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PERSPECTIVE

Establishing validity standards for iPSC modeling of neuropsychiatric disorders

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Neuropsychiatric disorders impact over 3 billion individuals globally, posing significant challenges due to their molecular complexity, phenotypic diversity, and limited clinical translation of genetic insights. Advances in induced pluripotent stem cell (iPSC) technology offer unprecedented opportunities to model these disorders in human-relevant contexts. Human iPSC-derived two-dimensional neurons and glia, and three-dimensional organoids recapitulate key aspects of brain development and cellular functions, enabling the study of disease mechanisms and therapeutic responses on the relevant genetic background. Pioneering studies have begun to demonstrate the potential of iPSC models for precision medicine. However, translating these findings to clinical applications at scale requires robust validity assessments. Building on established frameworks of construct, face, and predictive validity derived from animal models, this perspective examines their application within an iPSC context. These approaches offer valuable insights to refine iPSC-based modeling systems and enhance their translational relevance as well as address the complexities of modeling neuropsychiatric disorders.

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Introduction

Neuropsychiatric disorders are a molecularly complex group of disorders that impact over 3 billion individuals worldwide and profoundly shape the social, economic, and personal well-being of those affected (1). Over the past decade, significant strides have been made in uncovering the genetic underpinnings of both polygenic and monogenic neuropsychiatric disorders through genome-wide association studies, as well as exon and genome sequencing efforts. These advances have enhanced our understanding of the mechanisms underlying certain conditions, particularly those caused by monogenic factors. Despite this progress, a considerable gap persists between these genetic discoveries and their clinical application. Insights into disease mechanisms and potential therapeutic strategies have yet to be fully translated into effective and routine clinical practice, for example, prediction of drug response, outcome, and new therapeutic targets. Moreover, the substantial phenotypic diversity and varied treatment responses seen in these disorders underscore the urgent need for precision medicine approaches—not only to design targeted therapies but also to develop robust models for understanding disease mechanisms at the individual level.

The diverse clinical manifestations, complex etiology, and limited access to patient brain tissue have curtailed an effective understanding of the molecular framework of many of these disorders. Although animal models of relevance for neuropsychiatric disorders provide valuable insights into multiple aspects of these conditions, they are limited by inherent interspecies differences, including variations in the timing and trajectory of brain development, tissue architecture, and cell-type specificity (2). Human-derived induced pluripotent stem cell (iPSC) disease modeling offers an unprecedented opportunity to study neuropsychiatric disease within the appropriate genetic context and tissue or cell types of interest. Accumulating evidence suggests that iPSC-derived models have the potential to recapitulate various molecular and cellular features of neuropsychiatric disease (3–5). Thus far, protocols for reliably generating specific cell types have been established including glial cells such as astrocytes, oligodendrocytes, and microglia and neuronal subtypes such as glutamatergic, GABAergic, dopaminergic, serotonergic, cholinergic, and motor neurons (6–14). These iPSC-derived neural cell types can be cultured alone or in combination, in two-dimensional (2D) or three-dimensional (3D) organoids, to give rise to more complex systems to study various parameters such as excitatory-inhibitory balance or model brain regions of interest. Assessment of cellular morphology, functional electrophysiological parameters, protein expression, organelle structure, and transcriptional profile can be used to characterize iPSC-derived models of neural cell types.

Protocols pioneered by the Sasai group enabling the development of 3D optic cup (15) and cortical structures (16), laid the foundation for modeling embryonic development in 3D using embryonic and iPSC cells. Human iPSC-derived 3D cultures of neural development recapitulate key aspects of human brain development including self-organizing neural architecture, cell type formation, some electrophysiological parameters, and precise spatiotemporal signaling to establish regional identity. Transcriptomic and proteomic studies of iPSC-derived brain models indicate that these models display expression profiles akin to human fetal brain (17–20) between 8 and 16 weeks postconception (21) with neuronal classes from diverse developmental stages with heterogeneous cell intrinsic maturation states (22, 23). Disease modeling with organoids is complex but holds the potential to bridge the gap between humans and animal models, offering valuable insights into disease mechanisms and treatment strategies. Brain organoids can be used to assess known genetic risk factors for structure brain defections such as macrocephaly and microcephaly and screen potential therapeutic agents, as was demonstrated for Angelman syndrome where pharmaceutical attenuation of potassium channel activity with Paxillin normalized neuronal excitability (24).

