
Perspective

Brain-on-a-chip technology for modeling psychiatric disorders: A new frontier in precision psychiatry

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Abstract: Brain-on-a-chip (BoC) technology is an emerging human-relevant platform for investigating complex neuropsychiatric disorders, including major depressive disorder (MDD) and schizophrenia. By integrating microfluidic systems with human induced pluripotent stem cell (iPSC)-

derived neural cells, three-dimensional cultures, multiregion architectures, microelectrode arrays, and biosensors, BoC platforms enable controlled investigation of neural connectivity, network activity, and cellular interactions. iPSC-based models provide disease-relevant phenotypes that may support the development of more complex psychiatric BoC systems; however, dedicated and comprehensively validated BoC models for MDD and schizophrenia remain limited. Important challenges include incomplete cellular maturation and complexity, limited vascular and immune integration, technical variability, long-term stability, and insufficient clinical validation. Future advances integrating patient-specific cells, artificial intelligence, multi-omics, and standardized multimodal measurements may improve disease modeling and therapeutic research. With rigorous disease-specific validation and stronger links to clinically characterized data, BoC technology may contribute to the future development of precision psychiatry.

Keywords: brain-on-a-chip; organ-on-a-chip; psychiatric disorders; depression; schizophrenia; microfluidics; neuroengineering; induced pluripotent stem cells (iPSC)

1. Introduction

Psychiatric disorders, including major depressive disorder (MDD) and schizophrenia, represent a substantial global health burden. Despite extensive research, their pathophysiology remains incompletely understood because of the complexity of brain networks and the limitations of available experimental models [1]. Conventional animal models and two-dimensional (2D) cell cultures often fail to reproduce human-specific neurobiological systems or features [2]. These limitations highlight the need for experimental platforms that more closely recapitulate human neural biology while allowing controlled investigation of disease mechanisms and therapeutic responses. Brain-on-a-chip (BoC) technology has emerged as a promising approach to address these limitations by combining microengineering approaches with human-derived cells. These platforms can reproduce selected structural and functional characteristics of the human brain while providing precise control over cellular microenvironments and intercellular interactions [3]. Importantly, differentiated neural cells derived from human pluripotent stem cells can be used to investigate disease-associated phenotypes in a human-relevant experimental context. So, BoC systems can be a great addition to traditional animal models and simple in vitro cultures, allowing for the modeling of more physiologically relevant systems of complex neuropsychiatric disorders.

Subsequent advances have enabled more sophisticated microengineered systems and the integration of brain organoids into microfluidic platforms, commonly referred to as organoids-on-chip, with applications in disease modeling and drug screening [4–7]. These developments have broadened the potential of BoC platforms for investigating disease mechanisms in increasingly physiologically relevant experimental settings. In psychiatric research, the growing emphasis is on developing human-relevant models that can better represent the cellular and network-level complexity of disorders, such as MDD and schizophrenia. BoC and related organoid-based systems may therefore provide complementary approaches to conventional preclinical models and potentially improve the translational relevance of disease modeling and therapeutic testing [8,9]. However, despite these advances, the application of BoC technology to psychiatric disorders remains at an early stage. Dedicated and comprehensively validated BoC models for disorders, such as MDD and schizophrenia, are still limited,

particularly those capable of integrating disease-relevant cellular, molecular, and functional phenotypes. Addressing this gap will require greater integration of patient-derived cells, advanced functional monitoring, and standardized validation against clinically relevant phenotypes [4,10,11].

This perspective summarizes the development and core features of BoC technology, its applications in modeling psychiatric disorders, advances in multiregion and organoid-based platforms, integration of functional monitoring technologies, and the remaining biological, technical, and translational challenges. Finally, emerging approaches involving artificial intelligence, multi-omics, and personalized medicine are considered in the context of future applications of BoC technology in precision psychiatry.

