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Hepatic encephalopathy is associated with slowed and delayed stimulus-associated somatosensory alpha activity

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HIGHLIGHTS

- This study for the first time investigated alterations of oscillatory brain activity within the somatosensory system in hepatic encephalopathy (HE).
- The frequency of somatosensory alpha activity was slowed and its stimulation-induced rebound delayed with increasing HE severity.
- These findings provide further evidence for a global slowing of brain activity in HE and a deficit of somatosensory stimulus processing.

ABSTRACT

Objective: Hepatic encephalopathy (HE) is associated with motor symptoms and attentional deficits, which are related to pathologically slowed oscillatory brain activity. Here, potential alterations of oscillatory activity in the somatosensory system were investigated.
Methods: 21 patients with liver cirrhosis and varying HE severity and 7 control subjects received electrical stimulation of the right median nerve while brain activity was recorded using magnetoencephalography (MEG). Oscillatory activity within the contralateral primary somatosensory cortex (S1) and its stimulus-induced modulation were analyzed as a function of disease severity.
Results: Median nerve stimuli evoked an early broadband power increase followed by suppression and then rebound of S1 alpha and beta activity. Increasing HE severity as quantified by the critical flicker frequency (CFF) was associated with a slowing of the alpha peak frequency and a delay of the alpha rebound.
Conclusion: The present results provide the first evidence for a slowing of oscillatory activity in the somatosensory system in HE in combination with a previously unknown deficit of S1 in adjusting activation levels back to baseline.
Significance: These findings advance the understanding of the manifold symptoms of HE by strengthening the theory that disease related slowing of oscillatory brain activity also affects the somatosensory system.

1. Introduction

Hepatic encephalopathy (HE) is a frequent, neuropsychiatric complication of acute and chronic liver diseases comprising a range of different symptoms of varying severity, including vigilance, cognitive, and motor deficits (Butterworth, 2000; Ferenci et al., 2002; Häussinger & Blei, 2007; Prakash and Mullen, 2010). In the extreme, HE can lead to coma and death, but even in its mildest forms without overt clinical symptoms, HE impairs many aspects of daily life functioning (Groeneweg et al., 1998). Its pathophysiological mechanisms, however, are not yet fully understood.

HE has been associated with slowed and pathologically synchronized oscillatory brain activity. Magneto- and

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electroencephalography studies (M/EEG) demonstrated a slowing of the peak frequency of spontaneous brain activity (e.g. Kullmann et al., 2001; Montagnese et al., 2007; Amodio et al., 2009) and a stronger but slowed thalamo-cortico-muscular coupling was associated with the tremor-like motor symptoms of HE (Timmermann et al., 2002, 2003, 2008). In addition, a slowing and impaired attentional modulation of stimulus-induced visual activity in the gamma band was shown (Kahlbrock et al., 2012). Importantly, studies using the critical flicker frequency (CFF) as a behavioral oscillatory marker of HE severity (Kircheis et al., 2002; Romero-Gómez et al., 2007; Sharma et al., 2007; Prakash and Mullen, 2010) revealed a correlation between the slowing of oscillatory brain activity and the CFF (Timmermann et al., 2008; Kahlbrock et al., 2012). Hence, slowed oscillatory activity in the brain is thought to be a key pathophysiological mechanism underlying the different clinical symptoms in HE (Timmermann et al., 2005, 2008). Yet, it is not clear to what extent these pathophysiological alterations affect different sub-systems of the brain.

A predominant feature of the somatosensory system is oscillatory alpha activity (8 to 12 Hz), which is thought to reflect the degree of engagement/disengagement of a cortical region (Pfurtscheller et al., 1996; Jensen and Mazaheri, 2010; Foxe and Snyder, 2011). In early somatosensory cortices, the processing of simple somatosensory stimuli is associated with a characteristic modulation of alpha activity: It is initially suppressed, indicating cortical activation, and subsequently rebounds to and often briefly above baseline levels (Salenius et al., 1997; Nikouline et al., 2000; Della Penna et al., 2004). This well-known and reliable response of alpha activity to simple somatosensory stimulation represents a useful measure of oscillatory processing in the somatosensory system.