iPSC technology circumvents many obstacles currently impeding progress toward developing effective therapies for psychiatric illness. For the first time, we have the opportunity to track the developmental trajectory of neuropsychiatric disorders, investigate the role of genetic background, and study disease material throughout disease progression—rather than relying on postmortem samples taken at the end stage of disease. This approach allows us to examine disease dynamics in real time

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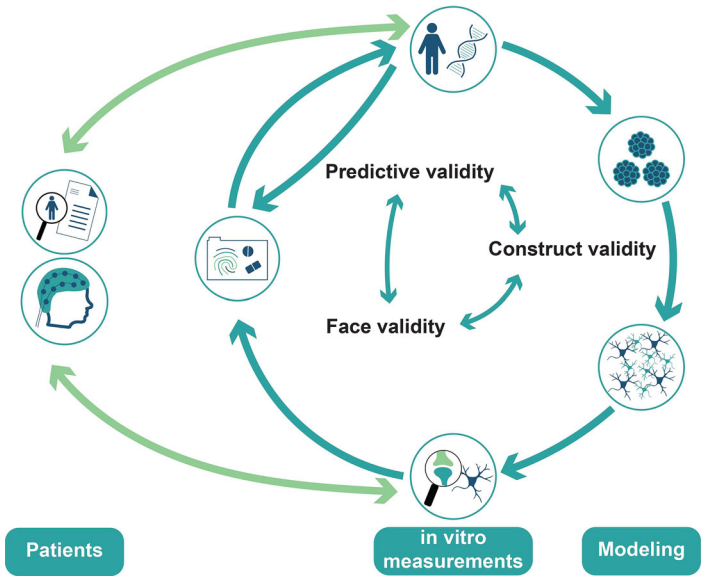

Figure 1. Interdependency of construct, face, and predictive validity. Construct, face, and predictive validity are highly interdependent. Depending on the available information, a model system can be built starting at any of the three validities. For example, if a patient's response to medication (predictive validity) and the appropriate in vitro measurement (face validity) are known, this can be used to define what cell types are needed (construct validity) to accurately model a neuropsychiatric disorder. By working closely together with clinicians, relevant patient information, like EEGs or questionnaires, can be informative to generate a patient iPSC-derived model system that has high construct, face, and predictive validity.

for fetal neurodevelopment (23, 25). However, while these advancements are promising, they also present challenges—many of which are shared with animal models. Of particular concern, how can we determine the validity of the chosen models and readouts to enable effective translation? This question is particularly pressing in the iPSC field, where bridging the translational gap remains a primary goal. To address this, we can draw valuable insights from the validity frameworks already established for animal models and by adapting such a framework, we may uncover solutions to ensure more reliable and impactful translational outcomes for iPSC models.

Classically animal models have been held to a multidimensional set of criteria of validities to be considered a relevant interface for human pathology, namely construct, face and predictive validity. The definition of construct validity in animal research is complex and the views on what it exactly entails are dependent on the author as has been extensively summarized in Lemoine and Belzung (2011). For iPCS-derived model systems, we define construct validity as follows: (1) The model system has the correct genetic etiology, for example, a relevant mutation in the causative gene for a specific disease, or a high or low polygenic risk score; (2) The biological processes underlying the disease in the relevant cell types are present (26–28). Face validity refers to the similarities between the model and the condition being modeled or essentially the extent to which a model measures the concept it is intended to measure and is therefore linked to assay validating readouts of cell-based assays. Predictive validity in animal science has traditionally been defined in one of two ways. Most commonly, predictive validity emphasizes the similarity in treatment responses between patients and the model system. However, it is sometimes defined as the model's ability to predict specific markers of the disease, referring to biomarkers used to monitor the disorder's progression (26). To achieve high predictive validity, both high construct validity and high face validity are essential. In this Perspectives, we assess the potential of this framework to be applied in the context of iPSC studies of neuropsychiatric disorders and explore how these validities pertain to such research. Below, we examine the three types of validity in detail (Figure 1).

