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Top-down and bottom-up processes in the extrastriate cortex of cirrhotic patients: An ERP study

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Abstract

Objective: This study aims to evaluate the efficiency of top-down and bottom-up processes in the extrastriate cortex of cirrhotic patients without overt hepatic encephalopathy (HE).

Methods: Reaction times (RTs), accuracy and event-related potentials (ERPs) were recorded during the execution of a visual Simon task in 17 cirrhotic patients and 10 healthy controls. Amplitude and latency of the P1 and N1 (indexes of bottom-up processes) and of the N2pc (index of top-down processes) were measured.

Results: Patients were slower than controls, and patients with minimal HE (MHE) were slower than patients without MHE. The distribution analysis of RTs showed that the Simon effect decays with slower RTs in all the groups and that the shape of the distribution was different in MHE patients.

No differences were found between cirrhotic patients and controls for P1 and N1 amplitude and latency. In contrast, N2pc latency was delayed in cirrhotic patients compared to controls independently of MHE.

Conclusions: In the extrastriate cortex of cirrhotic patients without HE, top-down processes are altered whereas bottom-up processes are preserved.

Significance: The analysis of exogenous and endogenous visual components of ERPs provides a model to study the functional dissociation between top-down and bottom-up processes inside the extrastriate cortex.

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Keywords: Cirrhotic patients; Minimal hepatic encephalopathy; Extrastriate cortex; Simon effect; P1; N1; N2pc; PCN

1. Introduction

Hepatic encephalopathy (HE) is a neuropsychiatric syndrome occurring in acute or chronic liver failure. In its subclinical or minimal expression, HE is characterized by the presence of cognitive and neurophysiological abnormalities in cirrhotic patients with normal or near-normal neurological and mental status (Gitlin et al., 1986; Rikkers et al., 1978; Tarter et al., 1984).

Minimal hepatic encephalopathy (MHE) is detectable in 20–60% of cirrhotic patients (Amodio et al., 2004; Ferenci et al., 2002). This neuropsychiatric syndrome is characterized by many neuropsychological dysfunctions concerning visual-constructive abilities, orienting of visual attention, psychomotor speed, inhibitory processes and executive functions (Amodio et al., 1995, 1998, 2005; Schiff et al., 2005; Weissenborn et al., 2001). Chronometric studies showed that in patients without overt HE (patient with or without MHE), the delay of simple reaction times

Abbreviations EEG, electroencephalogram; ERPs, event-related brain potentials; HE, hepatic encephalopathy; RTs, reaction times.

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(RTs) tasks is smaller compared to the delay of choice RTs tasks. Furthermore, there are evidences that MHE patients fail in cognitive tasks, which need higher levels of control and inhibition of non-relevant information (Amodio et al., 1999a, 2005; Rikkers et al., 1978; Schiff et al., 2005; Schomerus et al., 1981). These data suggest that when performance need the control of incoming information (top-down processes), patients show a worse performance.

Additional information about brain dysfunctions in cirrhotic patients come from brain imaging studies. Reduced brain metabolism was observed in MHE patients in the following associative cortical areas: the anterior cingulate cortex, the dorsolateral prefrontal cortex, the occipito-parietal cortex, the medial temporal cortex and the extrastriate cortex (Lockwood, 2000; Lockwood et al., 1993, 2002; Zafiris et al., 2004).

These neuropsychological and brain imaging findings suggest a correlation between the alterations observed in cirrhotic patients and top-down processes involved in stimulus discrimination and response selection during goal-directed behaviour (Corbetta and Shulman, 2002). Information inside the brain can travel from sensory input, through perceptual analysis, towards motor output, or from 'higher' associative cortices to 'lower' primary cortices involving feedback or re-entrant connections. The former types of processes are called bottom-up processes and are exogenous in nature (stimulus-driven); the latter are called top-down processes and are endogenous (goal-directed) in nature. Since, the control of visual and spatial selective attention affect information processing in extrastriate cortex (Corbetta and Shulman, 2002; Desimone and Duncan, 1995; Luck et al., 1997), it may be expected that a dissociation between the efficiency of top-down and bottom-up processes in cirrhotic patients with MHE may be detected in this area using event-related potentials techniques.

Event-related brain potentials (ERPs) are useful for the temporal analysis of cognitive processes (Rugg and Coles, 1995). ERPs reflect phasic modulations of brain activity, which are time-locked to the onset of an external or internal event. The abrupt onset of a visual stimulus evokes, independently of any task demand, two early ERP components named P1 and N1. Many reports claim that the origin of the P1/N1 lies in the extrastriate pathway and they represent the early multi- level analysis of visual information coming from V1 (Eimer, 1998; Heinze et al., 1994; Hillyard and Anllo-Vento, 1998; Hopfinger and Maxwell, 2005; Johannes et al., 1995; Mangun and Hillyard, 1995) However, a minority of reports claim that their origin, at least P1, lie in the striate pathway (Hashimoto et al., 1999; Hoshiyama and Kakigi, 2001).

Even if the amplitude of these two components can be modulated by selective attention, their nature is mainly exogenous (Eimer, 1998). Spatial attention can have an effect on P1 and N1 components in trial-by-trial cueing situations (Mangun et al., 1993), which indicates a spatially selective modulation of processing in the V1–IT pathway. When the stimulus located in the unattended visual field, these components are markedly attenuated.

