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Recent advances in nanomaterial-based brain organoid on-a-chip for drug evaluation

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ABSTRACT

Brain organoids have emerged as promising three-dimensional (3D) models that recapitulate key aspects of human brain development, neural circuit formation, and neurological disorders. However, conventional culture systems face critical limitations, including inadequate vascularization, restricted diffusion of nutrients and oxygen, insufficient neuronal maturation, and poor reproducibility, all of which hinder long-term stability and clinical translation. To address these challenges, organoid-on-a-chip technologies have been developed to provide controlled microenvironments, fluidic dynamics, and enhanced tissue integration; nevertheless, significant barriers remain. In recent years, nanomaterials have been increasingly incorporated into brain organoids and chip-based systems to overcome these limitations. Due to their unique structural, electrical, and biochemical properties, nanomaterials can mimic components of the extracellular matrix, promote cellular organization, enhance electrophysiological maturation, and enable advanced sensing modalities. Their integration with organoid-on-a-chip platforms further facilitates vascularization, supports long-term culture, and contributes to the generation of physiologically relevant neural models. This review provides a comprehensive overview of brain organoid technology, the functional roles of nanomaterials in these systems, and recent advances in nanomaterial-based brain organoid-on-a-chip platforms. Additionally, we summarize how these interdisciplinary approaches enhance the modeling of neurological diseases, improve drug evaluation including organoid-based biohybrid robot on-a-chip, and support the development of personalized medicine. Finally, we discuss persisting limitations and outline future directions toward the realization of intelligent, reproducible, and clinically translatable neural platforms. We hope this review will inspire innovative strategies and accelerate progress at the intersection of nanomaterials, organoid biology, and chip-based technologies, thereby advancing personalized and effective treatments in neuroscience and biomedicine.

1. Introduction

Brain organoids are three-dimensional (3D) neural tissue constructs derived from human pluripotent stem cells (hPSCs), including embryonic stem cells and induced pluripotent stem cells (Di Lullo and Kriegstein, 2017; Jeong et al., 2023; Koo et al., 2019). Through guided differentiation and intrinsic self-organization, brain organoids reproduce key structural and functional features of the developing human brain. They generate diverse neural and glial populations, establish regional identities, and form cytoarchitectures resembling early brain development, such as ventricular zone-like structures and layered cortical organization (Bock et al., 2021; Jain et al., 2025). Beyond morphological features, brain organoids exhibit functional maturation, including synaptogenesis, spontaneous neuronal firing, and emergent network activity. These characteristics make them powerful *in vitro* platforms for investigating human neurodevelopment, neurological disorders, and drug responses. Importantly, brain organoids provide insight into human-specific developmental and disease mechanisms that

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are often challenging to model in animals due to species-specific differences in brain organization, developmental timing, and genetic regulation (Agboola et al., 2021; Chang et al., 2020; Wang et al., 2018).

Despite these advantages, conventional brain organoid systems face major limitations that restrict their physiological relevance and translational potential. A primary challenge is insufficient mass transport to meet the oxygen and nutrient demands of growing 3D tissues (Agboola et al., 2021; Chang et al., 2020; Wang et al., 2023). As organoids increase in size and cellular density, oxygen gradients form, frequently resulting in hypoxia, metabolic stress, and necrotic cores. This compromises long-term culture viability and limits the ability of organoids to reach advanced maturation stages comparable to later developmental periods (Bhaduri et al., 2020; Boisvert et al., 2019; Fumadó Navarro et al., 2025). *In vivo*, brain tissue is supported by dense vascular networks that continuously supply oxygen and nutrients while removing metabolic waste; however, most brain organoids lack functional vascularization, leading to non-physiological metabolic environments and incomplete tissue maturation (LaMontagne et al., 2022; Sato et al., 2023). Another critical limitation is the absence of systemic connectivity and controlled microenvironmental regulation. In the human body, brain development and function depend on dynamic interactions with vascular, immune, and endocrine systems. Additionally, inter-organ axes such as the gut–brain pathway influence neurodevelopment, neuroinflammation, and neurodegeneration. Conventional organoid platforms also provide limited control over key environmental parameters, including biochemical gradients, oxygen tension, fluid-flow conditions, and the spatiotemporal delivery of growth factors (Sarieva and Mayer, 2021). These constraints reduce reproducibility and hinder the capacity to model complex physiological or pathological processes with high fidelity. Moreover, real-time functional monitoring remains a major challenge. Many analytical approaches still rely on destructive assays, such as immunostaining or transcriptomics, which require fixation. Although functional techniques like patch-clamp electrophysiology and calcium imaging offer valuable insights, they are constrained by limited accessibility in thick 3D tissues, restricted sampling, and the need for fluorescent labeling. Consequently, there remains a critical need for platforms that enable continuous, non-destructive monitoring of electrophysiological and biochemical dynamics within brain organoids.

To address these limitations, the integration of brain organoids with organ-on-a-chip systems has emerged as an advanced strategy, giving rise to brain organoid-on-a-chip platforms (Li et al., 2023; Park et al., 2019; Wang et al., 2023; Zhang et al., 2025). Microfluidic perfusion within these systems enables stable delivery of nutrients, efficient oxygen transport, and continuous waste removal, thereby mitigating hypoxia-induced necrosis and supporting long-term organoid viability. Additionally, organoid-on-a-chip technologies offer enhanced control over microenvironmental parameters, including flow patterns, biochemical gradients, and the temporal delivery of signaling molecules (Abdulla et al., 2023; Patel et al., 2024; Zhang et al., 2024a). This programmable and standardized regulation improves experimental reproducibility and facilitates systematic investigation of neurodevelopment, disease progression, and drug responses. A key advantage of brain organoid-on-a-chip platforms is their capacity for integrated, real-time monitoring (Saglam-Metiner et al., 2024; Zhao et al., 2026). Microelectrode arrays (MEAs) can be embedded within the chip to record electrophysiological activity over extended periods, allowing longitudinal assessment of neuronal firing, network synchronization, and oscillatory behavior. Complementarily, electrochemical biosensors enable real-time monitoring of neurotransmitter release, metabolic byproducts, and oxidative stress markers (Spitz et al., 2024; Zanetti et al., 2021). By combining electrophysiological data with biochemical readouts, these systems support dynamic phenotyping of brain organoids under physiologically relevant conditions. Moreover, organoid-on-a-chip platforms are compatible with automation and parallelization, facilitating higher-throughput experimentation for drug screening and toxicity testing. These platforms also offer the potential for multi-organ integration, expanding the scope for studying inter-organ communication (Chauhdari et al., 2025; Sakthivel et al., 2026; Tong et al., 2025). For instance, incorporation of vascular modules may enhance oxygen delivery and enable endothelial interactions; immune components can support modeling of neuroinflammation; and gut- or liver-associated modules may allow investigation of drug metabolism and systemic signaling. Such multi-organ systems enable more comprehensive modeling of human physiology and the complexity of disease mechanisms.

Nanomaterials further strengthen brain organoid-on-a-chip systems by enhancing bioelectronic interfaces and enabling highly sensitive, real-time sensing (Lee et al., 2025; Son and Jeong, 2025). Conductive nanomaterials, such as graphene, carbon nanotubes, and magnetic nanoparticles, improve electrode conductivity and reduce impedance, thereby increasing signal-to-noise ratios in electrophysiological recordings. Additionally, nanostructured surfaces expand the effective electrode area, promoting stable cell adhesion and supporting long-term recording performance. Nanomaterials also enhance electrochemical detection sensitivity by accelerating electron transfer and increasing analyte interaction, enabling label-free monitoring of neurotransmitters, cytokines, and oxidative stress biomarkers. Plasmonic nanomaterials further broaden sensing capabilities by enabling optical detection through signal amplification, thereby expanding the range of measurable biochemical dynamics. Beyond sensing, nanomaterials function as bioactive interfaces that influence neural development (Kim et al., 2023a; Park et al., 2022; Shi et al., 2024). Functionalized nanomaterials and nanostructured scaffolds can mimic extracellular matrix properties, modulate neuronal adhesion, and promote synaptic maturation. Moreover, they support vascularization strategies by enhancing endothelial cell proliferation and enabling controlled presentation of angiogenic cues. Through these multifunctional roles, nanomaterial integration significantly improves both the physiological relevance and sensing capabilities of organoid-on-a-chip systems (Kopic et al., 2025; Tran and Gautam, 2022; Yousuf et al., 2025). These advances position nanomaterial-based brain organoid-on-a-chip platforms as transformative tools that bridge conventional *in vitro* models with *in vivo*-like functionality. By integrating stem-cell-derived organoids, microfluidic control, bioelectronic sensing, and nanotechnology-enabled interfaces, these systems enhance viability, reproducibility, and real-time functional monitoring. Continued progress in this interdisciplinary field is expected to advance understanding of human brain development and disease mechanisms while accelerating translational research in drug discovery, toxicology, and precision neuroscience.

In this review, we present a selective overview of recent studies on brain organoids, the functional roles of nanomaterials in their development, and nanomaterial-based brain organoid-on-a-chip platforms for drug evaluation (Fig. 1). We begin by discussing various types of brain organoids, including cerebral, midbrain, and thalamic organoids, along with their distinguishing features. Next, we examine recent literature focused on the incorporation of specific nanomaterials in brain organoid systems and their functional contributions. We then explore nanomaterial-integrated brain organoid-on-a-chip platforms, with emphasis on applications in drug delivery, neuromodulation, and disease-specific pharmacological evaluation. We believe this review will underscore the unique advantages and potential of nanomaterials in advancing brain organoid technologies, while outlining future directions for the development and application of brain organoid-on-a-chip platforms in emerging biomedical fields.

2. Types of brain organoids and their features

Brain organoids are 3D neural tissues generated from hPSCs. Unlike two-dimensional (2D) neuronal cultures, organoids undergo coordinated cell fate decisions within a 3D environment, enabling the self-assembly of tissue structures that recapitulate aspects of the human brain (Di Lullo and Kriegstein, 2017; Koo et al., 2019; Scuderi et al.,

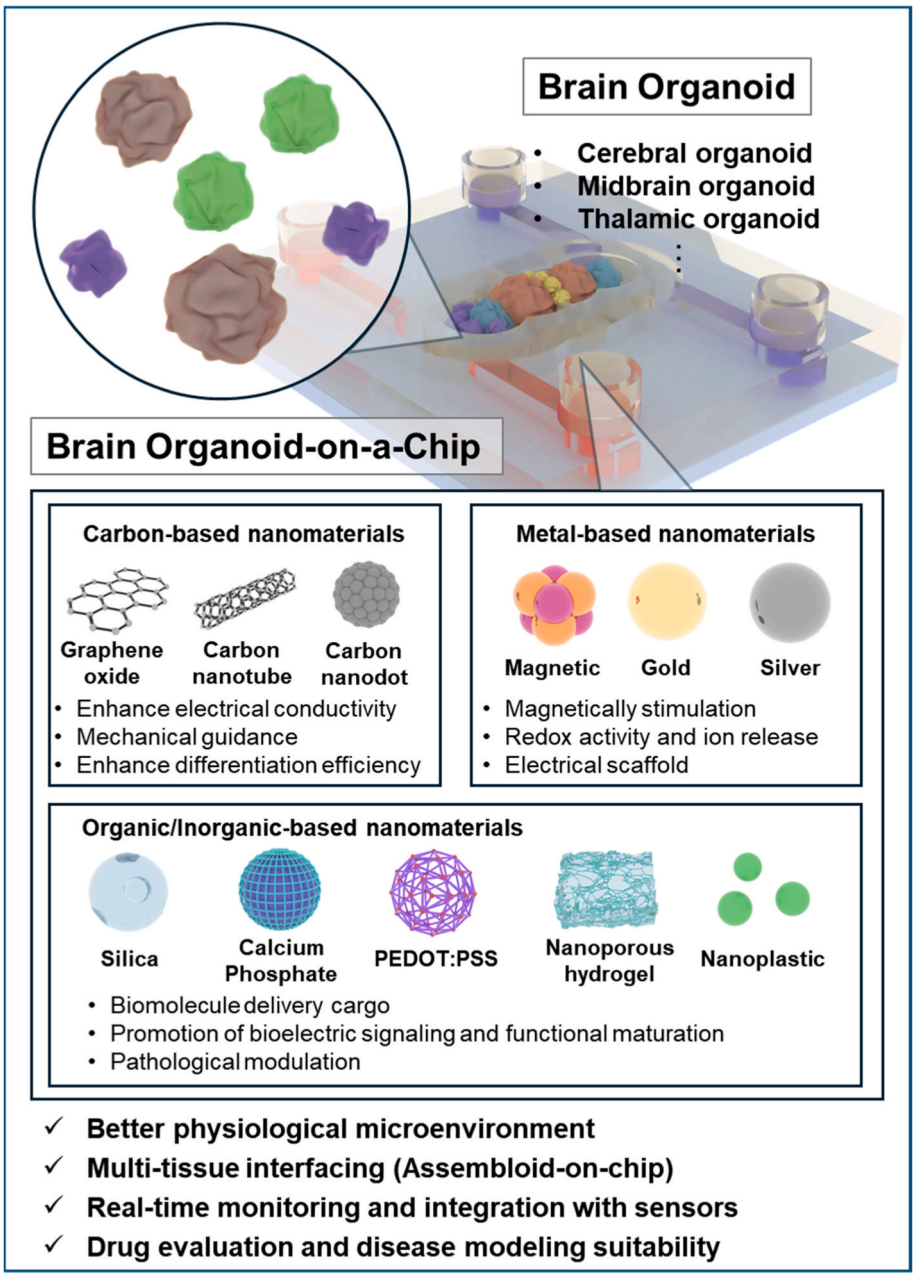

Fig. 1. Schematic image of the Brain organoid and Brain organoid-on-a-chip with nanomaterials for drug evaluation.

2021). During differentiation, stem cell-derived progenitors expand and organize into neuroepithelial-like domains, gradually differentiating into multiple neuronal and glial lineages. Consequently, brain organoids can mimic early human neurodevelopmental processes, including progenitor zone formation, neuronal migration-like behaviors, and the time-dependent maturation of synaptic connectivity (Borzou and Schwarz, 2022; Lancaster et al., 2017; Paşca, 2019). These properties have established brain organoids as specialized models for investigating developmental biology, disease mechanisms, and drug evaluation.

In brain organoid-on-a-chip systems, the choice of organoid type is not merely a technical detail but a critical factor for addressing biological questions specific to a given brain region and for determining which measurable parameters are reliable. Brain organoids used in these systems are generally classified into two major categories: (i) region-specific brain organoids and (ii) whole-brain (multi-region) brain organoids (Maisumu et al., 2025; Velasco et al., 2019; Zhang et al., 2022). Region-specific models are produced through directed differentiation strategies that promote the development of a defined brain region, resulting in stronger regional identity and often greater reproducibility. In contrast, whole-brain organoids rely on intrinsic patterning mechanisms that allow the emergence of multiple brain-like regions within a single construct, thereby increasing structural and cellular complexity.

Despite differences in protocols, brain organoids share core features that support their widespread adoption (Lancaster and Knoblich, 2014; Petersilie et al., 2024). They exhibit 3D cytoarchitecture, enabling spatially organized cell–cell interactions that more accurately reflect *in vivo* conditions than 2D cultures. They contain diverse cell types, including excitatory and inhibitory neurons as well as supportive glial cells, which are essential for forming functional neural tissue. Moreover, brain organoids are capable of generating synaptic activity and exhibiting network-level behaviors, thus enabling functional analyses that go beyond static measurements of gene expression or morphology. Because they are derived from human cells, organoids also provide insights into

human-specific developmental processes and disease phenotypes that are often not captured by animal models. These advantages make brain organoids highly suitable for engineering microphysiological systems that integrate long-term culture, controlled perfusion, and real-time sensing capabilities.