Construct Validity

Construct validity defines the extent to which an assessment accurately measures the concept it was designed to evaluate. For iPSC-based modeling of psychiatric diseases, two critical aspects underpin construct validity: the genetic framework and cell-type specificity. iPSCs can be generated from healthy individuals where a relevant mutation can be introduced using CRISPR-Cas9, or directly from patient material. The primary advantage of using patient-derived iPSCs is that the patient's genetic background is retained during reprogramming. However, it is important to acknowledge that genomic instability and genetic alterations may occur during or after the reprogramming process, where iPSCs generated via genome integrating methods have higher incidences of genomic aberrations compared to those generated by nonintegrating methods (29, 30). These changes include chromosomal aneuploidy, copy-number variants, or point mutations and may provide mutated iPSCs with a growth advantage during extended culture, thus introducing passage-dependent effects (31). In addition, iPSCs derived from fibroblasts accumulate more mutations and chromosomal abnormalities due to repeated exposure to ultraviolet light (32). iPSCs would therefore benefit from regular assessment of genomic integrity, to ensure they remain effective for disease modeling. This consideration is particularly pertinent for polygenic neuropsychiatric disorders, whose complexity is challenging to replicate in alternative models, underscoring the unique relevance of patient-derived iPSCs (33).

Experimental designs in iPSC studies generally employ either case-control approaches or gene-editing methods using isogenic controls. A key advantage of case-control studies is that the groups can be defined solely on a patient's clinical features or their polygenic risk score, eliminating the need to identify the exact causative mutations. However, a notable limitation of case-control studies is that they typically have limited cohort sizes, resulting in low statistical power. The use of multiple isogenic iPSC-lines can help mitigate this limitation for rare cases with monogenic contributions (34). While isogenic iPSC-based study designs are widely accepted as the gold standard, a major disadvantage is that there is no patient associated with an isogenic iPSC, limiting their translational applicability.

iPSCs can be differentiated into nearly any brain cell type, providing extensive versatility in neuropsychiatric disease modeling. However, this flexibility introduces challenges in selecting the appropriate cell types to include. Decisions about the model system are often driven by pragmatic considerations, such as speed, homogeneity, and reproducibility. iPSC-derived models range from simple 2D systems involving a single cell type

to complex 3D systems comprising diverse cell types. Simpler 2D models offer advantages in terms of rapid generation, uniformity, and reproducibility, making them ideal for high-throughput applications. However, they may lack the cellular complexity required to capture the full pathophysiology of neuropsychiatric disorders. Conversely, 3D models, while more time-intensive and variable, provide a more comprehensive representation of cellular interactions and the microenvironment, which are critical for understanding multifaceted disease mechanisms. Selecting the appropriate model system for a study requires careful consideration of the specific research question and available data. One valuable source of information is postmortem analysis. For example, a recent study using postmortem cortical brain samples from patients with autism spectrum disorder (ASD) and controls found that most alterations in neuronal gene expression were localized to glutamatergic neurons in the superficial layers of the cortex (35). Alternatively, insights can also be derived from the behavioral symptoms associated with a disorder and the regions of the brain implicated in these symptoms, or from the known mechanisms of action of medications used in treatment. For instance, in attention-deficit hyperactivity disorder, dysfunction is observed in areas such as the superior longitudinal fasciculus and cortico-limbic structures, and medications like methylphenidate are known to work by blocking presynaptic dopamine and norepinephrine transporters (36, 37). Additionally, single-cell data can provide further insights on the developmental trajectory of a specific disease gene (38).

