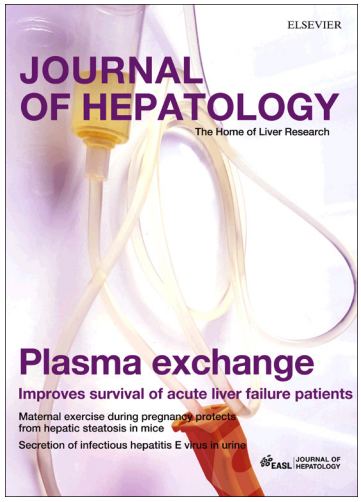

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Letter to the Editor

Tools and tactics for improving diagnosis of hepatic encephalopathy

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To the Editor,

We read with interest the paper from Montagenese *et al*. (2016) on the possible use of two novel approaches to determine ´neuropsychiatric normality´ in the context of a diagnosis of hepatic encephalopathy (HE) [1]. The authors challenge the conventional use of psychometric and neurophysiological testing based on reference to normative data and suggest that there may be advantages in defining 'normality' in terms of single patients' lifelong performance and/or in terms of risk. Three cases serve as examples for the relevance of the suggested approaches.

Better optimised tools and tactics for diagnosing HE would undoubtedly be welcomed; we do, however, have several concerns about both the proposed approaches. Semantic inconsistencies make it difficult to determine the exact approach in the system based on 'best performance'. First, it is unclear how the authors utilize the term ´baseline performance´. Thus, if a patient presents initially with overt HE, then any improvement/deterioration in their neuropsychiatric status would be judged against this baseline state. This, however, does not appear to be the way in which the term is applied; rather it appears that authors when referring to ´baseline performance´ actually mean 'best performance since the diagnosis of cirrhosis was established'. Second, it appears that this best performance is equated to ´top personal performance´ but these are far from the same; top personal performance is likely to have been attained before the person developed cirrhosis and could differ significantly from their best performance since that time. The arbitrary defined ´personal best` would also have to be adapted as the person ages. Third, neuropsychiatric comorbidities may compromise the ´personal best performance´ and thus bias the assessment of HE as illustrated in Case 2 where the authors state that an abnormal Mini Mental State Examination precluded testing for HE. We are not aware of any data that support this contention and are unsure why this patient was diagnosed with underlying alcohol-related, dietary-related, cerebro-vascular psychopathology rather than intractable, partially responsive chronic HE. The electroencephalogram (EEG) was grossly abnormal and although slowing of the mean cycle frequency may be observed in people with dementia, this degree of EEG abnormality if attributable to dementia *per se,* would be accompanied by a far greater degree of clinical abnormality than just 'inappropriateness' [2]. Finally, as neuropsychiatric comorbidities and age effects may compromise the ´personal best performance´, utilization of this information and, in the absence of normative reference data, its translation into guidelines useful for health systems and legislators would present considerable difficulties. Similar difficulties would arise with the utility of this system for clinical decision making, for example, in relation to driving [3].

The second proposed approach, for use in conjunction with the first or as a stand alone system, is to replace 'reference thresholds' with 'risk thresholds; defined by their ability to separate individuals who are likely or unlikely to develop an HE-related hospitalization in the future [1]. The authors provide illustrative,

but not validated data, showing that a PHES threshold of -2 and a spectral EEG Theta power threshold of 30% better predict the development of HE-related hospitalization over both 12 and 18 months than the current reference thresholds of -4 and 35% respectively. Selection of the risk thresholds was based on the lowest Cox-Mantel p value but performance data for these thresholds were not provided.

The major difficulty with these approaches is that they do not provide point diagnostic information and thus are not of value to clinicians who need to decide whether to treat a patient for HE at a given point in time; given the low toxicity of treatments prescribed for HE [4], it is hardly operational to wait for longitudinal data to see if the patient truly has HE or whether they may develop HE at some point in the future. As an alternative we would advocate retention of normative thresholds. These, however, need to be revisited, defined more appropriately, and validated prospectively to improve diagnostic and predictive validity. With this in mind we recently identified new spectral EEG thresholds for the diagnosis of any degree of HE and validated them in two independent populations and by reference to performance variables obtained using a machine learning technique [5]. The performance characteristics of these new thresholds, the most radical of which was the reduction in the theta activity threshold from <35% to <22.7%, are superior and better balanced than the thresholds currently employed [5]. Had Montagnese et al. [1] adopted these new EEG thresholds, and our paper was referenced in their text, then Cases 1 and 3 could have been correctly classified, based on their EEG findings. As such, the newly derived spectral thresholds may improve the utility of the EEG for the diagnosis of any degree of HE in clinical practice.

The major challenge in this patient population is the accurate diagnosis of neuropsychiatric impairment and a determination of its clinical relevance including, but not be confined to, a risk assessment. While the proposals have some merit, their practicality and utility must be questioned, at this time.

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