of RTs in the non-corresponding condition was 58% higher in cirrhotic patients than in controls, and the s-LRP onset latency during the execution of the Simon task was delayed in the non-corresponding condition, even in the cirrhotic patients without TMT-A and EEG alterations. This suggests that the cognitive processes preceding the activation of motor cortex were delayed, independent of any motor alteration. Moreover, the finding that such a delay was higher in the non-corresponding condition than in corresponding condition suggests the existence of executive dysfunction involving the control of inhibitory mechanism.

The higher cost of visuospatial interference in cirrhotic patients than in controls confirms the existence of executive dysfunction in cirrhotic patients. Such a dysfunction was suggested by the observation that the delay in simple RTs is smaller than the delay in choice RTs (Rikkers *et al*., 1978; Schomerus *et al*., 1981). In addition, even in patients in whom choice RTs are maintained, more complex cognitive paradigms, which need higher levels of control and inhibition of nonrelevant information, are altered (Amodio *et al*., 1999a). The same conclusions were reached by McCrea *et al*. (1996), using a nonchronometric approach, based on paper-and-pencil tests.

The detection of a prolonged r-LRP in the cirrhotic patients with TMT-A or EEG alterations can only be interpreted cautiously, because of the small number of subjects considered. At any rate, if confirmed, it suggests that also the processes occurring between the activation of motor cortex and motor response were altered in the patients with more advanced HE. In addition, the finding that such a delay is independent of the side of stimulus presentation reinforces the evidence of a pure disorder of motor execution and is in agreement with the observation by Jobges *et al*. (2003) that elegantly described the existence of a disorder in movement initiation in MHE.

The absence of alterations particularly related with HCV infection does not rule out the possibility of a direct minor adverse effect of HCV on the brain (Forton *et al*., 2002) that may need a more powerful study to be detected.

In conclusion, the present behavioral and electrophysiological study showed that in cirrhotic patients without overt HE a slowing of cognitive processes occurs and that such alteration precedes a motor execution disorder.

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