In the case of monogenic neuropsychiatric disorders, selecting the appropriate model system often depends on identifying which cell types express the gene of interest. For example, Timothy syndrome, caused by mutations in *CACNA1C* and associated with autism, bipolar disorder, and schizophrenia (SCZ) (39), exhibits the highest expression of *CACNA1C* in both excitatory and inhibitory neurons (40). Consequently, research using both mouse and iPSC-derived models has primarily focused on neuronal function. These iPSC-derived models are typically generated through an intermediate neural progenitor cell (NPC) stage, resulting in a system that includes a variety of cell types, including progenitors and multiple neuronal subtypes (41–43). However, these models often lack sufficient glial cells, which are crucial for neuronal development and function. This limitation could hinder the model's ability to fully represent the biological processes impacted by *CACNA1C* mutations. Future models incorporating glial cell populations could offer a more comprehensive understanding of *CACNA1C* deficiency. While patient iPSC-derived glial cells would be ideal to fully understand the full pathophysiology, healthy rodent glial cells have also been shown to support human neuronal function, as described by Frega *et al*., and can aid in characterizing the neuronal phenotype (14). One potential strategy is creating a chimeric model by transplanting human iPSC-derived organoids into rodent brains, as demonstrated by Chen *et al*. (2024). In this study, *CACNA1C*-deficient cortical organoids were transplanted into the somatosensory cortex of newborn rats to integrate into sensory and motivation-related circuits and evaluate an Antisense oligonucleotide (ASO)-based treatment strategy (44). This approach highlights the potential of combining in vitro patient-derived models with in vivo systems to study neuropsychiatric diseases, particularly when animal models fail to fully capture human genetics and pathophysiology. However, using animal-derived glial cells cannot exclude human-specific roles of a gene, as even low gene expression may still contribute to development of a disease.

Another example can be found in *SETD1A*, a gene with a significant, genome-wide association to SCZ (45, 46). All preclinical models, including both mouse and iPSC-derived models, for *SETD1A* have focused the role of SETD1A dysfunction in neurons (47). While it is true that, in the mouse brain, *Setd1a* is most expressed by neurons followed closely by astrocytes, in the human brain astrocytes have higher *SETD1A* expression followed closely by neurons (40, 48). For this reason, it follows logically that iPSC-derived model systems with good construct validity should contain both neurons and astrocytes with a *SETD1A* deficiency. To date, there are two studies using different iPSC-derived neuronal models, however, neither study has included *SETD1A*-deficient astrocytes (49, 50). While these studies have provided valuable insights into *SETD1A* deficiency in neurons, a key advantage of iPSC-based models is the capacity to incorporate diverse cell types. For *SETD1A* research, this means that a future model could integrate iPSC-derived astrocytes, allowing for a more comprehensive investigation into *SETD1A*-related pathology.

Although the concept of construct validity may seem straightforward when a disorder has a clear genetic cause, many neuropsychiatric disorders are understood to be highly polygenic, involving thousands of common and rare genetic variants (51). These genetic factors, combined with environmental risk factors, increase the likelihood for an individual to develop a neuropsychiatric condition. While the use of patient-derived iPSCs addresses the genetic etiology aspect of construct validity, identifying the relevant cell types and biological processes remains challenging when the specific genes involved in the disorder are unknown. In recent years, the Ziller lab has addressed this issue using a large cohort ($n = 104$) of iPSCs from healthy controls and individuals with SCZ, bipolar disorder, and major depressive disorder. They found differences in alternative polyadenylation (APA) in the 3′ untranslated region of many transcripts related to synapse biology between iPSC-derived neurons from patients with SCZ and healthy donors. These differences were associated with a reduction in synaptic density on the cellular level. In addition, they showed that 3′APA was highly correlated with SCZ polygenic risk and concluded that the cumulative effects of polygenic risk converge on 3′APA as a common molecular mechanism underlying synaptic impairment in SCZ (52). An alternative strategy could be to use models that encompass most cell types, like cerebral organoids, which may provide a more comprehensive understanding of polygenic risk in diverse cellular populations. In addition, it is important to calculate the polygenic risk score for each individual, not just for the disorder of interest.

Face Validity

Face validity is essentially the degree of descriptive similarity between a model and an individual affected by a neurobehavioral disorder. This concept was initially defined within the context of depression by Wilner to encompass both treatment and symptomatic features, specifically the response to pharmacological intervention and the experiential profile (27). Geyer and Markou, and Sarter and Bruno, expounded upon face validity to mean "the degree of phenomenological similarity between the model and the disorder to be modeled" (53, 54). This suggests that face validity corresponds to the ability of a model system to mimic (generally behavioral or cognitive) diagnostic criteria of psychiatric conditions, yet it remains largely uncharacterized at the molecular level. As psychiatric disorders are defined primarily based on behavior, something iPSCs are inherently unable to model, the focus of translational models must shift to the molecular and cellular level. Despite this necessity for physiological and molecular profiling, we currently lack clear biomarkers and cellular profiles of neuropsychiatric disorders. Additionally, for most studies it is difficult to assess face validity since there is often no golden standard data, such as fetal brain tissue from the case of interest.