In multi-stimulus array visual search tasks, it has recently been described a negative ERP component that occurs in the N2 latency-window in the posterior sites contralateral to target position. This location-specific processing modulations in the ventral pathway was called N2pc (Luck and Hillyard, 1994a,b). N2pc can be also observed when a target stimulus is laterally displayed and only a single irrelevant stimulus is presented simultaneously in the opposite visual field (Eimer, 1996; Oostenveld et al., 2001; Valle-Inclán, 1996; Wascher and Wauschkuhn, 1996; Wijers et al., 1997). From a functional point of view, the N2pc seems to reflect the spatial filtering of irrelevant information (Luck and Hillyard, 1994b). An alternative possibility is that the N2pc reflects the detection and the selection of the task-relevant information (Eimer, 1996). In any case, it is an index of visuospatial selective attention (Eimer, 1996, 1998). The most probable generator of the N2pc seems to be located in the ventro-lateral temporal cortex (Oostenveld et al., 2001; Praamstra and Oostenveld, 2003; Wijers et al., 1997; Woldorff et al., 2002), even if a small early contribute to this component was detected in the parietal cortex (Hopf et al., 2000). In recent models regarding the enhanced neural activity induced by selective attention in the extrastriate cortex, it was suggested that, during visual search tasks, the interaction between bottom-up and top-down processes can start early in the P1–N1 latency-window, but the N2pc is evoked only when target location is selected (Woldorff et al., 2002). For this reason, the latency of this attentional modulation can vary depending on the difficulty of the target localization (Shedden and Nordgaard, 2001; Wascher, 2005). Many authors, indeed, prefer to use the term posterior contralateral negativity (PCN) to dissociate this lateralized endogenous component from the N2 component (van der Lubbe et al., 2001; Wascher et al., 2001).

Albeit many studies (Amodio et al., 1999a, 2005; Rikkers et al., 1978; Schiff et al., 2005; Schomerus et al., 1981) suggest an impairment of top-down processes in MHE, there is not yet direct evidence for a clear dissociation between the efficiency of top-down and bottom-up processes in the extrastriate cortex of cirrhotic patients. In the present study we tested the integrity of these two kinds of processes in the extrastriate cortex in a group of cirrhotic patients with no signs of overt HE, in order to clarify this still unknown characteristic of MHE. For their obligatory nature, we used the P1 and N1 components as indexes of bottom-up (i.e. stimulus-driven) perceptual processing in the extrastriate cortex, and the N2pc, given its selective nature (Eimer, 1996), was used as an index of top-down (i.e. goal-directed) post-perceptual processing.

We used a choice RTs task involving visual discrimination. It is known that in a choice RTs task, if target stimuli are presented laterally with respect to a central fixation point, RTs are faster when the position of the responding

hand corresponds, spatially to the position of the target (Fitts and Deininger, 1954; Fitts and Seeger, 1953). This effect occurs even if the spatial position of the target is not relevant for the task. In this case it is called *Simon effect* (Simon and Rudell, 1967). In the Simon task it is assumed that stimulus localization process automatically activates a response code ipsilateral to the stimulus position (De Jong et al., 1994; Wascher et al., 2001). If the automatic activated response corresponds to the appropriate response, faster RTs follow. If the automatic activated response does not corresponds to the appropriate response, it has to be inhibited. This inhibitory process requires additional time that slows RTs down in the non-corresponding condition. Moreover, the response automatically activated by the irrelevant position of the target stimulus is assumed to be transient in nature. Many studies, using the distributional analysis of RTs, showed that the automatically generated response decays with time. Therefore, with the longest RTs the Simon effect tends to disappear (De Jong et al., 1994; Hommel, 1993, 1994; Nicoletti and Umiltà, 1994) at least under some conditions (Ansorge, 2003; Vallesi et al., 2005; Wascher et al., 2001; Wiegand and Wascher, 2005).

The first aim of the present study was to demonstrate a clear dissociation in the efficiency of bottom-up and top-down processing of cirrhotic patients in the extrastriate cortex using ERP correlates of early stimulus-driven processing, indexed by the P1 and N1, and of late goal-directed processing, expressed by the N2pc. To avoid exogenous perceptual asymmetries in the EEG signal an irrelevant distracter was displayed in the opposite visual field together with the target stimulus (Valle-Inclán, 1996). Under these conditions P1, N1 and the N2pc are frequently described (Eimer, 1996; Praamstra and Oostenveld, 2003; Valle-Inclán, 1996; Wascher and Wauschkuhn, 1996; Wascher et al., 2001). A second aim of the study was to evaluate the presence of any difference between controls and patients with regard to the Simon effect and its time-course. Distribution analysis of RTs provide a measure of RTs dispersion. In a previous study, Elssas and co-workers (1985) showed that this dispersion in RTs distribution in cirrhotic patients with overt HE was higher both compared to healthy controls and patients with brain damage. If this effect is associated with the presence of motor alteration in HE patients, this effect may be detectable also in patients with less severe motor or cognitive alteration.

2. Material and methods

2.1. Subjects

The population study comprised of 17 patients (4 females) with non-alcoholic cirrhosis and without evidence of overt HE and 10 healthy matched control participants (3 females) The mean age of the patients was 50 ± 10 years and the mean age of the controls was 48 ± 7 years (see Table 1).

