



Model Systems infrastructure of the German Center for Mental Health (DZPG): toward an integrated, mechanism-based framework for mental health research

Shima Safaiyan^{1,2} · Mathias V. Schmidt^{2,3} · Annemarie Zimprich^{2,4} · Johann Steiner^{5,6,7} · Eva C. Schulte^{2,8,9,10} · Claudia Böhm^{11,12} · Rainer Spanagel^{13,14} · Ekrem Dere^{15,16,17} · Armin Zlomuzica^{15,17} · Pamela Fischer-Posovszky^{18,19} · Jan Tuckermann^{19,20} · Iris-Tatjana Kolassa^{14,19,21} · Anita Hansson^{13,14} · Thomas Nickl-Jockschat^{5,7} · Stefan Remy^{7,22,23,24} · Elke Knappmann¹⁷ · Rudolf Starzengruber² · Sebastian Schmidt^{1,2} · Philipp Koch^{14,25,26,27} · Robert Kumsta^{15,28} · Sabine M. Höller^{2,4} · Josef Priller^{1,2,29,30}

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Abstract

Mental health is fragile and disorders are highly prevalent arising from complex interactions between genetic, developmental, psychological, social and environmental factors. The key mechanisms underlying resilience, vulnerability factors, brain repair systems, and recovery remain poorly understood, hindering the development of effective prevention and personalized treatment. The German Center for Mental Health (Deutsches Zentrum für Psychische Gesundheit, DZPG) addresses these challenges through a nationwide, interdisciplinary research network that integrates basic science with translational approaches across multiple sites. Its embedded “Model Systems” infrastructure provides a state-of-the-art platform to investigate brain–behavior mechanisms. Animal models are available to explore the links between genes, neural circuits, and behavior. Additionally, humanized model systems are established based on transgenesis and induced pluripotent stem cell (iPSC)-based models. Brain organoids further support research into neurodevelopment and multicellular interactions.

Critically, when combined with high-content/high-throughput screening, iPSC-derived models link disease mechanisms to therapeutic targets. Advanced techniques, such as machine learning-based behavior quantification, single-cell and spatial multi-omics analyses, and genome editing enable in-depth analysis of disease/patient-specific cellular phenotypes and networks. Patient and public involvement embedded within the Model Systems infrastructure secures the scientific and translational relevance of the activities and helps to link experimental findings in our model systems to clinical symptoms and behavioral dimensions. By integrating animal, cellular, and human data on a multi-systems level with clinically relevant symptoms, the DZPG leverages model systems to accelerate mechanistic discovery and translation in mental health research.

Keywords Mental health · Animal model systems · Patient and public involvement · Induced pluripotent stem cells · Brain organoids · Translation · Circuits · Dimensional frameworks

Introduction

Impairments of mental health represent a major global health challenge due to their high prevalence, complex etiology, and high individual and social burden of disease. Despite the progress made in recent decades, mental health research still lacks a robust mechanistic framework that links

multi-factorial causative processes, including environmental and genetic factors, cellular mechanisms, and behavioral phenotypes to clinically meaningful therapeutic outcomes [1–4]. Diagnostic frameworks remain largely descriptive with a significant symptom overlap between classical categorical diagnoses. For example, delusions are a defining feature of schizophrenia but are also prevalent in affective

Extended author information available on the last page of the article

and neurocognitive disorders. Anxiety defines a unique disease entity but is also a key symptom of psychosis, affective disorders, autism spectrum disorders and substance abuse. The translational success from laboratory models to patient care has been growing over the past decades [5–10]. The German Center for Mental Health (Deutsches Zentrum für Psychische Gesundheit, DZPG) was established in 2023 to address these challenges by fostering interdisciplinary translational research that accelerates the development of new diagnostic and therapeutic tools for mental health. The DZPG integrates expertise across six major research sites in Germany, emphasizing early detection, impact of environmental factors (e.g., early life stress, infection, migration, drug abuse) on disease development and the age of disease onset, detection of prodromal stages and inflection signals of imminent relapse, biological factors (e.g. genetics and sex across the lifespan), vulnerability, and resilience for pathological states and personalized treatment [11, 12]. To this end, one of the DZPG's research strategies is the systematic use of model systems ranging from in vivo animal models to human in vitro systems.

To address clinical heterogeneity and symptom overlap across traditional categorical boundaries, the model systems in the DZPG can be aligned with dimensional taxonomies of mental illness such as the Research Domain Criteria (RDoC), Hierarchical Taxonomy of Psychopathology (HiTOP), and clinical staging [13]. In contrast to traditional symptom-based diagnostic categories, like the Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD), these alternatives better accommodate transdiagnostic dimensions and can be investigated across levels of analysis, from molecular and cellular processes to behavioral and clinical outcomes [14, 15]. A particular emphasis rests upon the identification of translationally relevant neural circuits, which are dysfunctional in human mental health disorders and are subsequently studied in model organisms [16]. This endophenotypic circuit-centric approach yields the great advantage that behavioral changes in model organisms can be analyzed as a consequence of circuit dysfunction, and do not necessarily have to mimic closely human behaviors, which are generally difficult to model in rodents.

