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New spectral thresholds improve the utility of the electroencephalogram for the diagnosis of hepatic encephalopathy

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HIGHLIGHTS

- New spectral electroencephalogram thresholds for the diagnosis of any degree of hepatic encephalopathy have been identified using a modified receiver operating characteristic curve analysis and validated using a machine learning technique.
- The performance characteristics of these new thresholds are better balanced than the thresholds currently employed and hence their adoption would enhance diagnostic utility.
- Implementation of these new thresholds would not require any changes in data recording or collection.

ABSTRACT

Objective: The utility of the electroencephalogram (EEG) for the diagnosis of hepatic encephalopathy, using conventional spectral thresholds, is open to question. The aim of this study was to optimise its diagnostic performance by defining new spectral thresholds.
Methods: EEGs were recorded in 69 healthy controls and 113 patients with cirrhosis whose neuropsychiatric status was classified using clinical and psychometric criteria. New EEG spectral thresholds were calculated, on the parietal P3–P4 lead derivation, using an extended multivariable receiver operating characteristic curve analysis. Thresholds were validated in a separate cohort of 68 healthy controls and 113 patients with cirrhosis. The diagnostic performance of the newly derived spectral thresholds was further validated using a machine learning technique.
Results: The diagnostic performance of the new thresholds (sensitivity 75.0%; specificity 77.4%) was better balanced than that of the conventional thresholds (58.3%; 93.2%) and comparable to the performance of a machine learning technique (72.9%; 76.8%). The diagnostic utility of the new thresholds was confirmed in the validation cohort.
Conclusions: Adoption of the new spectral thresholds would significantly improve the utility of the EEG for the diagnosis of hepatic encephalopathy.

Abbreviations: PHES, Psychometric Hepatic Encephalopathy Score; ROC, Receiver Operating Characteristic; MV ROC, MultiVariable ROC; SVM, Support Vector Machine; SEDACA, Short Epoch, Dominant Activity, Cluster Analysis.

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Significance: These new spectral EEG thresholds optimise the performance of the EEG for the diagnosis of hepatic encephalopathy and can be adopted without the need to alter data recording or the initial processing of traces.

1. Introduction

Hepatic encephalopathy is one of the major complications of cirrhosis. In unselected populations approximately 30% to 45% of patients with cirrhosis will exhibit clinically apparent neuropsychiatric abnormalities, encompassing a wide spectrum of mental and motor disorders, and are classified as having *overt* hepatic encephalopathy; a further 22% to 75%, although apparently neuropsychiatrically unimpaired on clinical examination, will show significant abnormalities in both psychometric and neurophysiological performance and are classified as having *minimal* hepatic encephalopathy (Dhiman et al., 2010; Ferenci et al., 2002; Vilstrup et al., 2014). The presence of hepatic encephalopathy, whether minimal or overt, has a considerable impact on the execution of complex tasks, such as driving (Bajaj et al., 2009; Schomerus et al., 1981); health-related quality of life (Groeneweg et al., 1998; Montagnese et al., 2009); patient safety (Román et al., 2011); neurocognitive function post liver transplantation (Sotil et al., 2009); and, ultimately, survival (D'Amico et al., 2006; Stewart et al., 2007; Wong et al., 2015).

Electroencephalography (EEG) provides information useful for detecting, assessing and monitoring this complication of cirrhosis (Montagnese et al., 2004). The main electrophysiological characteristic of hepatic encephalopathy is slowing of the mean frequency from the alpha range towards the theta and delta ranges (Niedermeyer, 1998a).

The efficacy of the EEG for the diagnosis of hepatic encephalopathy is critically dependent on the type of analysis performed, as even those incorporating semi-quantitative classifications of the background frequency (Conn et al., 1977; Laidlaw, 1959), are subject to inter- and intra-operator variability. Thus, the reported sensitivity of *visual* analysis of the EEG, for the diagnosis of *overt* hepatic encephalopathy, ranges from 57% to 100% (Rehnstrom et al., 1977; Weissenborn et al., 1990), while the specificity ranges from 41% to 88% (Parsons-Smith et al., 1957; Weissenborn et al., 1990). Spectral analysis provides an automated estimate of the dominant EEG frequency (Van der Rijt et al., 1984) and, as such, is less inter- and intra-operator dependent (Amodio et al., 1996). Nevertheless, although frequency thresholds for the diagnosis of *overt* hepatic encephalopathy have been identified (Amodio et al., 1999; Van der Rijt et al., 1984) considerable variation is still observed in the reported diagnostic performance of spectral analysis, in this context, with sensitivities ranging from 43% to 100% (Van der Rijt et al., 1984; Weissenborn et al., 1990) and specificities from 64% to 81% (Weissenborn et al., 1990). To date, no thresholds have been identified, using conventional spectral analysis on the parietal P3–P4 lead derivation, to characterise patients with minimal hepatic encephalopathy.

Short Epoch, Dominant Activity, Cluster Analysis (SEDACA) is a technique for spatio-temporal decomposition of the EEG (Jackson and Sherratt, 2004; Montagnese et al., 2007). SEDACA-derived spectral estimates allow differentiation of patients with minimal hepatic encephalopathy from a reference population, whereas no such differentiation is possible using conventional spectral analysis (Montagnese et al., 2007). However, the SEDACA-derived spectral thresholds have not been independently validated, to date, and the technique is used primarily in a research setting.

Machine learning techniques explore the construction and study of algorithms to learn from and make predictions on data (Ortiz-Rosario and Adeli, 2013). Such algorithms operate by building a model from input examples to make data-driven predictions or decisions, without employing any theoretical *a priori* assumptions. There has been very little exploitation of these techniques to study EEG performance in patients with cirrhosis (Amodio et al., 2006).

The aims of this study were: (i) to derive new EEG spectral thresholds for the diagnosis of any degree hepatic encephalopathy on both the P3–P4 lead derivation and on SEDACA components; (ii) to validate the diagnostic performance of the newly derived thresholds in an independent cohort; and (iii) to validate the performance of the newly derived thresholds with a machine learning technique.

2. Subjects and methods

2.1. The study populations

2.1.1. The patient cohort

The patient cohort comprised of 226 patients (149 men: 77 women; mean [range] age 54.8 [26–80] yr) with biopsy-proven cirrhosis recruited from the Royal Free Hospital, London between 2008 and 2012. The aetiology of their liver injury was determined using clinical, laboratory, radiological and histological variables, whilst its severity was assessed using Pugh modification of the Child's grading system (Pugh et al., 1973). All were clinically stable at the time of the study. Patients were excluded if they were <25 or >80 years of age; if they had suffered an episode of major hepatic decompensation within seven days of assessment; had hyponatraemia or renal failure; significant cardiac or respiratory failure; insulin-dependent diabetes mellitus; 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 three months preceding assessment; if their manual dexterity was impaired; if they could not speak English; or were taking psychoactive medications.

2.1.2. The reference population

The reference population of 137 healthy volunteers (73 men:64 women: mean age 39 [17–75] yr) 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.

2.1.3. Creation of the identification and validation cohorts

The patients were ranked by their raw score on the Psychometric Hepatic Encephalopathy Syndrome (PHES) test battery of psychometric tests (Weissenborn et al., 2001) and then alternatively assigned to either an identification or a validation cohort. The 137 reference individuals were ordered by age before alternative assignment to one of the two cohorts. The terms identification