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Brain organoids: advances, applications, and limitations in neuroscientific and therapeutic research

Abstract

This article discusses the advances and limitations of brain organoids and stem cell–based therapies in neuroscience and regenerative medicine. Recent years have witnessed a rapid expansion of studies employing brain organoids ("mini-brains") and Induced Pluripotent Stem Cells (iPSCs) to model neurological and neurodegenerative diseases, test pharmacological compounds, and explore novel therapeutic approaches. The objective of this work is to provide an updated overview of the scientific progress achieved between 2013 and 2025, with special attention to breakthroughs in regenerative medicine and genetic engineering. The methodology adopted involves a systematic review of academic databases such as PubMed, ScienceDirect, and CAPES, complemented by a critical analysis of selected studies. Articles were evaluated based on their objectives, methods, study populations, interventions, outcomes, and conclusions. The results indicate that brain organoids represent reliable models for studying infectious, psychiatric, and degenerative diseases. Meanwhile, stem-cell–based therapies are increasingly showing clinical promise, particularly in conditions such as Parkinson's, amyotrophic lateral sclerosis, macular degeneration, and autoimmune disorders. Limitations persist regarding maturity, vascularization, and ethical issues, but technological innovations such as CRISPR, CAR-T, and organoids-on-chip point to a future in which highly personalized medicine may become feasible. Overall, this study highlights the transformative potential of stem cell and organoid technologies for modern biomedical science and therapeutic development.

Keywords: autoimmunity, brain organoids, including stem cells, genetic therapies, neurodegenerative diseases, regenerative medicine

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Introduction

Mini-brains, also called cerebral organoids, are one of the most notable innovations in biotechnology applied to neuroscience in the last two decades. These three-dimensional models, derived from embryonic stem cells or Induced Pluripotent Stem Cells (iPSCs), are capable of reproducing structural and functional aspects of the human brain in early stages of development. Using cell differentiation protocols under controlled conditions, mini-brains are organized into layers and regions that resemble the developing cerebral cortex, making them promising tools for studying mechanisms of neurodevelopment, neurological diseases, and drug action (Figure 1).[1,2]

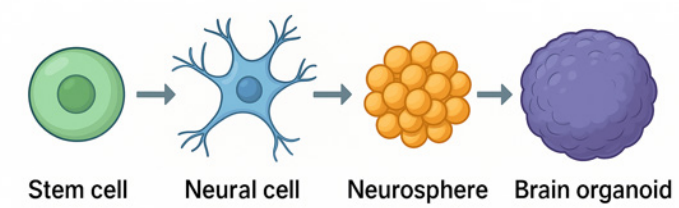

Figure 1 Process of generating a brain organoid from stem cells.

Limitations persist regarding maturity, vascularization, and ethical issues, but technological innovations such as CRISPR, CAR-T, and organoids-on-chip point to a future in which highly personalized medicine may become feasible. Overall, this study highlights the transformative potential of stem cell and organoid technologies for modern biomedical science and therapeutic development (Figure 2).[1,2]

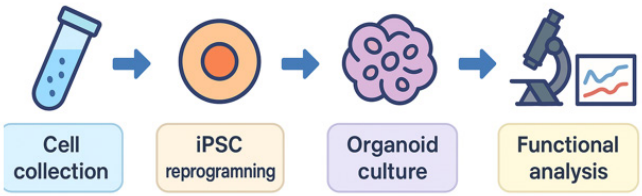

Figure 2 Experimental pipeline for brain organoid generation and analysis.