Besides clinical heterogeneity and symptom overlap, mental disorders share many of the same genetic risk factors. However, it remains unclear why these shared vulnerabilities lead to different mental illnesses in different individuals. To date, research efforts have largely attempted to link specific genetic manipulations directly to individual mental illnesses [17–20], an approach that has not always been successful and requires further investigation. One assumption is that specific environmental factors and/or the general individual genetic background serve to steer genetically

determined vulnerability toward distinct psychiatric disorders [21]. In the multidisciplinary environment of the DZPG, taking advantage of our Model Systems infrastructure, we assess how genetic disease factors like polygenic risk scores from genome-wide association studies (GWAS) interact with various environmental factors such as chronic mild stress, social defeat, maternal separation, chronic drug treatment, prenatal infections, malnutrition, overpopulation, brain trauma to ultimately result in different mental health disorders called depression, schizophrenia, anxiety disorders, autism, etc. This implies that the very same genetic risk factor, depending on the specific "environmental hit(s)" encountered, can lead to distinct behavioral symptoms that are, in turn, characteristic of (or mutually exclusive in) different disorders. By systematically comparing these interactions across standardized model systems and human data, the DZPG aims to identify convergent mechanisms underlying a "vulnerable brain".

While laboratory (animal and human) model systems offer the advantage of standardized controlled conditions that can be experimentally manipulated, the findings from different model systems are often not integrated or linked to clinical phenotypes [22–24]. Whereas animal models cannot fully reflect the complexity of human brain function, human cellular systems can provide some patient-derived biology but often lack organism-level complexity. To overcome these gaps, within the DZPG infrastructure, findings from different laboratory models are combined and linked to human behavior and neurobiological functioning. Such a synergistic approach avoids accumulating disconnected results and allows connecting findings across systems and levels of analyses. In the DZPG, all research activities are accompanied by participatory science engaging individuals with lived experience and the public, in research design and research decision-making. Patient and public involvement (PPI) ensures that the model systems adequately address the questions and needs of people at risk and with lived experience. PPI can also guide construct selection, outcome prioritization, acceptable biosampling procedures, and the communication of model system findings to people with mental health issues, their relatives, and the wider public [25].

In this Perspective article, we aim to discuss how the DZPG's Model Systems infrastructure that spans animal models, two- and three-dimensional human cellular systems can contribute to a more integrated and mechanism-based framework for mental health research in order to facilitate the development of biomarkers and effective treatment strategies (Fig. 1). By highlighting current practices, conceptual foundations, and emerging opportunities within the DZPG, we aim to demonstrate how dimensional taxonomies can be integrated with model systems and how convergence across