2. Technical components and physiological relevance of B-on-C systems

BoC systems are complex microfluidic devices that incorporate living neural cells into defined environments to mimic selected aspects of brain structure and function. The integration of human iPSC derived neurons, astrocytes and microglia provides the opportunity of disease modeling in a patient specific context. BoC platforms can recapitulate physiologically relevant microenvironments through control of spatial organization, mechanical cues, and biochemical gradients. This capacity enables detailed study of neuronal development and disease mechanisms in controlled conditions [12]. Microfluidic structures in BoC platforms enable precise control of fluid flow and exchange of nutrients and signaling gradients. They also allow compartmentalization of different brain regions or cell types, thus permitting the study of interregional connectivity and synaptic transmission [13]. The integration with microelectrode arrays (MEAs), biosensors, and high-resolution imaging allows analysis of neuronal activity in real time. These features enable dynamic, multiplexed, and potentially high-throughput analyses of neural networks. Compared with conventional 2D cultures, BoC systems may be more physiologically relevant because they allow 3D organization and complex cell–cell interactions [14,15]. They minimize differences between species and can more accurately mimic selected features of human neurobiology and disease than animal models. They also allow reproducible and precise control over the environment for mechanistic studies. These benefits render BoC platforms attractive for translational research and predictive drug screening [16]. BoC technology is transforming neuro-psychiatric research by enabling the modeling of complex neural circuits in disease-relevant micro-environments. Such platforms can be used to study synaptic dysfunctions, network-level disturbances, neuroinflammation, biomarker discovery and personalized treatment screening in patient-specific settings. Such approaches may help to bridge basic neuroscience, clinical translation and precision psychiatry [17,18]. BoC platforms integrate microfluidic engineering with human neural cells to reproduce selected structural, biochemical, and functional features of the brain microenvironment. Microfluidic architectures permit controlled fluid flow, nutrient delivery, chemical gradients, and spatial compartmentalization, enabling investigation of interactions between different neural cell populations under defined experimental conditions [19–21]. Recent engineering advances have further expanded BoC systems through integration of three-dimensional (3D) neural tissues, biosensors, and electrophysiological recording technologies [20].

MEAs provide an important functional interface for monitoring neuronal activity within engineered neural systems. MEAs can record extracellular electrical activity, including spontaneous firing, burst activity, network synchronization, and changes in electrophysiological responses following pharmacological or environmental stimulation. Their compatibility with human induced

pluripotent stem cell (iPSC)-derived neurons and increasingly with 3D neural models provides a means of assessing network-level function in real time [20,22]. Thus, MEA-based measurements can complement morphological, molecular, and biochemical analyses by providing direct functional readouts of neuronal network activity. Biosensors provide an additional layer of functional characterization by enabling dynamic monitoring of extracellular molecules and biochemical signals. Depending on platform design, biosensing systems can be used to investigate neurotransmitters, metabolites, ions, inflammatory mediators, and other secreted factors. Integration of biosensors with microfluidic neural cultures can therefore facilitate continuous monitoring of cellular responses and improve the temporal resolution of mechanistic and pharmacological studies [19,20].

3D culture approaches can further increase the physiological relevance of BoC models by providing spatial organization and cell–cell interactions that are difficult to reproduce in conventional two-dimensional cultures. Neural progenitor cells, neurons, astrocytes, microglia, and other relevant populations can be incorporated into extracellular-matrix-supported or scaffold-based environments. When combined with microfluidic compartmentalization, these systems can facilitate the investigation of interactions between anatomically or functionally distinct neural regions [20,23,24]. The physiological relevance of BoC systems nevertheless depends on how closely the engineered environment reproduces human neural organization and function. Incorporation of patient-derived iPSC populations can introduce disease-relevant genetic backgrounds, while electrophysiology, imaging, biosensing, and molecular profiling provide complementary functional and molecular endpoints. However, current platforms generally reproduce selected aspects of the human brain rather than its full cellular, vascular, immune, endocrine, and systemic complexity [19,21,25,26]. Accordingly, BoC models should be regarded as controlled human-relevant experimental systems that reproduce defined biological processes rather than complete replicas of the human brain. The BoC technology integrates microengineering and biological systems to provide dynamic and physiologically relevant modeling of brain function and pathology (Figure 1).