2.1. Region-specific brain organoids

Region-specific brain organoids are engineered to replicate defined areas of the human brain, capturing their distinct developmental trajectories in a controlled environment. Unlike unguided cerebral organoids that rely primarily on intrinsic self-organization, these specialized models are generated through directed differentiation protocols (Qian et al., 2018; Susaimanickam et al., 2022). In this approach, pluripotent

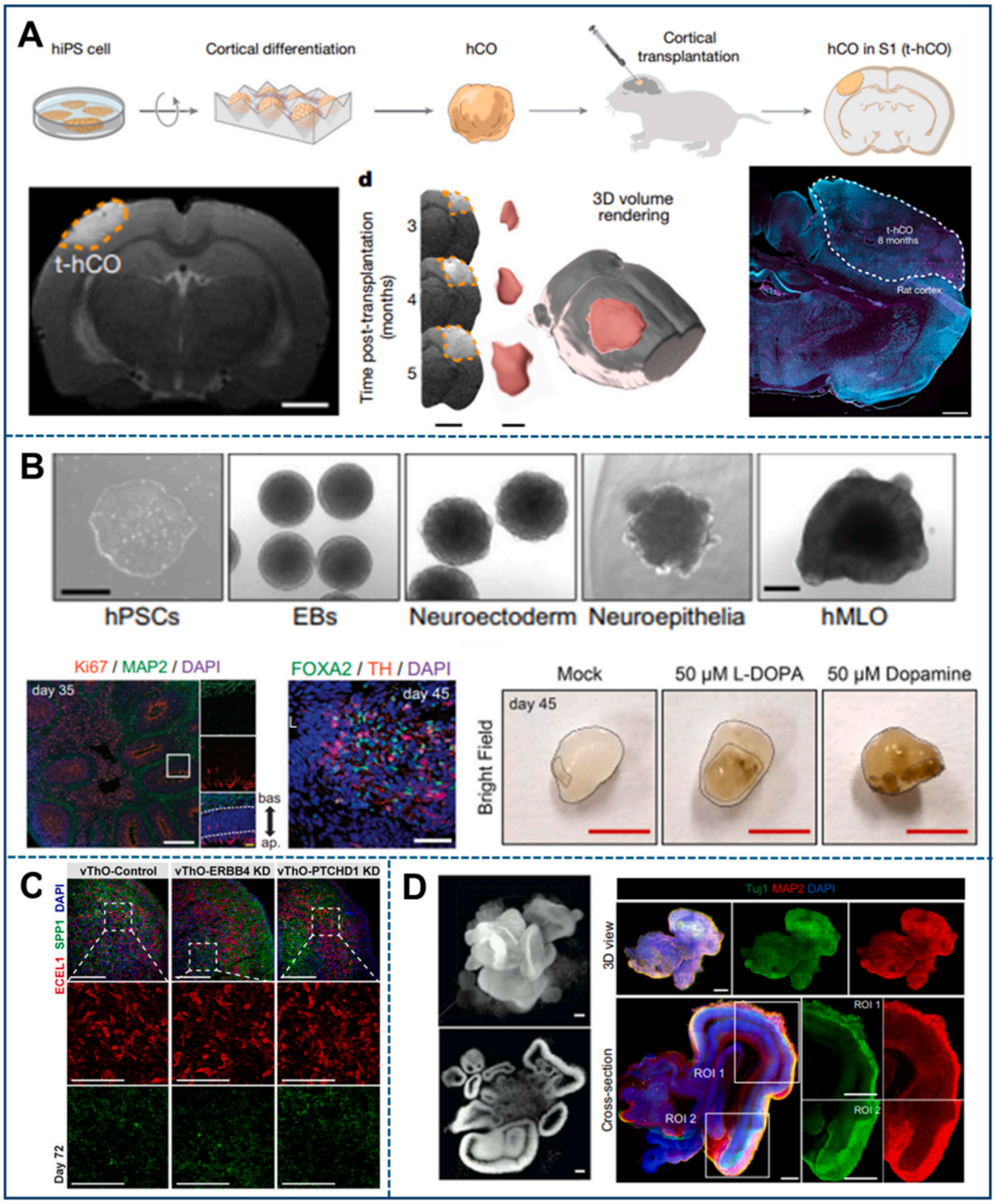

Fig. 2. (A) Schematic image of the generation of cortical organoid and their application of transplantation to the animal model. Reproduced with permission from Ref. (Revah et al., 2022). (B) Optical and immunostaining images of the generation of midbrain organoid and the generation of the portion of the dopaminergic neuron. Reproduced with permission from Ref (Jo et al., 2016). (C) immunostaining. images for the confirmation of the generated thalamic organoid. Reproduced with permission from Ref. (Kiral et al., 2023). (D) Structure of the cerebral organoid from the microfluidic system for enhancement to promote structural and functional maturation of human brain organoids. Reproduced with permission from Ref. (Cho et al., 2021).

stem cells are exposed to precisely timed morphogen signals and pathway modulators that steer early neuroectodermal differentiation toward specific dorsoventral and anteroposterior identities. This targeted guidance enriches for selected progenitor populations and their corresponding neuronal subtypes. As a result, region-specific organoids exhibit elevated expression of regional markers, reduced batch-to-batch variability, and improved reproducibility—features essential for quantitative testing, mechanistic investigations, and translational research.

From an organoid-on-a-chip standpoint, region-specific organoids are particularly advantageous, as microfluidic platforms and integrated sensing technologies benefit from standardized biological inputs. The ability to produce organoids with consistent cellular composition allows for more reliable comparisons across experimental conditions, including drug treatment, genetic perturbation, electrical stimulation, and inflammatory challenge. Moreover, region-specific models typically offer superior interpretability compared to multi-region organoids, as their phenotypes can be directly linked to defined neural circuits and neurotransmitter systems. This specificity is especially valuable when designing chips equipped with MEAs, electrochemical biosensors, optical readouts, or perfusion-controlled gradient generators, where the primary objective is to connect targeted stimuli with observable functional responses (Huang et al., 2022a; Spitz et al., 2024).

Among region-specific models, cortical organoids are the most extensively studied, owing to their relevance to human cortical expansion, neurodevelopmental timing, and higher-order cognitive functions (Fig. 2A) (Qian et al., 2020; Revah et al., 2022; Xiang et al., 2019). These organoids are designed to emulate dorsal forebrain development, typically forming neuroepithelial-like structures and ventricular zone–like proliferative regions enriched with radial glia–like progenitors and intermediate progenitor cells. Over time, cortical organoids give rise to excitatory glutamatergic neurons and may exhibit early hallmarks of cortical lamination, including layer-specific marker expression and organized patterns of neuronal migration. Critically, they progressively establish synaptic connections and develop spontaneous electrophysiological activity, supporting studies of network maturation. In organoid-on-a-chip systems, cortical organoids are often coupled with MEAs for long-term monitoring of firing rates, burst dynamics, synchrony, and oscillatory behavior. Microfluidic perfusion further enhances viability and functional stability by reducing hypoxic stress, improving nutrient delivery, and enabling controlled pharmacological exposure.

Midbrain organoids represent a major class of region-specific models, primarily focused on the generation of dopaminergic neurons (Fig. 2B) (Elvira et al., 2025; Jo et al., 2016; Nickels et al., 2020; Zagare et al., 2021). These organoids are patterned to acquire ventral midbrain identity, enabling the differentiation of dopamine-producing neurons that are highly relevant for modeling Parkinson's disease, dopaminergic neurotoxicity, and drug screening for neuroprotection or dopamine modulation. Their utility extends beyond cell-type specification: dopaminergic neurons can be functionally characterized using electrophysiological methods, while dopamine release can be dynamically quantified. As such, midbrain organoids are well-suited for integration into organoid-on-a-chip platforms incorporating electrochemical sensing elements, such as dopamine-sensitive electrodes, allowing real-time correlation between neurotransmitter release and electrical network activity. Hippocampal organoids are designed to model neural populations involved in learning and memory and are commonly used in studies of cognitive impairment, epilepsy-related circuit dysfunction, and neurodegenerative disease. These organoids typically require extended maturation to develop robust functional signatures, with their network properties evolving gradually over time (Fig. 2C) (Joo et al., 2025; Todd et al., 2013; Wu et al., 2024). Beyond these well-established models, ventral forebrain organoids represent a particularly impactful category, often patterned to resemble the medial ganglionic eminence (Sawada et al., 2024). These organoids generate progenitors of inhibitory interneurons that subsequently differentiate into GABAergic interneurons, including subtypes critical for cortical inhibition and network synchronization. This class is especially significant given the association of excitatory–inhibitory imbalance with neuropsychiatric disorders such as autism spectrum disorder, schizophrenia, and epilepsy. In organoid-on-a-chip systems, ventral forebrain organoids can be co-cultured with cortical organoids to introduce controlled inhibitory inputs, enabling the study of interneuron migration, inhibitory synapse formation, and their influence on circuit dynamics.

Thalamic organoids represent a critical class of region-specific models, as the thalamus functions as a central relay hub for sensory processing and cortical integration (Sawada et al., 2024). Thalamocortical connectivity plays a vital role in early neurodevelopment, sleep-related oscillations, and higher-order information processing (Angulo Salavarria et al., 2023; Shin et al., 2024a). Thalamic organoids can be co-cultured with cortical organoids to model thalamocortical circuit formation. In chip-based systems, this approach benefits significantly from microfluidic control, where defined spatial arrangements and precisely regulated diffusion gradients enhance reproducibility of inter-organoid interactions. Integrated electrophysiology is particularly informative in these systems, as thalamocortical coupling is reflected in altered synchrony and oscillatory dynamics. Hypothalamic organoids are region-specific constructs relevant to neuroendocrine regulation, feeding behavior, circadian rhythms, and hormonal signaling (Huang et al., 2021; Sarrafha et al., 2023). Compared to other brain regions, hypothalamic circuitry is more tightly coupled to systemic physiology, making these organoids uniquely compatible with multi-organ-on-a-chip systems. In such platforms, hormonal signals or metabolic cues from peripheral tissues (e.g., liver- or gut-on-a-chip modules) can be delivered via controlled perfusion. This design enables the investigation of systemic regulation of neural circuits, which cannot be achieved in isolated brain organoid cultures. Cerebellar organoids are increasingly employed to model motor coordination and cerebellum-related neurodevelopmental disorders. These constructs can generate cerebellar-like progenitors and may give rise to specialized neuronal phenotypes, including Purkinje cell–like populations, depending on the differentiation protocol and culture duration. As they often require prolonged maturation, chip-based perfusion systems are particularly beneficial, enhancing survival and supporting long-term development. Furthermore, electrophysiological monitoring on chip platforms allows real-time tracking of functional maturation and assessment of disease-associated circuit alterations. Choroid plexus organoids constitute a specialized region-specific model focused on cerebrospinal fluid (CSF) production and barrier-related functions (Pellegrini et al., 2020). They are relevant for studying central nervous system (CNS) homeostasis, molecular transport mechanisms, and signaling associated with neuroinflammation. In organoid-on-a-chip systems, choroid plexus organoids can serve as engineered modules that secrete CSF-like fluids and modulate local biochemical environments. When integrated with cortical or whole-brain organoids, they provide a platform to investigate barrier function and soluble factor exchange. Importantly, chip-based systems equipped with biosensors can quantify secreted factors and enable controlled fluid sampling for biochemical analysis. Although not strictly brain-derived, spinal cord organoids and related patterned neural tube models are frequently included in discussions of region-specific neural organoids due to their shared developmental frameworks (Lee et al., 2022; Sun et al., 2024). These constructs are particularly valuable for modeling motor neuron differentiation, neuromuscular signaling, and mechanisms of neurotoxicity. In organoid-on-a-chip platforms, spinal cord organoids are often integrated with muscle bundles or engineered contractile tissues to form neuromuscular systems. Region-specific patterning facilitates the directed formation of motor neuron populations.

Overall, region-specific brain organoids offer targeted biological relevance, enhanced interpretability, and improved experimental consistency. These attributes align closely with the demands of brain organoid-on-a-chip systems, where standardized culture conditions,

programmable stimulation, and integrated sensing technologies require reproducible tissue composition. By expanding the repertoire of region-specific organoids, including cortical, midbrain, hippocampal, ventral forebrain, striatal, thalamic, hypothalamic, cerebellar, choroid plexus, brainstem, and spinal cord-related models, researchers can select the most appropriate organoid module to address specific scientific questions.

2.2. Whole-brain (multi-region) brain organoids

Whole-brain organoids, often referred to as cerebral or multi-region organoids, represent a distinct approach in which tissue self-patterns into multiple brain-like domains. This strategy is particularly valuable for capturing broad developmental complexity or exploring emergent tissue-level organization arising from self-organization. A key advantage is their ability to model diverse developmental processes within a single construct. The formation of multiple neuroepithelial regions and their subsequent differentiation may recapitulate aspects of early embryonic brain organization, making whole-brain organoids attractive for investigating global neurodevelopmental mechanisms such as cellular diversification, progenitor expansion, and early neural patterning.

However, whole-brain organoids present inherent challenges due to their heterogeneity. Variations in the proportion and spatial arrangement of regions lead to significant batch-to-batch variability, complicating efforts to standardize them for applications requiring quantitative reproducibility. Organoid-on-a-chip approaches offer potential solutions to reduce such inconsistencies (Fig. 2D) (Cho et al., 2021). Microfluidic perfusion can stabilize the culture environment, minimize nutrient gradients, and reduce stress-induced artifacts, thereby indirectly improving the reliability of self-organized developmental trajectories. These organoids also serve as promising models for studying network-level physiological behaviors dependent on diverse neuronal subtypes. With sufficient culture time, they can develop synaptic networks capable of spontaneous firing, synchronized bursts, and oscillation-like activity (Fair et al., 2020). Recent advancements in whole-brain organoid platforms provide opportunities to investigate disease phenotypes associated with circuit dysfunction, including abnormal synchronization and seizure-like behaviors. Integration with chip devices equipped with embedded electrodes or sensor arrays allows continuous monitoring of electrophysiological activity, enabling observation of neural network development and responses to pharmacological interventions over time while preserving tissue integrity. Additionally, whole-brain organoids are essential for the development of advanced microphysiological platforms. Coupling with perfusable endothelial networks can enhance oxygen delivery and support physiologically relevant barrier interactions, while incorporation of immune components enables modeling of inflammatory signaling and neuroimmune communication. Connecting whole-brain organoids with peripheral organ-on-a-chip modules further facilitates investigation of systemic influences on the brain, such as metabolite signaling, cytokine-mediated effects, or drug metabolism–driven secondary neurotoxicity. In summary, whole-brain organoids emphasize complexity and self-organization, making them uniquely suited for studying brain-wide development and emergent neural function. Although heterogeneity remains a significant limitation, integration with chip-based engineering enhances environmental control and enables long-term functional monitoring, thereby improving their utility for advanced disease modeling and translational research.

3. Functional roles of nanomaterials in brain organoid development and maturation

Brain organoids have emerged as powerful 3D models for studying human brain development and disease; however, their growth and maturation are often constrained by limited control over cell differentiation, tissue organization, and functional development. Nanomaterials offer unique opportunities to address these limitations by providing physical, electrical, and biochemical cues that extend beyond the capabilities of soluble factors alone. Depending on their material properties and integration strategies, nanomaterials can guide neural differentiation, promote tissue-level organization, and enhance bioelectrical signaling within developing brain organoids. However, increasing evidence indicates that the effects of nanomaterials are highly context-dependent, with certain materials or exposure conditions leading to adverse developmental outcomes. This section examines the functional roles of nanomaterials in brain organoid systems, focusing on three key aspects: guiding neural differentiation and tissue organization, enhancing electrical signaling and functional maturation, and addressing safety considerations and context-dependent effects.