Besides their value as experimental models, mini-brains represent a significant advance over traditional animal models. Rodents and other organisms cannot faithfully reproduce the genetic, structural, and functional complexity of the human brain. For this reason, many results obtained in preclinical studies do not translate into effective benefits when applied to humans. In this sense, mini-brains emerge as innovative alternatives, allowing for the investigation of human conditions in a more realistic manner, although they still present limitations regarding cellular maturity and the lack of vascularization.[3,4]

Scientific interest in cerebral organoids has quickly grown across fields like virology, psychiatry, neurology, and pharmacology. During the Zika virus outbreak, for instance, mini-brains played a key role in showing how the virus directly impacts brain development, helping to explain the mechanisms behind microcephaly. This example highlighted the importance of organoids not just as basic research tools but also as resources for public health crises.[5,6]

Another promising avenue is the possibility of generating mini-brains from cells from patients with neurological or psychiatric diseases. This approach enables the study of individual-specific cellular and molecular phenotypes, bridging the gap between experimental biology and personalized medicine. This allows for a more precise understanding of how genetic mutations or epigenetic variations influence neuronal development and function, as well as the evaluation of potential targeted therapies.[7,8]

However, mini-brains still present significant challenges. The absence of circulatory systems limits the supply of oxygen and nutrients, restricting their growth and complexity. Furthermore, incomplete neuronal maturation makes it difficult to reproduce features of the adult brain, limiting the use of these models for studying processes that depend on advanced connectivity between different regions. Another relevant point concerns ethical implications, since technical developments may, in the future, bring these models closer to more complex cognitive functions.[9,10]

This article aims to review the main scientific advances related to mini-brains, discussing their applications in the study of neurological and psychiatric diseases, their use in pharmacological testing and personalized therapies, as well as their limitations and prospects.

Method

The research consisted of an integrative literature review, involving the identification, selection, and critical analysis of relevant studies. The objective was to understand the current state of scientific evidence and map gaps for future investigations. The search strategy used controlled terms and keywords such as stem cells, brain organoids, regenerative medicine, genetic therapies, neurodegenerative diseases, and autoimmune disorders, applied in databases such as PubMed, ScienceDirect, and CAPES (2013–2025). Studies that presented original data, methodological advances, or translational implications were included. Data extraction covered objectives, methods, samples, interventions, and main results. Thematic analysis identified recurring patterns in disease modeling, pharmacological testing, and therapy personalization, as well as limitations such as insufficient maturation and vascularization in organoids.

Results and discussion

Modeling neurological diseases

The results indicate that brain organoids represent reliable models for studying infectious, psychiatric, and degenerative diseases. Meanwhile, stem-cell–based therapies are increasingly showing clinical promise, particularly in conditions such as Parkinson's, amyotrophic lateral sclerosis, macular degeneration, and autoimmune disorders.

One of the main contributions of mini-brains to biomedical research is their capacity to model neurological diseases caused by genetic, infectious, or degenerative factors. Unlike animal models, which often do not accurately reflect human phenotypes, cerebral organoids allow for direct observation of cellular and molecular changes associated with specific diseases. A notable example happened during the Zika virus outbreak when mini-brains derived from human stem cells demonstrated how the infection disrupted neural progenitor growth, leading to microcephaly. This discovery had global importance, providing insight into how the virus impairs brain development and emphasizing the role of organoids as rapid-response models for public health emergencies (Table 1).[5,6]

Table 1 Brain organoids provide innovative models for studying human brain development, disease mechanisms, and drug discovery.

Application area	Main contributions	Study examples
Infectious diseases	Modeling Zika-associated microcephaly	Garcez et al.[6]; Cugola et al.[5]
Psychiatric disorders	Connectivity alterations in schizophrenia	Mariani et al.[11]; Quadrato et al.[7]
Neurodegenerative diseases	Pathological protein accumulation (Alzheimer's)	Choi et al.[12]; Raja et al.[13]
Pharmacological testing	Drug screening and personalized therapies	Bershteyn et al.[15]; Pellegrini et al.[14]

Beyond infectious diseases, mini-brains have been applied to understanding neurodevelopmental disorders such as autism and schizophrenia. Studies have shown that organoids derived from patients with mutations associated with these conditions exhibit alterations in synaptic formation, neuronal connectivity, and laminar organization—characteristics that cannot be fully reproduced in two-dimensional cultures.[7,11]

In neurodegenerative diseases such as Alzheimer's and Parkinson's, mini-brains have been used to investigate processes involving the accumulation of abnormal proteins, synaptic degeneration, and neuronal death. Organoid models have demonstrated, for example, the deposition of beta-amyloid plaques and hyperphosphorylation of the tau protein, classic Alzheimer's phenomena. This allows both the investigation of pathological mechanisms and the screening of potential pharmacological interventions (Figure 3).[12,13]

