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Editorial

Editorial on the focus point on breakthrough optics- and complex systems-based technologies of modulation of drainage and clearing functions of the brain

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1 Introduction

The crucial role of sleep in keeping health of the brain is an indisputable fact. Sleep has a critical function of clearance of unnecessary metabolites, and slow waves in neural activity contribute to memory consolidation. Deprivation of sleep contributes accumulation of toxins in the brain and the development of neurodegenerative diseases. It seems like that sleep scenarios of neural activity can be a crucial informative platform for the study of mechanisms underlying lymphatic clearance of waste and toxins from the brain as well as for early diagnosis and therapy of Alzheimer's and Parkinson diseases, dementia, sclerosis, etc. [1–4]. However, there are very limited methods for effectively extracting valuable diagnostic information from the analysis of neural rhythms during sleep.

This European Physical Journal Plus Focus Point is a collection of papers illustrating multidisciplinary approaches, some brave ideas and promising experimental and clinical results focusing on the study of therapeutic and diagnostic properties of sleep as well as the development of novel strategies for modulation of sleep functions. This issue refers to three main directions of active research in this field.

1.1 Nonlinear signal processing techniques

The development and application of modern approaches from complex systems science to treat this challenging problem is a promising research field, where in particular novel nonlinear signal processing techniques can reveal important information about the dynamics of the brain including modulation of its drainage and clearing functions. Due to the highly complex organization of physiological processes involving scale-invariant structures and a variety of rhythmic components as well as many factors complicating their processing, especially non-stationarity, artifacts, noise, etc., quite universal methods based on wavelet analysis, detrended fluctuation analysis, synchronization techniques, machine learning methods and other special techniques are applied and specified here. The given paper collection includes studies devoted to such universal methods. Thus, Pavlov et al. [5] investigate changes in the blood–brain barrier permeability in animals provoked by intermittent sound and reveal effects of the sound in the electrical activity of the brain. For this purpose, they combine the detrended fluctuation analysis and multiresolution wavelet analysis within an enhanced wavelet-based approach. Kurkin et al. analyze the oxygen saturation and electromyographic signals to study muscle activity during the single left- and right-hand movements. This paper hypothesizes that the dominant hand may require additional neuronal recruitment in the contralateral M1 cortex. Aiming to establish age-related changes in the electrical activity of the brain, Pavlov et al. [6] analyze the features of multichannel EEGs in groups of healthy elderly and younger adults during hand clenching and apply two wavelet-based methods. They reveal significant distinctions between these groups and show that characterization of age-related differences depends on the wavelet-based method used for signal processing. The paper by Pavlov et al. [7] offers a modified version of the fluctuation analysis, namely the extended detrended fluctuation analysis, which enables to evaluate two scaling exponents for a better quantification of inhomogeneous datasets, which are typical in Neuroscience. This work discusses effects of different types of non-stationarity on the method's performance and investigates the activation of brain lymphatic drainage during sleep. The proposed approach offers an indirect way to identify and characterize the nightly activation of the drainage and clearance of brain tissue. Runnova et al. [8] discuss spatial patterns in EEG activity during monotonous sound perception test. The problem of resistance to monotonous activity is of great interest, since monotonous activity accompanies

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almost any human activity—both creative and cognitive. This article examines the effect of monotonous exposure on volunteers complaining of severe daytime sleepiness. Short non-uniform periods of sleep have been demonstrated by all subjects during the neuropsychological testing. During the sleep periods, an increase in the interhemispheric difference in the spatial structures of brain EEG activity leads to an increase in both the speed of reaction and the duration of the subsequent stage of resistance to monotonous exposure. They found that the more complex the EEG structure was realized in the left hemisphere of the brain during a short period of sleep, the more successful was the subsequent period of the participant's cognitive response. Thus, such daytime sleepiness may be an adaptive mechanism for maintaining stability during prolonged monotonous exposure.

The blood–brain barrier plays a decisive role in protecting the brain from toxins and pathogens. The ability to analyze the BBB opening (OBBB) is crucial for the treatment of many brain diseases, but it is very difficult to noninvasively monitor OBBB. Semenova et al. [9] analyzed the EEG series of healthy rats with music-induced OBBB. Using machine learning technology, such as artificial neural network, authors effectively detected the number of fragments of EEG realizations recognized as OBBB that was confirmed by confocal imaging of OBBB.

1.2 Modeling of brain drainage mechanisms during sleep

The modeling of sleeping brain scenarios is one of the most evolving areas in neuroscience and sleep science. In this issue, we present several articles discussing new functional models that describe the complex processes of activation of brain drainage mechanisms during sleep.

In light of new findings about how much sleep can help clearing the brain of harmful metabolites, there is growing interest in different aspects of this process. For example, a change in the volume of the intercellular space is associated with the rhythm of sleep. The flow of water is carried out through AQP4 aquaporins, the expression of which, in turn, is controlled by the body's circadian clock. Usually, these rhythms are synchronized, and one may regard them as a single process. However, this is not always the case. Postnov et al. [10] apply a set of methods of nonlinear dynamics and synchronization theory to understand what situations can lead to desynchronization of the circadian rhythm and the sleep–wake cycle and how this happens. Importantly, the desynchronization scenarios found in this model study coincided with descriptions in the clinically accepted classification of sleep disorders.

