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Lowered frequency and impaired modulation of gamma band oscillations in a bimodal attention task are associated with reduced critical flicker frequency

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ABSTRACT

Visual attention is associated with occipital gamma band activity. While gamma band power can be modulated by attention, the frequency of gamma band activity is known to decrease with age. The present study tested the hypothesis that reduced visual attention is associated with a change in induced gamma band activity. To this end, 26 patients with liver cirrhosis and 8 healthy controls were tested. A subset of patients showed symptoms of hepatic encephalopathy (HE), a frequent neuropsychiatric complication in liver disease, which comprises a gradual increase of cognitive dysfunction including attention deficits. All participants completed a behavioral task requiring shifts of attention between simultaneously presented visual and auditory stimuli. Brain activity was recorded using magnetoencephalography (MEG). The individual critical flicker frequency (CFF) was assessed as it is known to reliably reflect the severity of HE.

Results showed correlations of behavioral data and HE severity, as indexed by CFF. Individual visual gamma band peak frequencies correlated positively with the CFF ($r = 0.41$). Only participants with normal, but not with pathological CFF values showed a modulation of gamma band power with attention.

The present results suggest that CFF and attentional performance are related. Moreover, a tight relation between the CFF and occipital gamma band activity both in frequency and power is shown. Thus, the present study provides evidence that a reduced CFF in HE, a disease associated with attention deficits, is closely linked to a slowing of gamma band activity and impaired modulation of gamma band power in a bimodal attention task.

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Introduction

Cortical gamma band activity (30–100 Hz) is known as a key correlate of cognition (Fries et al., 2008) and has been associated with various cognitive functions (Gray et al., 1989; Roelfsema et al., 1997; Tallon-Baudry et al., 1998), including attention (Fries et al., 2001; Hoogenboom et al., 2006, 2010; Kaiser et al., 2006; Lachaux et al., 2005; Steinmetz et al., 2000). The power of visually induced gamma band activity can be modulated by attention (Gruber et al., 1999; Kahlbrock et al., 2012; Siegel et al., 2008; Tallon-Baudry et al., 2005; Vidal et al., 2006; Wyart and Tallon-Baudry, 2008). The frequency of visually induced gamma band activity seems to be specific to certain cognitive operations. Vidal et al. (2006) showed in their study that distinct frequencies of gamma band oscillations are related to attention and grouping related activity, respectively. However, when stimuli, cognitive operation, and cognitive demand remain constant, gamma band power and frequency have been demonstrated to be very consistent across measurements within-subjects. Nevertheless, high inter-subject variability in power and frequency of gamma band responses can be observed (Hoogenboom et al., 2006; Muthukumaraswamy et al., 2010). The underlying causes of this variability have not been finally explained so far.

Two recent studies, including participants from first to fifth decade of life, have shown that the frequency of gamma band activity decreases with age (Gaetz et al., 2011b; Muthukumaraswamy et al., 2010). Moreover, in subjects suffering from schizophrenia, it has been shown that the frequency of phase-locked gamma band activity related to gestalt perception is decreased and correlates with specific symptoms of the disease, i.e. visual hallucinations, thought disorder, and disorganization (Spencer et al., 2004). Interestingly, these patients experience multiple cognitive deficits, which can be seen as core pathology of the disorder (Green, 1996).

Distinct oscillation features have been demonstrated in various neurological and psychiatric diseases (Schnitzler and Gross, 2005;

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Uhlhaas and Singer, 2006). Especially, a slowing of brain activity in lower frequencies, i.e. delta, alpha, and beta band activity has been demonstrated. For example, patients with brain infarct or brain tumor show increased activity in the delta band in perilesional areas (Butz et al., 2004; de Jongh et al., 2003). Patients with Alzheimer's disease show a reduction in resting state gamma band synchronization (Koenig et al., 2005).

Also in hepatic encephalopathy (HE), the neurological entity studied in the present work, spontaneous oscillatory activity and the mean resting activity electroencephalography (EEG) peak frequency have been shown to be progressively slowed (e.g., Amodio et al., 1999, 2009; Bajaj, 2010; Davies et al., 1991; Kullmann et al., 2001; Montagnese et al., 2007, 2011; Olesen et al., 2011; Parson-Smith et al., 1957; Van der Rijt et al., 1984). Alterations in the EEG are associated with the severity of HE (Marchetti et al., 2011). Hence, the EEG can be used to complement the neurological examination for HE, i.e., diagnosis, grading, and prediction (Amodio and Gatta, 2005; Guerit et al., 2009). HE is a frequent, potentially reversible, neuropsychiatric complication of chronic liver disease, involving multiple cognitive and motor symptoms, altered sleep patterns, and changes in vigilance state (for a review see Butterworth, 2000; Häussinger and Schliess, 2008). Of special relevance for the present study is one key symptom of HE — a gradual increase of attention deficits with increasing disease severity (Amodio et al., 2005; Kircheis et al., 2009; Pantiga et al., 2003; Weissenborn et al., 2001, 2005). Previous studies addressing the motor symptoms in HE revealed a pathologically slowed thalamo-cortico-muscular coupling with increasing severity of HE (Timmermann et al., 2002, 2003). Disease severity of HE can be quantified by determining the critical flicker frequency (CFF), which decreases with increasing disease severity (Kircheis et al., 2002; Prakash and Mullen, 2010; Romero-Gómez et al., 2007; Sharma et al., 2007). Accordingly, Timmermann et al. (2008) showed a strong correlation between the slowing of cortico-muscular coupling and the CFF. Based on the findings of slowed coupling in the motor systems of HE patients, Timmermann et al. (2005) hypothesized that a global slowing of oscillatory activity in various human cerebral subsystems could represent a key mechanism in the pathophysiology of HE. Along these lines, the question arises whether certain diseases that involve cognitive deficits are associated with a slowing of gamma band brain activity.

