Research Article

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Electroencephalogram variability in patients with cirrhosis associates with the presence and severity of hepatic encephalopathy

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Background & Aims: The outputs of physiological systems fluctuate in a complex manner even under resting conditions. Decreased variability or increased regularity of these outputs is documented in several disease states. Changes are observed in the spatial and temporal configuration of the electroencephalogram (EEG) in patients with hepatic encephalopathy (HE), but there is no information on the variability of the EEG signal in this condition. The aim of this study was to measure and characterize EEG variability in patients with cirrhosis and to determine its relationship to neuropsychiatric status.

Methods: Eyes-closed, awake EEGs were obtained from 226 patients with cirrhosis, classified, using clinical and psychometric criteria, as neuropsychiatrically unimpaired (n = 127) or as having minimal (n = 21) or overt (n = 78) HE, and from a reference population of 137 healthy controls. Analysis of EEG signal variability was undertaken using continuous wavelet transform and sample entropy.

Results: EEG variability was reduced in the patients with cirrhosis compared with the reference population (coefficient of variation: 21.2% [19.3–23.4] *vs.* 22.4% [20.8–24.5]; $p < 0.001$). A significant association was observed between EEG variability and neuropsychiatric status; thus, variability was increased in the patients with minimal HE compared with their neuropsychiatrically unimpaired counterparts (sample entropy: 0.98 [0.87–1.14] *vs.* 0.83 [0.75–0.95]; $p = 0.02$), and compared with the patients with overt HE (sample entropy: 0.98 [0.87–1.14] *vs.* 0.82 [0.71–1.01]; $p = 0.01$).

Conclusions: Variability of the EEG is associated with both the presence and severity of HE. This novel finding may provide new insights into the pathophysiology of HE and provide a means for monitoring patients over time.

Lay summary: Decreased variability or increased regularity of physiological systems is documented in several disease states. Variability of the electroencephalogram was found to be associated with both the presence and severity of brain dysfunction in patients with chronic liver disease.

Keywords: Biological variability; Cirrhosis; Continuous wavelet transform; Electroencephalogram; Hepatic encephalopathy; Sample entropy; Spectral analysis.

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Abbreviations: CWT, continuous wavelet transform; EEG, electroencephalogram; HE, hepatic encephalopathy.

Introduction

Hepatic encephalopathy (HE) is a common and potentially disabling complication of chronic liver disease. It encompasses a continuum of neuropsychiatric abnormalities ranging from discrete impairment of executive brain functions to profound coma [1]. The development of HE compromises daily living activities, reduces patients' life quality and has a significant negative effect on survival [2–5]. Nevertheless, there is still no 'gold standard' for the diagnosis of this syndrome; in particular the diagnosis of minimal HE remains difficult to establish due to the discrete nature of the cognitive abnormalities characterizing the lower end of the HE spectrum [1].

The electroencephalogram (EEG) reflects cortical neuronal activity and has been used to facilitate the diagnose of HE since the early 1950s [6]. The main electrophysiological characteristic of HE is slowing of the mean frequency from the alpha range towards the theta and delta ranges [7]. The diagnostic efficacy of the EEG, in this situation, is difficult to gauge because: (i) there is no diagnostic gold standard for comparison; and, (ii) results may vary depending on whether reports are based on visual inspection or spectral analysis. Thus, there is considerable variation in the reported performance of the EEG, with sensitivities, for the diagnosis of overt HE, ranging from 43 to 100% and specificities ranging from 41 to 88% [7].

A number of other EEG features have been observed in patients with HE including: transient fast activities [7]; distinct topographical changes over the temporal and frontal areas [7]; and dissociation and anteriorization of the posterior basic rhythm with disease progression [8–11]. However, the predominant use of frequency estimates, for diagnostic purposes, has resulted in

a relative disregard of these other EEG characteristics and hence little is known about their importance or diagnostic utility.

The EEG signal, like many physiological time series, is complex, as the information contained within the signal comprises of a multitude of fast and slow frequencies with changing potentials. In addition, and contrary to classical concepts of physiological control, the output fluctuates in a complex manner, even in the resting state [12]. Deceased variability or increased regularity of a number of physiological rhythms has been reported in a variety of clinical settings and is invariably associated with worsening disease severity and poorer outcomes [13]. It has been shown, for example, that the complexity of the EEG decreases up to 25 min before an epileptic seizure [14] and that complexity decreases in Alzheimer's disease [15].

The advent of mathematical techniques with a basis in chaos theory and nonlinear dynamics, and the parallel advancements in computational methodology have facilitated the measurement and characterization of the variability and complexity of time series [16]. Continuous wavelet transform (CWT) and sample entropy are techniques which, in addition to conventional spectral analysis, can be used to characterize variability and transient features of the EEG [10,17–19]. CWT has better time-frequency resolution than Fast Fourier Transform [19] which is the technique most often employed for spectral analysis of the EEG. Sample entropy can be used to investigate the temporal dynamics of the EEG; it quantifies the degree of regularity *vs.* the degree of unpredictability of the signal and thus provided a measure of its variability [18]. Regular time series are characterized by low sample entropy while random time series, which have greater disorder and complexity, are characterized by high sample entropy.