Despite challenges, there are credible examples of face validity within iPSC-derived models that demonstrate dimensions of neuropsychiatric disorders in large part due to the inclusion of patient data. de Vrij *et al*. adopted a family-based patient assessment approach for genetic discovery in SCZ coupled with functional analysis using patient-derived iPSCs to define variants in chondroitin sulfate proteoglycan 4 (*CSPG4*), an oligodendrocyte progenitor specific marker, as a potential cause of familial SCZ (55). This approach allowed researchers to characterize genetic and functional evidence of oligodendrocyte progenitor cell dysfunction in SCZ. In some cases, in vivo measurements in patients can be translated into molecular insights. 22q11.2 Deletion syndrome is associated with increased SCZ risk, in a pilot study, dopamine synthesis capacity was assessed via ^{18}F-DOPA PET imaging in patients with 22q11.2 deletions. By generating iPSC-derived dopaminergic neurons from these patients, they observed alterations in gene expression related to dopamine metabolism and signaling, with differences noted between 22q11.2 hiPSC lines corresponding to distinct clinical presentations (56) suggesting that dopamine metabolism dysfunction may contribute to SCZ.

Another potential strategy to circumvent the absence of behavior modeling is to focus on the underlying neuronal patterns that drive the behavior. For example, Romero-González *et al*. recently demonstrated

that in a cohort of children with ASD, those with greater impairment in executive functioning also exhibited abnormal epileptiform electroencephalography (EEG) activity (57). EEG abnormalities in patients are significantly elevated in patients with neuropsychiatric disorders, and current research is evaluating the use of EEG as a diagnostic tool (58, 59). Similar to EEGs, which measure the summation of synchronous activity in the brain (60), the synchronous activity of iPSC-derived neuronal models can be assessed using microelectrode arrays (MEAs). MEAs can be used to study neuronal activity patterns relevant to human neurological conditions in both 2D networks and brain organoids (61–63). For instance, Trujillo *et al*. showed that cortical organoids have similar developmental trajectories, specifically pertaining to frequency of oscillations and duration of events (63), in their functional neural network activity as those observed in neonatal human EEGs (64). These results indicate that interrogating developmental oscillatory patterns in neuropsychiatric and developmental disorders may offer valuable perspectives into both normal and abnormal brain development and function. These insights, coupled with the findings that administration of the benzodiazepine drug diazepam—known to facilitate GABAergic signaling—to organoids decreased spiking complexity within neural circuits, suggest that both neural circuitry abnormalities and neuropsychotropic drugs can be assessed via this platform (65).

Molecular insights into disease can be gleaned with the translation of patient data into in vitro studies which can then be translated back into the clinical setting. In ASD, Bruining *et al*. developed an algorithm to estimate the excitation-inhibition (E/I) ratio using EEG to assess neural oscillations, the functional E/I ratio was capable of detecting E/I shifts associated with pharmacological intervention in human EEG. E/I ratio profoundly affect optimal processing of stimuli (66) and aberrancies therein interrupt neuronal network dynamics and impair their function (67). This approach was validated in nonmedicated children with ASD and in healthy controls under pharmacological enhancement of GABAergic synaptic inhibition (68). Measuring the E/I ratio at the cellular level may provide a translational link between patient data informed in vitro models and the clinic. Additionally, using disease signatures of neural activity can offer insights into assessments of neural circuitry in patient-derived organoids. Using calcium imaging and extracellular recording to assess local field potentials, Samarasinghe *et al.* demonstrated that brain organoids derived from individuals with Rett syndrome (RTT), displayed complex circuitry dynamics akin to intact brain preparations and demonstrated a deficit in low frequency oscillations and frequent epileptiform-like activity (69). Additionally, they discovered that the antiapoptotic, p53 inhibitor pifithrin-α rescued many of these physiological parameters within the organoid model.

