



Advanced technologies and innovative strategies for neurotheranostics

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1 Introduction

Neurotheranostics is a rapidly growing field that includes promising technologies for the effective diagnosis of brain diseases and their personalized therapy, including preventive health technology [1–3]. It is expected that the market size is going to expand at an average annual growth rate of 10.87% between 2025 and 2035 and is anticipated to reach USD 1028.3 Billion by 2035, which is 3 times more than in 2024 [4]. The COVID-19 pandemic has further accelerated the shift toward neurotheranostics, especially when it became clear that the virus, even after infection, could contribute to the development of cognitive deficit [5]. This requires the creation of innovative approaches for neurotheranostics based on the search for new therapeutic targets, the development of wearable and AI-controlled preventive technologies for mass use, and the creation of novel scientific concepts that explain the fundamental mechanisms underlying the emergence of pioneering strategies for the treatment of brain diseases.

This European Physical Journal Special Topics is a collection of papers highlighting advanced technologies and innovative strategies for neurotheranostics, including a balanced number of articles devoted to preclinical and clinical directions. The contributions are subscribed into the following main areas.

2 Innovative strategies in neurotheranostics for practical medicine

Practical medicine is a translational platform for testing new strategies in the diagnosis and treatment of brain diseases. This issue presents 17 articles devoted to the application of innovative approaches to the treatment of stroke, cognitive dysfunction, traumatic brain injury (TBI) and other disorders in routine clinical practice.

Zaborova et al. [6] present a double-blind, placebo-controlled, parallel-group pretest–posttest clinical study of the short-term effects of neurochemical and enzymatic modulation (dopamine, acetylcholine, acetylcholinesterase inhibitor, and monoamine oxidase activity) on working memory and decision-making in 120 post-stroke patients (average age 40–70 years) using a quantitative, systems-oriented approach. The results revealed that targeted neurochemical modulation may influence specific domains of executive functioning after stroke. By linking biochemical indicators with cognitive outcomes, this work provides an interdisciplinary perspective on post-stroke cognitive rehabilitation and offers a framework for future studies using longer intervention periods and longitudinal follow-up. In another cohort of 144 patients (average age 40–75 years), the same group found that short-term cognitive training combined with citicoline may yield greater improvements in selected executive functions than either intervention alone in stroke patients. The study supports the use of controlled experimental paradigms for investigating multimodal approaches to post-stroke cognitive rehabilitation (Zaborova et al. [7]).

Demareva et al. [8] demonstrate acoustic markers of task-induced stress during transitions from baseline to cognitively demanding conditions in 20 participants (18 females, 2 males; average age 20.8 years). Analyzing speech and heart rate variability, the authors revealed that while acoustic features enable above-chance detection of

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task-induced cognitive stress under subject-independent conditions, their generalizability across different cognitive contexts is limited. The results highlight the importance of accounting for task-specific acoustic variability and support the need for multimodal and context-aware approaches to stress monitoring.

Interesting results in the new paradigm of lymphatic drainage were presented from the Bukhara branch of the Republican Scientific Centre for Emergency Medical Care. Clinical results were obtained between 2021 and 2025 on a total of 85 patients with severe TBI, which were divided into the control group (41 patients) receiving standard intensive care and the main group (44 patients) receiving the new anti-edema, lymphotropic and anti-neuroinflammatory therapy. Shoyimkulovich et al. [9] found that the main group shows a statistically significant reduction in pro-inflammatory cytokines (IL-6, IL-8, IL-1 β , IL-6, IL-8) and in marker of microglia health (TNF- α) in both the blood and the cerebrospinal fluid. However, in the control group, the indicated changes were less pronounced. The clinical efficacy of the proposed new therapeutic method was also confirmed by an improvement in the level of consciousness on the Glasgow Coma Scale, a more rapid recovery of neurological functions, and a reduction in the severity of perifocal edema as assessed by multislice computed tomography. In the main group, a return to consciousness was observed in 78.6% of patients, compared with 54.2% in the control group. The mortality rates were 15.9% and 41.5%, respectively. The use of the new therapy also reduced the length of stay in the intensive care unit from 17.4 ± 3.6 to 11.7 ± 2.4 days in the main vs. control groups. Authors concluded that the new method for improving brain drainage for TBI therapy is highly effective and promising.