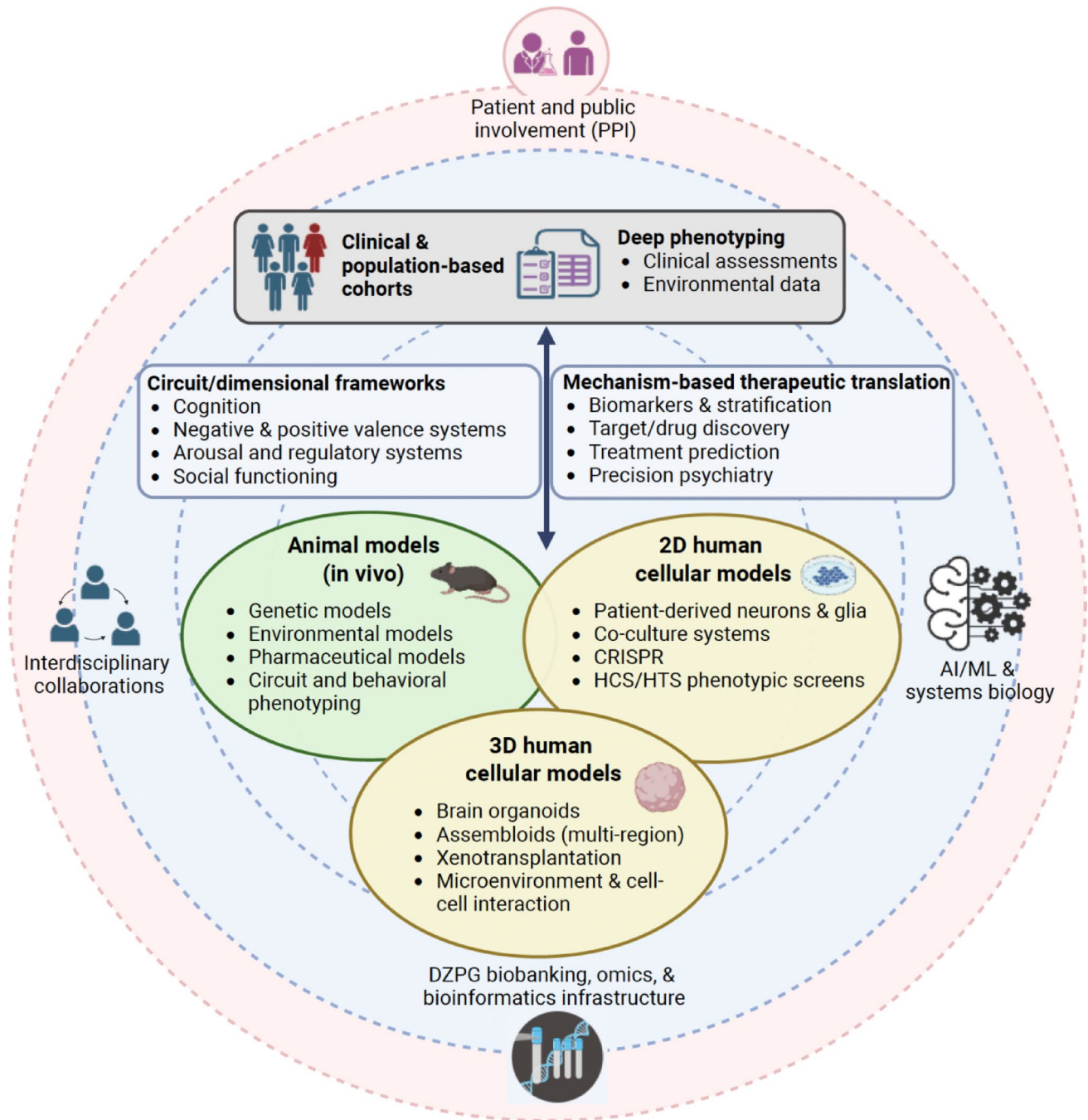


Fig. 1 Schematic overview of the DZPG infrastructure 'Model Systems'

model systems can enhance translational research and facilitate progress beyond symptom-based classification.

The Model Systems infrastructure aims to leverage therapeutic translation by integrating deeply phenotyped clinical and population-based cohorts with complementary model systems across scales of biological organization and levels of analyses. The model systems include in vivo animal models, two-dimensional (2D) and three-dimensional (3D) human cellular models. The causal relationships between

genes, environmental disruption, neuronal circuits, neurodevelopmental mechanisms, brain tissue homeostasis, and behavior are assessed within circuit/dimensional frameworks across these models. Patient and public involvement is key to the success of all activities within the infrastructure. AI/machine learning as well as biobanking, omics and the bioinformatics infrastructure of the DZPG support data integration/validation and convergence analyses. The coordinated and mechanism-based Model Systems infrastructure

facilitates biomarker and drug discovery by bridging pre-clinical model systems with clinical phenotypes. Dashed circles represent continuous interaction across all elements.

Model systems in mental health research: limitations and integration

The application of model systems in the field of mental health research remains fragmented. Animal studies provide controlled experimental conditions and mechanistic insights but often struggle with linking behavioral readouts to specific psycho(patho)logical or biological processes relevant to human brain function [26]. Human cellular studies generate rich molecular data but frequently lack interpretative anchors in behavior or cognition. Clinical research, in turn, provides detailed descriptions of patient characteristics but often remains weakly connected to underlying mechanisms on the molecular, cellular, circuit, and systems levels [27, 28]. This fragmentation has significant consequences: findings sometimes fail to connect with clinical symptomatology or fail to replicate across laboratories and model systems, contributing to inconsistent evidence and limited progress in biomarker and therapy development [29–31]. In our view, the main limitation is not the quality of individual model systems, but the lack of comprehensive integration across models and human brain function.

We argue that mental health researchers may want to ensure whether findings from different levels of research, including animal models, cellular models, and human studies are consistent with each other when addressing the same psycho(patho)logical or biological processes. In other words, construct validity should be placed at the center of translational research [32]. This approach benefits from dimensional and circuits-based frameworks for core psycho(patho)logical and biological functions, which can then be integrated with experimental paradigms in animal models, human cellular systems, and human studies. In practice, this construct-based approach can be implemented through convergence-oriented study designs, in which the same taxonomy-defined construct (e.g., stress/threat) is examined across different model systems with relevant methodology and conceptually aligned readouts. For example, we reached consensus that stress- or emotion-related regulation can be assessed through behavioral paradigms in laboratory animals, cellular stress responses in patient-derived cells, and physiological or neuroimaging measures in humans. Coordinated research infrastructures, such as the DZPG, provide the framework necessary to implement this approach systematically.