The diagnosis of cirrhosis was made on the basis of historical, clinical, laboratory, endoscopic and ultrasonographic findings; histological confirmation was obtained when needed (12 patients). With one exception, none of the patients had ever manifested overt bouts of HE and none was on maintenance treatment for this condition. Moreover, none had evidence of overt HE at the time of the study. 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 tremor).

None of the study participants had a history of past or current alcohol misuse, a history or current evidence of neurological disease (i.e. transitory ischemic attach, stroke, head trauma, or epilepsy), systemic disease likely to affect cerebral functioning (i.e. diabetes, cardiovascular, respiratory or renal insufficiency, neuropsychiatric disorders or dementia), none used psychotropic medications and none had uncorrected impairment of visual acuity or was colour blind.

The presence of visuo-motor alterations abilities were assessed in all patients on the basis of their performance on the Trail-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, 2002). Spectral analysis of digitalized EEG was also considered for patient characterization (Quero et al., 1996). Details on EEG analysis were reported previously (Amodio et al., 1999b, 2001). In brief, the EEG was considered to be abnormal if the mean dominant frequency (MDF) was ≤ 7.3 Hz or the theta relative power $\geqq 35\%$ (Amodio et al., 1999b). Seven patients who showed

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

		Cirrhotic patients	Healthy controls
Age (years)[a]		51 (11)	50 (11)
Females (%)		25%	30%
Education (years)[a]		8 (5)	13 (8)
Aetiology (N°)	HBV	3	
	HCV	10	
	Other	4	
Child–Pugh class (N°)	A	3	
	B	8	
	C	6	
Biochemical data[a]	Albumin (g/L)	31 (13)	
	Prothr. activity (%)	61 (18)	
	Total bilirubin (mmol/L)	40 (26)	
	AST (UI)	88 (71)	

No of Cirrhotic patients with MHE (TMT-A or EEG alteration): 7/17.
[a] Median (interquartile interval).

abnormalities in the TMT-A or EEG were considered to have 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.

2.2. Behavioural task

During the experimental session, participants were seated in front of a computer screen with their head positioned in an adjustable head-and-chin rest with a distance between the eyes and the screen fixed at 80–85 cm. The target stimuli were 4×4 red-and-black or green-and-black checkerboards 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 to the left of a central fixation cross on a constantly white background. A 4×4 black-and-white checkerboard was used as contralateral distracter. Stimuli were displayed for 176 ms.

Participants were encouraged to maintain fixation on the cross in the centre of the screen and 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 target was red-and-black, and the right button (the letter 'M') with their right index finger if it was green-and-black, independently of its spatial position. The remaining participants were given opposite instructions. A practice run of 40 trials was performed and then each colour by 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 a random fashion. RTs and accuracy were recorded for each trial.

2.3. Electrophysiological recordings

The electroencephalogram (EEG) was continuously recorded (Equipment: Micromed System Plus, Mogliano Veneto, Italy) by Ag/AgCl electrodes from 29 standard locations according to the international 10/20 system (American Electroencephalographic Society, 1994), using a pre-cabled elastic cap. FPz was used as ground and reference was provided by the earlobe electrodes sorted together. Two electrodes were placed on the outer cantus and under the left eye, respectively, to record eye movements (horizontal and vertical EOG). Each channel had its own analogical-to-digital converter (ADC). The EEG and EOG signals were digitalised on-line with a frequency rate of 512 Hz and a conversion resolution of 0.19 μV/digit.

Impedance was kept lower than 5 kΩ. Signals were digitally filtered in the 0.03–30 Hz range.

2.4. Data analysis

The maximal RT allowed was 1500 ms. All trials with incorrect response were excluded from further analyses. Trials with erroneous or anticipated responses (RT < 150 ms), trials without response and those with artefacts (e.g. EOG variations exceeding ±50 μV, or variations of any scalp electrode exceeding ±100 μV), were automatically excluded from further analyses.

EEG and EOG signals were epoched off-line in the interval starting with 100 ms prior to stimulus onset and ending at 900 ms after. Baseline correction was applied using the sample points recorded 100 ms prior to stimulus onset.

The electrodes O1/2, PO3/4, T5/6, P3/4 were considered. Component peak latencies were defined as the sample point with maximal value, for the P1, and minimal values for the N1 and the N2pc in the 80–180, 120–250, 180–300 latency-windows, respectively. Component peak amplitudes were defined as the amplitude of the same sample points. The N2pc was computed as the difference between the waves ipsilateral and contralateral to the target in the T5/T6 electrodes, where the component has been found to have the highest amplitude (Wascher and Wauschkuhn, 1996).

2.5. 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 ± SD; 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 ANOVA was used, with the group (cirrhotics vs. controls or patients with MHE vs. without MHE) as the between-subjects factor, and Simon task condition (corresponding vs. non-corresponding) as the within-subjects factor.

To analyse the time course of the Simon effect, RTs were divided in quintiles (bins) from the fastest to the slowest, separately for corresponding and non-corresponding trials and a repeated-measures ANOVA was performed with the group as between-subjects factor, the Simon task conditions and the Bin (5 quintiles from the fastest to the slowest) as within-subjects factors.

For the significant effects, Post-hoc analysis was carried out using the Tukey HDS test.