The results of clinical studies on the application of new strategies in the treatment of cerebral drainage disorders underlie the pioneering direction of studying the representation of lymphatic vessels in human brain tissue. Shirokov [10] and Navolokin [11] presented pilot results obtained on human brain tissue, clearly indicating the presence of a lymphatic system in the central nervous system (CNS), which performs the important function of drainage and clearance of the brain. These results open up new perspectives in the search for new markers of brain water homeostasis and key targets for the treatment of brain edema, such as those based on non-invasive photobiomodulation (PBM). So, Trofimov et al. [12] present a retrospective clinical study of evaluation of the dynamics of cerebral edema, quantified by net water uptake, in relation to endovascular thrombectomy outcomes using the extended Thrombolysis in Cerebral Infarction scale and treatment results in 93 patients (44 men, 49 women; average age 68.7 years) with acute ischemic stroke. These results indicate that the dynamics of net water uptake might be a promising biomarker for cerebral edema following endovascular thrombectomy in acute ischemic stroke. In another clinical study on 78 patients (average age 35.1 years, 40 men, 38 women) with TBI, this research group highlights a new diagnostic method of severity TBI based on the evaluation of shear-mediated stress in the middle cerebral artery using biophysical characters of diffuse and focal injury patterns (Trofimov et al. [13]). Zaborova et al. [14] discuss in a review the emerging approaches in neurotheranostics for TBI, including an analysis of the epidemiology of neurologic (epilepsy, stroke, neurodegenerative disorders) and psychiatric (substance use, psychopathology, affective and cognitive disorders) problems in patients after TBI obtained in military, civilian, and sports settings. Ali et al. [15] demonstrate PBM as a promising method for an improvement of brain activity after stress.

A series of clinical studies presented by Kirichenko et al. [16], Kunitsyna et al. [17], Kryshchopava et al. [18], Lazareva et al. [19], Timoshenko et al. [20], Samsonov et al. [21], Lyanenko et al. [22], and Kastyro et al. [23] highlight innovative solutions in the diagnosis of sensory, psychological and regulatory disorders in the brain.

3 Promising strategies in neurotheranostics for sleep medicine

Recent discoveries have shown that sleep is a natural factor in the active removal of metabolites and waste products from CNS [24]. Therefore, sleep is regarded as a systemic marker for the development of many brain diseases, including Alzheimer's, Parkinson's, apnea-induced cognitive impairment, and other pathologies [24]. This section presents 12 articles highlighting modern approaches and promising strategies for both the diagnosis and assessment of brain disease progression based on sleep pattern analysis.

Zhuravlev et al. [25], Lazarenko et al. [26], Guyo et al. [27], Khanadeev et al. [28], and Adushkina et al. [29] present pioneering developments in characterizing the activity of the sleeping brain for the diagnosis of age-related changes in sleep and brain pathologies using mathematical modeling and nonlinear dynamic methods.

A recently emerging field is the development of markers of cognitive and neurodegenerative disorders based on the study of brain activity during sleep. Madaeva et al. [30], Berdina et al. [31], Orlova et al. [32], and Sergeev et al. [33] present new approaches to assessing the risk of developing cognitive dysfunction in patients with apnea and acute sleep deprivation as well as in people with Parkinson's disease.

Emelyanova et al. [34] and Putilov [35, 36] discuss innovative methods for assessing sleep patterns, including the analysis of cognitive brain function in healthy people.

Simonyan [37] in a review highlights modern trends toward integrating advanced technological solutions into specific research challenges, fostering the development of automated systems for analyzing sleep architecture and

potential “special” sleep events using photoplethysmographic waveform data. These systems exhibit high sensitivity and specificity compared to polysomnographic studies.

4 Preclinical breakthrough directions in neurotheranostics

The series of preclinical studies presented in this issue focuses on three directions and includes 19 articles. The first direction involves the development of promising mathematical models for neurotheranostics. These models are based on current trends in the study of brain drainage and clearance and describe the regulatory mechanisms of the neurovascular unit. The second area is related to the development of innovative approaches to the treatment of brain diseases, including TBI and glioma. The third area is dedicated to the development of new methodological approaches in experimental research.

Recent experimental studies characterize CNS not as a collection of independent cells, but as a closely integrated system of neurons, astrocytes, and blood vessels. According to this paradigm, there is a clear tendency to combine all these three components into a single system, and hence the concept of the neuroglyovascular unit. Lukin et al. [38] present a model of arachidonic acid metabolites modulation of neuronal activity via vasomodulatory pathways. This model includes astrocytic calcium, neural and vascular dynamics taking into account the synthesis of arachidonic acid and its metabolites by the astrocytes. The authors suggest that vascular dynamics acts by stimulating arachidonic acid metabolites, which directly affects synaptic activity. Elucidating the internal processes of the neuroglyovascular unit and its multi-unit network is an essential prerequisite for advancing the diagnosis and treatment of neuropathologies.

Verisokin et al. [39] demonstrate a model for a simulation-based personalized treatment of neuropathological conditions and prediction of intervention outcome. This model includes the neuroglyovascular unit and simulates the changes in neuronal activity in response to variations in norepinephrine concentration (stimulation) and gamma-aminobutyric acid level (inhibition).