By promoting shared conceptual definitions, harmonization of paradigms, PPI and cross-site collaboration, the

DZPG enables the interconnection of results from model systems with human phenotypes. In this context, construct validity counts not as a single assay or model property, but as an outcome of coordinated, multi-level investigation, supporting a more integrated and mechanism-focused approach for translational mental health research [33, 34]. We also integrate computational analysis of comprehensive phenotype data from mouse models with advanced digital tools for brain research to enable a synergistic investigation of mouse and human brain function, thereby facilitating translation [35, 36]. Additionally, sex and age are reported and analyzed as biological variables. Cross-site consensus on standard operating procedures (SOPs) helps to provide high-quality metadata and batch-effect documentation.

Animal models

Animal models are essential for mental health research because they provide opportunities to test correlations between biological processes and behaviors/symptoms in humans although they do not reproduce (the full spectrum of) human mental health disorders. Unlike most human studies, animal experiments allow researchers to directly manipulate genes, neural circuits, and environmental conditions in controlled settings. Across the DZPG sites, we are developing new animal models that better reflect core aspects of human mental health disorders as well as hitherto rather neglected effects of mental disorders on conscious cognitive information processing and disease-related mental processes [37–39]. These models allow us to dissect gene–brain–behavior relationships and experimentally test mechanisms involved in vulnerability, resilience and treatment response. Our work focuses mainly on rodent systems. Nevertheless, where appropriate, we complement these models with other established model organisms to further explore the links between genes, neural circuits and behavior. Our animal models combine genetic and environmental disease risk factors through targeted genetic manipulations (e.g., CRISPR) and environmental perturbations such as stress exposure and developmental manipulations [40, 41]. For instance, we use functionally selective and conditional mutant mouse strains to target the stress axis, including catecholamine and glucocorticoid receptors [42, 43]. These models enable tissue-specific and mechanistic dissection of stress responses, and more specifically the crosstalk between the central nervous system (CNS) and peripheral organs. To keep the construct-validity logic explicit, we distinguish between model systems (the biological organism, genotype, cell type, or perturbation), paradigms/assays (the experimental task or challenge), and readouts (the measured behavioral, neural, physiological, omics, or biomarker endpoints). This distinction helps align animal and human

studies around shared constructs rather than around seemingly similar phenotypes.

The DZPG animal research approach follows a coordinated, multi-institutional effort that involves a broad spectrum of established and advanced behavioral paradigms in rodents. These include, but are not limited to, focused behavioral assays such as open field, elevated plus maze, zero maze, light–dark box, fear conditioning, startle paradigms for negative valence systems; sucrose preference, operant reward learning, conditioned place preference for positive valence systems; reversal learning, attentional set shifting, touchscreen-based cognitive tasks for cognitive systems; locomotor activity, home-cage monitoring, telemetry-based physiological measures for arousal and sleep regulatory systems, as well as social interaction paradigms and social preference assays for social processes. These assays can be combined with deep behavioral phenotyping approaches utilizing computer vision- and machine learning (ML)-based long-term behavioral quantification to understand and map the underlying structure of behavior and link it to brain function [44]. Using these approaches in the DZPG, we can make fingerprints across the diurnal cycle in settings, allowing for the continuous and uninterrupted capture of behavior across multiple domains of dimensional taxonomies [45, 46]. Also, we can use highly standardized behavioral assays as well as more naturalistic settings to study social interactions, group dynamics, and collective behavior [47, 48]. Additional metabolic phenotyping is performed using non-invasive methodologies, including indirect calorimetry and body composition assessment, thereby strengthening the link between mental health disorders and metabolic dysfunction.

Behavioral paradigms and functional assessments become meaningful when interpreted in relation to constructs such as threat processing, cognitive control, reward learning, arousal regulation, or sleep [22]. Also, when applying dimensional taxonomies, assays of exploratory behavior, stress responsivity, or learning and memory can serve as tools to identify processes that are relevant for brain function in health and disease [49, 50].

This approach supports construct validity across paradigms and can help to relate mouse and human behavior. Building on this cross-species interpretation, the integration of behavioral assay batteries with longitudinal deep phenotyping enables a paradigm shift from traditional group-level comparisons to individual diagnostics also in animal models. While conventional experimental designs often focus on mean differences between cohorts (e.g., stress vs. control or knock-out vs. wild type), we can identify stratified subgroups of individuals that are truly affected within specific domains by leveraging high-resolution behavioral fingerprinting. This granular stratification allows for better investigation of

mechanisms that are linked to the extreme phenotypes of a given behavioral dimension, by utilizing the full spectrum of available technologies including genetic manipulation based on GWAS hits, single-cell omics and spatial transcriptomics, projection-specific circuit manipulations, and real-time biosensors. Crucially, this creates a key point of convergence with human *in vitro* model systems. Because these findings are resolved at the level of specific cell types and circuits, they provide a biological template that can be assessed in parallel within human-derived cellular models. Ultimately, this integrated approach moves beyond broad phenotypic descriptions towards a precise, multi-scale understanding of the mechanisms underlying mental health and driving disease across species and model systems.