Additional examples of face validity within iPSC-derived neural systems include the ability to recapitulate macrocephaly and microcephaly in neural organoids, which is validated by their clear structural readout. Urresti *et al*. demonstrated that cortical organoid model the macrocephalic and microcephalic effects of the reciprocal deletion and duplication, respectively, of the 16p11.2 region associated with ASD (70). Morphological measures of the brain could also serve this purpose. For Williams syndrome, Chailangkarn *et al*. generated patient iPSC-derived NPCs and cortical neurons, demonstrating that increased NPC proliferation and apoptosis could be traced to a single gene, FZD9, within the Williams-Beuren Syndrome Critical Region. These findings were further supported by morphological abnormalities observed in postmortem brain tissue, particularly in neurons from cortical layers V and VI (71). Non-neuropsychiatric disorders, including epilepsy and neurodegenerative diseases, offer a potentially more straightforward approach for modelling diseases using iPSCs, owing to their distinct cellular phenotypes and potential for electrophysiological readouts. However, these models face shared challenges with neuropsychiatric disorders that need to be fully realized for accurate disease modeling, such as reflecting developmental timepoints that may precede disease onset by decades.

Predictive Validity

To assess the validity of a model system, the inclusion of positive and negative controls is essential. Considering that there are currently no known biomarkers for neuropsychiatric disorders, we will define predictive validity as the ability of the model system to replicate treatment responses observed in patients using relevant measurements. For example, lithium has been widely used to treat mania in bipolar disorder. Mertens *et al*. generated iPSC-derived hippocampal dentate gyrus granule-like neuronal networks from both lithium responders and nonresponders. Their study showed that lithium treatment induced significant changes in the neuronal networks of lithium responders, while it had no apparent effect on the neuronal networks of nonresponders (72). Interestingly, this suggests that a model containing only iPSC-derived dentate gyrus cells could suffice for building a predictive model for bipolar disorder, as it effectively differentiates between lithium responders and nonresponders. This study highlights the value of incorporating clinical insights at the individual level to guide experimental design. An extension of this study showed this could also be replicated in cortical organoids derived from lithium responders and nonresponders (73). Instead of prioritizing construct and face validity first, identifying known medication responders and nonresponders can help determine the most suitable iPSC-derived model for a disorder. It is worth noting that it may be difficult to accurately define treatment-resistant groups and therefore, close collaboration with clinicians and use of established guidelines or standards for diagnosing treatment resistance is advantageous.

Another study that utilized this concept used iPSCs from clozapine responders and nonresponders. Here, they showed that clozapine increased activity in neuronal networks from both control and clozapine responders, while there was no effect for clozapine nonresponders (74). Unfortunately, the available clinical information is not always applied effectively. In one study, researchers used iPSC-derived neuronal cultures from a patient that clinically has no response to clozapine, yet they did not include clozapine as a positive control (75). In contrast, there are instances where clinical information is unavailable. For example, a study aiming to model disease predisposition used iPSCs lines from multiple patients attempted to investigate whether antipsychotic manipulation could rescue deficits in NPC migration during in vitro neurodevelopment. However, the absence of detailed medication histories made it unclear whether the tested medications had been clinically effective for those patients (76). That being said, the readouts used in this study did not reflect aspects of adult treatment efficacy, suggesting limitations in the model's face validity and highlighting how all three validities contribute to a valid stem cell model.

Recently, the US Food and Drug Administration (FDA) approved a new therapy for RTT, consisting of a peptide fragment of insulin-like growth factor 1 (IGF-1) which was shown to restore multiple aspects of RTT pathology in a mouse model (77, 78). This information was later used to develop a predictive iPSC-derived model for RTT by Marchetto *et al*. (2015), who generated both NPCs and neurons from clinically affected female patients with RTT. Here, they showed that RTT patient-derived neurons have reduced number of synapses and dendritic spines, as was previously shown in the mouse model. In addition, IGF-1 treatment was able to recover the synapse number back to control levels (79), suggesting that this iPSC-derived model can be used for translational purposes and discovery of additional novel treatments for RTT.