Lavrova et al. [40] discuss a new fast computational method for evaluating Caputo fractional derivatives when the argument’s interval spans many orders of time. In this approach, the weakly singular kernel of the fractional derivative is approximated by a hierarchical, multiscale weighted sum of exponential functions, thereby converting the original convolution into a system of ordinary differential equations. The formulation ensures numerical stability and allows an efficient parallel implementation, making it suitable for analyzing long and oscillatory signals. Using intracellular data from neocortical pyramidal neurons, the authors show that the method accurately reproduces the firing-rate adaptation and reveals a spectrum of characteristic time scales consistent with ion-channel kinetics and slow electrogenic processes. The proposed approach offers a computationally efficient framework for modeling systems with long-term memory and for processing experimental neurophysiological data.

Loshkarev et al. [41] present a computational study of different BOLD responses to a single stimulus, as demonstrated by “sleeping” and “awake” neuroglyovascular units. Using a detailed quantitative mathematical model with sets of control parameters, the authors assess the differences in BOLD responses to external stimuli in sleep and wake states. The results revealed that for a certain range of stimulus strengths, the BOLD response during sleep is, on average, below the baseline, while during wakefulness, the opposite is true. Importantly, this also applies to local sleep states, when systemic noradrenaline levels remain high. Authors propose an explanation for this result based on the idea that a weaker response to incoming stimuli during sleep leads to weaker reactive hyperemia, while neuronal oxygen consumption changes less significantly. Furthermore, the authors discuss possible applications of the results to the analysis of experimental data.

Merkulova et al. [42] employ mathematical modeling to estimate the hydrodynamic resistance of cerebrospinal fluid flow within parenchymal channels. The authors introduce a method for post-processing previously acquired imaging datasets and provide a comparative evaluation of the hydrodynamic characteristics of the cerebral lymphatic vessels. They develop an approach for estimating hydrodynamic resistance in channels of arbitrary cross-sectional shape and present calculated results for channel fragments identified in the parenchyma of laboratory animals. This method might be useful for the analysis of the pathways by which beta-amyloid is transported from the brain to the meningeal lymphatic vessels, including the perivascular spaces of small blood vessels, the interstitial space of the brain parenchyma, and the cerebral lymphatic vessels located adjacent to perivascular spaces.

Komleva et al. [43] discuss *in vitro* and *ex vivo* models used to study microglia, ranging from classical primary cultures and immortalized cell lines to advanced human-relevant platforms, including induced pluripotent stem cell-derived microglia, organotypic brain slices, neuroimmune organoids, and microphysiological systems. Particular emphasis is placed on the capacity of these technologies to support neurotheranostic development by enabling mechanistic dissection of microglial aging, immunosenescence, and inflammasome-driven neuroinflammation, with a focus on NLRP3 signaling. The authors further discuss emerging integrative strategies that combine advanced neuroimmune platforms with artificial intelligence, machine learning, and digital twin frameworks to enhance data

integration, predictive modeling, and translational relevance. Together, these approaches position neuroimmune organoids and microphysiological systems as enabling technologies for next-generation neurotheranostics targeting age-associated neuroinflammatory processes.

Illarionova et al. [44], Evsiukova et al. [45], Ishbulatov et al. [46], Bogotskoy et al. [47], and Adrianov et al. [48] demonstrate the innovative methodological results. Illarionova et al. [44] show a new method of analysis of synchronization between the electroencephalogram, electrocardiogram, respiration, and blood pressure recordings. Evsiukova et al. [45]⁴⁵ discuss that brain drainage depends on the mouse strain and is most suitable for preclinical studies C57BL/6 mice vs. BALB/c. Ishbulatov et al. [46] describe a mathematical model for the investigation of autonomic blood pressure control. Bogotskoy et al. [47] develop a novel approach based on exercise training for protection of cerebral blood flow autoregulation from the impairment by carotid stenosis in rats. Adrianov et al. [48]⁴⁸ show a new method based on accelerometry and thermometry for the study of formation of colonies of experimental animals.

Bragina et al. [49], Tsoy et al. [50], and Zaborova et al. [51] discuss new approaches in neurotheranostics for TBI, including innovative modifications of electromagnetic stimulation and original approaches to assessing the severity of TBI based on new methods of analyzing metabolism and markers in cerebrospinal fluid and blood.

In a series of studies presented by Vaziri et al. [52], Shirokov et al. [53], Korolev et al. [54], Bulava et al. [55] and Kotov et al. [56], the new non-invasive methods based on PBM for glioma and stress therapy are discussed.

5 Outlook

The issue collected articles highlighting the innovative clinical and preclinical strategies in neurotheranostics, including promising mathematical models for assessing brain drainage and clearance; nonlinear dynamics methods for assessing biological signals to search for new markers of brain diseases; pioneering approaches to the diagnosis and treatment of cognitive impairments, sensory systems, TBI, and brain tumors; and original methodological protocols for experimental studies of brain disease development. Overall, this issue is a unique collection of modern interdisciplinary trends in neurotheranostics that provide impetus for the development of breakthrough technologies for preventive and personalized medicine.

Data availability No new data were created or analyzed in this study. Data sharing is not applicable.

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