Moreover, behavioral assays are combined with neural recordings, including electrophysiological methods [51] and calcium imaging, to capture cellular-resolution neural dynamics as behavior unfolds in real time. A key advantage of this approach is that recordings are obtained during active behavior, allowing for the detection of changes in neuronal activity precisely when and where they most likely manifest upon social encounters, in anxiety-provoking contexts, or a cognitively challenging task [52, 53]. This allows us to move beyond static snapshots of brain state and characterize how specific neural circuits are involved, adapt, and may be disrupted across behaviorally relevant situations. These methods can also reveal how genetic risk factors, developmental, or environmental perturbations such as stress exposure or targeted circuit manipulations reshape coordination between brain regions, disrupt neural ensemble dynamics, or alter neural dynamics during learning or behavioral adaptation. Linking these readouts to well-defined behavioral constructs within the framework of dimensional taxonomies further strengthens their translational relevance, as it grounds observed network-level changes in dimensions of function that map onto human psycho(patho)logy.

Finally, despite the power of transgenic animal models, their limitations are evident and from an ethical perspective, efforts should be made to replace, reduce and refine animal experiments according to the 3R principles. The Model Systems infrastructure of the DZPG contributes to these efforts by combining model systems, patient-derived stem cells and organoids, and the direct assessment of patients. This integrated approach is essential for tackling the complex questions in mental health research.

Human cellular models (two-dimensional)

Patient-derived induced pluripotent stem cell (iPSC) models represent a significant advance in mental health research. iPSC-derived neurons and glial cells retain the complete endogenous genetic architecture of the donor, including

the complex polygenic backgrounds and rare variants that collectively shape disease risk. Thus, they provide a human cellular system in which the genetic complexity underlying mental disorders can be studied experimentally in a scalable and patient-related manner. This distinguishes iPSC-based approaches from transgenic animal models, which typically isolate the effects of single genes or defined genetic variants. Furthermore, iPSC-derived systems enable researchers to directly examine cellular and molecular features that differ not only between patients and healthy individuals but also between individuals with the same clinical diagnosis [54, 55]. This makes it possible to identify biologically defined subgroups of patients who share common cellular phenotypes such as changes in synaptic function, neuronal excitability, immune factors, metabolic state, or other cellular responses [7, 55, 56]. By enabling the identification of shared cellular mechanisms, iPSC-based systems support a shift from symptom-based diagnostic classification toward a more mechanism-based understanding of mental disorders. Studies indicating differential cellular phenotypes associated with treatment response, e.g. lithium responsiveness in bipolar disorder, illustrate this potential [55]. More recent work emphasizes that iPSC models can reveal clinically meaningful cellular heterogeneity across individuals and disorders [23]. Additionally, transcriptomic and functional alterations in patient-derived neurons continue to reveal novel phenotypes [57, 58]. The integration of CRISPR-based editing further strengthens causal inference, allowing researchers to study specific risk variants within isogenic backgrounds [56, 59]. Furthermore, the application of high-throughput approaches like CRISPR-based perturbation screens (e.g., Perturb-seq) or massively parallel reporter assays (MPRAs) [60, 61] enables the functional annotation of genes and genetic variants at scale. These approaches allow for the systematic mapping of gene-regulatory networks in iPSC-derived brain cells, providing critical insights into the common downstream mechanisms that alter mental health-related gene function both individually and at a network scale [62, 63]. To date, iPSC-derived neurons remain the most common cell type employed in mental health research. However, human iPSC-derived glial cells are increasingly incorporated into research projects [64].

The DZPG iPSC platforms utilize both two-dimensional (2D) neuronal cultures and more complex 3D systems (see below) to generate a diverse array of neural cell types, including cortical excitatory, ventral inhibitory (GABAergic), hippocampal neurons, induced excitatory neurons, induced astrocytes, oligodendrocytes [65, 66] and microglia [67]. The DZPG is at the forefront of human microglia research [67, 68], reflecting growing recognition of their critical roles in neurodevelopment, synaptic regulation and neuroimmune processes relevant to mental health. Similarly,

iPSC-derived astrocytes provide access to cell-autonomous and non-cell-autonomous mechanisms related to metabolic support, neurotransmitter homeostasis, and modulation of synaptic activity [69, 70]. Within the DZPG, these glial models are combined with patient-derived neuronal cultures to generate the 2D co-culture systems or 3D organoid or assembloid systems (see below). These tools enable the investigation of neuron–glia and glia–glia interactions under controlled human-relevant conditions and support mechanistic analyses of neuroimmune and developmental processes that cannot be captured in neuron-only or glia-only models. The iPSC lines are frequently derived from well-characterized clinical cohorts, including individuals with autism spectrum disorder, bipolar disorder, schizophrenia spectrum disorders, and depression, allowing for associations between cellular phenotypes and clinical features such as neuroimaging, behavioral assessments or longitudinal outcomes.