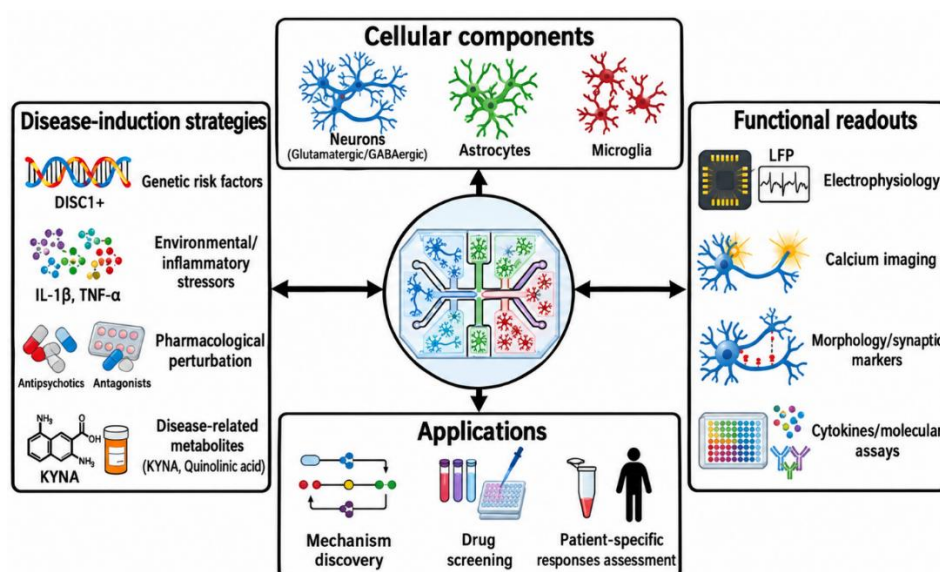


Figure 1. Key Opportunities of BoC Technology in Neuropsychiatric Research.

3. Modeling depression using BoC systems

MDD is a complex psychiatric disorder involving interactions among neuronal dysfunction, synaptic alterations, neurotransmitter imbalance, neuroinflammatory processes, and changes in neural circuitry. The biological heterogeneity of MDD and the limited accessibility of living human brain tissue present substantial challenges for investigating disease mechanisms and treatment responses. Conventional animal models and two-dimensional neuronal cultures have contributed substantially to understanding depression-related mechanisms; however, they may not fully reproduce the cellular diversity, human-specific genetic background, and complex microenvironment associated with the human disorder. BoC technology provides an emerging human-relevant platform through which selected aspects of these processes can be investigated under controlled experimental conditions [19–21]. Patient-derived iPSC models have provided evidence that MDD-associated cellular phenotypes can be investigated in human neuronal systems. Depression patient-derived cortical neurons have demonstrated differences in synaptic connectivity and morphology as well as gene-expression patterns associated with antidepressant response [27]. Other studies using patient-derived serotonergic neurons have reported altered neurite morphology and serotonin-associated neuronal activity in individuals with SSRI-resistant MDD [28,29]. In addition, patient-derived GABAergic interneurons and forebrain organoids have demonstrated altered neuronal morphology, firing activity, calcium signaling, and transcriptional profiles in severe MDD [30]. These findings support the potential of patient-derived neural models for investigating disease-associated cellular phenotypes and therapeutic responses.

Importantly, these findings should be distinguished from evidence generated directly using dedicated MDD-specific BoC platforms. Although iPSC-based neuronal and organoid models provide disease-relevant cellular phenotypes, the incorporation of such phenotypes into validated microfluidic BoC systems remains an emerging area. Therefore, current evidence supports the feasibility and potential of combining patient-derived MDD neural cells with BoC technologies, but it should not be interpreted as evidence that MDD has already been comprehensively modeled on a chip. At present, a dedicated and comprehensively validated MDD-specific BoC model has not yet been established. Future MDD-on-a-chip platforms could integrate patient-specific neuronal and glial populations with controlled inflammatory or stress-related environments, electrophysiological monitoring, neurotransmitter sensing, and molecular profiling to investigate disease mechanisms and treatment responses. Neuroinflammation represents another important biological process that could potentially be investigated using MDD-oriented BoC systems. Increasing evidence has implicated interactions among neurons, astrocytes, microglia, and inflammatory mediators in the pathophysiology of depression [31,32]. Conventional neuronal cultures often provide limited opportunities to reproduce these multicellular interactions, whereas microfluidic systems can provide spatially controlled environments in which different neural and glial populations can be maintained and experimentally manipulated [20]. Incorporating microglia and astrocytes into patient-derived neural systems may therefore provide opportunities to investigate how inflammatory signaling affects neuronal activity, synaptic function, and cellular responses. However, such applications should currently be regarded as prospective extensions of BoC technology rather than established MDD-specific models.

The controlled microenvironment of BoC systems may also provide opportunities for investigating therapeutic responses. Patient-specific neural cells could potentially be exposed to antidepressant compounds under controlled conditions while electrophysiological, morphological, biochemical, and molecular responses are monitored. Such approaches may complement conventional

drug-screening models by allowing treatment-associated cellular responses to be examined in a human genetic background. The use of compartmentalized microfluidic systems could additionally permit the independent manipulation of neuronal and inflammatory environments, potentially enabling investigation of interactions between pharmacological treatment and disease-associated cellular processes [19–21]. Integration of biosensors, MEAs, imaging, and molecular profiling may further increase the utility of BoC systems for depression research. Electrophysiological measurements can provide functional information regarding neuronal activity and network organization, while biosensors may enable monitoring of neurotransmitters and other extracellular signaling molecules. These functional measurements can be combined with transcriptomic, proteomic, or metabolomic analyses to generate multidimensional profiles of cellular responses. Such multimodal approaches may be particularly valuable for investigating heterogeneous disorders, such as MDD, in which no single cellular or molecular phenotype is sufficient to capture the complexity of the disorder [20,22].