Astrocytes are deeply involved in many regulatory processes in the neurovascular unit. Unlike neurons, these cells are not electrically excitable and do not generate spikes. Instead, intracellular calcium waves serve as a universal messenger. They arise in response to neuronal activity and control a variety of types of astrocyte response, from the release of potassium into the perivascular space of the nearest blood vessel to the formation of network patterns of activity. Understanding these functions raises many questions; in particular, if in a neuron its electrical activity is due to transmembrane currents, then in an astrocyte, the mechanism for generating the calcium spike itself is located inside the cell and consists in the release of calcium from internal storage. Known ways to trigger this process from outside the cell require the production of a second messenger, the inositol triphosphate IP3. However, it is not entirely clear whether the astrocyte has other, possibly faster pathways for activating the calcium response. Verisokin et al. [11] discuss a version of events. Analyzing the properties of Na/Ca-exchanger, they suggest that under certain conditions it can work like voltage-sensitive channels of a neuron, triggering a calcium wave in response to an increase in extracellular sodium concentration, which is somewhat similar to a neuron. Thus, the authors propose to expand the view on modeling the behavior of an astrocyte, taking into account extracellular sodium in the models as another player.

In another work by the same group of authors, the focus is on the network dynamics of astrocytes. Verveyko et al. [12] discuss the reasons for the amazing rhythmicity of spontaneous calcium dynamics, which suggests a possible complex organization of the corresponding information processing. Using an intricate network model built on 2D projections of real astrocytes, the authors show that the complex morphology of astrocytes and the random spread of their contacts with each other is sufficient to create a highly periodic "winning" wave pattern.

1.3 Optical methods

The development of understanding of the complex and interrelated processes in the brain parenchyma relies on the growing multimodality of optical methods, which make it possible to track two or more processes simultaneously. Usually, this requires additional fluorescent tracers, additional channels or new equipment. Kurochkin et al. [13] offer a fairly straightforward way to get new information through more detailed data analysis. They start with the fact that conventional microscopic imaging does not show the entire circulatory network, leaving the smallest of them invisible, the capillaries. This happens because with label-free imaging, the vessels are visible only by the erythrocytes filling them. Small vessels may be rarely visited by erythrocytes and remain invisible. The authors propose a way to track and remember the passage of each individual erythrocyte for subsequent ingenious work with their images. As a result, a branched and complex structure of the vascular tree becomes indeed visible where there are only a couple of vessels in a conventional image. Having obtained an accurate vessel map, the authors apply the well-known PIV method to it to construct a velocity map. Of course, nothing is completely free. To do all of this requires a longer blood flow record and good stability of a living object.

Postnikov et al. [14] presented a model of diffusion assessment through image processing: beyond the point-source paradigm. This work addresses the problem, which arises when one needs to find the diffusion coefficient of the brain's parenchyma processing realistic recordings of marker's spread under physiological experimental conditions in vivo. The latter implies that the source of the leakage is a complicatedly shaped vessel and the spread emerges due to the penetration of the blood–brain barrier. This situation drastically differs from the "point-source paradigm" applicable to the artificially constructed measurement scheme. The proposed method of image processing overcomes the mentioned difficulty by using the frame-by-frame comparison between the simulated pictures of spread from the realistically shaped sources and actual recordings. Maximization of the correlation coefficient between these two pictures gives the required parameter that is confirmed by using both the simulated surrogate data and the set of fluorescent images of the isolated event of blood–brain barrier opening. In addition, the work demonstrates that algorithms developed for image processing (such as blurring) can be used not only for artistic goals but are also able to be used for research purposes to study transport processes.

The recent discovery of the existence of meningeal lymphatic vessels states the completely new problem of explaining how the fluid propagates in such micro-channels. Lavrova et al. [15] propose a model, which can reproduce features revealed in live imaging of the intracranial lymph-mediated trafficking in zebrafish. The model belongs to the class of Barnblatt-Pattle nonlinear diffusion equations, but, in contrast to their conventional area of application, it operates not with a compressible gas moving through a solid porous matrix, but introduces an incompressible fluid (lymph), which deforms the surrounding elastic tube (lymphatic vessel). Due to the discussed duality of the mathematical descriptions, the latter case also results in the emergence of lymphatic flows which accurately correspond to the spatiotemporal dynamics observed in the living organism. Thus, this original approach opens promising perspectives for the quantitative modeling of lymph-mediated cerebral waste clearance processes.

Near-infrared spectroscopy (fNIRS) is a promising optical technology for noninvasive measurement of concentrations of oxygenated (HbO) and deoxygenated (HbR) hemoglobin in the brain tissues. Borchardt et al. [16] for the first time demonstrate that fNIRS has potential also for measuring concentrations of cerebral water in healthy people. Authors performed fNIRS measurements during rest to study fluctuations in concentrations of cerebral water, HbO and HbR in healthy control subjects (HC) and 18 acutely sleep-deprived HC. The results clearly show that fNIRS can become the bedside, safe and noninvasive technology for the measurement of functions of lymphatic system of the brain and for prognosis of brain diseases associated with injury of removing of toxins and wastes from the central nervous system. Kurkin [17] demonstrates that fNIRS is useful tool for the study of the brain oxygen saturation associated with the changes of electromyographic signals during muscle activity. Optic measurements depend on skin temperature, which changes significantly during wakefulness and during sleep. Salwa et al. [18] demonstrate the dependence of the effectiveness of optical measurements on skin temperature.

2 Outlook

The issue collected pilot studies in a pioneering direction to study the activation of drainage processes during sleep. For the first time, the possibility of assessing the state of the permeability of the blood–brain barrier only according to EEG data has been shown. A unique platform has been developed for modeling the complex processes of regulation of brain drainage processes during sleep, as well as for understanding the mechanisms underlying the nocturnal activation of lymphatic excretion of metabolites and waste compounds from the central nervous system.

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Data availability The data that support the findings of this study are available on request from the corresponding author.

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