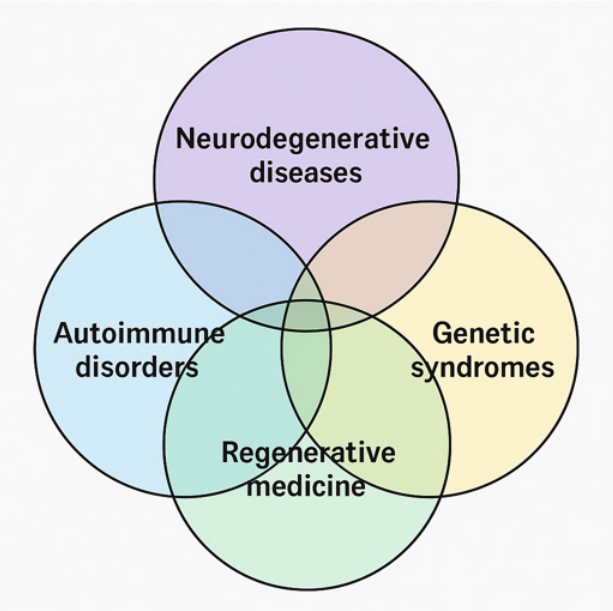

Figure 3 Therapeutic potential of brain organoids.

This set of applications demonstrates that mini-brains are powerful tools for bridging basic research and clinical reality, providing a more accurate and flexible platform for studying complex human diseases.

Pharmacological applications

Mini-brains have also established themselves as innovative platforms for drug screening and toxicity assessment. Unlike traditional assays based on two-dimensional cultures or animal models, brain organoids possess a three-dimensional architecture that

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is closer to reality, enabling more reliable results regarding therapeutic efficacy and safety (Table 2).

Table 2 Organoids reproduce key structural and functional features of the brain, offering ethical and scalable alternatives to animal models.

Aspect	Advantages	Limitations
Biological relevance	Reproduce human characteristics	Immature, resembling fetal brains
Disease modeling	Neurological, infectious, degenerative	Limited interaction with other systems
Pharmacological testing	Drug screening and personalized medicine	Limited extrapolation to adult brains
Infrastructure	Reduce dependence on animal models	High cost, restricted technology centers

One of the main advances is the possibility of using organoids derived from stem cells from specific patients, creating personalized models for studying drug response. This allows not only the identification of more effective compounds for specific population groups but also the prediction of adverse effects in individuals with specific genetic predispositions. This approach brings research closer to so-called precision medicine, in which therapies are tailored to the biological characteristics of each patient.[8]

Furthermore, organoids have been used to assess drug penetration and action in the central nervous system. The presence of blood-brain barriers similar to the blood-brain barrier in mini-brains represents an important advantage, as it allows for the study of whether molecules can actually reach deep regions of neural tissue. This is essential in diseases such as epilepsy and amyotrophic lateral sclerosis, where many drugs fail because they do not adequately cross this barrier.[14]

Another relevant point is toxicity investigation. Several compounds that demonstrate efficacy in animal models end up failing in clinical trials due to serious side effects in humans. Because mini-brains exhibit human physiological characteristics, they help identify potential risks in the early stages of drug development, reducing costs and increasing process safety.[15]

Therefore, as pharmacological platforms, mini-brains offer dual benefits: they enable the discovery of new drugs and increase the safety of translating results into clinical practice, reducing the exclusive reliance on animal models and improving the predictability of studies.