Artificial intelligence (AI) and machine-learning approaches may further facilitate analysis of the complex datasets generated by advanced BoC platforms. Integration of electrophysiological, imaging, molecular, and biochemical measurements could potentially enable identification of disease-associated patterns and prediction of cellular responses to candidate treatments. AI-assisted analysis has increasingly been proposed for integrating multidimensional biomedical data and supporting translational drug-development workflows [33,34]. Nevertheless, the application of AI to MDD-specific BoC systems remains prospective and will require sufficiently large, standardized, and independently validated datasets before reliable predictive models can be established.

4. BoC models for studying schizophrenia

Importantly, technical neural-circuit reconstruction should not be equated with disease-specific modeling. Corticostriatal and nigrostriatal platforms demonstrate circuit-level feasibility, but they should be considered schizophrenia-on-chip models only when patient-derived cells or established schizophrenia-associated phenotypes are incorporated and validated. Schizophrenia is a heterogeneous neuropsychiatric disorder characterized by positive symptoms, negative symptoms, and cognitive impairment, with evidence of abnormalities in synaptic function, neuronal development, and brain connectivity [35]. However, schizophrenia-specific BoC models remain at an early stage compared with the broader field of human iPSC and microfluidic neural-circuit modeling. Therefore, it is important to distinguish findings obtained directly from schizophrenia patient-derived cells or schizophrenia-relevant experimental paradigms from studies that primarily demonstrate the technical feasibility of reconstructing human neural circuits. Patient-derived iPSC models have provided evidence for cellular and electrophysiological phenotypes relevant to schizophrenia. For example, electrophysiological measurements from human iPSC-derived neurons have been associated with clinical features of individual donors, with alterations in neuronal sodium-channel properties associated with the severity of positive symptoms and differences in spontaneous excitatory synaptic currents associated with negative symptoms and cognitive performance [36,37]. These findings are important because they establish measurable cellular phenotypes that can be linked to clinically characterized schizophrenia features. However, these studies were performed primarily in iPSC-derived neuronal systems rather than fully integrated schizophrenia-specific BoC platforms. Their findings therefore provide biological targets and phenotypes that future BoC systems could reproduce and quantify rather than constituting evidence that schizophrenia has already been comprehensively modeled on-chip [38].

Genetic risk mechanisms provide another route for establishing schizophrenia-relevant phenotypes. Studies of a rare DISC1 mutation in patient-derived and isogenic iPSC-derived cortical neurons have demonstrated reduced synaptic density, impaired synaptic vesicle release, and reduced excitatory synaptic transmission. The mutation was associated with increased expression of phosphodiesterase-4 (PDE4)-related signaling, while pharmacological inhibition of PDE4 or activation of the cAMP pathway rescued the synaptic abnormalities. These findings provide a mechanistic link between a schizophrenia-associated genetic alteration, intracellular signaling, and measurable synaptic dysfunction. They also demonstrate an important criterion for disease modeling: a phenotype is more informative when it can be traced to a defined genetic perturbation and subsequently rescued by a mechanism-directed intervention. Nevertheless, this DISC1 work was performed in patient-derived iPSC neuronal cultures and animal models rather than in a dedicated BoC platform and should therefore be interpreted as a foundation for, rather than direct evidence of, schizophrenia-on-chip modeling [39].

The interaction between metabolic and immune mechanisms provides another schizophrenia-relevant phenotype that may be particularly suitable for future BoC approaches. Kynurenic acid (KYNA), a metabolite of the kynurenine pathway, has been implicated in schizophrenia-related neurobiological abnormalities. Recent patient-derived cellular and organoid studies indicate that elevated KYNA can reduce neuronal activity and promote microglia-mediated elimination of synaptic material. Inhibition of KYNA-producing pathways has been investigated as a means of modifying these effects [40]. These observations are relevant to BoC technology because microfluidic systems can potentially place neurons and microglia within controlled, spatially organized environments, allowing investigators to examine how metabolic signals influence neuronal activity and synaptic maintenance [41]. Importantly, the evidence currently comes from iPSC-based co-culture and organoid models rather than a validated schizophrenia-specific BoC platform; therefore, the findings should be regarded as disease-relevant biological mechanisms that could be incorporated into future on-chip models rather than as established schizophrenia-on-chip evidence.