3.1. Nanomaterials-mediated control of stem cell differentiation and fate

Early neurodifferentiation and tissue organization represent critical bottlenecks in brain organoid development, as small variations in initial signaling can lead to substantial differences in organoid structure and cellular composition. Increasing evidence suggests that nanomaterials can directly regulate these early events by serving as physical, electrical, or biochemical interfaces between cells and their microenvironment. Unlike uniformly diffused soluble factors, nanomaterials deliver localized and continuous signals at nano–bio interfaces, influencing cell immersion and spatial organization.

Graphene-based nanomaterials are among the most extensively studied systems for promoting neural differentiation. Park et al. demonstrated that culturing human neural stem cells on graphene substrates significantly enhanced neuronal differentiation compared with glass controls (Park et al., 2011). This effect was attributed to graphene's high electrical conductivity and surface chemistry, which enhanced cell adhesion and modulated membrane-associated signaling. Notably, differentiation occurred without altering soluble factors, indicating that the material interface itself functioned as an instructive signal. In brain organoids, this mechanism suggests that graphene-coated scaffolds or inserts could bias early neural fate decisions within 3D aggregates. Moving beyond planar substrates, Solanki et al. showed that graphene–silica nanoparticle hybrid structures provide both conductive and topographical cues for neural stem cells (Fig. 3A) (Solanki et al., 2013). In their system, nanoscale features promoted axonal alignment and directional neurite extension, while the conductive graphene backbone supported neuronal differentiation. The resulting networks displayed improved structural organization compared with those grown on non-patterned surfaces. This is particularly relevant to brain organoids, where disorganized neurite outgrowth often compromises tissue architecture; integrating nanostructured graphene interfaces could mitigate this issue. More complex tissue organization has been achieved using biohybrid nanomaterial systems. Shin et al. reported that graphene-based biohybrid motor neuron spheroids, incorporating both endothelial and neural cells, exhibited enhanced electrical communication and spatial organization (Fig. 3B) (Shin et al., 2025a). Here, the conductive graphene facilitated signal propagation, while the multicellular architecture supported physiologically relevant tissue assembly. This work demonstrates how nanomaterials can be incorporated into organoid-like systems to guide differentiation and enable functional interfacing simultaneously. The dependence of neural outcomes on nanomaterial properties was further elucidated by Capasso et al., who reported that neuronal adhesion, morphology, and differentiation varied significantly with the structural features and electrical conductivity of graphene films (Capasso et al., 2021). By systematically comparing graphene materials with different degrees of order and conductivity, they showed that subtle nanoscale variations led to pronounced biological effects. These findings underscore the need for precise tuning of graphene properties to optimize their application in brain organoid systems, rather than adopting a one-size-fits-all strategy.

Topographical control of neural differentiation has also been

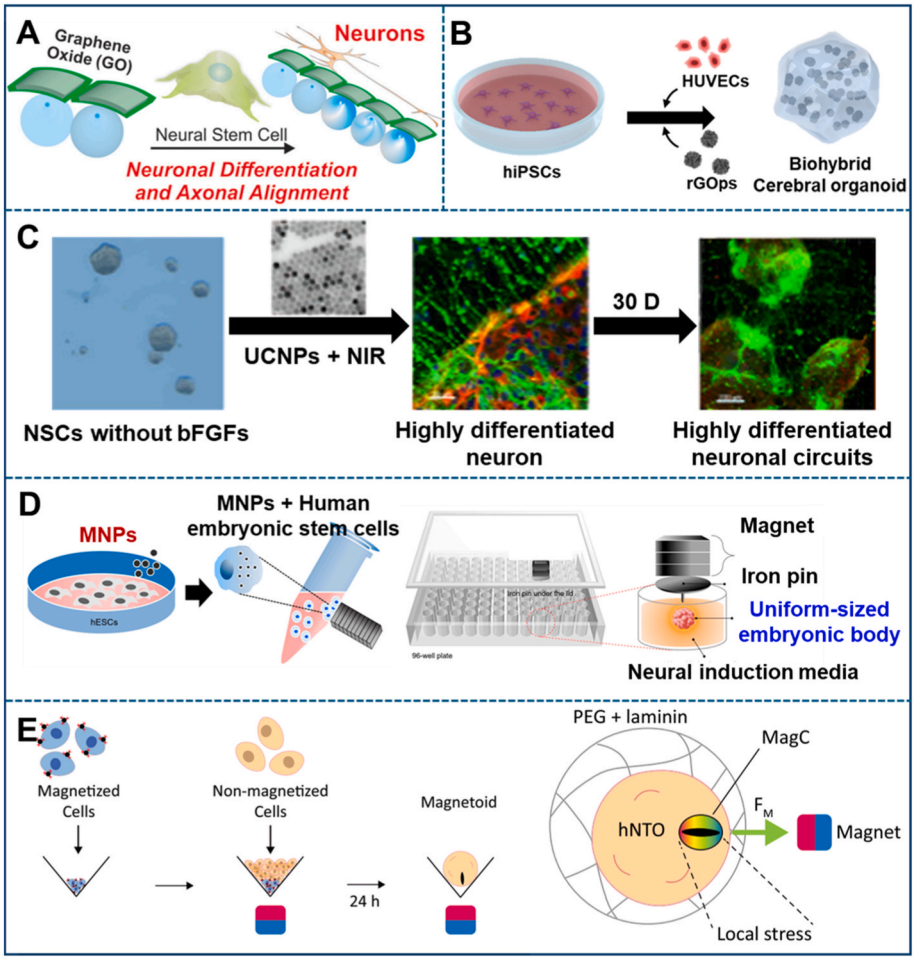

Fig. 3. (A) Graphene–nanoparticle hybrid structures offer combined electrical conductivity and nanoscale topographical cues that promote axonal alignment and neuronal differentiation, representing a strategy to enhance network organization in brain organoids. Reproduced with permission from (Solanki et al., 2013) (B) Graphene-based biohybrid cerebral organoid incorporating neural and endothelial cells improves electrical communication and spatial organization through conductive graphene-mediated signal propagation in organoid-like neural tissues. Reproduced with permission from (Shin et al., 2025a) (C) Rare-earth metal–based upconversion nanoparticles ($NaYF_4$:Yb^{3+}/Tm^{3+}) enable non-invasive optical control of neural fate via NIR-triggered intracellular photoreceptive signaling, promoting neuronal differentiation and axonal stability. Reproduced with permission from (Zhang et al., 2024b) (D) Magnetic nanoparticle–mediated modulation of embryoid body size using external magnetic fields achieves more uniform neural induction, addressing size-dependent variability in early brain organoid development. Reproduced with permission (Son et al., 2024). (E) Magneto-mechanical stimulation of magnetically labeled cells activates mechanotransduction pathways that influence cytoskeletal organization and neural differentiation, enabling remote control of early tissue patterning in brain organoids. Reproduced with permission from (Abdel Fattah et al., 2023).

achieved using non-carbon nanostructures. Harberts et al. demonstrated that densely spaced spiky silicon nanowire arrays promote robust neuronal differentiation of human iPSC-derived neural progenitor cells (Harberts et al., 2021). The sharp nanoscale features influenced focal adhesion formation and cytoskeletal tension, resulting in increased expression of neuronal markers. Although shown in 2D cultures, this study offers a clear mechanistic basis for incorporating nanoscale topographies into brain organoid systems to guide tissue organization during early development. Zhang et al. reported that rare-earth metal–based upconversion nanoparticles (UCNPs) can bias neural stem cell fate toward neuronal lineages while simultaneously enhancing axonal stability (Fig. 3C) In their study, UCNPs composed of $NaYF_4$ doped with Yb^{3+} and Tm^{3+} were internalized by neural stem cells, where near-infrared (NIR) irradiation induced upconversion emission in the blue and ultraviolet ranges. This optical activation triggered intracellular photoreceptive signaling pathways, promoting neuronal differentiation and suppressing astrocytic lineage commitment. Additionally, UCNPs improved axonal stability and sustained intercellular connectivity during long-term culture. Although demonstrated in neurosphere-based systems, this approach presents a compelling framework for brain organoids, where non-invasive, spatiotemporal control over neural fate specification and tissue stability remains a key challenge.

Magnetic nanomaterials offer a fundamentally distinct strategy for guiding neural differentiation by enabling remote physical control. Son et al. reported that embedding magnetic nanoparticles during embryoid body formation allows precise regulation of aggregate size via external magnetic fields (Fig. 3D) (Zhang et al., 2024b) As embryoid body size strongly influences neural inductivity, this approach resulted in more uniform and efficient neural differentiation. In brain organoids, where size heterogeneity significantly contributes to batch-to-batch variability, magnetic size control provides a powerful tool for improving reproducibility. Zhang et al. demonstrated that magnetic graphene oxide nanoparticles deliver synergistic biochemical and physical cues that enhance neural differentiation efficiency (Son et al., 2024). In their study, graphene oxide sheets decorated with magnetic nanoparticles were introduced into neural stem cell cultures. The graphene oxide promoted cell adhesion and surface-mediated signaling, while the magnetic core enabled external field–mediated positioning and mechanical stimulation. This dual functionality accelerated neuronal

differentiation and improved cytoskeletal organization compared with non-magnetic or non-graphene controls. The combined use of surface interaction and magnetic responsiveness suggests that magnetic graphene oxide nanoparticles may be particularly effective in brain organoid systems, where both spatial organization and differentiation efficiency must be tightly regulated. Mechanical cues mediated by magnetic nanomaterials have also been shown to influence tissue development. Fattah et al. demonstrated that targeted magnetic stimulation of magnetically labeled cells activates mechanotransduction pathways associated with cytoskeletal remodeling and neural differentiation (Fig. 3E) (Abdel Fattah et al., 2023) This form of magneto-mechanical stimulation offers a non-invasive means of directing tissue organization and fate decisions, which may be especially valuable for modulating early patterning events in developing brain organoids.

At the scale of 3D tissues, nanomaterials have also been employed as structural scaffolds to support organoid growth. Tejchman et al. showed that carbon fiber scaffolds enhance the structural integrity and organized growth of midbrain organoids during long-term culture (Tejchman et al., 2020). By providing both mechanical support and guidance cues, these scaffolds mitigated tissue collapse and promoted more reproducible organoid morphology, addressing a common limitation of conventional organoid cultures.

Nanoparticles have also been employed as delivery platforms to regulate neural differentiation through controlled molecular signaling. Chao et al. reported that calcium phosphate (CaP) nanoparticles enable efficient intracellular delivery of nucleic acids and proteins to neural stem cells while maintaining high biocompatibility (Chao et al., 2024) By modulating intracellular pathways associated with differentiation, these delivery systems offer a means to locally control signaling within brain organoids, where uniform exposure to soluble factors is challenging to achieve. Stimuli-responsive nanoparticles further advance this approach by allowing temporal control over differentiation cues. Abueva et al. demonstrated that near-infrared photocleavable nanoparticles releasing brain-derived neurotrophic factor (BDNF) enable precise spatiotemporal regulation of neuronal regeneration (Abueva et al., 2025). Although applied in regenerative contexts, this strategy provides a conceptual framework for dynamically modulating neural differentiation or patterning within brain organoids at defined developmental stages.

Taken together, these studies suggest that nanomaterials function as active regulators of neural differentiation and tissue organization rather than passive culture additives. Through diverse mechanisms—including substrate-mediated electrical and adhesion cues, nanoscale topographical guidance, optically triggered intracellular signaling, magnetic regulation of spatial organization, and mechanically supportive scaffolding—nanotechnologies offer precise control over early developmental events in brain organoids. Importantly, these findings establish that neural fate specification and tissue architecture can be finely tuned through rational nanomaterial design, laying a foundation for the subsequent enhancement of functional maturation, as discussed in the following section.

3.2. *Enhancement of electrical conductivity and neural signal transmission*

While appropriate neural differentiation and tissue organization are essential for brain organoid formation, functional maturation requires the establishment of robust bioelectrical signaling and coordinated neural network activity. Native brain development depends heavily on electrical coupling, action potential propagation, and activity-dependent synaptic maturation—processes that are often insufficiently replicated in conventional organoid cultures. Recent studies suggest that nanomaterials can address these limitations by creating electrically active microenvironments, accelerating bioelectrical maturation, and enabling active neuromodulation and functional monitoring within neural tissues.

Electroconductive hydrogel-based nanocomposites represent one of the most widely explored strategies for enhancing bioelectrical signaling. Tondera et al. reported that nanoclay-doped hydrogels provide a highly conductive, stretchable, and cell-adhesive matrix capable of supporting neural cell growth while preserving brain-like mechanical softness (Tondera et al., 2019). The incorporation of nanoclay nanosheets increased both ionic and electronic conductivity without compromising elasticity, thereby facilitating electrical signal propagation between neighboring cells. Such conductive yet compliant matrices are particularly suited to brain organoids, where mechanical mismatch between rigid materials and soft neural tissue can impair long-term maturation.

Building on this concept, Tringides et al. demonstrated that conductive hydrogel scaffolds with tunable electrical properties enable systematic control over neural differentiation and maturation (Tringides et al., 2023) By modulating scaffold conductivity, they observed corresponding changes in neurite extension and neuronal marker expression, indicating a direct relationship between the electrical microenvironment and neural functional development. This tunability provides a critical design parameter for brain organoid systems, where stage-specific electrical requirements may vary during maturation.

Conductive polymer–nanoparticle composites further expand the material palette for bioelectrical regulation. Guan et al. reported that incorporating conductive poly(3,4-ethylenedioxythiophene): polystyrene sulfonate (PEDOT:PSS) nanoparticles into carboxymethyl chitosan and gelatin hydrogels significantly enhanced neural stem cell proliferation and electrical coupling (Guan et al., 2022) The nanoparticle-based approach enabled uniform dispersion of conductive domains within the soft polymer matrix, resulting in improved electrical communication across the scaffold. Such hybrid systems could be readily adapted for brain organoid cultures to promote synchronized network activity during later developmental stages.

Advances in fabrication techniques have also enabled 3D patterning of conductive matrices. Han et al. reported that 3D-printable gelatin methacryloyl–chitosan hydrogels assembled with conductive components support neural cell growth while permitting spatial control over scaffold architecture (Fig. 4A) (Han et al., 2024). The ability to print conductive hydrogels in predefined geometries provides a powerful strategy to engineer organoid-scale electrical pathways, potentially guiding neural network formation and functional integration within complex brain organoids.

Beyond bulk conductive matrices, carbon-based electroconductive nanoparticles have been shown to directly enhance bioelectrical maturation at the cellular level. Lomboni et al. demonstrated that collagen matrices embedded with carbon nanodots form electroconductive nanocomposites that promote rapid neurite outgrowth and enhanced neurogenic differentiation (Lomboni et al., 2024). The carbon nanodots created localized conductive hotspots within the ECM-like collagen scaffold, facilitating electrical coupling and accelerating the development of electrically active neuronal phenotypes. This study exemplifies how nanoscale conductivity can translate into faster functional maturation, an essential requirement for brain organoid applications.

Carbon-based nanostructures have also been integrated with external stimulation strategies. LaMontagne et al. showed that graphene–polymer nanofibers enable optically induced electrical responses, allowing light-triggered modulation of neural activity (Fig. 4B) (LaMontagne et al., 2025). By embedding conductive graphene within polymer nanofibers, the system converted optical inputs into electrical signals capable of influencing neuronal behavior. Such opto-electrical platforms offer unique opportunities for non-invasive control of neural activity in brain organoids, where precise temporal modulation of network dynamics is challenging to achieve using conventional electrodes.