Importantly, the translational value of iPSC-based disease models extends beyond mechanistic understanding when these models are integrated into systematic drug screening and repurposing workflows. High-content and high-throughput screening (HCS/HTS) platforms enable the phenotypic profiling of patient-derived neurons and glia at scale, allowing for the identification of compounds that reverse or ameliorate disease-associated cellular phenotypes. This approach has already yielded tangible therapeutic leads: a large-scale repurposing screen in iPSC-derived neural cells from patients with Leigh syndrome identified sildenafil as a candidate that has received orphan drug designation by the European Medicines Agency and is advancing toward clinical trials [71]. Similarly, population-scale phenotypic screening in iPSC-derived motor neurons from over 100 individuals with sporadic amyotrophic lateral sclerosis identified a combinatorial drug regimen with translational potential, while also demonstrating that the iPSC-based platform could retrospectively predict the failure of compounds that had previously been ineffective in clinical trials [72]. Within the DZPG, this translational trajectory from iPSC-derived disease modeling to pharmacological intervention is already being realized: using human neurons carrying *MYT1L* mutations associated with autism spectrum disorder, sodium channel blockers were identified that reversed electrophysiological hyperactivation and autism-associated phenotypes in both human neurons and mice, and compassionate-use treatments in affected patients are now underway [73]. To enable such translational screening at the scale required for mental health indications, the DZPG has established fully automated HCS/HTS infrastructure specifically designed for iPSC-derived neural cell models, including robotic cell handling optimized for the extended cultivation periods (weeks to months), automated

compound dispensing, and multi-parametric high-content image analysis. This infrastructure is located at the ZI (Zentralinstitut für Seelische Gesundheit) Mannheim and can be contacted through this link: <https://www.zi-mannheim.de/forschung/abteilungen-ags-institute/translationale-hirnforschung.html>.

When combined with the clinical cohort and biobanking infrastructure of the DZPG, screening hits identified in patient-derived cells can be cross-validated against phenotypic and longitudinal outcome data, thereby linking cellular mechanisms to clinical relevance within the construct-based framework outlined above.

As a note of caution, interpretation of iPSC models must account for donor-line variability, batch effects, differences in differentiation protocols, and the developmentally immature state of these cell types. Consequently, their translational potential is strongest when they are used as a complementary component of an integrated research framework rather than in isolation. Within this DZPG-endorsed framework, findings from human cell models can help shape experiments in animals, while results from animal studies, in turn, can guide focused analyses in patient-derived cells [33].

Beyond brain-derived cellular models, the DZPG projects also use patient-derived immune cells as experimentally accessible systems for investigating immune-metabolic processes, and the interaction of peripheral immune cells/factors with the CNS in mental disorders. Stress and environmental factors (e.g. alcohol consumption) can profoundly affect immune function, raising the question of whether immune cells contribute causally to the pathogenesis or maintenance of mental illness, or are simply a pathological epiphenomenon of disturbed homeostatic processes [74]. Since cellular metabolism shapes pro- and anti-inflammatory states [75], immune-metabolic processes can be studied *ex vivo* in patient-derived blood cells at single-cell resolution and related to mental health symptoms such as anxiety, depression, or other psychiatric symptoms [76, 77]. Beyond assessing basal metabolic states, this system enables the modeling of cellular responses to stressors such as glucocorticoids, toxins, LPS stimulation, and nutritional conditions [78].

Human cellular models (three-dimensional)

Brain organoids and related three-dimensional culture systems, such as brain assembloids, further extend the model systems available for mental health research [79, 80]. Organoids act as a bridge between human cellular models and animal models in controlled laboratory conditions. Unlike conventional 2D cultures, which primarily allow for the investigation of individual cell properties, the

three-dimensional (3D) organoids reflect aspects of tissue architecture and multicellular organization that more closely resemble the developing human brain. This approach facilitates the study of intercellular crosstalk between neurons, astrocytes, oligodendrocytes and microglia, providing insights into both neurodevelopmental trajectories and the maintenance of adult tissue homeostasis. Because many brain disorders are thought to originate from subtle alterations in neurodevelopmental processes, organoid models offer a unique tool to study underlying mechanisms that may trigger long-term vulnerability after development [81, 82]. Studies demonstrating spontaneous network activity and oscillatory dynamics in cortical organoids illustrate the potential of these systems to model emergent properties of developing neural circuits [83, 84]. It should be noted that organoids serve primarily as models of selected developmental and multicellular processes, rather than as representations of adult brain function.