Early schizophrenia iPSC studies have also identified developmental phenotypes, including altered neural progenitor migration and abnormalities in cellular signaling and oxidative processes. Microfluidic migration assays have demonstrated reduced migration of schizophrenia-derived forebrain neural progenitor cells compared with control cells, providing a quantitative phenotype that can be evaluated under controlled spatial conditions [42]. Such findings illustrate one advantage of combining patient-derived cells with microfluidic technologies: cellular behavior can be measured under defined physical and biochemical conditions rather than inferred from conventional culture alone. However, interpretation of iPSC-derived phenotypes is complicated by the small sample sizes typically feasible in patient-specific studies. In addition, variability can arise from differences among patient cell lines, reprogramming-associated effects, genetic and epigenetic background, differentiation efficiency, cellular composition, maturation state, and experimental protocols [43].

Another important limitation is that many schizophrenia phenotypes emerge from interactions among multiple brain regions rather than from abnormalities in an isolated neuronal population. This makes multiregion microfluidic systems particularly relevant. Cortico-striatal circuits provide an example because they integrate cortical glutamatergic signaling with striatal circuits strongly influenced by dopaminergic transmission. Altered dopamine–glutamate interactions and abnormalities in corticostriatal communication have been implicated in schizophrenia [44]. A connected model therefore permits investigation of how abnormalities originating in one neuronal population influence

signal propagation, synaptic function, and network activity in another region. Rather than simply measuring the properties of cortical or striatal neurons separately, an interconnected system can examine circuit-level phenotypes, such as altered calcium dynamics, synaptic-vesicle cycling, and network synchrony [45]. These systems provide valuable technological foundations for schizophrenia research because they reproduce defined neuronal connections and permit region-specific manipulation and functional monitoring. However, the existing corticostriatal platforms should not automatically be considered validated schizophrenia models unless schizophrenia patient-derived cells or experimentally established schizophrenia phenotypes are incorporated and demonstrated.

Similarly, other multiregional systems have demonstrated the general feasibility of reconstructing interconnected brain regions and measuring their functional responses. For example, multiregional BoC systems have been used to connect different neuronal populations and examine how a pharmacological perturbation applied to one region affects activity in interconnected regions. Such studies demonstrate the importance of network context for interpreting brain function, but they do not by themselves establish a schizophrenia-specific disease phenotype. The distinction is important because a sophisticated neural circuit is not equivalent to a disease model unless the system reproduces a phenotype associated with the disorder and demonstrates appropriate validation. The same distinction applies to human nigrostriatal on-chip models. Human iPSC-derived dopaminergic neurons and striatal medium spiny neurons have been incorporated into microfluidic systems to reconstruct the nigrostriatal pathway and investigate mitochondrial or dopaminergic abnormalities, while other microfluidic platforms have enabled continuous monitoring of dopamine homeostasis [46–48].

These studies demonstrate important capabilities for constructing human neural circuits, monitoring dopamine dynamics, and manipulating interconnected neuronal populations. However, the nigrostriatal studies were developed primarily in the context of neurodegenerative disease or dopaminergic-cell biology rather than schizophrenia. They therefore should not be presented as direct evidence of the current state of schizophrenia-on-chip research. Instead, they illustrate technological approaches that may be transferable to schizophrenia studies in which dopaminergic circuitry is investigated using schizophrenia-relevant patient-derived cells or genetic and environmental perturbations. Overall, current evidence suggests that schizophrenia research has established several disease-relevant cellular phenotypes including altered neuronal migration, synaptic dysfunction, electrophysiological abnormalities [49], genetic-risk-associated signaling changes, and metabolic or microglial effects on synaptic function, but these findings have largely emerged from patient-derived iPSC cultures, organoid systems, or specialized microfluidic models rather than from fully integrated schizophrenia-specific BoC platforms [38].

The major opportunity for schizophrenia-on-chip research is therefore to combine these validated disease phenotypes with compartmentalized, multiregion microfluidics, multiple neural and glial cell types, real-time electrophysiological measurements, and patient-specific genetic backgrounds [50]. Such integration could enable direct testing of how genetic risk, neurodevelopmental abnormalities, neurotransmitter dysregulation, neuroimmune interactions, and altered circuit connectivity converge to produce schizophrenia-relevant phenotypes. At present, however, rigorous validation using patient-derived cells, appropriate controls, reproducible phenotypes, and clinically relevant endpoints remains necessary before these systems can be considered effective models for precision schizophrenia research.