Personalized medicine

Mini-brains are playing an increasingly central role in the consolidation of personalized medicine, as they allow the reproduction of each patient's unique characteristics on a laboratory scale. By reprogramming somatic cells into iPSCs, it is possible to generate organoids that carry an individual's genetic and epigenetic profile, enabling the investigation of specific phenotypes and particular responses to external stimuli or medications.[10]

This approach is especially relevant in genetically based neurological diseases, such as refractory epilepsies, autism spectrum disorders, and neurodegenerative diseases. Studies have shown that patient-derived organoids can reveal subtle changes in neuronal development, synapse formation, and electrical activity, which are often not detectable in traditional cell cultures or animal models.[11,16]

"Brain organoids are emerging as a cornerstone of personalized medicine, allowing patient-derived iPSCs to be used in organoid modeling and drug testing for individualized therapeutic strategies" (Figure 4).[8]

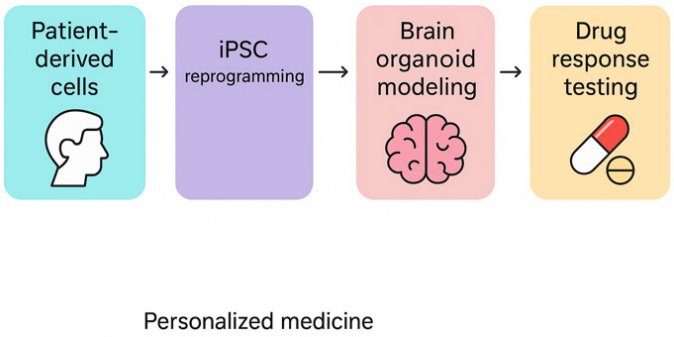

Figure 4 Personalized medicine with brain organoids.

Therefore, integrating mini-brains into personalized medicine represents a unique opportunity to overcome historical barriers between basic research and clinical practice, bringing laboratory knowledge closer to patients' real needs and enabling significant advances in the diagnosis and treatment of complex neurological conditions.

Current limitations

Despite significant advances, mini-brains still have considerable limitations that limit their translational application. The main one is the lack of vascularization, which prevents adequate oxygen and nutrient supply to more complex structures. As a result, many central regions of the organoids end up necrotic, limiting their growth beyond a few millimeters and compromising cellular maturation.[3,17]

Another important obstacle is functional immaturity. Mini-brains correspond to embryonic or fetal stages of brain development and, therefore, cannot fully reproduce the characteristics of an adult brain. This limitation restricts the investigation of neurodegenerative diseases or conditions that depend on complex neural networks, such as late-stage schizophrenia or cognitive decline associated with aging (Figure 5).[8,10]

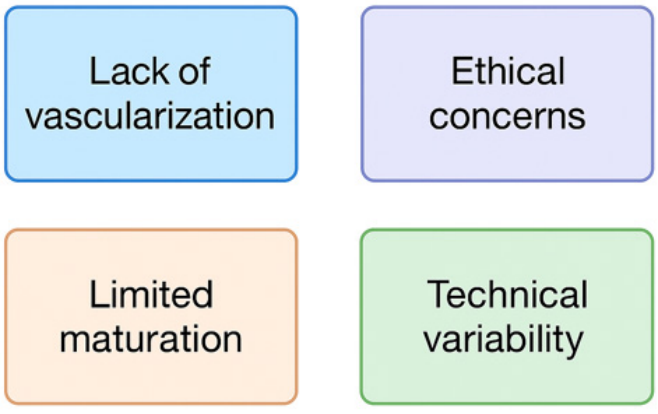

Figure 5 key obstacles in the field of brain organoids, including limited vascularization, ethical concerns, restricted maturation, and technical variability, which remain critical barriers to their translational applications.

The lack of interactions with other biological systems is also a key issue. In real organisms, the brain heavily interacts with the immune system, the endocrine system, and other organs. In mini-brains, such interactions are missing or significantly reduced, which limits the study of inflammatory processes, immune responses, or the systemic effects of medications.[2,14]

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Finally, there are ethical challenges related to the technological evolution of organoids. Although current mini-brains do not exhibit consciousness or cognition, advances in neuronal maturation and connectivity techniques raise bioethical questions about the limits of using these models. Some experts advocate the creation of strict guidelines to ensure that future research does not cross sensitive ethical boundaries.[9,18]

These limitations reinforce the need to develop complementary technologies, such as 3D bioprinting, microfluidics, and co-culture with endothelial and glial cells, to overcome current challenges and expand the applicability of mini-brains in biomedical research.