In addition to passive conductivity, active electrical stimulation has been shown to further enhance neural functional maturation. Garrudo

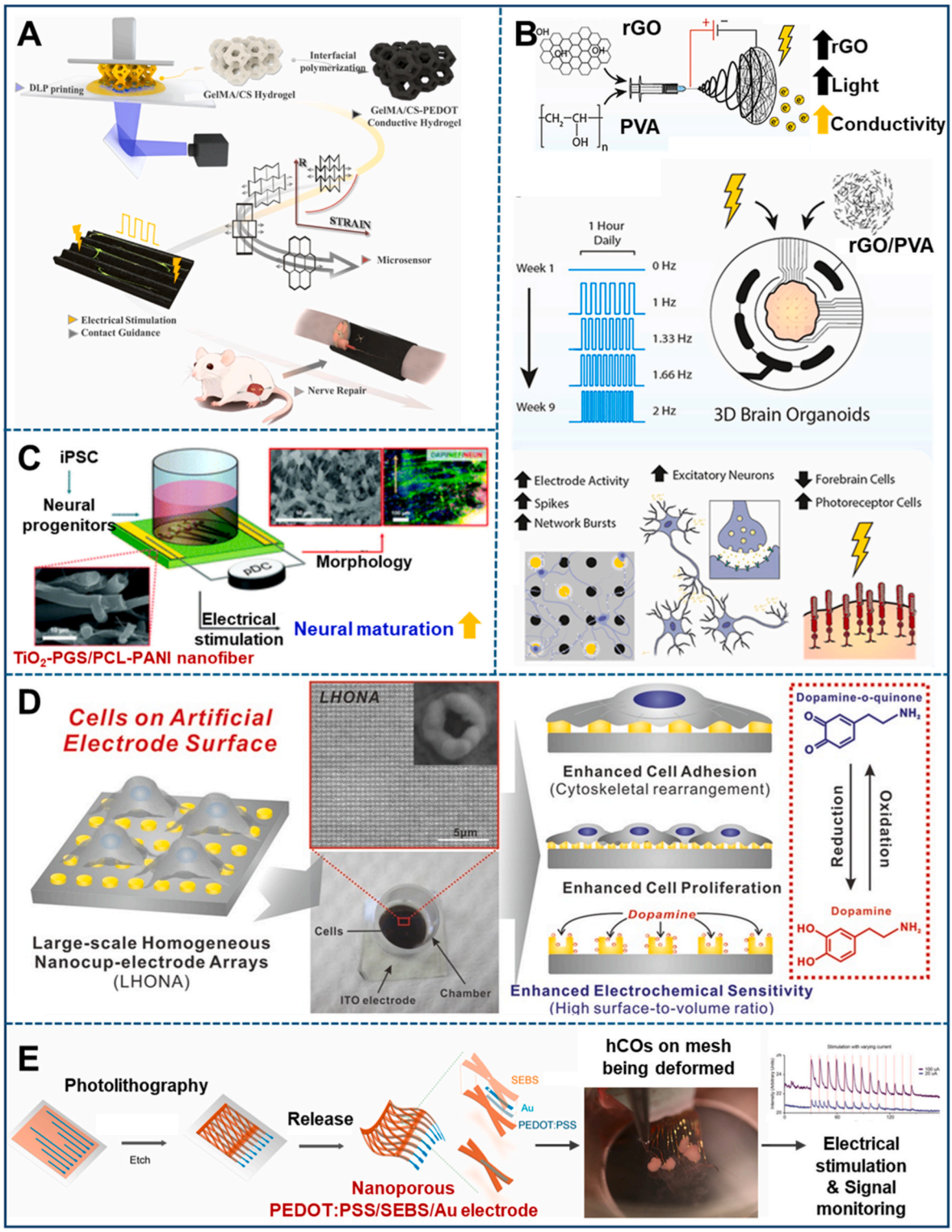

Fig. 4. (A) Three-dimensionally printable gelatin methacryloyl–chitosan conductive hydrogels enable spatially defined electrical pathways that support neural cell growth, guide network formation, and promote functional integration. Reproduced with permission from (Han et al., 2024). (B) Graphene–polymer nanofibers transduce optical stimulation into electrical signals, enabling non-invasive, light-triggered modulation of neural activity and temporal control of network dynamics in brain organoid systems. Reproduced with permission from (LaMontagne et al., 2025). (C) TiO_2–PGS/PCL–PANI conductive nanofibers, combined with controlled electrical stimulation, accelerate bioelectric development, enhancing neuronal firing, synaptic connectivity, and overall functional maturation. Reproduced with permission from (Garrudo et al., 2021). (D) Large-scale nanoelectrode arrays enable high-resolution, real-time monitoring of dopaminergic differentiation and electrophysiological activity, providing a quantitative assessment of functional maturation beyond conventional imaging. Reproduced with permission from (Kim et al., 2015). (E) Stretchable mesh microelectronics composed of nanoporous PEDOT:PSS/SEBS/Au conformally integrate with human neural organoids, enabling simultaneous stimulation and recording while maintaining tissue integrity and long-term functionality. Reproduced with permission from (Li et al., 2022).

et al. demonstrated that applying controlled electrical stimulation during neural differentiation accelerates bioelectric development when using TiO_2-PGS/PCL-PANI nanofibers, leading to increased firing activity, improved synaptic connectivity, and enhanced neural maturation (Fig. 4C) (Garrudo et al., 2021). These findings indicate that combining nanomaterial-enabled conductive environments with external electrical cues can synergistically promote functional development.

Consistent with this observation, Guo et al. reported that the bioelectric functional development of neural stem cells can be significantly accelerated by optimizing electrical stimulation protocols (Guo et al., 2016). Their results underscore that the timing, amplitude, and duration of electrical cues are critical parameters that interact with the underlying material environment, emphasizing the importance of an integrated material–stimulation design for brain organoid maturation.

Magneto-responsive nanomaterials introduce an additional layer of control by coupling mechanical and electrical signaling. Tay et al. demonstrated that a 3D magnetic hyaluronic acid hydrogel enables magnetomechanical neuromodulation by transmitting external magnetic forces to embedded neurons (Tay et al., 2018). This approach activates mechanotransduction pathways while simultaneously influencing electrical signaling, indicating that functional maturation is governed by tightly coupled electromechanical cues. Such systems may be leveraged in brain organoids to modulate network activity without direct physical contact.

To assess functional maturation, nanoelectronic interfaces have been developed for real-time monitoring of neural activity. Kim et al. showed that large-scale nanoelectrode arrays enable continuous monitoring of dopaminergic differentiation and electrophysiological activity with high spatial resolution (Fig. 4D) (Kim et al., 2015). These platforms not only enhanced cell proliferation but also provided quantitative readouts of functional maturation that are difficult to obtain using conventional imaging-based methods. Similarly, Lee et al. demonstrated that graphene–Au hybrid nanoelectrode arrays allow nondestructive, real-time monitoring of enhanced stem cell differentiation by recording electrical activity over extended periods (Lee et al., 2018). The high conductivity and stability of the hybrid electrodes supported long-term measurements, making them well suited for brain organoid cultures requiring prolonged maturation times.

Beyond electrophysiology, chemical signaling has also been integrated into nanoelectronic systems. Kang et al. demonstrated that graphene oxide–wrapped hierarchical gold nanopillar hybrids enable real-time, non-destructive dopamine sensing in neurons and midbrain organoids (Kang et al.). This work illustrates that nanomaterials can be employed not only to stimulate and record electrical activity but also to directly monitor neurotransmitter release, providing a more comprehensive assessment of functional maturation.

Organoid-level integration of nanoelectronics has also been achieved using soft, stretchable systems. Li et al. reported that stretchable mesh microelectronics composed of nanoporous PEDOT: PSS/poly(styrene-ethylene-butylene-styrene) (SEBS)/Au can seamlessly integrate with human neural organoids, enabling both stimulation and recording without compromising tissue integrity (Fig. 4E) (Li et al., 2022). By conformally interfacing with growing organoids, these systems bridge the gap between nanoscale materials and macroscale tissue function, representing a critical step toward fully integrated brain organoid platforms.

Overall, these studies demonstrate that nanomaterial-based strategies play a central role in promoting electrical signaling and functional maturation in brain organoid systems. Through the use of electroconductive hydrogels, carbon-based nanostructures, and responsive nano–bio interfaces, nanotechnologies establish electrically active microenvironments that accelerate neurite outgrowth, synchronize network activity, and enhance bioelectric development. Furthermore, the integration of external stimulation modalities and nanoelectronic interfaces enables both active modulation and real-time monitoring of functional maturation, thereby bridging the gap between structural differentiation and physiological relevance. Collectively, these advances underscore that the rational design and integration of nanomaterials are essential for achieving mature, functionally competent brain organoids, setting the stage for subsequent discussions on safety considerations and context-dependent effects.

3.3. *Pathological modulation of brain organoid development by nanomaterials*

While nanomaterials are increasingly employed to guide neural differentiation and enhance functional maturation in brain organoid systems, accumulating evidence indicates that specific nanomaterial properties can pathologically redirect developmental trajectories. Brain organoids, which recapitulate key aspects of human neural development in three dimensions over extended culture periods, are particularly sensitive to such pathological modulation. In these systems, nanomaterial-induced perturbations often manifest as altered lineage specification, disrupted network formation, or abnormal tissue organization. Importantly, these deviations do not merely reflect nonspecific toxicity but instead generate disease-relevant phenotypes, positioning nanomaterial-treated brain organoids as powerful platforms for modeling pathological neurodevelopment.

Redox-active metal nanoparticles represent a prominent class of pathological modulators due to their high oxidative potential. Huang et al. demonstrated that exposure to silver nanoparticles (AgNPs) induces developmental neurotoxicity by disrupting neural progenitor proliferation and neuronal differentiation (Fig. 5A) (Huang et al., 2022b). In their study, AgNPs increased intracellular oxidative stress and altered the expression of neurodevelopmental genes, resulting in delayed neuronal maturation and imbalanced lineage commitment. Within brain organoids, such redox-driven perturbations mimic pathological trajectories characteristic of neurodevelopmental disorders involving impaired neuronal differentiation and oxidative stress–mediated damage.

Carbon-based nanomaterials further exemplify how nanoscale properties can pathologically modulate neural development. Jiang et al. reported that multi-walled carbon nanotubes suppress neuronal nitric oxide synthase (nNOS) expression in 3D brain organoids, thereby disrupting nitric oxide–mediated signaling pathways essential for neural communication and network maturation (Jiang et al., 2020). This suppression led to impaired neuronal connectivity and altered network dynamics—phenotypes that parallel those observed in neuropsychiatric and neurodevelopmental disorders associated with dysregulated nitric oxide signaling. Notably, these effects were substantially amplified in 3D organoid systems compared to 2D cultures, underscoring the necessity of organoid-based evaluation.

At the same time, Cellot et al. showed that carbon nanotubes can enhance neurite extension and electrical coupling under carefully controlled conditions; however, slight deviations in concentration, length, or surface functionalization rapidly shifted their effects toward pathological outcomes (Cellot et al., 2009). Elevated doses or unfavorable physicochemical parameters resulted in reduced cell viability and aberrant differentiation patterns. This narrow functional window highlights how carbon-based nanomaterials can act either as developmental enhancers or as pathological modulators, depending on precise material design—reinforcing the concept of disease-mimicking modulation rather than binary toxicity.

Environmental nanoplastics have emerged as potent pathological modulators of early neurodevelopment. Huang et al. reported that early-life exposure to polypropylene nanoplastics induces neurodevelopmental abnormalities in both animal models and human iPSC-derived cerebral organoids (Fig. 5B) (Huang et al., 2025). In organoid cultures, nanoplastic exposure disrupted neural progenitor differentiation, reduced neuronal marker expression, and altered tissue architecture. These phenotypes resemble developmental delays and cortical disorganization observed in neurodevelopmental disorders, suggesting

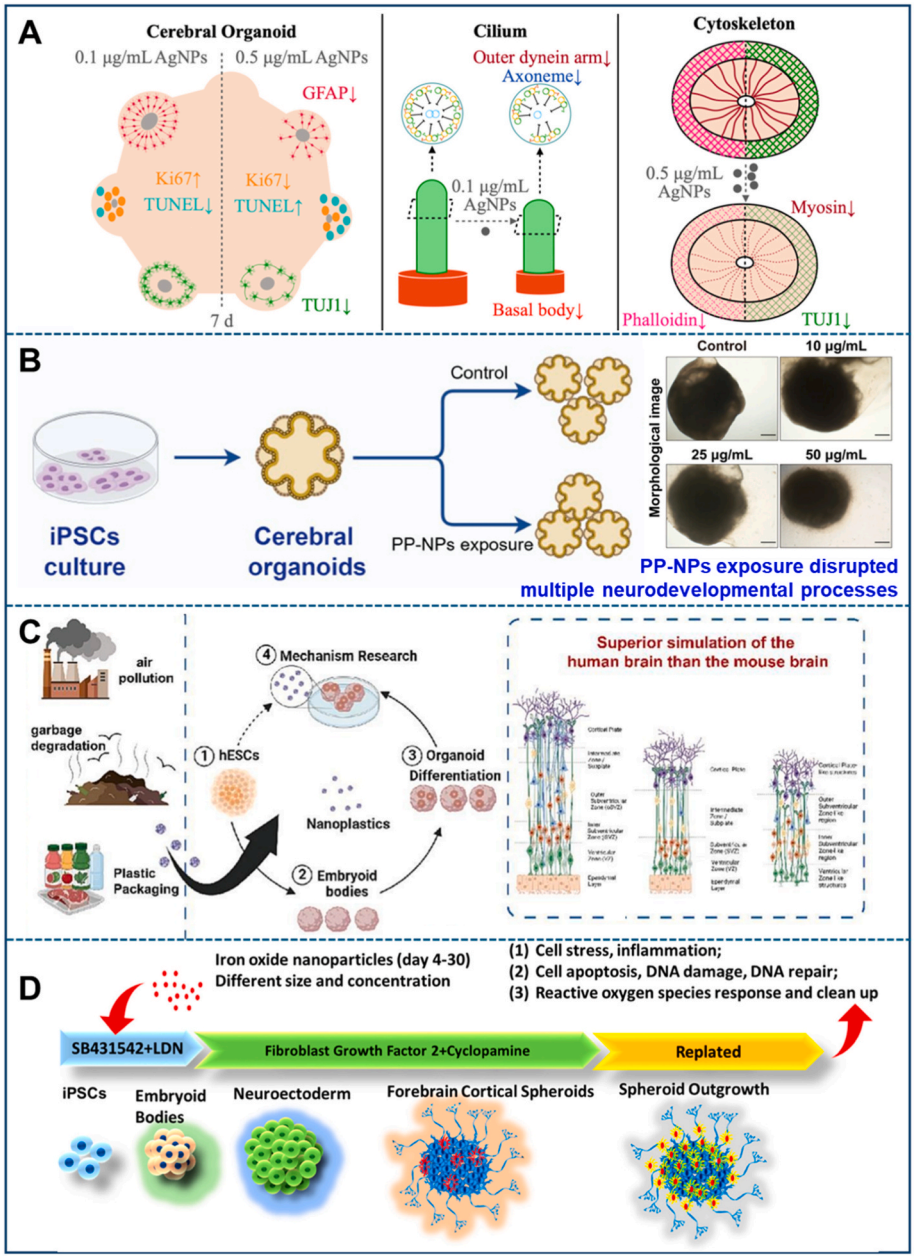

Fig. 5. (A) Redox-active silver nanoparticles pathologically modulate brain organoid development by elevating intracellular oxidative stress, disrupting neural progenitor proliferation, and delaying neuronal maturation, in a manner resembling oxidative stress–linked neurodevelopmental disorders. Reproduced with permission from (Huang et al., 2022b). (B) Polypropylene nanoplastics pathologically alter cerebral organoid development by impairing neural progenitor differentiation, reducing neuronal marker expression, and disrupting tissue architecture, generating disease-relevant phenotypes associated with developmental delay and cortical disorganization. Reproduced with permission from (Huang et al., 2025). (C) Nanoplastic-induced oxidative stress and inflammatory signaling dysregulate neurodevelopmental gene networks, leading to cumulative and progressive pathological trajectories in embryonic brain models, which are effectively captured in long-term brain organoid cultures. Reproduced with permission from (Chen et al., 2023). (D) Prolonged exposure to nanoscale magnetite pathologically alters the growth and differentiation of forebrain-like cortical spheroids, demonstrating exposure duration–dependent modulation that mirrors late-onset or progressive neurodevelopmental abnormalities in brain organoid systems. Reproduced with permission from (Henderson et al., 2022).

that nanoplastics can redirect organoid development toward disease-relevant states.

