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Editorial

Brain Organoids: From Lab Bench to Neural Repair

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1. Experimental Insights

Brain-organoid-transplantation techniques represent a significant advancement in neuroscience, offering unprecedented opportunities to model human brain development and neurological disease. Derived predominantly from human induced pluripotent stem cells, brain organoids recapitulate essential developmental processes including neuronal differentiation, cortical patterning, and synapse formation [1]. Initially developed to study disorders like microcephaly [2], these structures have quickly evolved into robust tools for investigating neurodegenerative conditions, neuroinflammation, and CNS infections [3]. However, despite substantial advancements, translating brain organoid technology into effective clinical therapies remains challenging.

Experimental studies have recently offered compelling proof-of-principle evidence for the therapeutic potential for transplantation of cortical or cerebral organoids (COs), highlighting their ability to repair neurological damage and restore lost function (Fig. 1, Ref. [4–9]). In ischemic stroke models, transplanted COs reduced infarct volume, stimulated angiogenesis and neurogenesis, and improved motor function—even when transplantation was delayed up to 24 hours post-injury [4,5]. Similarly, COs transplanted into traumatic brain injury models successfully countered neuronal loss and inflammation, and impaired connectivity. Notably, younger (55-day-old) organoids demonstrated superior survival and integration than did older organoids, emphasizing optimal developmental timing [6].

In addition to studies on motor recovery, a recent study has illustrated the capacity of organoid transplantations for functional integration within sensory-specific circuits. Revah and colleagues [7] transplanted human COs into neonatal rat somatosensory cortex, demonstrating substantial integration into host thalamocortical and corticocortical circuits. The organoids exhibited mature synaptic properties and active responses to sensory stimuli, and effectively reconstructed damaged sensory networks. Similarly, transplantation of human forebrain organoids into experimental adult rat visual-cortex lesions resulted in robust reciprocal synaptic connections, selective neuronal responses to visual stimuli, and impressive vascular integration [8,9]. However, precise cortical laminar architecture remained incompletely restored, highlighting room for structural refinement [9].

Those transplantation studies revealed critical insights into mechanisms that underlie organoid-driven neural repair. Transplanted COs not only supported direct neuronal replacement but also significantly enhanced endogenous neuroregeneration, including increased neurogenesis in the hippocampus and subventricular zones [5,6]. Axonal sprouting, synaptic reconstruction, and successful vascular integration between host and graft were consistently reported [4,7,9]. Additionally, organoid transplantation was accompanied by reduced neuroinflammation and decreased neuronal apoptosis that indicated an active immunomodulatory role that enhances neuronal survival and functional integration [6].

2. Translational Barriers and Limitations

Despite their profound impact as research models, significant limitations still impede the translation of CO transplantation into clinical therapies. Notably, key challenges such as organoid size constraints and random tissue organization remain relevant. For instance, current COs typically contain approximately 2.5 million neurons, dramatically fewer than the approximately 86 billion neurons in the human brain [10]. Although *in vitro* organoids lack physiological sensory inputs, transplantation a recent study has demonstrated that once transplanted, organoids can indeed integrate into existing host sensory circuits, thus alleviating this limitation post-transplantation [7].

Another significant limitation frequently cited as "limited vascularization" requires a nuanced interpretation. Although organoids *in vitro* remain avascular, resulting in limited size and complexity, transplantation *in vivo* incorporates the host's existing vasculature, which effectively infiltrates and supports the graft. Nevertheless, this beneficial vascular integration is constrained by organoid size; larger grafts may exceed the spontaneous vascularization capacity of the host, resulting in ischemia or poor graft survival [9,11]. Therefore, enhancing vascularization artificially remains critical, especially for repairing extensive tissue damage requiring larger, structurally more complex organoid transplants [12].