Recent advances in brain organoid research (2025)

Brain organoids are three-dimensional tissue models generated from pluripotent stem cells (PSCs), offering unique opportunities to study the human brain in vitro. They provide an alternative to traditional animal models and overcome some of the limitations caused by the inaccessibility of human neural tissue. By mimicking aspects of brain development, organoids have opened new avenues for investigating neurodevelopmental and neurodegenerative conditions (Figure 6).[1]

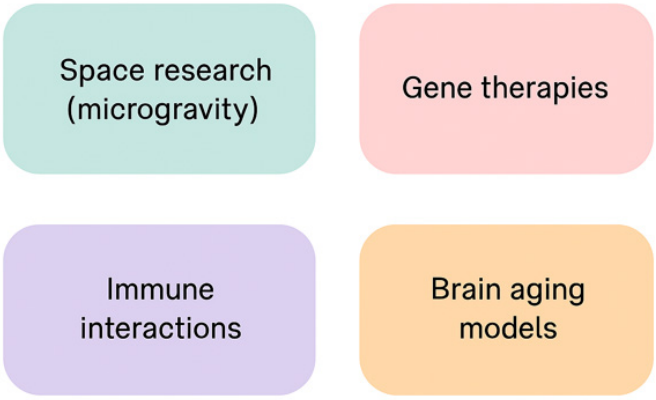

Figure 6 Recent advances in brain organoid research.

Recent progress has been made to address these limitations. Scientists are now able to generate more sophisticated organoids that integrate multiple brain regions, allowing interactions between distinct neuronal populations. These "assembloids" reproduce in vitro some of the connectivity observed in vivo, making them more representative models of brain physiology and pathology.[10]

Another breakthrough has been reconstructing neural circuits within organoids. By fostering synaptic connections and activity across different neuronal subtypes, researchers have created systems that better mimic actual human brain functions. These models not only improve understanding of core neurobiology but also serve as more accurate platforms for testing pharmacological and genetic interventions.[14,19]

Future perspectives

The field of mini-brains is rapidly growing and offers exciting opportunities for overcoming current limitations and expanding its scientific and clinical influence. One of the most important research areas is the development of artificial vascular systems, either through tissue bioengineering or by integrating endothelial cells. These advancements have already shown promising results, allowing for increased growth and viability of organoids (Table 3).[17]

Table 3 Advances in bioengineering, vascularization, and integration with microfluidic systems will enhance organoid complexity and functionality.

Innovation area	Main strategy	Potential impact in biomedical research	References
Bioengineering	Artificial vascularization	Greater viability of complex organoids	Cakir et al.[17]
Organs-on-chip	Integration with microfluidics	Study of systemic drug effects	Park et al.[20]
CRISPR-Cas9	Precise genetic editing	Modeling of specific mutations	Birey et al.
Artificial inteligente	Biological Data Analysis	Prediction of personalized therapies	Pașca[21]

Another emerging trend is the combination of mini-brains with 3D bioprinting and microfluidics technologies, known as "organs-on-a-chip." This type of integration offers the possibility of creating more complete models, in which the brain interacts with other artificial organs, such as the liver or heart, enabling the study of systemic drug effects and complex pathophysiological processes (Figure 7).[20]

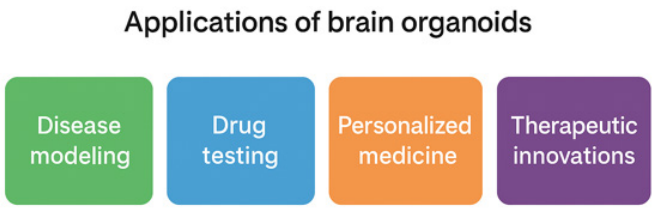

Figure 7 Future applications of brain organoids.