3. Results

3.1. Behavioural data

Behavioural results are summarized in Table 2. The Simon effect (i.e. slower RTs in the non-corresponding

Table 2
Mean reaction times and accuracy of cirrhotic patients and controls

		Conditions of the Simon task	
		S–R corresponding	S–R non-corresponding
Reaction times (ms)	Cirrhotic patients	623 (138)**	655 (134)*·***
	Cirr. without MHE	537 (93)	575 (91)*·***
	Cirr. with MHE	745 (89)**·****	772 (94)*·**·***
	Healthy controls	473 (76)	497 (73)*
Correct responses (%)	Cirrhotic patients	93 (7)	91 (8)*
	Cirr. without MHE	95 (4)	93 (6)
	Cirr. with MHE	89 (9)**	88 (9)**
	Healthy controls	97 (2)	95 (3)

*$P<0.05$ vs. corresponding condition; **$P<0.05$ vs. controls; ***$P<0.05$ vs. cirrhotics without MHE. Values expressed as mean (SD).

condition) was observed both in cirrhotic patients ($P<0.0001$) and healthy controls ($P<0.005$). Accuracy in non-corresponding trials was found significantly lower than the corresponding one in control subjects ($P<0.005$), but not in cirrhotic patients. In cirrhotic patients, RTs for both the corresponding and non-corresponding conditions were significantly delayed compared to healthy controls ($P<0.005$). Accuracy was not significantly reduced in cirrhotic patients compared to controls, even if a trend for a lower accuracy was observed (see Table 2). No interactions involving groups and task conditions were found, even if a trend for a grater Simon effect in cirrhotic patients than in controls was detectable (32 vs. 24 ms, $P=0.32$).

In patients with MHE the RTs were significantly slower than in the other groups ($F_{2,24}=22.1$, $P<0.01$; post hoc test: MHE vs. non-MHE, and MHE vs. controls: $P<0.001$), in both the Simon task conditions. In contrast, patients without MHE showed slower RTs compared to controls only in the non-corresponding condition (post hoc test: $P=0.05$). Patients with MHE performed the task with a lower accuracy than both controls and patients without MHE (ANOVA: $F_{2,24}=6.4$, $P<0.05$; post hoc test: MHE vs. controls and MHE vs. non-MHE: $P<0.05$).

The RT distributional analysis revealed a significant group effect (ANOVA: $F_{2,24}=22.1$, $P<0.001$): cirrhotic patients with MHE showed slower RT than either controls or patients without MHE (post hoc tests: $P<0.05$); a significant within effect of task conditions (ANOVA: $F_{1,24}=37.6$, $P<0.001$): slower RT in the non-corresponding condition; as expected, a significant interaction between bins and task conditions (ANOVA: $F_{4,96}=24.4$, $P<0.001$): the Simon effect disappears with slower RTs. Planned comparisons between consecutive pairs of bins revealed that the Simon effect decreased significantly from the forth bin to the fifth in both controls and patients (for all $P<0.01$). An additional bin x group interaction was found (ANOVA: $F_{4,96}=24.394$, $P<0.001$): patient with MHE showed slower RTs with later bins compared with both controls and patients without MHE (see Fig. 1).

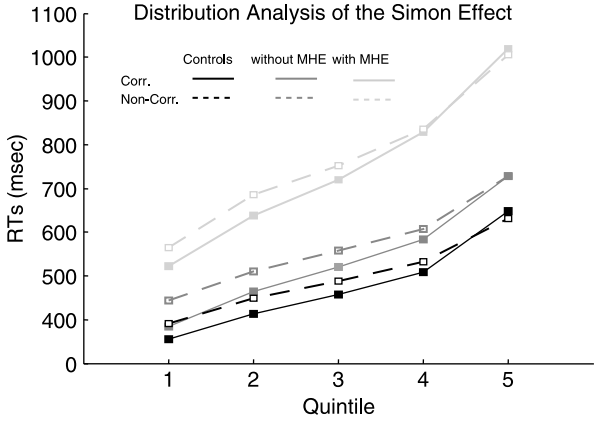

Fig. 1. The graph represents the temporal evolution of the Simon effect in controls subjects (black lines), cirrhotic patients without MHE (dark grey lines) and with MHE (bright grey lines). Corresponding condition is depicted with solid lines and the non-corresponding condition is depict with dashed lines. Even if a shift along the temporal dimension is evident, the decay of the Simon effect with slower RTs is present in all 3 groups. Patients with MHE showed a higher increase of RTs with bins compared to both controls and patients without MHE.

3.2. Electrophysiological data

Mean amplitude and latency of the P1, N1 and N2pc ERP components, measured in T5/T6 derivations, both in patients and controls, are reported in Table 3.

Repeated-measures ANOVAs were performed for both latency and amplitude of P1 and N1 components. Group was used as between-subjects factor and electrode site (O1/2, PO3/4, T5/6 and P3/4) as within-subjects factor.

No significant differences between cirrhotic patients and controls and between patients with and without MHE were found in P1 and N1 latency. Moreover, no significant differences between cirrhotic patients and controls and between patients with and without MHE were found for P1 and N1 amplitude. A significant effect of electrode site was found for both P1 and N1 amplitude ($F_{3,75}=2.8$; $P<0.05$ and $F_{3,75}=6.05$; $P<0.001$, respectively). Concerning P1 amplitude, post-hoc analysis showed no significant differences among various electrode sites. In contrast, for N1 the effect of electrode site is due to a significant difference between P3/4 and the others electrodes in patients without MHE (post hoc test: $P<0.001$).

