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Engineering Human Brain Organoids for Understanding Substance Use Disorders

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Substance use disorders (SUDs) are complex mental health conditions involving a problematic pattern of substance use. Challenges remain in understanding its neural mechanisms, which is likely to lead to improved SUD treatments. Human brain organoids, brain-like 3D in vitro cultures derived from human stem cells, can recapitulate the molecular, cellular, structural, and functional features of a human brain, holding remarkable potential in understanding SUDs. However, the function and phenotype of current human brain organoids are still limited by insufficient diffusion of oxygen, nutrients, metabolites, signaling molecules, and substances. Herein, we present Vascular network-Inspired Diffusible (VID) scaffolds to fully recapture the benefits of physiological diffusion physics for generating functional brain organoids and phenotyping their drug response. In a proof-of-concept application, the VID scaffolds, 3D-printed meshed tubular channel networks, support the successful generation of engineered human midbrain organoids almost without necrosis and hypoxia in commonly used well-plates. Compared to conventional organoids, these engineered organoids develop with more physiologically relevant features and functions including midbrain-specific identity, oxygen metabolism, neuronal maturation, and network activity. Moreover, these engineered organoids also better recapitulate pharmacological responses, such as neural activity changes to fentanyl exposure, compared to conventional organoids with significant diffusion limits. Combining these unique scaffolds and engineered organoids may provide insights for organoid development and therapeutic innovation for SUDs.