5. Integration of multiregion brain models

Multiregion BoC platforms should likewise be distinguished from disease-specific models. Reconstructing interconnected circuits demonstrates technical capability but does not establish a schizophrenia model without patient-derived cells or validated disease-associated phenotypes. A key development in BoC technology is the inclusion of multiple brain regions into one microfluidic device. Unlike traditional monoculture or single-region systems, multiregion BoC models are intended to approximate the complex interregional connectivity that underlies higher-order brain functions [51]. This approach is especially relevant for psychiatric disorders, where dysfunction is increasingly understood as a network-level phenomenon rather than as a localized pathology. Recent advances have allowed the co-culture and functional coupling of different brain regions, such as cortex, hippocampus, amygdala, and striatum, in compartmentalized microfluidic environments. These methods allow for selective axonal outgrowth and synaptic connectivity between regions, making it possible to study long-range neuronal transmission and circuit dynamics [52,53]. For example, *in vitro* reconstruction of cortico-hippocampal and corticostriatal circuits has revealed information about processes, such as memory, emotional regulation, and reward, that are strongly implicated in disorders, such as depression and schizophrenia [48,54]. From a mechanistic perspective, multiregion BoC models provide a valuable opportunity to investigate how abnormal connectivity patterns develop and propagate across neural networks. In depression, impaired communication between the prefrontal cortex and limbic regions is associated with deficient emotional regulation; in schizophrenia, altered connectivity within corticostriatal-thalamic circuits are associated with cognitive and perceptual abnormalities [55,56].

Integrated electrophysiological tools, such as MEAs and calcium imaging, enable real-time monitoring of these interactions in multiregion chips and the measurement of network synchronization, signal propagation, and changes in plasticity following pharmacological or environmental perturbations. From a translational perspective, multiregion BoC systems represent an important step toward more predictive and therapeutically relevant models. These systems, by embedding patient-derived iPSCs in interconnected brain regions, may be able to capture individual-specific patterns of network dysfunction. This approach may create new opportunities for precision psychiatry by allowing the evaluation of therapeutic responses at the cellular and functional circuit level. The same platform could be used to investigate region-specific pharmacological effects (e.g., differential modulation of cortical versus limbic activity), thereby providing a more complete picture of treatment mechanisms. Still, technical difficulties remain in integrating multiple regions [57]. Long-term integration into the tissue, retention of regional cellular identity, and reproducibility across platforms are challenges that are still being worked on. Moreover, current approaches are not fully incorporating other physiological components, such as vascularization and immune signaling, that are important for a more complete model of brain-wide interactions [25,58].

6. Technical, biological, translational, and ethical limitations

The current limitations of BoC technology can be considered at several interconnected levels, including biological fidelity, technical reproducibility, translational validity, and ethical and regulatory considerations. These limitations affect the interpretation, reproducibility, scalability, and eventual clinical translation of BoC models. Biological limitations include incomplete representation of the cellular diversity, maturation, vascularization, immune interactions, and systemic signaling of the

human brain [19,21,23,25,58,59]. Technical limitations include device fabrication, material selection, fluidic control, long-term culture stability, and integration of multiple analytical modalities [19,20,60].

Translational limitations concern the validation of chip-derived phenotypes against human disease and clinical outcomes [26,61,62]. The limitations discussed in this section represent recognized constraints of currently available platforms. The major biological, technical, translational, and ethical/regulatory challenges; current limitations; and priority directions for BoC technology in psychiatric disease research are summarized in Table 1. Specific scientific questions that remain insufficiently investigated are considered separately in Section 7, whereas potential technological and translational strategies for addressing these challenges are discussed in Section 8.

Table 1. Key biological, technical, translational, and ethical/regulatory challenges, current limitations, and priority directions for BoC technology in psychiatric disease research.

Category	Key challenge	Current limitation	Priority direction
Biological	Cellular complexity	Current platforms reproduce selected neural populations but incompletely represent neuronal, glial, vascular, and immune diversity [19,21,23,25].	Incorporate multicellular and patient-specific systems with improved maturation.
Biological	Neural maturation	iPSC-derived neural cells may exhibit developmental immaturity and inter-line variability [25].	Establish standardized differentiation and maturation protocols.
Technical	Fabrication and reproducibility	Differences in device architecture, materials, flow conditions, and cell-loading procedures can affect experimental outcomes [19,20,60].	Develop standardized fabrication and quality-control procedures.
Technical	Multimodal measurement	Integration of electrophysiology, imaging, biosensing, and molecular analyses remains technically demanding [19,20].	Develop interoperable multimodal readout systems.
Translational	Disease-specific validation	Technical neural platforms should not automatically be classified as psychiatric disease models without disease-relevant cells or phenotypes [26,61,62].	Establish disease-specific biological endpoints and validation criteria.
Translational	Vascular and systemic interactions	Many models incompletely reproduce vascular, immune, endocrine, and systemic interactions [23,25,58].	Develop vascularized and multicompartiment platforms.
Translational	Clinical validation	Relationships between chip-derived phenotypes and patient outcomes or treatment responses remain insufficiently established [26,61,62].	Benchmark models against clinically characterized patient-derived data.
Ethical/Regulatory	Standardization and governance	Increasing model complexity creates challenges for reproducibility, reporting, ethical oversight, and regulatory qualification [63–65].	Establish consensus standards and appropriate regulatory frameworks.