In contrast to P1 and N1 exogenous components, N2pc latency (but not its amplitude) was found to be significantly different in cirrhotic patients compared with controls ($t_{25}=3.1$, $P<0.01$). The latency of N2pc was delayed in cirrhotic patients with respect to controls (265 ± 25 vs. 237 ± 20 ms). No difference was found between patients with and without MHE (see Fig. 2).

Table 3
Mean amplitude and latency of P1, N1 and N2pc ERPs components

		Amplitude (μV)	Latency (ms)
P1	Cirrhotic patients	2.9 (2)	112 (31)
	Cirr. without MHE	2.2 (2.4)	106 (22)
	Cirr. with MHE	3.9 (2.4)	121 (36)
	Healthy controls	2.3 (1.5)	109 (12)
N1	Cirrhotic patients	−4.1 (4.2)	161 (23)
	Cirr. without MHE	−5.6 (2.5)	158 (13)
	Cirr. with MHE	−2.4 (2.1)	166 (34)
	Healthy controls	−3.9 (1.8)	155 (16)
N2pc	Cirrhotic patients	−3.1 (1.6)	265 (25)*
	Cirr. without MHE	−3.2 (1.9)	270 (18)*
	Cirr. with MHE	−2.8 (0.8)	260 (33)*
	Healthy controls	−2.3 (0.9)	237 (20)

*$P < 0.05$ vs. controls. Values measured in T5/T6 expressed as mean (SD).

4. Discussion

In this study, the efficiency of bottom-up and top-down mechanisms involved in perceptual and post-perceptual selective processes of the extrastriate cortex of cirrhotic patients without overt HE was explored. To that purpose, ERPs were recorded during the execution of a visual discrimination Simon task. The analysis of the ERPs revealed that the early stages of visual information processing (P1 and N1 components) are maintained even when target selection processes are altered (N2pc), and that an alteration of these processes is detectable even in patients without MHE.

Deficit of visual selective attention is a well recognised feature that may occur in cirrhotic patients, even in those without overt HE (Amodio et al., 1995, 1998, 2005; Weissenborn et al., 2001). Visual input travels from V1 through two possible pathways: the ventral and dorsal stream (Ungerleider and Mishkin, 1982). The ventral pathway connects V1 and V2 with V3 and V4 and these areas, in turn, with the inferotemporal cortex (IT). Its main function is object discrimination and identification. The dorsal pathway connects V1 and V2 to the posterior parietal cortex and its main function is the analysis of spatial aspects of visual objects. The interaction between these two pathways allows goal-directed selection. This interaction is also modulated by sub-cortical structures such as the thalamus and the superior colliculus (LaBerge, 1995). P1 and N1 latencies provide temporal markers of those processes involved in the analysis of visual input flowing from V1 to IT along the ventral stream. In contrast, N2pc latency provides a temporal marker of the top-down modulation coming from the posterior parietal cortex and dorsolateral prefrontal cortex (Eimer, 1998).

In the present study the analysis of visual P1 and N1 amplitudes and latencies showed that cirrhotic patients' extrastriate bottom-up processes are maintained while the extrastriate top-down processes reflected by the N2pc are already altered. These findings are in agreement with a previous study of Kugler et al. (1994), who studied a group of cirrhotic patients recording P1, N250 and P300 latency evoked by a visual oddball task. They found that patients

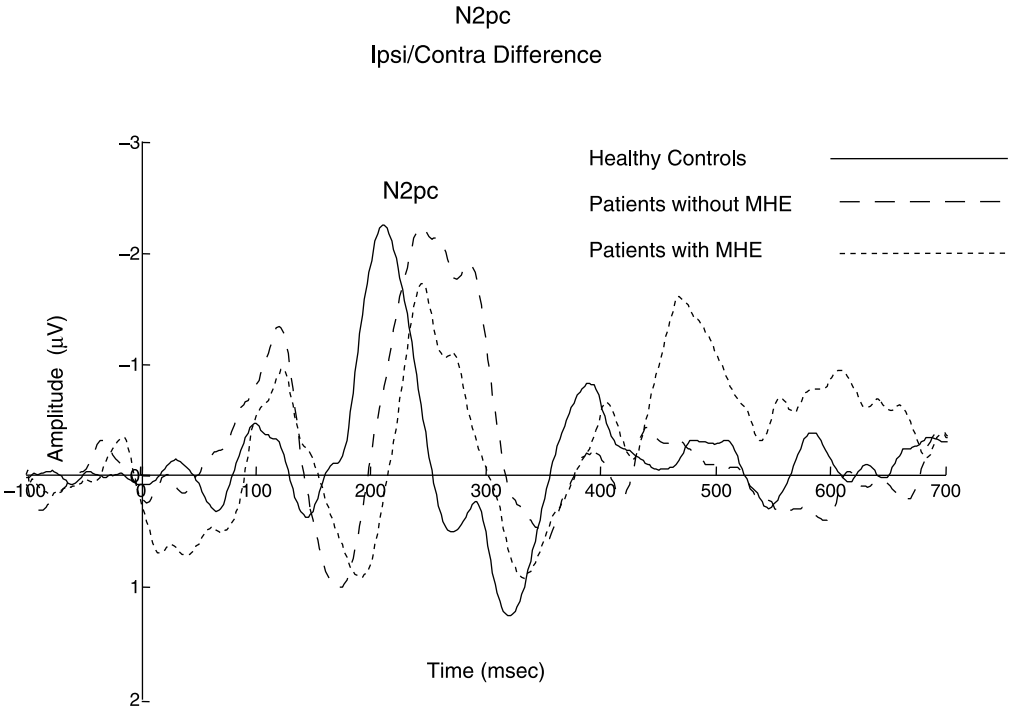

Fig. 2. Target ipsi/contra difference of ERPs recorded in T5/T6 derivation sites in control subjects (solid line), cirrhotic patients without MHE (dashed line) and with MHE (dotted line). The N2pc is the component with its negative peak between 200 and 300 ms. The latency of this component is delayed in cirrhotic patients compared with controls. No difference was found between patients with and without MHE.

without overt HE showed delayed N250 and P300 latency but a normal P1. The latency of the P1 increased significantly only in patients with overt HE (Kugler et al., 1994).