Mechanistic insights into nanoplastic-induced pathology were further provided by Chen et al., who demonstrated that nanoplastics impair embryonic brain development through oxidative stress, inflammatory signaling, and dysregulation of neurodevelopmental gene networks (Fig. 5C) (Chen et al., 2023). The nanoscale dimensions of these particles facilitated direct interactions with neural cells, resulting in cumulative and progressive developmental abnormalities. Brain organoids proved particularly effective in capturing these chronic and subtle pathological trajectories, which may be overlooked in short-term or reductionist models.

Oxide-based nanomaterials, often considered biocompatible, also exhibit pathological modulation under prolonged exposure. Henderson et al. found that long-term exposure to nanoscale magnetite alters the development of human forebrain-like cortical spheroids (Fig. 5D) (Henderson et al., 2022). Sustained nanoparticle accumulation disrupted tissue growth patterns and neural marker expression, producing phenotypes reminiscent of late-onset or progressive neurodevelopmental abnormalities. These findings highlight exposure

duration as a critical determinant of pathological modulation in brain organoid systems.

Similarly, Chen et al. suggested that graphene oxide induces concentration- and oxidation state–dependent pathological effects in 3D neural models (Chen et al., 2026). Elevated oxidation levels and prolonged exposure impaired neuronal differentiation and tissue organization, leading to abnormal developmental patterns that are not fully recapitulated in 2D cultures. These findings demonstrate that the surface chemistry and physicochemical tuning of nanomaterials directly influence whether brain organoid development follows physiological or pathological trajectories.

Beyond identifying pathological effects, organoid-based platforms have been developed to systematically interrogate nanomaterial-induced disease-like modulation. Baek et al. proposed that a novel organoid culture system enables improved assessment of nanomaterial-driven developmental perturbations by capturing organoid-specific endpoints, including lineage dynamics, tissue architecture, and functional integrity (Baek et al., 2024). Such platforms provide a mechanistically informed framework that leverages pathological modulation not merely to catalog adverse effects but to model neurodevelopmental disease processes.

Taken together, these studies demonstrate that nanomaterials can pathologically modulate brain organoid development by redirecting normal developmental trajectories toward disease-relevant states. Through mechanisms involving redox imbalance, disruption of signaling pathways, chronic exposure, and surface chemistry–dependent interactions, nanomaterials induce aberrant differentiation patterns, network dysfunction, and disorganized tissue architecture. Importantly, these pathological modulations are not solely indicators of material-associated risk but also represent mechanistically informative phenomena that can be exploited to model neurodevelopmental disorders in human-relevant brain organoid systems.

To systematically analyze the nanomaterial strategies discussed, Table 1 provides an integrated overview of the nanomaterials applied to brain organoid systems and their corresponding functional roles. The table categorizes nanomaterials by type, composition, and underlying physicochemical mechanisms, mapping each system to reported functional outcomes such as neurodifferentiation, functional maturation, and pathological regulation. By organizing these studies within a unified framework, the table highlights how specific nanomaterial properties can be strategically applied to brain organoid models.

4. Nanomaterial-based brain organoid-on-a-chip for drug evaluation

Early brain organoid-on-a-chip systems primarily utilized microfluidics to enhance nutrient delivery and waste removal, thereby improving organoid survival and growth compared to static cultures. More recently, the incorporation of nanomaterials has introduced new functional capabilities. Within the organoid, bioactive and nanoporous nanomaterials help recreate an extracellular matrix–like environment that supports neuronal differentiation, promotes vascularization, and enhances long-term structural stability. Concurrently, the integration of nanomaterials into sensing interfaces has expanded chip functionality. Conductive nanostructures such as graphene, carbon nanotubes, and gold nanodots increase the fidelity of electrophysiological recordings, while plasmonic and optical nanomaterials enable highly sensitive, label-free detection of neurotransmitters and disease biomarkers. By simultaneously enhancing the biological performance of brain organoids and advancing real-time sensing capabilities, nanomaterial-enabled brain organoid-on-a-chip platforms are emerging as powerful tools for studying neurodevelopment, modeling neurological diseases, and evaluating pharmacological compounds with improved accuracy and reproducibility. From a functional perspective, nanomaterials integrated into brain organoid-on-a-chip platforms can be broadly categorized into three roles: (i) passive carriers that facilitate targeted drug delivery, (ii) active therapeutic or pathological modulators that directly influence cellular signaling and tissue development, and (iii) enabling biointerfaces that enhance electrical coupling, signal transduction, or biosensing performance. While certain multifunctional systems may span more than one category, explicitly distinguishing these roles provides a clearer conceptual framework for interpreting nanomaterial-driven biological effects and pharmacological outcomes.

4.1. Nanomaterial-enabled bioelectronic and multimodal readouts for drug evaluation

The incorporation of nanomaterials into brain organoid-on-a-chip platforms has fundamentally reshaped the evaluation of drug responses in complex human neural models. Traditional organoid-based drug testing strategies primarily rely on endpoint analyses such as immunohistochemistry, bulk transcriptomics, or viability assays, which offer limited insight into the dynamic and functional consequences of pharmacological interventions. These approaches often fail to capture subtle changes in neural circuit activity, neurotransmitter release, or intracellular signaling that precede overt phenotypic alterations. In contrast, nanomaterial-enabled bioelectronic and multimodal readout systems introduce interfaces capable of continuously interrogating brain organoids with high temporal, spatial, and functional resolution, thereby transforming organoid-on-a-chip platforms into quantitative and predictive tools for drug evaluation.

A key contribution of nanomaterials in this context is the development of 3D, conformable nano/microelectrode systems that overcome the intrinsic mechanical mismatch between rigid planar electrodes and the soft, curved architecture of organoid tissues. Torres et al. developed a 3D flexible self-folding MEA that autonomously transitions from a planar structure to a 3D configuration, enveloping brain organoids (Pesantez Torres et al., 2025). This self-folding behavior, enabled by stress-engineered nanolayers, ensures intimate and uniform electrical contact across the cortical surface, significantly reducing electrode–tissue impedance. Consequently, the platform enables stable, long-term recordings of spontaneous neural activity and provides a robust bioelectronic interface for detecting drug-induced modulation of firing patterns and network dynamics.

To address the inherent heterogeneity in organoid size and morphology, Ozaki et al. introduced a 360° size-adjustable MEA system designed to mechanically adapt to individual organoids (Ozaki et al., 2025). Fabricated using flexible nanoscale thin-film metal microelectrodes, the platform offers a low-impedance interface that accommodates mechanical deformation without compromising electrical performance. By dynamically adjusting the electrode geometry, the system maintains consistent electrode coverage and stable electrode–tissue coupling across cerebral organoids of varying diameters. As a result, electrophysiological features such as firing rate and burst activity can be recorded with improved reproducibility, effectively reducing variability caused by organoid heterogeneity. Through the combination of mechanically adaptive design and nanoscale bioelectronic interfaces, this platform establishes a robust foundation for standardized functional assessments in pharmacological and disease-modeling studies. Beyond conformability, advances in electrode density and functional integration have further expanded the analytical capabilities of brain organoid-on-a-chip systems. Shin et al. reported a 3D high-density MEA that integrates electrical recording with optical stimulation and localized microfluidic drug delivery, enabling simultaneous perturbation and monitoring of neural circuit dynamics within brain organoids (Shin et al., 2021). Although this study focuses primarily on microscale architectural integration rather than nanomaterial engineering, it offers an important reference for multifunctional bioelectronic system design—one that may be further enhanced by incorporating nanomaterial-enabled interfaces in future pharmacological applications.

Advanced nanofabrication techniques, including printing-based approaches, have expanded the design space of bioelectronic interfaces for

Table 1
Summary of nanomaterial composition, functional roles, applications, and readout strategies in brain organoid-on-a-chip systems.

Nanomaterial class	Material composition	Functional Role	Target Application	Key Readout Modality	Functional role in brain organoid systems	Reference
Carbon-based nanomaterials	Graphene sheets	Conductive biointerface	Neural differentiation enhancement	Gene expression/ lineage analysis	Promotion of neuronal differentiation and lineage biasing	Park et al. (2011)
	Graphene films (tunable conductivity)	Tunable conductive substrate	Regulation of neuronal adhesion & maturation	Differentiation efficiency assays	Modulation of neuronal adhesion and differentiation efficiency	Capasso et al. (2021)
	Multi-walled carbon nanotubes	Network-interacting scaffold	Pathological neural network modeling	Network formation/ NO signaling	Pathological impairment of neural network formation	Jiang et al. (2020)
	Graphene oxide	Surface-mediated modulator	Concentration-dependent differentiation control	Morphology/lineage markers	Concentration-dependent pathological modulation of neural differentiation	Chen et al. (2026)
	Graphene oxide	Electrical coupling interface	Organized neural assembly & biosensing	Electrophysiology/ biosensing	Organized neural tissue assembly and biosensing	Shin et al. (2025a)
	Carbon fiber scaffolds	Structural reinforcement	Midbrain organoid stabilization	Structural analysis/ viability	Structural stabilization of midbrain organoids	Tejchman et al. (2020)
Carbon-based hybrid nanomaterials	Graphene–silica nanoparticle hybrid structures	Conductive topographical scaffold	Axonal alignment & network organization	Neurite alignment imaging	Axonal alignment and neural network organization	Solanki et al. (2013)
	Magnetic graphene oxide nanoparticles	Magneto-responsive interface	Spatial neural differentiation control	Morphology/ differentiation assays	Enhanced neural differentiation and spatial organization	Zhang et al. (2026)
	Collagen–carbon nanodots	Electroconductive ECM mimic	Accelerated neurite outgrowth	Neurite length/ electrophysiology	Accelerated neurite outgrowth and bioelectric functional maturation	Lomboni et al. (2024)
	Graphene–polymer nanofibers	Photo-electrical converter	Light-triggered neural modulation	Optical stimulation response	Light-triggered modulation of neural activity	LaMontagne et al. (2025)
	Graphene–Au nanoelectrode arrays	Stable sensing interface	Long-term neural monitoring	Electrophysiological recording	Long-term, nondestructive electrical monitoring	Lee et al. (2018)
	Graphene oxide–wrapped gold nanopillars	Electrochemical amplifier	Dopamine sensing in organoids	Electrochemical sensing	Dopamine sensing in neurons and midbrain organoids	(Kang et al.)
Magnetic nanomaterials	Iron oxide (Fe_3O_4)	Magnetic aggregation control	Regulation of organoid size & inductivity	Aggregate size/ differentiation	Regulation of aggregate size and neural inductivity	Son et al. (2024)
		Mechanotransductive actuator	Tissue development modulation	Morphology/ maturation markers	Mechanotransduction-mediated tissue development	Abdel Fattah et al. (2023)
		Chronic exposure modulator	Pathological forebrain modeling	Long-term structural analysis	Progressive pathological alteration of forebrain-like organoids	Henderson et al. (2022)
Metal-based nanomaterials	AgNP	Redox-active pathological modulator	Disease-like phenotype induction	Oxidative stress/ morphology	Pathological redirection toward disease-like phenotypes	Huang et al. (2022b)
Inorganic-based nanomaterials	Calcium phosphate nanoparticles (CaP)	Intracellular delivery carrier	Neural differentiation modulation	Intracellular signaling assays	Modulation of neural differentiation via intracellular signaling	Chao et al. (2024)
	Rare-earth UCNPs ($NaYF_4$:Yb/Tm)	NIR-responsive optical modulator	Optical control of differentiation	Fluorescence imaging	Optical control of neural differentiation and axonal stability	Zhang et al. (2024b)
	Stretchable mesh microelectronics	Conformal nanoelectronic interface	Organoid-level stimulation & recording	Electrical recording	Organoid-level stimulation and recording	Li et al. (2022)
Organic	Polypropylene nanoplastics	Stress-inducing pathological agent	Neurodevelopmental abnormality modeling	Stress markers/ morphology	Disease-relevant neurodevelopmental abnormalities	Huang et al. (2025)
	Mixed nanoplastics	Inflammatory signaling inducer	Embryonic brain pathology modeling	Oxidative/ inflammatory assays	Pathological modulation of embryonic brain development	Chen et al. (2023)
Conductive hydrogel nanocomposites	Nanoclay-doped hydrogels	Ionic/electronic conductive scaffold	Functional maturation enhancement	Bioelectric signaling	Promotion of bioelectric signaling and functional maturation	Tondera et al. (2019)
	Tunable conductive hydrogels	Conductivity-regulated matrix	Controlled neural differentiation	Electrophysiology	Controlled acceleration of neural functional maturation	Tringides et al. (2023)
Conductive hydrogel nanocomposites	PEDOT NP–incorporated chitosan/gelatin hydrogels	Uniform conductive domains	Neural proliferation & synchronization	Network activity analysis	Enhanced neural proliferation and synchronized activity	Guan et al. (2022)
	3D-printable GelMA–chitosan conductive hydrogels	Programmable conductivity scaffold	Organoid-scale pathway engineering	Electrical mapping	Organoid-scale electrical pathway engineering	Han et al. (2024)
Nanoelectronic interfaces	Large-scale nanoelectrode arrays	High-resolution recording interface	Dopaminergic differentiation monitoring	Real-time electrophysiology	Real-time monitoring of dopaminergic differentiation	Kim et al. (2015)

organoid electrophysiology and pharmacology-relevant studies. Zips et al. demonstrated aerosol jet–printed, high-aspect-ratio microneedle electrodes fabricated via a high-resolution additive nanofabrication process, enabling penetration into 3D organoid tissue (Fig. 6A) (Zips et al., 2023). Unlike planar surface electrodes, these microneedle structures access deeper neural layers, allowing electrophysiological signals from internal neuronal populations to be recorded with improved fidelity. The increased effective surface area and reduced impedance resulting from the nanostructured, high-aspect-ratio geometry enhance the signal-to-noise ratio, yielding a bioelectronic interface well suited for detecting subtle functional changes in thick, multilayered brain organoid systems. Complementarily, inkjet-printed 3D sensor arrays, refined using focused ion beam (FIB) processing, have enabled low-noise amperometric recordings in hiPSC-derived brain organoids) (Fig. 6B) (Kopic et al., 2025). This platform integrates scalable inkjet printing of silver nanoparticle ink with nanoscale electrode refinement, allowing precise control over the electroactive area and significantly reducing background noise. The resulting improvement in signal fidelity supports stable, long-term electrochemical monitoring in 3D neural tissues, demonstrating how the combination of scalable fabrication and nanoscale engineering can yield robust bioelectronic interfaces for functional and chemically resolved interrogation of brain organoid systems.