Prospects also involve applications in areas such as environmental neurotoxicology and research on neurodiversity. Organoids can be exposed to pollutants or chemicals to assess their impact on human brain development, generating relevant data for public health policies. Similarly, models derived from neurodivergent individuals, such as those with autism or ADHD, can help elucidate the biological underpinnings of these conditions, while respecting their specificities (Figure 8).[16,21]

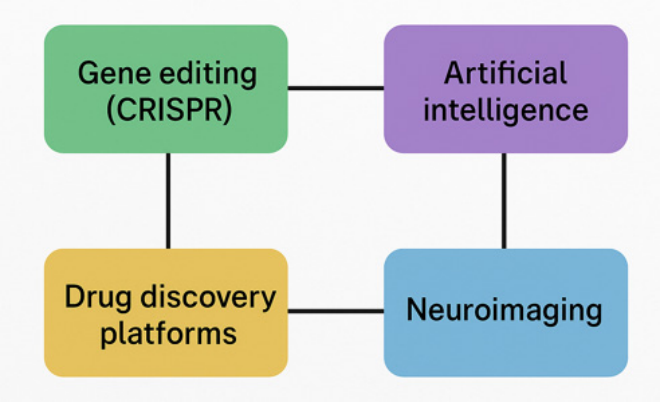

Figure 8 Integration of brain organoids with emerging technologies.

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Special section: Microgravity experiments

Due to the effects of microgravity on the ISS, mini-brains develop in a manner more similar to what occurs in the human body than in test tubes on Earth. Understanding how neurological conditions arise during development, including multiple sclerosis and Parkinson's disease, benefits from these space-based models (Figure 9).[22–24]

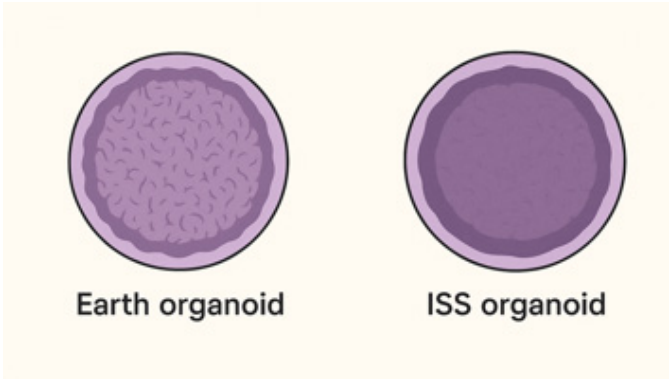

Figure 9 Comparative analysis of brain organoids cultivated on Earth and in microgravity (ISS).

The experiment was developed at Scripps Research and the New York Stem Cell Foundation. Although the tests occurred in 2019, results were published in Stem Cells Translational Medicine only recently, reporting enhanced gene expression linked to maturation and reduced proliferation, stress, and inflammation in space-exposed organoids (Figure 10).[22–24]

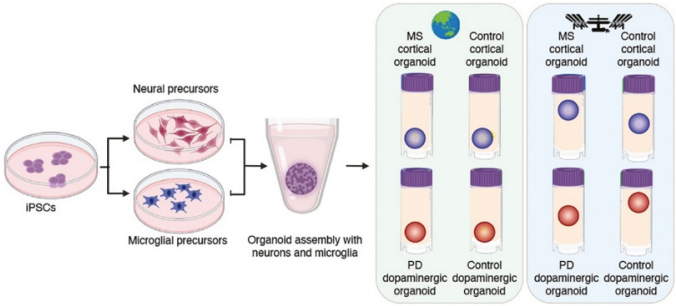

Figure 10 Experiment discovers how mini-brains behave in space, under the effect of microgravity.

In an interview with Jornal da CBN, [Alysson Muotri] from the University of California San Diego explained: "mini-brains are neural structures derived from stem cells of a living person, making it possible to recreate the brain of a patient with Alzheimer's to understand disease development." Muotri also highlighted graphene-based photostimulation to accelerate neuronal maturation, with implications for personalized interventions and early detection.[22–24]

Optic vesicle–containing brain organoids

Human brain organoids derived from iPSCs have become essential platforms to model early neural development and disease. A remarkable recent advance has been the demonstration that these organoids are capable of generating bilateral, optic vesicle–like structures within a single three-dimensional system. This finding moves beyond the traditional 'assembloid' approach, in which distinct organoids are fused, and instead reveals the intrinsic capacity of cerebral organoids to self-organize into complex sensory structures.[3,25]

