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Early markers of neural dysfunction and compensation: A model from minimal hepatic encephalopathy

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HIGHLIGHTS

- Patients with MHE showed attention deficits, as revealed by the lower P3a and impaired performance.
- Patients without MHE did not show a decline in performance, although they displayed a P3a reduction.
- Patients without MHE showed an enhancement of the N2 and nogo-P3 amplitudes compared to controls.
- The N2 and nogo-P3 increase reflects compensatory mechanisms recruited by patients without MHE.

ABSTRACT

Objective: The Inhibitory Control Task (ICT) was used to detect minimal hepatic encephalopathy (MHE). ICT assesses attention, working memory and inhibition by evaluating performance in *detect*, *go* and *nogo* trials, respectively. The event-related potentials (ERPs) elicited by the ICT provide insight into neural mechanisms underlying the cognitive alterations associated with MHE.
Methods: The performance and the ERPs elicited by ICT were measured in 31 patients with cirrhosis (13 with and 18 without MHE) and in 17 controls. The latency and amplitude of the N2, P3a, P3b and nogo-P3 were compared among the groups.
Results: Patients with MHE performed worse in all ICT trials compared to patients without MHE and controls. Cirrhotic patients, both with and without MHE, displayed a reduction in P3a amplitude, selectively in the *detect* trials. Patients without MHE exhibited greater N2 and nogo-P3 amplitudes compared to patients with MHE and controls.
Conclusions: Both patients with and without MHE displayed neural alterations reflecting attentional deficits (i.e., P3a attenuation). However, patients without MHE coped with such dysfunctions by recruiting compensatory neural mechanisms, as suggested by the enhancement of the nogo-P3 and N2 amplitudes coupled with a normal ICT performance.
Significance: The study suggests how initial brain dysfunction might be compensated for by recruitment of additional neurocognitive resources.

1. Introduction

Hepatic encephalopathy (HE) is a brain dysfunction caused by liver insufficiency and/or portal-systemic shunting, and manifests a wide spectrum of neurological and psychiatric alterations. In its subclinical form, HE causes a kind of minimal cognitive impairment, affecting selective attention, visuomotor ability, psychomotor speed, executive function and response inhibition (Weissenborn et al., 2001; Amodio and Gatta, 2005) as well as

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neurophysiological alterations (Amodio et al., 2004; Bersagliere et al., 2013). This condition is called Minimal HE (MHE) (Ferenci et al., 2002) and can be considered as a paradigm to study reversible mild cognitive dysfunction.

Recently, the Inhibitory Control Task (ICT) has been proposed as a useful test for the diagnosis of MHE (Bajaj et al., 2008). The ICT is an adapted version of the paradigm used by Garavan et al. (1999), and provides information about several cognitive functions, from low-level or '*basic*' abilities (i.e., selective and sustained attention) to higher-level functions, such as working memory updating and response inhibition (Cona et al., 2013a,b). This distinction between low-level and high-level functions is based on the fact that the latter require the former but not *vice versa*. Indeed, a successful ICT performance requires: (i) to focus attention on the relevant stimuli (selective attention) and maintain it over time, throughout the task (sustained attention), (ii) to store and continuously update the representations of the upcoming stimuli in memory (working memory updating), and (iii) to inhibit possible prepotent but inappropriate, responses (response inhibition).

In a previous study designed to assess the usefulness of the ICT for purposes of MHE diagnosis, Amodio et al. (2010) observed that performance on '*go trials*' (i.e., trials requiring to press a key in response to a relevant visual stimulus on the computer screen) could discriminate patients with MHE from controls, while this was not the case for '*nogo trials*' (i.e., trials in which the upcoming visual stimuli were associated with the inhibition of key pressing). The authors suggested that this was due to the fact that in a condition of insufficient attention, the measurement of the ability to inhibit a response is less meaningful. In other words, a correct non-response can be the result of a lapse in attention rather than the result of an efficient inhibitory process. Thus, behavioral ICT measures alone do not seem sufficient to establish which cognitive functions are affected by a pathological process.

In the present study, the excellent temporal resolution of ERPs was utilized to better define which of the cognitive processes involved in performing the ICT are affected in patients with MHE. In this respect, ICT is a suitable task to have an overview of MHE-related cognitive alterations, since it assesses a set of processes, including attention, working memory updating and inhibition. Moreover, ERPs are more effective than behavioral measures to address this issue, since an electrical brain response is evoked even for trials where no overt behavioral response is required (i.e.'nogo trials').