Mechanical compatibility between electronic interfaces and neural tissue has emerged as a decisive factor for achieving stable, long-term electrophysiological recording in 3D brain organoid systems. Yang et al. developed kirigami-inspired nanoelectronics fabricated from ultrathin, nanoscale metal thin-film electrodes that unfold and conform to the curved surfaces of cortical organoids (Fig. 6C) (Yang et al., 2024). This mechanically adaptive design minimizes tissue stress while preserving electrical performance, enabling weeks-long monitoring of neural activity without compromising organoid viability. By providing a stable and compliant bioelectronic interface, the platform facilitates chronic electrophysiological observation of neural development and network dynamics, laying the groundwork for future integration into long-term functional and pharmacology-relevant studies. Similarly, stretchable mesh nanoelectronics embedded within developing brain organoids enable 3D, single-cell–resolved chronic electrophysiology (Fig. 6D) (Le Floch et al., 2022). In this system, ultrathin, stretchable mesh nanoelectronics composed of nanoscale Au and Pt electrode interconnects are distributed throughout the organoid tissue, forming a mechanically compliant and electrically stable interface. This architecture supports long-term tracking of neural activity at single-cell resolution during organoid development. Notably, pharmacological perturbation using synaptic antagonists such as CNQX and AP5 suppressed neuronal firing and network activity, which were directly recorded through the embedded mesh. These results demonstrate the capacity of mesh nanoelectronics to resolve drug-induced modulation of synaptic transmission and network dynamics in 3D brain organoids with unprecedented spatial and temporal resolution. Liquid metal-based 3D neuro-interfaces further advance brain organoid-on-a-chip platforms by enabling direct evaluation of organoid responses to chemical stimulation via mechanically compliant bioelectronic interfaces. Wu et al. employed nano- and micrometer-scale gallium–indium (GaIn) liquid metal particles dispersed within an elastomeric matrix to construct soft, deformable neuro-interfaces that conformally integrate with human hippocampal organoids (Fig. 6E) (Wu et al., 2024). The particulate liquid metal forms a percolating conductive network that maintains electrical continuity while minimizing mechanical mismatch and preserving tissue integrity during long-term interfacing. Upon glutamine-induced chemical stimulation, region-specific electrophysiological responses were directly recorded through the liquid metal–based interface. The observed modulation of neural activity demonstrates that soft bioelectronics based on liquid metal particles can sensitively resolve drug- and toxin-induced functional responses in 3D brain organoids. This capability underscores the potential of such nano-enabled interfaces for assessing pharmacological and neurotoxic effects in organoid-on-a-chip systems without compromising tissue viability.

In parallel with electrophysiological readouts, nanomaterial-enabled chemical sensing has provided complementary functional metrics for brain organoid analysis. Nasr et al. developed a self-organized nanostructure-modified microelectrode in which spontaneously formed nanoscale features significantly enhanced electrochemical sensitivity for neurotransmitter detection (Nasr et al., 2018). Using this platform, real-time electrochemical monitoring of glutamate was achieved within stem cell-derived brain organoids, enabling direct observation of excitatory neurotransmission dynamics associated with neuronal activity. By providing a quantitative biochemical readout closely linked to synaptic signaling and excitotoxic processes, this nanostructured electrochemical interface establishes a valuable foundation for evaluating drug- or toxin-induced modulation of neurotransmitter release in brain organoid-on-a-chip systems.

In a related approach, Kang et al. reported graphene oxide–wrapped hierarchical gold nanopillar hybrids that enable real-time, non-destructive electrochemical sensing of dopamine in neurons and midbrain organoids (Fig. 6F) (Kang et al.). The combination of a high-surface-area hierarchical gold nanopillar architecture with a graphene oxide coating produces a conductive interface that enhances dopamine sensitivity without compromising cellular integrity. This platform enabled continuous monitoring of dynamic dopaminergic signaling associated with neuronal activity in midbrain organoids. By directly measuring dopaminergic neurotransmission, the system offers a functional readout relevant to Parkinson's disease–related dysfunction and provides a basis for assessing drug- or toxin-induced modulation of dopamine signaling in organoid models.

Nanomaterial-based sensing strategies have also been extended to molecular biomarkers indicative of disease-specific pathological processes in brain organoids. Lee et al. developed peptide-imprinted conductive polymer nanotubes in which nanoscale tubular architectures, combined with molecular imprinting, enabled selective recognition of α-synuclein (Lee et al., 2020). Using this nanomaterial-engineered sensing interface, α-synuclein was sensitively detected within human brain organoids, providing a disease-relevant molecular readout associated with neurodegenerative pathology. By moving beyond general viability or electrophysiological metrics, this work demonstrates how nanomaterial-based molecular recognition platforms can support organoid-level assessment of pathological protein aggregation and enable future evaluation of therapeutic interventions targeting disease-specific biomarkers.

Complementarily, nanopore-based single-molecule counting assays have been employed to quantify extracellular vesicle cargo released from cerebral organoids, offering a non-invasive strategy for monitoring organoid development, health, and stress-related responses. In this approach, solid-state nanopores enable sensitive, label-free detection and quantification of small extracellular vesicle cargo at the single-molecule level (Saiduzzaman et al., 2025). Applied to cerebral organoids, this platform allows longitudinal assessment of organoid state without perturbing tissue integrity. By providing a non-invasive molecular readout linked to cellular stress and functional status, nanopore-based sensing establishes a versatile framework suitable for integration with drug or toxin exposure studies to track organoid responses over time.

Optical and photoacoustic nanomaterial-enabled readouts further extend drug evaluation into volumetric and intracellular dimensions. Barulin et al. developed an axially multifocal metalens composed of submicrometer-thick titanium oxide nanopillars that enables 3D volumetric photoacoustic imaging of neuromelanin in live brain organoids (Barulin et al., 2025). This label-free technique provides spatially resolved visualization of a disease-relevant intracellular biomarker throughout intact organoids, offering an optical complement to extracellular molecular sensing as well as to electrical and chemical readouts in neurodegenerative disease modeling.

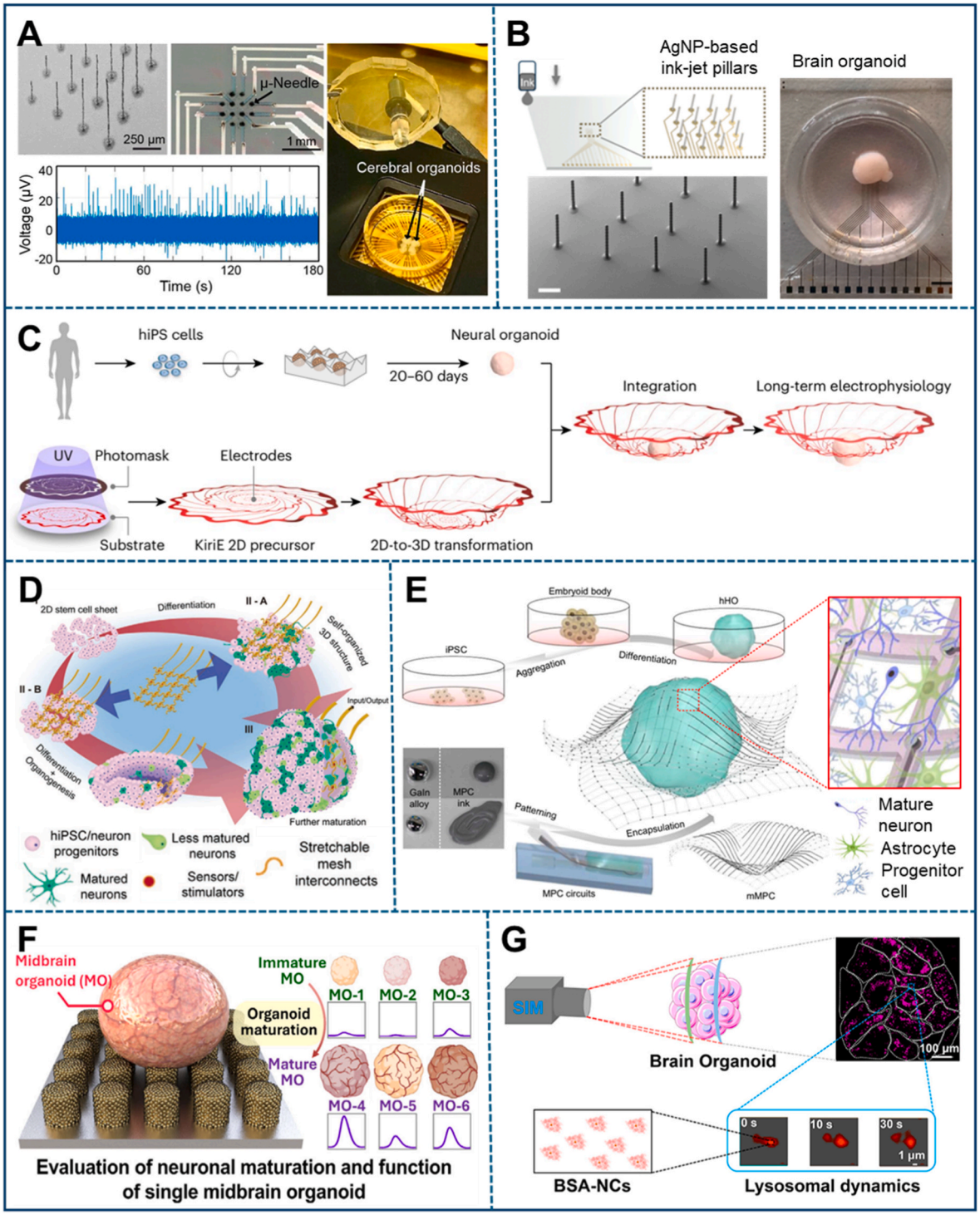

Fig. 6. Nanomaterial-enabled bioelectronic and multimodal readout strategies for functional interrogation of brain organoid-on-a-chip systems. (A) Aerosol jet–printed, high–aspect ratio microneedle electrodes penetrating brain organoids to access deep neuronal layers and enhance electrophysiological signal quality. Reproduced with permission from (Zips et al., 2023). (B) Inkjet-printed, 3D sensor arrays fabricated with silver nanoparticle ink and refined via focused ion beam processing for low-noise electrochemical recording in hiPSC-derived brain organoids. Reproduced with permission from (Kopic et al., 2025). (C) Kirigami-inspired nanoelectronic interfaces conformally wrapping brain organoids to enable stable, long-term electrophysiological monitoring with minimal mechanical stress. Reproduced with permission from (Yang et al., 2024). (D) Stretchable mesh nanoelectronics embedded within developing brain organoids, allowing chronic, single-cell–resolved electrophysiological recording and monitoring of drug-induced synaptic modulation. Reproduced with permission from (Le Floch et al., 2022) (E) Liquid metal–based soft neuro-interfaces composed of gallium–indium particles that conform to hippocampal organoids for assessing chemically induced electrophysiological responses. Reproduced with permission from (Wu et al., 2024). (F) Graphene oxide–wrapped hierarchical gold nanopillar hybrids enabling real-time, non-destructive dopamine sensing in midbrain organoids. Reproduced with permission from (Kang et al.). (G) Near-infrared–emitting noble metal nanoclusters for ultralong-term super-resolution imaging of lysosomal dynamics and drug-induced intracellular alterations in brain organoids. Reproduced with permission from (Qiu et al., 2022). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

At a finer intracellular scale, Qiu et al. demonstrated that near-infrared–emitting noble metal nanoclusters enable ultralong-term super-resolution tracking of lysosomes within brain organoids (Fig. 6G) (Qiu et al., 2022). These ultrasmall nanoclusters exhibit exceptional photostability and low phototoxicity, allowing continuous visualization of lysosomal trafficking over extended periods in 3D tissue. Chemical perturbation with carbonyl cyanide m-chlorophenylhydrazone (CCCP) was applied to the organoids, and the resulting alterations in lysosomal positioning and intracellular transport dynamics were directly observed, revealing drug-induced modulation of autophagy-related and metabolic processes at the subcellular level. Together, these optical nanomaterial-based platforms illustrate how volumetric and intracellular imaging modalities complement non-invasive extracellular sensing by capturing disease- and drug-related responses in brain organoids across multiple spatial scales.

Collectively, these studies demonstrate that nanomaterial-enabled bioelectronic and multimodal readout platforms fundamentally advance brain organoid-on-a-chip systems into comprehensive tools for drug evaluation. By enabling continuous, high-resolution interrogation of electrophysiological, biochemical, molecular, and intracellular responses, these approaches establish a multidimensional framework for assessing drug efficacy, toxicity, and mechanisms of action in physiologically relevant human neural models.

4.2. *Nanomaterial-based platforms for drug delivery, neuromodulation, and disease-specific pharmacological evaluation*

Beyond their role as sensing and readout interfaces, nanomaterials have increasingly been employed as active components for drug delivery, neuromodulation, and therapeutic intervention within brain organoid-on-a-chip platforms. In this context, nanomaterials function not merely as passive carriers or probes, but as engineered therapeutic agents whose physicochemical properties enable controlled delivery, targeted action, and enhanced efficacy in complex 3D neural tissues. The integration of such nanomaterial-based therapeutic platforms with brain organoids has opened new avenues for disease-specific pharmacological