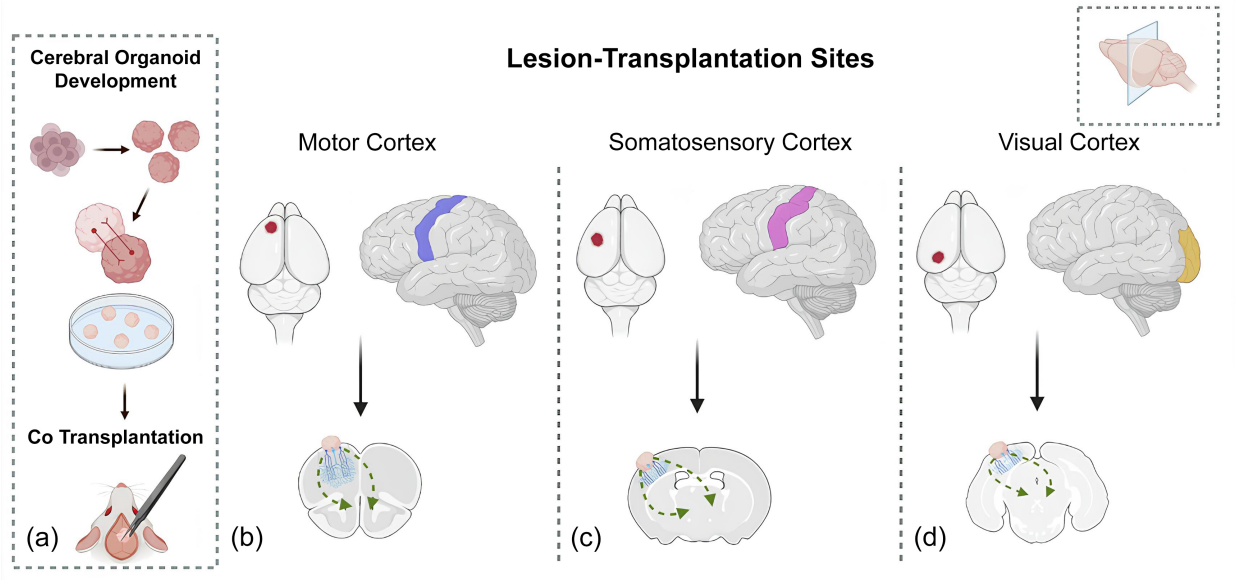

Fig. 1. Experimental transplantation of cerebral organoids (COs) into rodent brains. Schematic illustration summarizing experimental protocols from recent preclinical studies involving transplantation of COs into defined lesion sites in rodent brains. Representative coronal sections illustrate transplantation sites, subsequent neural integration, and their corresponding homologous areas within the human brain. (a) General outline of CO formation followed by surgical transplantation into rodent brain lesions using microsurgical techniques. (b) Transplantation sites targeting ischemic stroke lesions that were induced in the rodent motor cortex (M1/M2), adapted from previous studies [4–6]. (c) Non-specific experimental cortical lesions focusing on the rodent primary somatosensory cortex (S1), based on protocols previously described [7]. (d) Cortical lesion and CO transplantation studies targeting visual cortex (V1) injuries, adapted from previous studies [8,9]. Figure was created in BioRender.com.

It is important to note that several transplantation-specific limitations remain critically under-addressed. First, the prolonged developmental timelines for CO maturation commonly exceed optimal clinical therapeutic windows after acute neurological injuries [5,7]. Second, significant uncertainty persists regarding the physiological mechanisms that underlie successful integration into host neural circuits, thereby complicating the direct translation from animal models to human patients [4]. Current transplantation studies mainly evaluate only short-term histological and electrophysiological outcomes, and lack robust longitudinal data on sustained functional integration, stability, and long-term therapeutic efficacy [7,9]. Furthermore, immune compatibility, graft longevity, and host-graft interactions remain poorly explored, posing critical challenges that must be rigorously investigated [11]. Finally, the elucidation of the precise developmental stages that optimize graft viability, integration, and regenerative capacity remains essential yet unresolved.

3. Future Perspectives: Emerging Strategies and Important Directions

Addressing transplantation-specific limitations demands focused interdisciplinary strategies integrating stem-cell biology, bioengineering, immunology, neurophysiology, and clinical expertise. Standardizing CO protocols that define optimal maturation timeframes, improve structural complexity and vascularization for larger grafts, and outline comprehensive longitudinal studies, represents crucial steps forward. Refinements in transplantation methods, including bioengineered scaffolds or minimally invasive surgical approaches may significantly enhance graft survival, integration, and overall therapeutic outcomes. In parallel with these steps, the exponential rise of artificial intelligence (AI) in biomedical research is opening new frontiers that may benefit CO technology. AI has already demonstrated its potential in areas such as organoid culture optimization, high-content image analysis, and predictive modeling of cellular differentiation. These computational tools could assist in analyzing patient-specific data, monitoring integration dynamics, and refining graft-host compatibility in a personalized manner.

Although the application of AI to organoid transplantation is still in its early conceptual stages, its theoretical potential is substantial. Specifically, brain-inspired AI models, particularly neural networks that mimic biological principles of neural network, have begun to inform new ways of thinking about dynamic tissue modeling and integration. These conceptualizations, inspired by the structure and function of the human brain, may one day offer insights into how to model plasticity and circuit adaptation, or even simulate host-graft interactions. Conceptual frameworks drawing from such models have recently been explored in

the context of artificial neural systems that parallel cerebral architecture, providing theoretical tools to bridge computational neuroscience with regenerative biology [13].

Finally, as CO transplantation moves closer to clinical implementation, ethical considerations must remain a guiding force. The increasing anatomical and functional integration observed in preclinical studies raises complex questions surrounding potential cognitive enhancement, changes in self-awareness, and the moral status of chimeric models. Transparent ethical frameworks, continuous multidisciplinary oversight, and public engagement will be vital to ensure responsible innovation and societal trust.

4. Conclusion

Transplantation of brain organoids occupies a pivotal position at the intersection of experimental neuroscience and regenerative medicine. As evidence of their structural and functional integration in preclinical models continues to grow, so too does their potential as therapeutic tools for previously untreatable neurological conditions. Realizing this promise will require overcoming key translational barriers through coordinated interdisciplinary efforts, advancing bioengineering strategies, and critically integrating insights from computational and AI-based models. Equally essential is a proactive ethical framework to guide the responsible application of this technology. With continued scientific rigor, innovation, and ethical foresight, the clinical translation of brain organoid transplantation is no longer a distant prospect, but a rapidly approaching frontier in neurology and restorative medicine.

Author Contributions

PT designed the study and wrote the manuscript. GA performed the research and wrote the manuscript. MEM was involved in the analysis and interpretation of the data presented in the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

Given his role as the Guest Editor, Paschalis Theotokis had no involvement in the peer-review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Graham Pawelec. The authors declare no conflict of interest.

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