Note: Technical development of a microfluidic neural platform should be distinguished from disease-specific validation. The reproduction of neural connectivity, neurotransmitter signaling, or multiple brain regions does not by itself establish a psychiatric disease model. Disease-specific classification requires incorporation of relevant disease-associated cellular, genetic, or molecular phenotypes together with appropriate validation.

7. Research gaps and unsolved questions

Beyond the technical and biological limitations described in Section 6, several scientific questions remain unresolved. One major gap concerns the relationship between chip-derived phenotypes and clinically meaningful psychiatric features. It remains necessary to determine whether electrophysiological, molecular, synaptic, inflammatory, or neurotransmitter-related measurements obtained from BoC systems correspond reliably to clinically characterized disease phenotypes and treatment responses [26,61,66]. A second gap concerns disease heterogeneity. Psychiatric disorders are biologically heterogeneous, and patient-derived models may capture only subsets of disease-associated mechanisms. Determining how genetic background, disease subtype, treatment history, environmental exposure, and cellular composition influence BoC phenotypes will therefore be important for developing robust precision-psychiatry applications [66]. A third gap involves the establishment of standardized functional endpoints. Although MEA recordings, calcium imaging, biosensing, transcriptomics, and proteomics can generate complementary information, their reproducibility and clinical relevance across different BoC platforms remain insufficiently established [26]. Finally, it remains unclear whether disease-specific BoC systems can produce reproducible and predictive treatment-response profiles across independent laboratories and patient populations. Addressing this question will require standardized protocols, adequately characterized patient-derived cell lines, cross-platform benchmarking, and independent validation [26,34,61]. These gaps represent the next stage of scientific validation rather than simply additional engineering challenges.

8. Future directions

Future development of BoC technology should prioritize biological relevance while simultaneously improving reproducibility, scalability, and analytical capacity. Integration of vascularized compartments, immune and glial populations, and controlled endocrine or metabolic interfaces may enable more comprehensive representation of the brain microenvironment. These developments could address several of the biological limitations discussed in Section 6 [19,21,23,25,58]. Patient-specific iPSC-derived cells represent another important direction for precision psychiatry. MDD and schizophrenia iPSC studies have demonstrated that patient-derived neural systems can reveal disease-associated cellular and molecular phenotypes. Incorporating these cells into standardized microfluidic platforms could allow investigation of patient-specific disease mechanisms and therapeutic responses while maintaining controlled experimental conditions [28,29,61].

Integration of electrophysiology, high-content imaging, biosensing, transcriptomics, proteomics, and metabolomics may provide multidimensional characterization of disease phenotypes. Artificial intelligence and machine-learning approaches could subsequently assist with the integration and interpretation of these datasets, although their predictive value will depend on sufficiently large, standardized, and independently validated datasets [19,20,34]. Automation and standardized manufacturing will also be important for improving reproducibility and enabling higher-throughput

applications. Ultimately, successful translation will depend not only on increasing model complexity but also on demonstrating reproducibility, defining clinically meaningful endpoints, and establishing relationships between chip-derived measurements and human disease phenotypes. In this context, BoC systems are best viewed as complementary experimental tools that can bridge cellular disease modeling and translational research rather than as complete replacements for clinical or in vivo models [19,26,61,62]. Figure 2 depicts a prospective roadmap of the major milestones and interdisciplinary efforts needed to drive BoC technology toward precision psychiatry and clinical application.