The present study aimed to test the relation of disease severity and the frequency of attention-related visually induced gamma band activity in a population of HE patients. In addition, the subject's capacity to modulate attention and concurrently modulate the power of attention-related occipital gamma band activity was scrutinized. Subjects completed a behavioral task requiring shifts of attention between simultaneously presented visual and auditory stimuli, while brain activity was recorded using magnetoencephalography (MEG). A reduction in attention-related gamma band peak frequencies with increasing disease severity was hypothesized, adhering to the hypothesis of slowed oscillatory brain activity as a key phenomenon in the pathophysiology of HE. Due to the known attentional deficits in this disease, a reduced capacity to modulate gamma band power with attention was expected.

Methods

Participants

Patients and controls

26 patients with liver cirrhosis, confirmed by sonography or fibroscan (>13 kPa) and 8 healthy, age-matched controls underwent a comprehensive clinical assessment including blood tests, neuropsychometric computer tests (Vienna test system, WINWTS, Version 4.50, 1999), assorted subtests of the test battery of Tests of Attentional Performance (TAP; PSYTEST, Herzogenrath, Germany), and CFF measurements (Eberhardt, 1994). As described in Kircheis et al. (2002) and according to *West-Haven* Criteria (Conn and Lieberthal, 1979) and psychometric test results, patients were classified into three groups: (i) HE0, i.e. patients showing no signs of HE, (ii) minimal HE (mHE), i.e., patients showing no clinical signs of HE, but pathological results in at least two psychometric tests, and (iii) HE1, i.e. manifest HE of grade 1, patients showing clinical signs of HE. The fourth group constituted of healthy control participants, i.e., (iv) controls (please see Table 1 for further details about subjects' characteristics). 24 patients performed the tests for grading of HE stage within two days, two patients within a week before or after the MEG measurement. All subjects had normal or corrected to normal vision and normal hearing. All of them gave their written informed consent. The study was approved by the local ethics committee (study no. 2895) and was performed in accordance with the Declaration of Helsinki.

General exclusion criteria were neurological/psychiatric illness, intake of psychoactive drugs, the existence of an HIV infection, Wilson's disease, Korsakoff's syndrome, and chronic pain syndrome. Patients with liver cirrhosis stemming from alcohol abuse had to be abstinent from alcohol for at least 6 months. To further control for this, blood

Table 1
Participant data.

Group	Subj. no.	Age	Sex	CFF	Cirrhosis etiology	Child Pugh Score
Control	1	51	m	44.3	–	–
	2	46	f	41.1	–	–
	3	67	m	39.8	–	–
	4	71	m	–	–	–
	5	69	f	40.8	–	–
	6	58	f	41.4	–	–
	7	61	f	38.4	–	–
	8	73	m	38.1	–	–
	n = 8	**62.0 ± 3.5**		**40.6 ± 0.8**		
HE0	9	55	f	39.4	Ethanol	A
	10	53	m	43.0	Ethanol	B
	11	48	m	41.8	Hepatitis C	C
	12	44	f	41.3	PBC	A
	13	69	f	38.4	Hepatitis C	A
	14	60	m	42.3	Ethanol	A
	15	70	m	39.0	Hepatitis C	A
	16	59	m	39.1	Hepatitis B	A
	n = 8	**52.3 ± 3.3**		**40.5 ± 0.6**		
mHE	17	60	m	38.6	Cryptogenic	B
	18	59	f	39.1	Hepatitis C	A
	19	57	m	38.3	Ethanol	A
	20	65	f	39.0	Ethanol	A
	21	56	m	35.7	Ethanol	B
	22	57	m	37.2	Ethanol	A
	23	62	m	39.9	Cryptogenic	A
	24	52	m	39.4	Hepatitis C	A
	n = 8	**58.5 ± 1.3**		**38.4 ± 0.5**		
HE1	25	69	m	38.6	Ethanol	B
	26	67	m	36.2	Autoimmune	C
	27	70	m	38.3	Hepatitis A/B	B
	28	72	m	35.5	Hepatitis C	B
	29	75	f	38.3	Cryptogenic	B
	30	65	f	37.7	Ethanol	C
	31	45	m	34.8	PSC	C
	32	45	f	32.6	Autoimmune	C
	33	63	m	36.4	Ethanol	A
	34	59	m	32.4	Ethanol	C
	n = 10	**63.0 ± 3.3**		**36.1 ± 0.7**		

Individual participant specific data are shown. For age and CFF, group mean values ± standard errors of the mean are given. Gender is coded as f = female and m = male. Etiology of liver cirrhosis was assessed by each patient's medical history, PSC = Primary sclerosing cholangitis, PBC = Primary biliary cirrhosis. Grading of liver cirrhosis was done according to the European Child-Pugh-classification (Pugh et al., 1973).

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