By around day 30 of culture, developing brain organoids begin to show signs of optic vesicle formation. Within approximately 60 days, these vesicles become bilaterally symmetric and visibly integrated into the forebrain-like tissue. The organoids contain a diverse repertoire of cell types, including lens- and cornea-like epithelial cells, retinal pigment epithelia, retinal progenitors, axon-like projections, and electrically active neurons. The bilateral symmetry observed parallels early embryonic retinal development, highlighting the degree of self-organization achievable under optimized conditions.[26–28]

Functional analyses have provided further evidence of the complexity of these structures. Transcriptomic profiling confirmed the presence of retinal, corneal, and lens-associated gene signatures, while immunostaining demonstrated cortical neurons, synapsin-1 expression, and the presence of microglia. Importantly, these organoids also exhibited functional connectivity between the cortical tissue and the optic vesicle-like domains. Exposure to varying light intensities induced photosensitive activity, which could be restored even after transient bleaching, underscoring their sensory-like capabilities (Figure 11).[26–28]

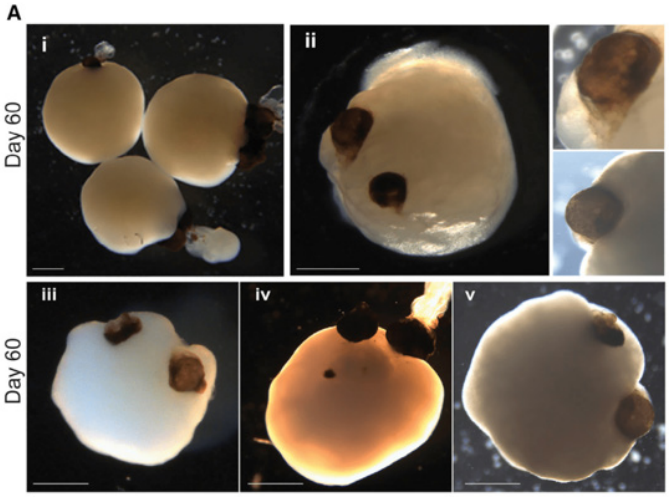

Figure 11 Brain organoids with primitive eye-like structures.

The implications of these findings are significant. For the first time, brain organoids have been shown to generate integrated optic vesicles that establish primitive neuronal circuitry with forebrain-like tissue. This offers opportunities to explore interorgan interactions, early human eye development, and disease mechanisms within a single in vitro platform. Nonetheless, limitations remain. Current protocols raise concerns regarding the long-term viability of optic vesicle–containing brain organoids (OVB-organoids). Their ability to survive beyond 60 days is limited, reducing the likelihood of producing mature retinal subtypes. Furthermore, variability across induced pluripotent stem cell donors presents challenges for reproducibility. Addressing these issues will be critical for advancing their application in translational research.[26,27,28]

Conclusion

Beyond disease modeling, these organoids have emerged as tools for pharmacological screening and the advancement of personalized medicine. The possibility of generating mini-brains from patient cells allows us to understand genetic and epigenetic particularities, as well as predict individual responses to medications. This potential brings basic research closer to clinical needs, establishing an essential link for translating discoveries into more effective therapeutic

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practices. However, the remaining limitations, such as the lack of vascularization, neuronal immaturity, and the lack of integration with other physiological systems, require caution when interpreting the results. Ethical issues also emerge as technological advances make organoids more complex, reinforcing the need for clear regulations to guide their responsible use. Despite these challenges, prospects are promising. The development of bioengineering, microfluidics, and genome editing techniques is likely to overcome current barriers, expanding the applicability of mini-brains and solidifying them as indispensable tools in contemporary science. Thus, cerebral organoids represent an innovative bridge between experimental biology and clinical practice, contributing to a deeper understanding of the human brain and the creation of personalized therapies in the future.

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Conflicts of interest

The authors declare that there are no conflict of interest.

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