In HE, the study of somatosensory evoked potentials has already allowed the first insights into somatosensory processing. A prolongation of peak and inter peak latencies in combination with a deformation or loss of somatosensory evoked components was demonstrated, indicating altered and delayed processing of simple somatosensory stimuli (Yang et al., 1985; Chu and Yang, 1987; Davies et al., 1991; Blauenfeldt et al., 2010). However, oscillatory activity and in particular oscillatory alpha activity has not yet been studied in this context.

The objective of the present work was to investigate potential alterations of oscillatory activity in primary somatosensory areas in association with stimulation of the median nerve in HE using MEG. Our findings provide evidence for a slowing of somatosensory alpha activity and a delayed stimulus-associated alpha rebound. Thereby, they extend the notion of slowed oscillatory brain activity as a key phenomenon in HE to the somatosensory system and advance the understanding of the disease.

2. Methods

2.1. Subjects and clinical evaluation

21 patients with liver cirrhosis and 7 healthy controls underwent a clinical assessment and standard blood examination including venous ammonia levels. Single subject characteristics are given in Table 1. Liver cirrhosis was verified by sonography or fibroscan (>13 kPa). The etiology of liver cirrhosis was assessed by examining each patient's medical history. Liver function was estimated according to the Child Pugh score (Pugh et al., 1973).

For the assessment of HE severity, we chose a twofold approach: We used both (i) the well-established *West-Haven*-Criteria (Ferenci et al., 2002) and (ii) the critical flicker frequency (CFF), which was suggested as a new and more fine-graded measure of HE (Kircheis et al., 2002).

Table 1
Participant data. Data are summarized using mean values ± standard deviation (Controls = healthy control subjects, HE0 = cirrhotic patients showing no signs of hepatic encephalopathy (HE), mHE = minimal HE, HE1 = HE grade 1, M = male, F = female, CFF = critical flicker frequency, ALC = alcoholic, PSC = primary sclerosing cholangitis, HCV = hepatitis C virus, CRYP = cryptogenic, PBC = primary biliary cirrhosis).

Group	Subj. No.	Age (y)	Sex	CFF (Hz)	Etiology of cirrhosis	Child Pugh score
Controls	1	52	M	44.6	–	–
	2	58	F	41.4	–	–
	3	61	F	39.4	–	–
	4	74	M	38.1	–	–
	5	67	M	46.2	–	–
	6	48	M	39.3	–	–
	7	69	M	38.1	–	–
	n = 7	**61.3 ± 9.4**		**41.0 ± 3.2**		
HE0	8	50	M	43.2	ALC	A
	9	44	F	43.3	PSC	A
	10	70	F	42.2	HCV	A
	11	76	F	39.6	CRYP	B
	12	62	F	39.6	PBC	A
	13	54	M	42.7	HCV	A
	n= 6	**59.3 ± 12.2**		**41.8 ± 1.7**		
mHE	14	67	F	40.2	HCV	A
	15	63	M	39.3	ALC	A
	16	52	M	39.3	HCV	A
	17	62	M	40.4	CRYP	A
	18	56	M	42.0	HCV	A
	19	77	M	-	HCV	A
	20	53	F	41.3	ALC	B
	21	43	F	37.1	ALC	C
	n = 8	**59.1 ± 10.4**		**39.9 ± 1.6**		
HE1	22	57	M	38.0	ALC	B
	23	58	M	36.7	HCV	C
	24	45	M	36.2	PSC	B
	25	61	M	35.5	HCV	C
	26	70	M	37.6	ALC	A
	27	63	M	36.7	ALC	A
	28	47	M	36.2	ALC	B
	n = 7	**57.3 ± 8.8**		**36.7 ± 0.9**		