The neurobiology of higher sensitivity of top-down than bottom-up processes to the neurotoxins causing HE is far to be explained. Both differences in neuromediators-receptors and synaptic pathways can be hypothesized. At any rate, behavioural studied measuring RTs showed that the higher is task complexity, the higher is the difference between the performance of cirrhotic patients and healthy subjects. Since, high complex tasks require high top-down control, it is arguable that these processes are more involved in the first stages of HE. Furthermore, hypo-metabolism in specific target associative brain areas suggest an impairment of the control of tasks demands.

A second aim was to study the Simon effect and its time course in cirrhotic patients. We found that cirrhotic patients without overt HE showed delay RTs in the non-corresponding condition of the Simon task compare to controls and that patients with MHE have delayed RTs also in the corresponding condition compared to both patients without MHE and controls. Distributional analysis of RTs showed that the Simon effect decays parallel to the increase in RTs both in controls and in patients with and without MHE. Moreover, the interaction between bin and groups showed that patients with MHE had slower RTs especially in the latest bins compared to patients without MHE and to controls. A similar result was previously described by Elssas and collaborators (Elsass et al., 1985) with a simple RT task. These authors showed that the slowest RTs discriminate better the performance of controls from that of patients with HE compared to the fastest RTs. The difference in the distribution of RTs between patient with MHE and controls may be ascribed to the impairment at the stage of response selection that is detectable in patients with MHE (Joebges et al., 2003; Schiff et al., 2005).

As suggested by Wascher (2005), the N2pc latency seems to be related to the time course of the Simon effect. The decay hypothesis of the Simon effect postulates a dependency between the timing of stimulus localization and response execution (Hommel, 1993, 1994; Wascher, 2005). Following this hypothesis, if target localization (indexed by N2pc latency) is delayed in cirrhotic patients also the decay of the Simon effect should be shifted along the temporal dimension. In accordance with this prediction, our data showed that cirrhotic patients delayed RTs and N2pc latency, but the time course of the Simon effect were found to be normal. In contrast, patients with MHE showed longer RTs than controls and patients without MHE, while their N2pc latency was delayed compared to controls, but not compared to patients without MHE. However, it is important to underline that the processes involved in target localization and selection are not the only ones involved in the Simon task. Pre-motor and motor processes are also modulated by task conditions (Oostenveld et al., 2001; Praamstra and Oostenveld, 2003; Valle-Inclán, 1996; Vallesi et al., 2005; Wascher et al., 2001; Wiegand and Wascher, 2005). In a recent study, Schiff et al. (2005) showed, using the *lateralized readiness potential* (LRP), that spatial code interferes at pre-motor level with response selection in both cirrhotic patients with and without MHE; in contrast, motor processes are delayed in MHE patients only. These data corroborate our finding of a greater difference between patients with MHE and without MHE in the slowest part of RTs distribution.

In conclusion, the present study showed that: (1) in cirrhotic patients a functional dissociation between top-down and bottom-up processing efficiency in the extrastriate cortex dose exist; (2) the alteration of top-down, but not bottom-up, extrastriate processes contributes to the slowing of RTs detectable in cirrhotic patients without overt HE; (3) RTs delay in patients with MHE increases with bins.

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References

Amodio P, Marchetti P, Del Piccolo F, Sartori G, Prior M, Merkel C, Gatta A. Visual attention orienting in liver cirrhosis without overt hepatic encephalopathy. Metab Brain Dis 1995;10:335–45.

Amodio P, Marchetti P, Del Piccolo F, Campo G, Rizzo C, Iemmolo RM, Gerunda G, Caregaro L, Merkel C, Gatta A. Visual attention in cirrhotic patients: a study on covert visual attention orienting. Hepatology 1998; 27:1517–23.

Amodio P, Del Piccolo F, Marchetti P, Angeli P, Iemmolo R, Caregaro L, Merkel C, Gerunda G. Gatta A.Clinical features and survivial of cirrhotic patients with subclinical cognitive alterations detected by the number connection test and computerized psychometric tests. Hepatology 1999a;29:1662–7.

Amodio P, Marchetti P, Del Piccolo F, de Tourtchaninoff M, Varghese P, Zuliani C, Campo G, Gatta A, Guerit JM. Spectral versus visual EEG analysis in mild hepatic encephalopathy. Clin Neurophysiol 1999b;110: 1334–44.

Amodio P, Del Piccolo F, Petteno E, Mapelli D, Angeli P, Iemmolo R, Muraca M, Musto C, Gerunda G, Rizzo C, Merkel C, Gatta A. Prevalence and prognostic value of quantified electroencephalogram (EEG) alterations in cirrhotic patients. J Hepatol 2001;35:37–45.