DZPG iPSC models are further strengthened by advanced methodologies, including live-cell and calcium imaging, single-cell transcriptomics, CRISPR-based genome editing, and xenotransplantation approaches [85]. These advanced methods allow for the investigation of human brain development and disease-relevant processes with dynamic, causal, and single-cell resolution. Xenotransplantation of brain organoids is particularly valuable because it enables the maturation and functional assessment of human cells, including microglia, within a vascularized host brain environment [85]. These systems can support integration into host tissue networks and provide translationally relevant platforms for disease modeling, target validation, and therapy development [79]. In addition, brain assembloid models are becoming an important component of the DZPG research portfolio. By combining regionally patterned organoids or defined neural and glial cell populations, assembloids make it possible to model tissue organization, interregional communication, and neuronal network interactions that are difficult to capture in 2D cultures or single-region organoids [86, 87]. Together, these complementary model systems offer powerful tools to investigate how genetic risk, environmental perturbations and altered neurodevelopmental or neuroimmune processes contribute to mental disorders [88]. Importantly, they preserve patient-specific genetic backgrounds while enabling controlled experimental perturbations, making them well suited to study long-term effects on human brain tissue homeostasis and function.

Clinical-translational biomarker interface: linking model systems with DZPG Biobanking, Omics and Bioinformatics infrastructures

Within the DZPG, the Model Systems infrastructure is embedded in a bidirectional clinical-translational interface rather than treated as a stand-alone preclinical platform. In the forward-translational direction, mechanisms determined in animal models, human iPSC-based systems and organoids/assembloids can be prioritized for validation in deeply phenotyped clinical cohorts. In the reverse-translational direction, molecular signatures from patients can inform the selection of cohorts, experimental perturbations, cell types, behavioral paradigms, and readouts in model systems. This creates an iterative bench-to-bedside-to-bench loop in which candidate mechanisms are tested across levels of analysis and refined when human data support, qualify or challenge model-system findings [6].

The DZPG-wide Biobanking, Omics and Bioinformatics infrastructure provides the natural interface for this loop by harmonizing access to biomaterials, omics data, meta-data, and bioinformatic workflows across sites. Blood and cerebrospinal fluid (CSF) and, where available, human brain-derived readouts can serve as *in vivo* human molecular anchors for mechanisms determined in model systems, particularly when linked to dimensional phenotypes, neuroimaging measures, treatment response and longitudinal outcomes. Depending on the construct, relevant readouts may include immune, metabolic, endocrine, proteomic, synaptic, glial, neuroaxonal, and cell-type-specific molecular markers in collaboration with the DZPG Biobanking, Omics and Bioinformatics infrastructure. Further relevant information can be found in the following link under the DZPG Biobanking, Omics, and Bioinformatics section: <https://www.dzpg.org/forschung/infrastrukturen>.

From cells to brain networks: integrative human systems approaches

A further extension of the DZPG Model Systems infrastructure is provided by rodent and human brain imaging approaches that incorporate genetic and other molecular information and operate at the level of whole-brain systems in humans and thus capture the highest level of biological and behavioral complexity. Importantly, multimodal neuroimaging serves as an excellent translational approach because its findings often translate effectively from rodent models to the human brain [89–93]. By combining genomic and other -omics data (e.g., polygenic scores, gene expression-based indices, genome-wide interaction signals, or metabolomics/lipidomics) with multimodal neuroimaging,

these approaches enable the systematic mapping of distributed genetic and (multi)omic variation onto large-scale brain network organization and, ultimately, behavior [94–96]. Moving beyond single-variant or region-specific associations, this framework characterizes how genetic and molecular risk is instantiated in the topology and dynamics of whole-brain systems, including structural and functional connectomes, and how these relate to dimensional constructs such as affect regulation, cognitive control, and reward processing [97, 98]. Critically, this line of work can serve as a central integration layer across model systems: mechanistic insights derived from cellular and animal models can be tested in humans at the level of network architecture, while brain-based intermediate phenotypes provide biologically grounded targets for experimental manipulation in controlled systems. Within the DZPG, this bidirectional integration enables a scalable and iterative variant-to-function framework, in which genetic discoveries are translated across levels of organization from molecular and cellular mechanisms to neural circuits and behavior. Conversely, the systems-level phenotypes refine the identification of functionally relevant genetic variation. In this way, human imaging approaches not only link genes to behavior, but also operationalize convergence across model systems, strengthening causal inference and advancing a mechanistic understanding of mental health and disease.