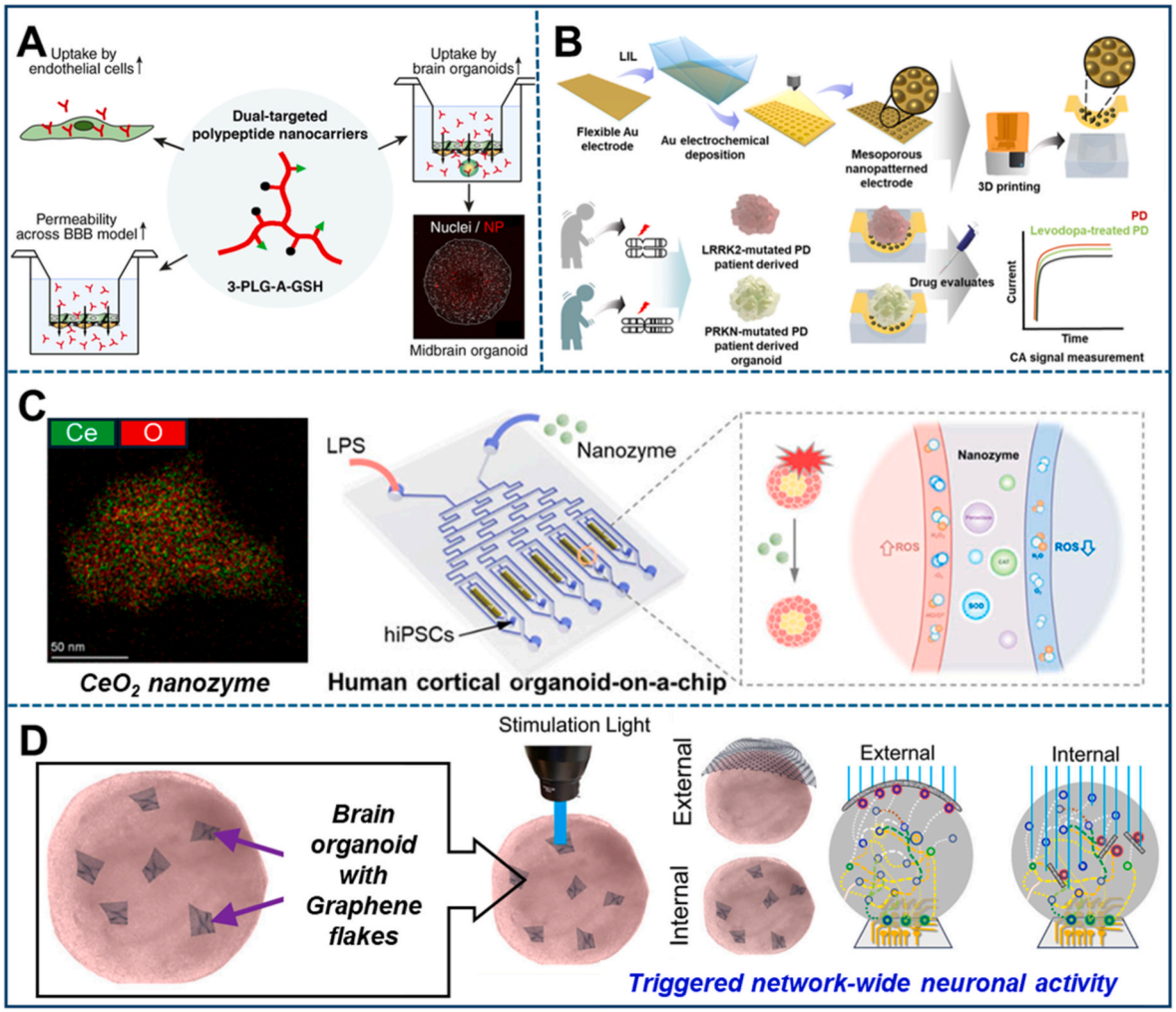

Fig. 7. Nanomaterial-based platforms for drug delivery, neuromodulation, and disease-specific pharmacological evaluation in brain organoid-on-a-chip systems. (A) Glutathione- and alanine-functionalized polypeptide nanocarriers evaluated in a human endothelial cell–based blood–brain barrier (BBB) model coupled to midbrain organoids, enabling assessment of BBB permeability and post-barrier accumulation within 3D neural tissue. Reproduced with permission from (Mészáros et al., 2023). (B) Ultrasmall gold nanoparticles (~2 nm) functionalized with doxorubicin for targeted drug delivery in disease-relevant brain organoids, allowing comparison of pharmacological efficacy and off-target toxicity between normal and glioblastoma organoids. Reproduced with permission from (An et al., 2024). (C) CeO_2 nanozyme-based therapeutic screening in a human cortical brain organoid-on-a-chip platform, where the nanozyme serves as a catalytic agent to modulate oxidative stress and neuroinflammatory responses under defined pathological conditions. Reproduced with permission from (Wu et al., 2025) (D) Graphene-based optoelectronic actuators integrated with brain organoids for non-genetic neuromodulation, enabling spatially controlled, light-triggered activation of neural networks for functional studies in disease-relevant models. Reproduced with permission from (Molokanova et al., 2025). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

evaluation, offering models that more faithfully recapitulate human brain physiology than conventional 2D cultures or animal models.

A critical challenge in brain drug development is the delivery of therapeutic agents across the blood–brain barrier (BBB), a process poorly captured by conventional *in vitro* assays. To address this limitation, Mészáros et al. developed a polypeptide nanocarrier system functionalized with glutathione and alanine to enhance transport across a human endothelial cell–based *in vitro* BBB model (Fig. 7A) (Mészáros et al., 2023). By systematically tuning the nanocarrier surface chemistry, the study demonstrated that glutathione- and alanine-mediated targeting significantly improves trans-endothelial transport efficiency. Importantly, the BBB model was coupled with human midbrain organoids to verify post-BBB accumulation and localization of the nanocarriers within 3D neural tissue, providing biologically relevant validation of brain-targeted delivery. Rather than focusing on therapeutic efficacy, this platform enables quantitative assessment of BBB-crossing capability and neural tissue exposure, establishing a critical screening interface between nanomaterial-enabled drug delivery and downstream organoid-based neuropharmacological studies. This work underscores the importance of nanomaterial design in early-stage evaluation of brain-targeted drug delivery platforms.

Nanoparticle-mediated drug delivery has also been evaluated directly within 3D brain tumor and disease-relevant organoid models. Kostka et al. investigated ultrasmall gold nanoparticles (~2 nm) functionalized with doxorubicin and examined their pharmacological responses in both normal brain organoids and glioblastoma organoids (Kostka et al., 2024). The ultrasmall particle size enabled efficient penetration throughout dense 3D organoid tissue, facilitating uniform drug exposure within the organoid interior. By directly comparing drug-induced responses between healthy and tumor organoids, this platform enabled disease-specific assessment of anticancer activity alongside evaluation of off-target toxicity in normal neural tissue. This study demonstrates how nanomaterial-based drug carriers can support differential pharmacological evaluation in physiologically relevant brain organoid models, highlighting their value for early-stage screening of brain tumor therapeutics.

Disease-specific pharmacological evaluation has been further advanced through the integration of patient-derived brain organoids into organoid-on-a-chip platforms. An et al. reported a Parkinson's disease patient–derived midbrain organoid-on-a-chip system that enables assessment of pharmacological modulation of dopaminergic neural function within a genetically relevant disease background (Fig. 7B) (An et al., 2024). Using this platform, clinically relevant neurotransmitter-related drugs, including levodopa, norepinephrine, and isoprenaline, were applied, and drug-specific functional responses of the midbrain organoids were quantitatively evaluated. Although engineered nanoparticles were not used as drug carriers, the system incorporated micro- and nanoscale bioelectronic interfaces to enable sensitive monitoring of neuronal activity under pharmacological perturbation. This work demonstrates how patient-specific organoid-on-a-chip platforms can support disease-context drug evaluation and pharmacological stratification beyond conventional cell-based assays.

Similarly, Kim et al. investigated the effects of a novel mica-based nanoparticle (STB-MP) using Alzheimer's disease patient–derived cortical brain organoids (Kim et al., 2023b). In this study, the nanomaterial functioned as a drug-like therapeutic candidate rather than as a delivery vehicle, enabling direct assessment of its biological activity within a disease-relevant neural context. The organoid-on-a-chip platform allowed systematic evaluation of nanoparticle-induced modulation of Alzheimer's disease–associated phenotypes, including changes in neuronal viability, cytotoxicity, and pathological marker expression. By employing patient-specific cortical brain organoids, this work demonstrates how nanomaterials can be screened directly as pharmacological agents in human-relevant brain models, underscoring the utility of organoid-on-a-chip platforms for disease-specific nanomedicine evaluation.

Nanomaterials have also been engineered to function as catalytic or reactive therapeutic agents rather than conventional drug carriers. Wu et al. developed a CeO_2 nanozyme-based platform to screen anti-inflammatory and neuroprotective effects using human cortical brain organoids integrated into an organoid-on-a-chip system (Fig. 7C) (Wu et al., 2025). In this study, the CeO_2 nanozyme acted as an active therapeutic agent, modulating oxidative stress and inflammation-related signaling pathways within neural tissue. Neuroinflammatory conditions were first induced in the organoids, after which nanozyme treatment enabled systematic evaluation of dose-dependent neuroprotective responses, alterations in inflammatory marker expression, and potential cytotoxic effects. This work demonstrates how brain organoid-on-a-chip platforms can support direct screening of nanomaterial-based therapeutics in human-relevant neural models, highlighting their utility for evaluating the efficacy–toxicity balance in emerging nanomedicine strategies.

Beyond chemical therapeutics, nanomaterial-based platforms have enabled non-genetic neuromodulation strategies for functional intervention in brain organoid models. Molokanova et al. developed graphene-based optoelectronic actuators capable of modulating neural activity in response to optical stimulation (Fig. 7D) (Molokanova et al., 2025). When integrated with brain organoid systems, these graphene interfaces enabled precise, spatially controlled excitation of neural networks without the need for genetic modification. This platform was applied to disease-relevant neural models and stem cell–derived tissues, demonstrating how optoelectronic neuromodulation can influence neural maturation and functional states. Although this approach does not involve direct chemical drug screening, it establishes a pharmacologically relevant neuromodulation framework that can complement or substitute for conventional drug-based interventions.

The microenvironment in which brain organoids are cultured plays a crucial role in determining drug responsiveness, and nanomaterial-integrated microfluidic systems have been developed to better recapitulate *in vivo* conditions. Cho et al. designed a microfluidic brain organoid platform incorporating brain extracellular matrix components together with oxygen-sensitive phosphor nanoparticles composed of Pt(II) meso-tetra(pentafluorophenyl)porphine (PtTFPP) embedded in a poly(urethane acrylate nonionomer) (PUAN) matrix (Cho et al., 2021).These PtTFPP–PUAN nanoparticles enabled real-time monitoring of oxygen distribution and the metabolic microenvironment within developing organoids, providing quantitative insight into tissue maturation under perfused culture. By promoting structural organization, neuronal connectivity, and physiologically relevant oxygenation, this nanomaterial-integrated platform generated mature brain organoids that are better suited for downstream pharmacological interrogation. Although the nanoparticles do not function as therapeutic agents, they play a critical role in establishing and monitoring a drug-relevant microenvironment, thereby improving the reliability of pharmacological evaluation in brain organoid-on-a-chip systems.

Taken together, these studies demonstrate that nanomaterial-based platforms significantly expand the applications of brain organoid-on-a-chip systems in drug-related research. By facilitating drug delivery across physiological barriers, enabling non-genetic modulation of neural activity, and supporting disease-specific pharmacological testing in human-relevant organoids, nanomaterials offer practical tools for investigating neural tissue responses to therapeutic interventions. Rather than functioning as drugs themselves in all cases, nanomaterials often serve as enabling components that enhance control, measurement, and biological relevance in organoid-based studies. Collectively, these strategies increase the utility of brain organoid-on-a-chip platforms in early-stage neuropharmacology and drug development by integrating materials engineering with functional neural models.

4.3. Next-generation platforms: Assembloids and organoid-based biohybrid robot on-a-chip systems

As brain organoid-on-a-chip technologies evolve toward higher-order physiological modeling, next-generation platforms increasingly incorporate assembloids and biohybrid systems that integrate multiple neural regions or couple living neural tissues with artificial actuators and sensors. These advanced architectures enable the interrogation of neural function beyond isolated organoids by capturing inter-regional signal transmission, coordinated network activity, and system-level outputs. Within this context, nanomaterials serve as pivotal functional interfaces that enhance electrical coupling, signal fidelity, and

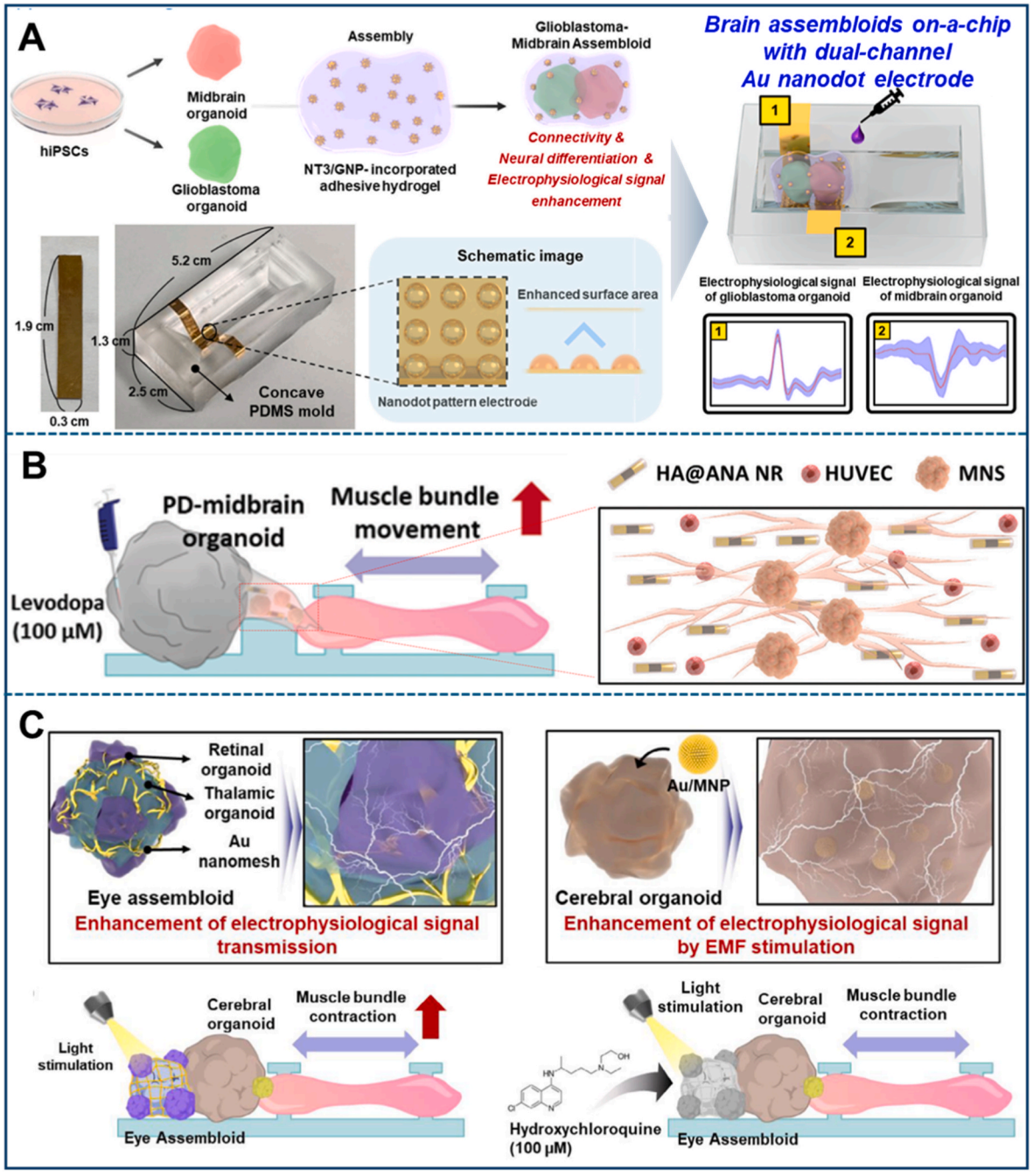

Fig. 8. Nanomaterial-assisted assembloid and brain organoid-based biohybrid robot-on-a-chip platforms for system-level drug and toxicity assessment. (A) Glioblastoma–midbrain assembloid-on-a-chip integrated with Au nanodot–decorated microelectrodes and neurotrophin-3–functionalized gold nanoparticles (NT3-GNPs), enabling high-sensitivity electrophysiological interrogation at the tumor–neuron interface and concurrent evaluation of anticancer drug efficacy and neurotoxicity. Reproduced with permission from (Park et al., 2026). (B) Motor system–based biohybrid robot-on-a-chip linking brain organoid–derived neural tissue with muscle actuators via Au-based microelectrodes and hyaluronic acid–coated anisotropic nanorods (HA@ANA NRs), allowing functional drug testing by translating glutamate- and levodopa-induced neural modulation into quantifiable neuromuscular outputs. Reproduced with permission from (Shin et al., 2024b). (C) Nervous system–based biohybrid robot-on-a-chip incorporating brain organoids and eye assembloids encapsulated by an Au nanomesh, with Au-coated magnetic nanoparticles (Au/MNPs) embedded in cerebral organoids to enhance neural signal transmission, enabling sensitive detection of hydroxychloroquine-induced neurotoxicity through altered electrophysiological signals and motor responses. Reproduced with permission from (Shin et al., 2025b). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

transduction efficiency, thereby supporting drug and toxicity evaluation at levels of biological organization that more closely approximate *in vivo* neural systems.