To assess the potential for precision therapy in early infantile epileptic encephalopathy type 13, also known as SCN8A-related epilepsy, Tidball *et al.* treated iPSC-derived excitatory neuron from three patients with missense variants in *SCN8A* (80). They were able to show within their model system that iPSC-derived neurons displayed altered sodium currents and treatment with riluzole, a drug used to treat amyotrophic lateral sclerosis, reduced spontaneous firing and heightened the action potential firing threshold. As a result of this study, riluzole was prescribed off-label to 2 patients whose iPSC-derived neurons demonstrated responsiveness.

Many neuropsychiatric disorders are managed through antipsychotics, antidepressants, mood stabilizers, and stimulants. Despite significant efforts, the current psychiatric medications show little improvement in effectiveness or functional outcomes compared to the original treatments introduced over 50 years (81). The development of patient-derived iPSC-based model systems offer the potential for testing future novel medications in a more personalized manner. For example, the FDA has

recently approved a new therapy for schizophrenia (82). Inclusion of known responders and nonresponders from these clinical trials in iPSC studies could validate these models, resulting in a model that is more suited for forward translation and discovery of new therapeutic approaches. To achieve this, it is essential to establish a model system with high predictive validity. However, before a model can provide meaningful insights into the efficacy of new medications, its predictive validity must be established using positive and negative controls based on a patient's medical history at the individual level.

Discussion

One limitation of iPSC-derived model systems is their restriction to early prenatal neurodevelopmental stages. For instance, on a gene expression level, brain organoids replicate cell states normally observed in the first and second trimester but generally fail to capture later developmental stages (23, 83). Similarly, 2D neuronal cultures most closely resemble fetal brain tissue (17, 84, 85). Considering that neuropsychiatric disorders can emerge anywhere from childhood through adulthood, iPSC-derived models are therefore best suited to study disease predisposition rather than fully modeling the disease itself. A critical challenge in iPSC-based research is therefore identifying measurable features that are related to clinical manifestations of the disorder. For example, neuropsychiatric disorders are primarily defined by behavioral characteristics, a trait that iPSC-derived model systems inherently cannot replicate. This limitation not only affects the ability to model these disorders but also complicates the validation of these models and requires alternative approaches to capture this aspect of the disorder. One potential strategy could be to compare electrophysiological MEA recordings from patient iPSC-derived neuronal models to a control cohort to reveal neuronal mechanisms underlying the behavioral symptoms, functioning as an effort to capture a phenomenon that iPSCs are inherently unable to model and providing a basis for model validation. Another possible approach is to analyze the transcriptional signature underlying brain activity. Although establishing a direct correlation between brain activity and transcriptomics in the human brain is ethically and clinically challenging, Bahl *et al*. recently developed a deep learning toolbox designed to predict neuronal activation based on transcriptomic signals (86). Likewise, transcriptional signatures of iPSC-derived neuronal networks can be directly integrated with electrophysiological profiling using MEA recordings (87). This integration enables the identification of disorder-related pathways and opens opportunities for future therapeutic strategies.

The development of iPSC-derived models in recent years has revolutionized the study of human brain development, providing opportunities to model complex disorders *in vitro*. However, these advancements have also introduced new challenges, particularly in selecting the most appropriate model to address specific research questions. Drawing on examples from animal models of neuropsychiatric disorders, the well-established validity framework can serve as a foundation for selecting the most suited iPSC model. This framework is built upon three key types of validity, specifically construct, face, and predictive validity, each of which plays a critical role in model development and is interdependent. Conceptually, any of the three validities could serve as a starting point. For instance, in the case of monogenic disorders, it would be logical to start with construct validity. Alternatively, clinical data could be informative for the predictive validity, particularly when information about known responders and non-responders to a specific medication is available. With proper rigor and validity standards, iPSC modeling of neuropsychiatric disorders stands to provide insights that contribute to elucidating disease mechanisms as well as prognostic and preventative indicators of disease. Predictive iPSC modeling of disease would benefit from the synthesis of data from patients and data gleaned from current cellular models to generate prediction models of biological patterns and mechanisms and how they relate to disease.

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Author Contributions

N.K., A.C.V., N.N.K., and B.L.L. conceived the ideas and wrote the manuscript.

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