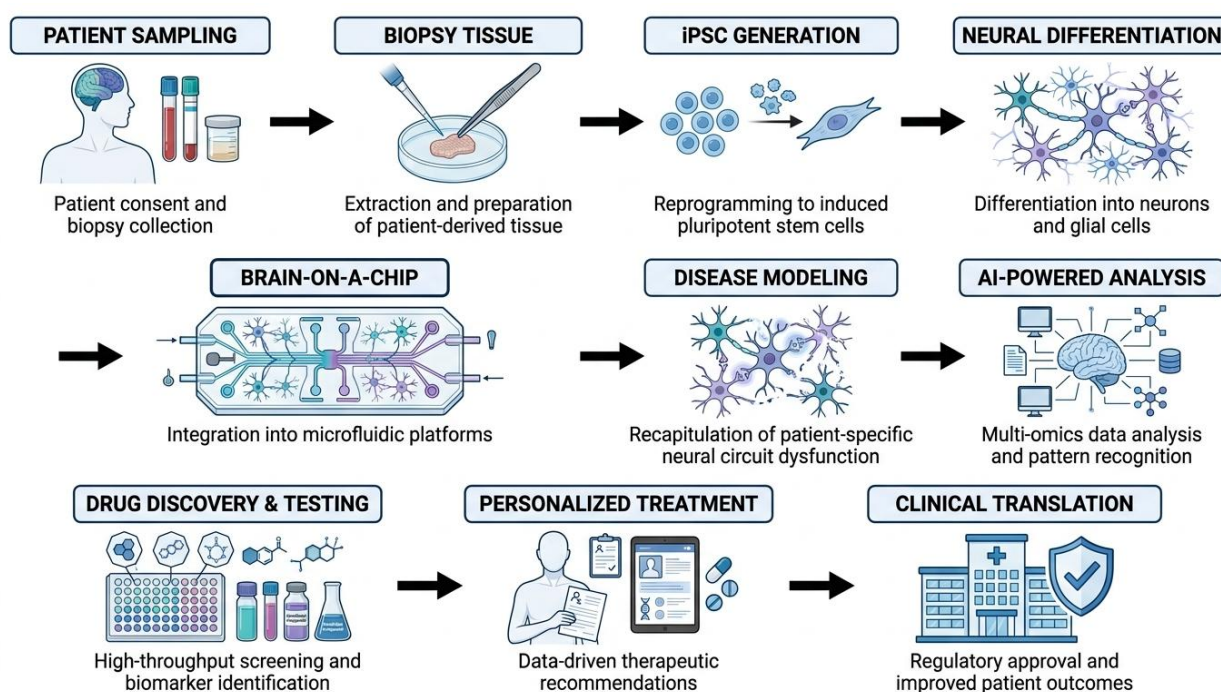


Figure 2. Proposed translational workflow of BoC technology for psychiatric research and future precision-psychiatry applications.

9. Conclusions

BoC technology provides an emerging human-relevant platform for investigating selected structural, cellular, electrophysiological, and biochemical features of the brain under controlled experimental conditions. Its integration with human iPSC-derived neural cells, three-dimensional culture systems, multiregion architectures, microelectrode arrays, biosensors, and advanced imaging creates opportunities to study neural connectivity, synaptic function, network activity, and neuroinflammatory processes relevant to psychiatric research. However, the current evidence should be interpreted cautiously. Many existing platforms primarily demonstrate technical capabilities for reproducing neural organization or function rather than fully validated models of specific psychiatric disorders. In particular, dedicated and comprehensively validated BoC models for MDD and schizophrenia remain limited. Future development should therefore focus on increasing cellular maturation and complexity, incorporating vascular, immune, and other relevant physiological interactions; improving fabrication and experimental standardization; and establishing reproducible disease-specific functional endpoints. Patient-derived iPSC models, multimodal measurements,

artificial intelligence, and multi-omics approaches may further improve the characterization and interpretation of complex neural phenotypes. Most importantly, the translational value of BoC systems will depend on rigorous validation against clinically characterized human data and treatment-related outcomes. With continued interdisciplinary development and appropriate validation, BoC technology may become a valuable complementary platform for psychiatric disease modeling, therapeutic research, and the future development of precision-psychiatry approaches.

Use of Generative-AI tools declaration

No AI tools other than those used for basic grammar correction and language polishing were employed in the preparation of this manuscript. The authors independently developed the scientific content, data interpretation, and conclusions. All AI-assisted text was carefully reviewed and edited by the authors for accuracy, and the authors take full responsibility for the content of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

Authors' contributions

Taslim Uddin: Conceptualization, Supervision, Writing Original–Draft; Adel Gouri: Supervision, Writing- Review & Editing; Faria Sharmin: Resources, Investigation; Khadidja Belhouala: Writing- Review & Editing; Nusrat Jahan Nisha: Formal analysis, Resources; Nazifa Anjum: Investigation, Formal analysis; Susmita Biswas: Project Administration, Validation; Sajid Asgar: Project Administration, Validation; Sarah Tahera Mahmud: Writing- Review & Editing, Supervision; Afia Asma: Literature review, Investigation; Nayeemul Islam: Investigation, Visualization; Bachir Benarba: Supervision, Project Administration, Writing- Review & Editing.

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