Amodio P, Wenin H, Del Piccolo F, Mapelli D, Montagnese S, Pellegrini A, Musto C, Gatta A, Umiltà C. Variability of Trail Making Test, Symbol Digit Test and Line Trait Test in normal people. A normative study taking into account age-dependent decline and sociobiological variables. Aging Clin Exp 2002;14:116–31.

Amodio P, Montagnese S, Gatta A, Morgan MY. Characteristics of minimal hepatic encephalopathy. Metab Brain Dis 2004;19:253–67.

Amodio P, Schiff S, Del Piccolo F, Mapelli D, Gatta A, Umilta C. Attention dysfunction in cirrhotic patients: an inquiry on the role of executive control, attention orienting and focusing. Metab Brain Dis 2005;20:115–27.

Ansorge U. Influences of response-activating stimuli and passage of time on the Simon effect. Psychol Res 2003;67:174–83.

Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 2002;3:201–15.

De Jong R, Liang CC, Lauber E. Conditional and unconditional automaticity: a dual-process model of effects of spatial stimulus–response correspondence. J Exp Psychol: Hum Percept Perform 1994;20:731–50.

Desimone R, Duncan J. Neural mechanisms of selective visual attention. Annu Rev Neurosci 1995;18:193–222.

Eimer M. The N2pc component as an indicator of attentional selectivity. Electroencephalogr Clin Neurophysiol 1996;99:225–34.

Eimer M. Mechanism of Visuospatial Attention: Evidence from Event-related Brain Potentials. Visual Cogn 1998;5(1/2):257–86.

Elsass P, Christensen SE, Mortensen EL, Vilstrup H. Discrimination between organic and hepatic encephalopathy by means of continuous reaction times. Liver 1985;5:29–34.

Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy–definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. Hepatology 2002;35:716–21.

Fitts PM, Seeger CMS-R. S-R compatibility: spatial characteristics of stimulus and response codes. J Exp Psychol 1953;46:199–210.

Fitts PM, Deininger RLS-R. S-R compatibility: correspondence among paired elements within stimulus and response codes. J Exp Psychol 1954;48:483–92.

Gitlin N, Lewis DC, Hinkley L. The diagnosis and prevalence of subclinical hepatic encephalopathy in apparently healthy, ambulant, non-shunted patients with cirrhosis. J Hepatol 1986;3:75–82.

Hashimoto T, Kashii S, Kikushi M, Honda Y, Nagamine T, Shibasaki H. Temporal profile of visual evoked responses to pattern-reversal stimulatin analyzed with whole-head magnetometer. Exp Brain Res 1999;125:375–82.

Heinze HJ, Mangun GR, Burchert W, Hinrichs H, Scholz M, Munte TF, Gos A, Scherg M, Johannes S, Hundeshagen H. Combined spatial and temporal imaging of brain activity during visual selective attention in humans. Nature 1994;372:543–6.

Hillyard SA, Anllo-Vento L. Event-related brain potentials in the study of visual selective attention. Proc Natl Acad Sci USA 1998;95:781–7.

Hommel B. The role of attention for the Simon effect. Psychol Res 1993;55: 208–22.

Hommel B. Spontaneous decay of response-code activation. Psychol Res 1994;56:261–8.

Hopf JM, Luck SJ, Girelli M, Hagner T, Mangun GR, Scheich H, Heinze HJ. Neural sources of focused attention in visual search. Cereb Cortex 2000;10:1233–41.

Hopfinger JB, Maxwell JS. Appearing and disappearing stimuli trigger a reflexive modulation of visual cortical activity. Brain Res Cogn Brain Res 2005;25:48–56.

Hoshiyama M, Kakigi R. Effects of attention on pattern-reversal visual evoked potentials: foveal field stimulation versus peripheral field stimulation. Brain Topogr 2001;13:293–8.

Joebges EM, Heidemann M, Schimke N, Hecker H, Ennen JC, Weissenborn K. Bradykinesia in minimal hepatic encephalopathy is due to disturbances in movement initiation. J Hepatol 2003;38:273–80.

Johannes S, Munte TF, Heinze HJ, Mangun GR. Luminance and spatial attention effects on early visual processing. Brain Res Cogn Brain Res 1995;2:189–205.

Kugler CF, Petter J, Taghavy A, Lotterer E, Wensing G, Hahn EG, Fleig WE. Dynamics of cognitive brain dysfunction in patients with cirrhotic liver disease: an event-related P300 potential perspective. Electroencephalogr Clin Neurophysiol 1994;91:33–41.

LaBerge D. Attentional processing: the brain's art of mindfulness. Harvard University Press; 1995.

Lockwood AH. What's in a name? Improving the care of cirrhotics J Hepatol 2000;32:859–61.

Lockwood AH, Murphy BW, Donnelly KZ, Mahl TC, Perini S. Positron-emission tomographic localization of abnormalities of brain metabolism in patients with minimal hepatic encephalopathy. Hepatology 1993;18:1061–8.

Lockwood AH, Weissenborn K, Bokemeyer M, Tietge U, Burchert W. Correlations between cerebral glucose metabolism and neuropsychological test performance in nonalcoholic cirrhotics. Metab Brain Dis 2002;17:29–40.

Luck SJ, Hillyard SA. Electrophysiological correlates of feature analysis during visual search. Psychophysiology 1994a;31:291–308.

Luck SJ, Hillyard SA. Spatial filtering during visual search: evidence from human electrophysiology. J Exp Psychol: Hum Percept Perform 1994;1000–14.