As for the ERP components investigated, the P3a is a positive wave occurring roughly 300 ms post-stimulus over frontal and central regions. The P3a is considered to be associated with attentional processes (Escera et al., 2000; Polich, 2007).

The P3b is a positive deflection reaching its maximum amplitude over the parietal sites of the scalp. The peak latency of the P3b occurs roughly at 300–400 ms after the onset of the stimulus. The P3b is the best-known ERP correlate of updating information in working memory (Polich, 2007).

The electrophysiological indexes of response inhibition are: the N2, expressed over central and fronto-central regions as a negative potential developing between 180 and 400 ms post-stimulus, and the nogo-P3, a positive deflection over central sites peaking between 300 and 600 ms post-stimulus (e.g., Falkenstein et al., 1999; Bokura et al., 2001). While the inhibitory-related significance of the nogo-P3 has been consistently demonstrated (Kok et al., 2004), the functional meaning of the N2 is more debated. More specifically, several studies have suggested that the N2 reflects the detection of a conflict between alternative responses, rather than inhibition *per se* (Donkers and Van Boxtel, 2004; Randall and Smith, 2011). Likewise, a recent review suggests that the N2 might be better conceived as a general correlate of cognitive control (Folstein and Van Petten, 2008).

The present study was aimed at increasing our insight into the neurocognitive alterations related to MHE. Specifically, we focused on investigating the effect of MHE on the behavioral and electrophysiological correlates of attention, working memory and inhibition processes. We hypothesized that, if MHE is associated with a deficit in a given cognitive process (e.g., in attention or inhibition) this would be revealed by an alteration in the pertinent ERP correlate (e.g., delayed and/or attenuated attention-related ERP 'P3a' or inhibition-related ERP nogo-P3, respectively).

2. Materials and methods

2.1. Participants

A convenient sample of 48 participants was enrolled in the study: 31 patients with liver cirrhosis (age: 54 ± 10 years, mean ± SD; 25 males; education level: 11 ± 4 years), and 17 age-matched healthy controls (age 54 ± 13 years; 7 males, education level: 15 ± 2 years). Demographic data are reported in Table 1. None of the patients had cardiac, renal, neurological or psychiatric co-morbidity, nor did they take psychoactive medication or were alcohol misusers at the moment of the evaluation. The diagnosis of cirrhosis was made on historical, clinical, laboratory, endoscopic and radiological data and, where needed, confirmed by a liver biopsy (see Table 1 for more details on clinical features of the sample). The severity of hepatic failure was assessed by Pugh's modification of the Child score (Pugh et al., 1973) and the MELD (model for end-stage liver disease) score (Malinchoc et al., 2000). These are the most widely used scores for classifying the stage of liver disease. On the day of study, none of the patients had evidence of symptomatic hepatic encephalopathy (HE). Participants were always tested in the morning (at around 10 am), after a light breakfast.

The clinical evaluation of HE was performed by expert neuropsychologists (S.S. and G.C.) and a clinician with high international

Table 1
Demographic and clinical variables and ICT measures of the sample. Weighted lure was calculated as follows: $WL = L/(GoAcc)^2$.

	Patients with MHE	Patients without MHE	Controls
Demographic and clinical variables			
Number	13	18	17
Age (years)	54 ± 5	53 ± 11	54 ± 13
Education (years)	9 ± 3	13 ± 4	15 ± 2
Aetiology of cirrhosis (virus/alcohol/mixed) (N)	3/6/4	9/6/3	–
CHILD (a/b/c) (N)	3/4/6	7/6/5	–
MELD	14 ± 5	11.5 ± 5	–
Bilirubin (μmol/L)	44.5	70	–
Albumin plasma level (g/L)	36	37.8	–
Prothrombin time (%)	58	47	–
Esophageal varices (N)	8	6	–
Prior episodes of HE (N)	8	5	–
P3–P4 MDF	8.8	11	–
P3–P4 beta (%)	14	28	–
P3–P4 alpha (%)	31	48	–
P3–P4 theta (%)	48	17	–
P3–P4 delta (%)	6.48	6.42	–
PHES score	−1.3	1	–
ICT measures			
Detect accuracy (%)	86 ± 10	91 ± 13	95 ± 8
Go accuracy (%)	74 ± 20	89 ± 17	94 ± 2
Nogo accuracy (%)	67 ± 14	79 ± 14	82 ± 10
Detect RTs (ms)	565 ± 80	534 ± 70	521 ± 47
Go RTs (ms)	615 ± 86	576 ± 76	566 ± 52
Weighted lure (WL)	60 ± 114	11 ± 15	8 ± 5