The aims of the present study were: i) to characterise EEG rhythmicity and its topography based on CWT spectral analysis; ii) to characterize the variability of the EEG signal using dynamic CWT estimates and sample entropy; and, iii) to investigate possible interactions between EEG variability measures, neuropsychiatric status, and the aetiology and severity of the underlying liver disease.

Subjects and methods

Study populations

The patient population comprised of 226 patients (149 men: 77 women; mean [range] age 54.8 [26–80] years) with biopsy-proven cirrhosis, recruited at the Royal Free Hospital, London between 2008 and 2012. The aetiology of the liver injury was determined using clinical, laboratory, radiological and histological variables, while its severity was assessed using the model for end-stage liver disease (MELD) score and the Child-Pugh grading system [20]. All patients were clinically stable at the time of the study. Patients were excluded if they were under 25 or over 80 years of age; if they had suffered an episode of major hepatic decompensation within seven days of the assessment date; had hyponatraemia or renal failure; had significant cardiac or respiratory failure; insulin-dependent diabetes mellitus or non-insulin-dependent diabetes mellitus with poor glycaemic control; cerebrovascular disease; epilepsy; a history of significant head injury or other conditions likely to affect cerebral function. Patients were also excluded if they had misused alcohol or drugs in the previous three months or were taking psychoactive medications, including hypnotic drugs.

The reference population of 137 healthy volunteers (73 men: 64 women: mean age 38 [17–75] years) was recruited from amongst family, friends and staff working at the Royal Free Hospital, London and individuals who had experienced an isolated episode of fainting/dizziness but in whom clinical examination, the EEG, and cerebral imaging were completely normal. None had a history of liver disease, drank alcohol in excess of 20 g daily, or took prescription or over-the-counter medicines.

The study was conducted according to the Declaration of Helsinki (Hong Kong Amendment) and Good Clinical Practice (European guidelines). The protocol was approved by the Royal Free Hampstead NHS Trust Ethics Committee. All participating subjects, or their appropriately appointed guardians, provided written, informed consent.

Overall study procedures

Each recruited subject was assessed in a single session lasting approximately two hours. All assessments, apart from the EEG, were completed in the same quiet and well-lit room. The EEGs were performed in a dedicated recording room by a trained neurophysiologist. The procedures were always carried out in the same order using a standard set of instructions from scripted texts.

Mental state and psychometric assessment

Patients were clinically assessed by two hepatologists, working independently, and their mental state classified, using West Haven criteria [21], as either clinically unimpaired or as showing features of overt HE. Psychometric performance was assessed using the Psychometric Hepatic Encephalopathy Score (PHES) battery [22], which comprises of five paper and pencil tests *viz*: digit symbol, number connection A and B, serial dotting and line tracing, which has both time and error components. The PHES data were adjusted and scored using UK normative reference data [23]. Composite scores of less than two standard deviations below mean reference values were considered abnormal.

EEG recording

EEGs were recorded on one of two digital EEG systems, *viz*. Walter-Graphtek PL-Winsor (Walter-Graphtek GmbH, Emmendingen, Gerrmany) or MicroMed SystemPlus EVOLUTION (Micromed Sp.A., Mogliano, Veneto, Italy). Recordings were undertaken for six minutes, in a state of eyes-closed, relaxed wakefulness, using 23 silver-silver chloride electrodes placed according to the International 10–20 system. The impedance of the electrodes was kept below 5 KΩ.

Classification of neuropsychiatric status

Neuropsychiatric status was classified, on day of study, as: (i) unimpaired: no clinical evidence of HE and no psychometric abnormalities; (ii) minimal HE: no clinical abnormalities but impaired psychometric performance (*supra vide*); (iii) overt HE: clinically evident, characteristic neuropsychiatric disturbances.

EEG analysis

EEG pre-processing

A consecutive, 60–100 sec of eyes-closed, artefact-free recording was selected from each recording for EEG analysis. If the length of artefact-free recoding available for analysis was insufficient, the selection criteria were relaxed to allow use of sections that were artefact-free on the P3–P4 derivation.

CWT spectral and variability estimates

CWT is based on a mother wavelet function which can be translated and dilated to calculate time-frequency coefficients. The mother wavelet function can be chosen from a set of infinite functions. For purposes of this study a complex Morlet wavelet function with a bandwidth of 10 Hz and a centre frequency of 1 Hz was used. Scales for the mother wavelet were chosen to match frequencies ranging from 1–32 Hz with a 0.5 Hz between-scale frequency interval. The wavelet coefficients were divided into standardized frequency bands *viz*: delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz) and beta (12–32 Hz) and averaged over time; the scales contained within each frequency band were summated to provide a measure of absolute activity. The relative activity was calculated separately for each channel by dividing individual frequency bands with the summated energy for all bands and multiplying by 100. EEG variability was calculated using Matlab 2012a (The Matworks, Inc., Natick, MA, USA) as the coefficient of variation (CV) for the wavelet coefficients. Hence, for each frequency band successive epochs of 2 sec were extracted from the CWT output and the CV calculated as the standard deviation of the wavelet coefficient divided by its mean. The average CV across all frequency bands was used to provide a single measure of EEG variability for analysis.