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Editorial

Hepatic encephalopathy revisited: Beyond the triphasic waves

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Brain function is of universal interest for both clinical practitioners and neuroscience researchers. Scalp electroencephalography (EEG) is a non-invasive technique to evaluate brain activity not only in patients with consciousness disturbance and/or neurodegenerative disorders but also healthy subjects. Along with the recent utilization of continuous EEG monitoring on the intensive care unit, growing evidence has accumulated for the value of scalp EEG analysis especially in ischemic-hypoxic brain injury and traumatic brain injury (Caricato et al., 2018). Though a crystallized wisdom of successful EEGers, the strong dependence of conventional EEG interpretation upon visual inspection still prevents EEG from wide application. By using functional connectivity analysis, Olesen et al. (2019) in this issue of *Clinical Neurophysiology* successfully underscored the importance of EEG in a large cohort of patients with liver cirrhosis. They found widespread disruption in functional connectivity with increases in connectivity in the theta (4–8 Hz) band, and decreased connectivity in the delta (1–3.5 Hz), alpha (8.5–13 Hz) and beta (13.5–26.5 Hz) bands, even in the absence of psychometric impairment (Olesen et al., 2019).

Over more than 6 decades, hepatic encephalopathy, one of the most important complications of cirrhosis, has been evaluated by EEG analysis (Foley et al., 1950). Besides the well-known triphasic waves, the main EEG feature of hepatic encephalopathy is slowing of the mean frequency in occipital leads from the alpha range to the theta or even delta range, reflecting the postulated pathophysiology that hyperammonemia, hyponatremia, or inflammatory cytokines, leading towards astrocyte dysfunction and neural oscillation disturbance (Schomer and Da Silva, 2012). However, semiquantitative classification of the background frequency is subject to inter- or even intra-rater variability (Parsons-Smith et al., 1957). Spectral analysis, a more consistent and reproducible method, revealed a relative theta power threshold for identifying patients with hepatic encephalopathy (Jackson et al., 2016).

Connectivity analysis has emerged by viewing the brain as a complex network and led toward identifying functional networks (Stam et al., 2007), beyond the notion of conventional EEG interpretation based on the analysis of waveform, frequency, and localization, and beyond the concept of the automated analysis of power analysis in different frequency bands. There are two major kinds of connectivity analyses using EEG data: functional connectivity and effective connectivity. Functional connectivity refers to the interaction between two or more neural systems, reflected by a statistical dependence of a variable indicating the activation or deactivation of a certain system (Friston, 2011). Functional connectivity analysis provides the predominant pattern of correlations that are useful to classify subjects into distinct groups. One of the essential limitations is that the resulting classification does not test or prove any hypothesis that classified groups have distinct connectivity. Another methodological problem is the contamination by neural activity generated in remote cortical regions and spread due to volume conduction (Blinowska et al., 2017). In contrast, effective connectivity measures causal influences from one neural system to another and can be analyzed by using Granger causality, transfer entropy, or directed transfer function.

Other than phase lag index (PLI), which is a measure of the amount of stable phase lags between two signals used by Olesen et al. (2019), there are several methods for exploring functional connectivity or interaction. Coherence analysis is a correlation of frequency spectra and a classical method for functional connectivity (Bendat and Piersol, 1980), generally preferred in the field of coma research (Stefan et al., 2018). In addition, measures such as phase locking value using phase difference between signals (Lachaux et al., 1999) and mutual information using the concept of entropy (Xu et al., 1997) have been proposed to separate the effects of amplitude and phase. However, these measures are susceptible to artificial interaction or volume conduction. For overcoming these obstacles, imaginary coherence (Nolte et al., 2004) and PLI (Stam et al., 2007) were proposed. For the imaginary coherence analysis, the imaginary part depends on the amplitude of the signal and the magnitude of the phase delay between the two signals (Hatz and Fuhr, 2018). Both imaginary coherence and PLI have been widely used; however, to the best of our knowledge, no report has proved significant superiority of one over the other for evaluating functional connectivity (Stam et al., 2007, Palva et al., 2018).

Functional connectivity analysis in the study of Olesen et al. (2019) has clarified the neural network disturbance in the absence of neuropsychological symptoms and provided distinctive features from conventional background activity analysis or spectral analysis. Though relatively complex and time-consuming, several reports have demonstrated potential utility of functional connectivity as biomarker for schizophrenia (Micheloyannis et al., 2006), autism (Peters et al., 2013), and Alzheimer disease (Blinowska et al., 2017). Further data accumulation will enable

us to determine cut-off values for early detection and monitoring of the effects of therapeutic interventions in patients with various neurological disorders.

EEG plays an important role in prognosis prediction. In anoxic encephalopathy, various markers of conventional EEG and connectivity analysis are proposed for evaluating brain function or predicting the outcome of patients (Wijdicks et al., 2006, Tjepkema-Cloostermans et al., 2017). In comatose patients after cardiac arrest, the revised Cerebral Recovery Index, based on continuous data extraction and the combination of a large set of quantitative EEG features and machine learning techniques, is reported to be a sensitive and reliable predictor of neurological outcome (Nagaraj et al., 2018). Recent wide-band EEG analysis has shed light on infraslow activity for predicting the prognosis or occurrence of acute symptomatic seizures (van Putten et al., 2015, Togo et al., 2018). The study by Olesen et al. (2019) demonstrates that now is the time to also revisit hepatic encephalopathy from the viewpoint of advanced EEG computational analysis.

Conflict of interest

The authors have no potential conflicts of interest to be disclosed.

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