A foundational example of assembloid-based modeling is the generation of cortico-striatal circuitry through the assembly of region-specific brain organoids. Miura et al. reported the formation of human striatal organoids and their fusion with cortical organoids to produce cortico-striatal assembloids that recapitulate key features of inter-regional neural connectivity (Miura et al., 2020).While this biological assembly establishes an anatomical framework for multiregional brain models, quantitative evaluation of functional coupling and pharmacological modulation across compartments requires sensitive interfacing and recording strategies capable of resolving bidirectional signal transmission. As assembloid platforms scale toward larger sizes and greater structural complexity, they encounter challenges such as structural instability and diffusion limitations that impair long-term culture and functional assessment. Addressing these limitations, Xu et al. developed an artificial meshed vessel–induced platform for dimensional breaking growth of human brain organoids and multiregional assembloids. In this system, engineered polymeric mesh architecture functioned as artificial vasculature, facilitating nutrient transport, guiding tissue organization, and mechanically stabilizing interfaces between distinct neural regions (Xu et al., 2024). By supporting the sustained growth and functional integration of interconnected organoids, this scaffold-based framework provides a structural foundation for reliable electrophysiological interrogation and downstream drug evaluation in large-scale assembloid-on-a-chip systems. Importantly, functional drug evaluation in assembloid-on-a-chip platforms has also been demonstrated using electrophysiological monitoring approaches that do not explicitly rely on nanomaterials. In a human brain–spinal cord assembloid system, electrophysiological monitoring of neurochemical-based signal transmission enabled assessment of functional coupling between central and peripheral neural tissues; the effects of caffeine as a pharmacological stimulant were evaluated through drug-induced modulation of inter-regional neural signal propagation (Son et al., 2022). Although this platform utilized conventional microscale electrodes, it provides clear proof of concept that assembloid-on-a-chip systems can support functional drug evaluation at the level of inter-regional neural communication, while simultaneously underscoring the limitations in sensitivity and resolution that motivate the integration of nanomaterial-enabled sensing interfaces.

The limitations of microscale electrode interfaces become particularly evident in disease-relevant assembloid models that demand high sensitivity and spatial resolution. Park et al. developed a glioblastoma–midbrain assembloid platform integrated with gold nanodot–decorated microelectrodes, where densely distributed Au nanodots significantly increased the effective electroactive surface area and reduced electrode impedance (Fig. 8A) (Park et al., 2026). In addition to the nanodot-engineered sensing interface, neurotrophin-3–functionalized gold nanoparticles (NT3-GNPs) were incorporated to promote neuronal viability and functional stability within the midbrain compartment, enabling sustained electrophysiological interrogation in the presence of tumor tissue. This combined nanomaterial strategy enabled high signal-to-noise recordings at the tumor–neuron interface, allowing real-time resolution of subtle, drug-induced changes in neuronal firing patterns and tumor-associated electrical disruptions. By leveraging Au nanodots for signal amplification and NT3-GNPs for biological interface stabilization, the platform facilitated simultaneous evaluation of anticancer drug efficacy and neurotoxicity within a single assembloid system, illustrating how nanomaterial-enabled sensing can overcome the sensitivity limitations of conventional microscale electrode approaches.

Beyond neural–neural assemblies, biohybrid robot-on-a-chip systems represent a further advancement toward system-level drug evaluation by coupling neural tissues with artificial actuators. A representative example is the human motor system–based biohybrid robot-on-a-chip developed by Shin et al., in which human neural tissues were functionally integrated with muscle actuators to recapitulate neuromuscular signal transmission (Fig. 8B) (Shin et al., 2024b).In this platform, Au-based microelectrodes were employed to establish stable electrical coupling and enable long-term recording of neural activity. Additionally, hyaluronic acid–coated anisotropic nanorods (HA@ANA NRs) were incorporated as functional nanomaterials to enhance neural interface stability and facilitate efficient transmission of neural signals to the muscle component. Using this biohybrid system, glutamate was applied to induce excitatory neural stimulation, while levodopa was evaluated as a dopaminergic therapeutic relevant to neurodegenerative disease models. Drug-induced modulation of neural activity was reliably transduced into measurable muscle contraction and macroscopic motion, enabling quantitative assessment of pharmacological effects through system-level motor outputs. This work highlights how nanomaterial-assisted biohybrid robot-on-a-chip platforms enable functional drug evaluation beyond conventional electrophysiological readouts by linking neural pharmacology to integrated neuromuscular behavior.

In a toxicity-focused biohybrid study, Shin et al. developed a human nervous system–based robot-on-a-chip that integrates brain organoids with nanomaterial-assisted signal amplification for functional neurotoxicity screening (Fig. 8C) (Shin et al., 2025b). In this platform, an eye assembloid composed of retinal and thalamic organoids was encapsulated by an Au nanomesh, which enhanced electrophysiological signal transmission between sensory and neural tissues while maintaining biocompatibility and molecular permeability. In parallel, Au-coated magnetic nanoparticles (Au/MNPs) were incorporated into cerebral organoids to promote neuronal maturation and amplify intrinsic neural activity under electromagnetic stimulation, thereby enhancing central signal processing. Leveraging these complementary nanomaterial interfaces, the biohybrid platform translated organoid-level neural dysfunction into macroscopic motor outputs. Using hydroxychloroquine as a model neurotoxic agent, drug-induced impairment of light-evoked neural signaling was quantitatively captured through reduced muscle contraction, demonstrating how nanomaterial-enabled, brain organoid–based biohybrid systems allow sensitive, system-level toxicity evaluation beyond conventional viability assays. Collectively, these next-generation assembloid and brain organoid-based biohybrid robot-on-a-chip platforms represent a decisive shift from static, single-organoid assays toward integrated, system-level functional evaluation frameworks. By combining multiregional neural assemblies with nanomaterial-enabled sensing and actuation interfaces, these systems allow drug and toxicity responses to be assessed not only at the cellular and molecular levels but also through emergent phenomena such as inter-regional signal propagation, neuromuscular output, and coordinated network dynamics.

Nanomaterials play a central role in this transition by addressing the limitations of conventional microscale interfaces in terms of sensitivity, stability, and scalability, thereby enabling high-fidelity electrical coupling, signal amplification, and long-term functional monitoring in complex neural constructs. Importantly, the ability to translate pharmacological perturbations into quantitative, system-level readouts establishes assembloid- and biohybrid-based platforms as powerful testbeds for evaluating therapeutic efficacy and safety in human-relevant neural models. As these technologies continue to mature, nanomaterial-assisted assembloid and biohybrid systems are expected to become essential tools in neuropharmacology, bridging simplified *in vitro* assays with the complex functional behavior of the human nervous system.

However, despite their promising functional integration and biomimetic complexity, the scalability and reproducibility of biohybrid robot-on-a-chip systems remain critical considerations for routine drug screening applications. The fabrication of hybrid platforms that combine living tissues with nanoengineered components often involves multistep assembly processes and precise material–cell interfacing, which

may introduce device-to-device variability. Furthermore, throughput limitations associated with customized microfabrication and organoid integration can restrict large-scale pharmacological testing. The development of standardized fabrication workflows, automated assembly strategies, and modular design architectures will therefore be essential to enhance reproducibility and enable broader implementation of biohybrid systems in high-throughput drug evaluation settings.

4.4. Translational and reproducibility considerations

Despite the significant technological advances described above, several translational and methodological considerations must be addressed to ensure reliable drug evaluation using nanomaterial-enabled brain organoid-on-a-chip platforms. Beyond functional enhancement, the biocompatibility of nanomaterials remains a critical determinant of pharmacological interpretation and clinical relevance.

Carbon-based nanomaterials such as graphene derivatives and carbon nanotubes have been widely employed for neural interfacing and signal enhancement due to their electrical conductivity and structural robustness. However, their biological responses are strongly influenced by physicochemical parameters including size, surface functionalization, oxidation state, and administered dose. Under certain exposure conditions, oxidative stress generation, membrane perturbation, and altered neural differentiation have been reported, indicating that safety optimization must accompany performance enhancement. Similar design-dependent effects have also been observed in metallic and polymeric nanoparticles, underscoring that biocompatibility is not intrinsic to a material class but rather depends on dosage, surface engineering, and exposure duration.

Importantly, discrepancies may arise when extrapolating organoid-based *in vitro* findings to *in vivo* biological systems. In living organisms, nanoparticle biodistribution and long-term fate are governed by systemic clearance pathways, including hepatic and renal elimination, dynamic protein corona formation, and immune surveillance mechanisms such as microglial activation. In contrast, brain organoids lack fully developed vascular and immune systems, which may alter nanoparticle retention, diffusion dynamics, and local accumulation. Such differences can influence both therapeutic efficacy and toxicity assessment, potentially limiting direct translation of *in vitro* results to *in vivo* contexts (Liu et al., 2024).

In the specific context of drug evaluation, nanoparticle-mediated delivery strategies introduce additional considerations related to dose normalization and retention kinetics. The absence of physiological elimination mechanisms in organoid models may lead to prolonged nanoparticle persistence within extracellular matrices or intracellular compartments. This extended exposure can amplify apparent therapeutic responses or toxicity profiles, thereby influencing pharmacological interpretation. Careful dose calibration, temporal monitoring of nanoparticle distribution, and consideration of diffusion gradients within three-dimensional organoid architectures are therefore essential to avoid overestimation of drug efficacy or adverse effects.

Furthermore, biological variability inherent to brain organoid systems presents additional challenges for reproducible drug screening. Batch-to-batch differences in organoid size, cellular composition, and maturation state can result in heterogeneous baseline functional readouts. Patient-derived or disease-specific organoids may exhibit substantial inter-individual variability in genetic background and signaling dynamics, which can affect responsiveness to nanomaterial-mediated drug delivery or neuromodulation strategies. Standardized culture protocols, quantitative benchmarking metrics, and integration of nanomaterial-enabled real-time sensing platforms may help mitigate such variability and improve cross-sample comparability.

Collectively, addressing these translational and reproducibility considerations will be essential for realizing the full predictive potential of nanomaterial-based brain organoid-on-a-chip systems in neuropharmacology and personalized medicine.

5. Conclusion and future perspective

Brain organoid-on-a-chip platforms have rapidly emerged as advanced microphysiological systems that integrate stem cell–derived brain organoids with microfluidic technologies. Compared to conventional static cultures, these chip-based platforms offer a more controlled microenvironment through regulated perfusion, stable oxygen and nutrient delivery, and efficient waste removal. This engineering-based regulation addresses key limitations of brain organoids, including diffusion-limited mass transport, hypoxia-induced necrotic core formation, and inconsistent biochemical cue exposure. Notably, these systems also overcome the lack of continuous, quantitative monitoring of neural function. By incorporating integrated sensing and bioelectronic modules, brain organoid-on-a-chip platforms enable longitudinal assessment of electrophysiological activity and dynamic biochemical signaling, transforming organoids from descriptive models into measurable, functional testbeds with enhanced translational relevance.

Nanomaterial-enabled strategies further augment these platforms by enhancing both neural differentiation and sensing performance. Conductive nanomaterials and nanostructured electrode interfaces improve electrical coupling between soft organoid tissues and recording devices, reduce interfacial impedance, and increase signal fidelity for long-term electrophysiological monitoring. Additionally, nanomaterials facilitate amplified electrochemical and optical detection of critical biomarkers, including neurotransmitters, metabolites, inflammatory mediators, and oxidative stress indicators, thereby supporting multimodal monitoring under physiologically relevant conditions. These advancements underscore that future brain organoid-on-a-chip platforms will depend not only on refined culture environments but also on integrated nanotechnologies that enable real-time, functional phenotyping at the level of neural circuits and biochemical dynamics.

Despite substantial progress, brain organoid-on-a-chip systems require further advancement in biological realism, standardization, and system integration. The incorporation of perfusable vasculature and barrier components remains a critical priority. Vascularization is essential for sustaining long-term maturation and maintaining metabolic homeostasis, while blood–brain barrier-like modules are necessary for realistic modeling of drug permeability, neurovascular dysfunction, and systemic exposure profiles. Furthermore, the integration of immune and inflammatory components is increasingly important, as neuroimmune signaling not only contributes to brain development but also plays a central role in the pathogenesis of neurodegenerative and neuroinflammatory disorders. Perfusion systems offer unique opportunities to temporally and spatially control inflammatory stimuli, enabling precise dosing and continuous monitoring of functional consequences. Next-generation platforms are also expected to evolve beyond single-region organoids toward integrated, circuit-level models. Multi-region assembloids and modular neural assemblies will facilitate the investigation of inter-regional communication and long-range connectivity, enabling more faithful modeling of complex phenotypes such as excitatory–inhibitory imbalance, altered synchrony, and circuit-level dysfunction. Microfluidic architectures can support spatial compartmentalization and guided axonal projections, while integrated recording systems provide quantitative assessment of network maturation and pathological disruptions. Concurrently, future chip designs will expand functional readouts beyond electrophysiology by combining electrical recordings with biochemical biosensing. This multimodal approach is expected to enhance sensitivity for detecting early or subtle drug effects, particularly when perturbations in neurotransmitter dynamics, metabolism, or oxidative stress occur prior to overt morphological changes.

Long-term stability and maturation remain key challenges, as many brain organoids retain fetal-like characteristics that limit their relevance for modeling age-associated disorders. Advancing long-term perfusion conditions, introducing maturation-promoting cues, and implementing chronic monitoring strategies will be essential to extend brain organoid-on-a-chip applications to aging and neurodegeneration research.

Translational scalability will also depend on standardized differentiation protocols, reproducible chip manufacturing, automated culture workflows, and robust quality-control metrics. In parallel, data-driven analytics and machine learning (ML) approaches will become increasingly important for interpreting high-dimensional datasets and for establishing reproducible functional models in disease modeling and pharmacological screening. Furthermore, the application of ML approaches is increasingly relevant for the analysis of data generated from brain organoid-on-a-chip platforms (Cai et al.). These systems typically produce high-dimensional datasets that include electrophysiological recordings, biochemical sensing outputs, and longitudinal functional measurements. The integration of nanomaterial-enabled bioelectronic and biosensing interfaces further increases data by improving temporal resolution, signal stability, and multimodal measurement capability. As a result, the datasets obtained from such platforms are well suited for data-driven analytical approaches that can capture relationships between neural activity, biochemical dynamics, and pharmacological perturbations without relying solely on predefined metrics.

In particular, nanomaterial-based readouts provide practical advantages for computational analysis by reducing noise, measurement error, and inter-device variability, which are common challenges in training and validating ML models. Continuous and label-free monitoring of neural electrophysiology, neurotransmitter release, and metabolic indicators enables the construction of feature spaces that reflect functional organoid states over time. These datasets can support established ML approaches such as feature extraction, pattern recognition, and classification of drug-induced responses, as well as time-series analysis of maturation or disease-related changes. From a translational standpoint, the combination of standardized organoid-on-a-chip platforms with reproducible nanomaterial-enabled sensing may facilitate comparative analysis across experiments and laboratories, thereby supporting more reliable data-driven evaluation of neuroactive compounds.

In conclusion, brain organoid-on-a-chip platforms represent a transformative convergence of organoid biology, microfluidic engineering, and nanomaterial-based bioelectronics. Continued advances in vascularization, immune system integration, circuit-level assembly, multimodal sensing, and standardization are expected to accelerate their development into reliable, human-relevant systems for mechanistic neuroscience and predictive drug evaluation.

CRediT authorship contribution statement

Minkyu Shin: Writing – original draft, Writing – review & editing. **Myeong-Jun Lee:** Writing – original draft, Writing – review & editing. **Sangeun Lee:** Investigation. **Ki-Bum Lee:** Conceptualization, Supervision, Writing – review & editing. **Jeong-Woo Choi:** Conceptualization, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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