Luck SJ, Chelazzi L, Hillyard SA, Desimone R. Neural mechanisms of spatial selective attention in areas V1, V2, and V4 of macaque visual cortex. J Neurophysiol 1997;77:24–42.

Mangun GR, Hillyard SA. Mechanisms and models of selective attention. In: Rugg D, Coles MGH, editors. Electrophysiology of mind: Event-related potentials and cognition. 1995: 86-131.

Mangun GR, Hillyard SA, Luck SJ. Electrocortical substrates of visual selective attention. In Meyer D, Kornblum S, editors. Attention and Performance XIV. 1993:219-243.

Nicoletti R, Umiltà C. Attention shifts produce spatial stimulus codes. Psychological-Research/Psychologische-Forschung 1994;56:144–50.

Oostenveld R, Praamstra P, Stegeman DF, van Oosterom A. Overlap of attention and movement-related activity in lateralized event-related brain potentials. Clin Neurophysiol 2001;112:477–84.

Osman A, Moore CM, Ulrich R, Bisecting RT. with lateralised readiness potentials: precue effects after LRP onset. Acta Psychologica 1995;90: 111–27.

Praamstra P, Oostenveld R. Attention and movement-related motor cortex activation: a high-density EEG study of spatial stimulus–response compatibility. Brain Res Cogn Brain Res 2003;16:309–22.

Quero JC, Hartmann IJ, Meulstee J, Hop WC, Schalm SW. The diagnosis of subclinical hepatic encephalopathy in patients with cirrhosis using neuropsychological tests and automated electroencephalogram analysis. Hepatology 1996;24:556–60.

Rikkers L, Jenko P, Rudman D, Freides D. Subclinical hepatic encephalopathy: detection, prevalence, and relationship to nitrogen metabolism. Gastroenterology 1978;75:462–9.

Rugg MD, Coles MGH. Electrophysiology of mind. Oxford: Oxford University Press; 1995.

Shedden GM, Nordgaard GL. ERP time course of perceptual and post-perceptual mechanisms of spatial selection. Cogn Brain Res 2001;11: 59–75.

Schomerus H, Hamster W, Blunck H, Reinhard U, Mayer K, Dölle W. Latent portasystemic encephalopathy. I. Nature of cerebral functional defects and their effect on fitness to drive. Dig Dis Sci 1981;26:622–30.

Simon JR, Rudell AP. Auditory S-R compatibility: the effect of an irrelevant cue on information processing. J Appl Psychol 1967;51: 300–4.

Schiff S, Vallesi A, Mapelli D, Orsato R, Pellegrini A, Umilta C, Gatta A, Amodio P. Impairment of response inhibition precede motor alterartion in the early stage of liver cirrhosis: a behavioral and electrophysiological study. Metab Brain Dis 2005;20:381–92.

Tarter RE, Hegedus AM, Van Thiel DH, Schade RR, Gavaler JS, Starzl TE. Nonalcoholic cirrhosis associated with neuropsychological dysfunction in the absence of overt evidence of hepatic encephalopathy. Gastroenterology 1984;86:1421–7.

Ungerleider L, Mishkin M. Two cortical visual systems. In: Ingle DJ, Goodale MA, Mansfield RJW, editors. Analysis of visual behavior. 1982.

Valle-Inclán F. The locus of interference in the Simon effect: an ERP study. Biol Psychol 1996;43:2–147.

Vallesi A, Mapelli D, Schiff S, Amodio P, Umilta C. Horizontal and vertical Simon effect: different underlying mechanisms? Cognition 2005;96: B33–B43.

van der Lubbe RHJ, Jaskowski P, Wauschkuhn B, Verleger R. Influence of time pressure in a simple detection task, a choice-by-location task and the Simon task. J Psychophysiol 2001;15:241–55.

Wascher E. The timing of stimulus localisation and the Simon effect: an ERP study. Exp Brain Res 2005;163:430–9.

Wascher E, Wauschkuhn B. The interaction of stimulus- and rensponse-related processes measured by event-related lateralizzations of the EEG. Electroencephalogr clin Neurophysiol 1996;99: 149–62.

Wascher E, Schatz U, Kuder T, Verleger R. Validity and bountary conditions of automatic response activation in the Simon task. J Exp Psychol: Hum Percept Perform 2001;27:731–51.

Weissenborn K, Ennen JC, Schomerus H, Ruckert N, Hecker H. Neuropsychological characterization of hepatic encephalopathy. J Hepatol 2001;34:768–73.

Wiegand K, Wascher E. Dynamic aspects of stimulus-response correspondence: evidence for two mechanisms involved in the Simon effect. J Exp Psychol Hum Percept Perform 2005;31:453–64.

Wijers AA, Lange JJ, Mulder G, Mulder LGM, An ERP. study on visual spatial attention and letter target detection for isoluminant and non isoluminant stimuli. Psychophysiology 1997;553–65.

Woldorff MG, Liotti M, Seabolt M, Busse L, Lancaster JL, Fox PT. The temporal dynamics of the effects in occipital cortex of visual-spatial selective attention. Brain Res Cogn Brain Res 2002;15:1–15.

Zafiris O, Kircheis G, Rood HA, Boers F, Haussinger D, Zilles K. Neural mechanism underlying impaired visual judgement in the dysmetabolic brain: an fMRI study. Neuroimage 2004;22:541–52.