Conclusion

Mental health research has experienced numerous methodological innovations over the last decades. However, the accumulation of increasingly large multidimensional datasets within fragmented or poorly integrated frameworks remains an obstacle to translation. Approaches that align different model systems across levels of analysis offer a promising strategy to build reliable, mechanism-based knowledge in mental health research. When animal experiments, human cell models, clinical studies and biobank-derived molecular readouts focus on the shared biological processes, researchers can better identify meaningful patient subgroups, find more precise treatment targets, and develop treatments tailored to individual patients instead of broad diagnostic categories.

In this regard, the value of coordinated infrastructures such as the DZPG Model Systems infrastructure and embedded PPI activities lies in the potential to move mental health neuroscience away from fragmented findings towards an integrated science of mechanisms that can be targeted therapeutically.

To get direct access to the DZPG Model Systems infrastructure, we provide the following link: <https://forms.clou>

[d.microsoft.com/c/Z9DU1UxcA](https://doi.org/10.1007/s00127-023-02503-0). This will allow the readers to receive expert advice on technical matters, establish collaborations within the DZPG and beyond, and also have access to original data.

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Author contributions S.S wrote the main manuscript text, and prepared Fig. 1. All authors provided expert input and additional information regarding the DZPG infrastructure and critically reviewed the manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

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Authors and Affiliations

Shima Safaiyan^{1,2} · Mathias V. Schmidt^{2,3} · Annemarie Zimprich^{2,4} · Johann Steiner^{5,6,7} · Eva C. Schulte^{2,8,9,10} · Claudia Böhm^{11,12} · Rainer Spanagel^{13,14} · Ekrem Dere^{15,16,17} · Armin Zlomuzica^{15,17} · Pamela Fischer-Posovszky^{18,19} · Jan Tuckermann^{19,20} · Iris-Tatjana Kolassa^{14,19,21} · Anita Hansson^{13,14} · Thomas Nickl-Jockschat^{5,7} · Stefan Remy^{7,22,23,24} · Elke Knappmann¹⁷ · Rudolf Starzengruber² · Sebastian Schmidt^{1,2} · Philipp Koch^{14,25,26,27} · Robert Kumsta^{15,28} · Sabine M. Hölter^{2,4} · Josef Priller^{1,2,29,30}

✉ Josef Priller
josef.priller@tum.de

- ¹ Department of Psychiatry and Psychotherapy, TUM Klinikum Rechts der Isar, Technical University of Munich, Munich, Germany
- ² German Center for Mental Health (DZPG), Partner Site Munich-Augsburg, Munich, Germany
- ³ Research Group Neurobiology of Stress Resilience, Max Planck Institute of Psychiatry, Munich, Germany
- ⁴ Institute of Experimental Genetics and German Mouse Clinic, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany
- ⁵ Department of Psychiatry and Psychotherapy, Otto-von-Guericke-University Magdeburg, Magdeburg, Germany
- ⁶ Laboratory of Translational Psychiatry, Otto-von-Guericke-University Magdeburg, Magdeburg, Germany
- ⁷ German Center for Mental Health (DZPG), Partner Site Halle-Jena-Magdeburg, Magdeburg, Germany
- ⁸ Department of Psychiatry & Psychotherapy, University Hospital Bonn, University of Bonn, Bonn, Germany
- ⁹ Institute of Human Genetics, University Hospital Bonn, University of Bonn, Bonn, Germany
- ¹⁰ Institute of Psychiatric Phenomics & Genomics, LMU University Hospital, LMU Munich, Munich, Germany
- ¹¹ Department of Psychiatry and Neuroscience, Charité, Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität, Berlin, Germany
- ¹² German Center for Mental Health (DZPG), Partner Site Berlin-Potsdam, Berlin, Germany
- ¹³ Medical Faculty Mannheim, Institute of Psychopharmacology, Central Institute of Mental Health, Heidelberg University, Mannheim, Germany
- ¹⁴ German Center for Mental Health (DZPG), Partner Site Mannheim/Heidelberg/Ulm, Heidelberg, Germany

- ¹⁵ Mental Health Research and Treatment Center, Ruhr-University Bochum, Bochum, Germany
- ¹⁶ Unité de Formation et de Recherche des Sciences de la Vie (UFR 927), Sorbonne Université. Institut de Biologie Paris-Seine, Paris, France
- ¹⁷ German Center for Mental Health (DZPG), Partner Site Bochum/Marburg, Marburg, Germany
- ¹⁸ Department of Pediatrics and Adolescent Medicine, Ulm University Medical Center, Ulm, Germany
- ¹⁹ German Center for Child and Adolescent Health (DZKJ), Partner Site Ulm, Ulm, Germany
- ²⁰ Institute of Molecular Endocrinology and Physiology, Ulm University, Ulm, Germany
- ²¹ Institute of Psychology & Education, Clinical & Biological Psychology, Ulm University, Ulm, Germany
- ²² Department of Cellular Neuroscience, Leibniz Institute for Neurobiology, Magdeburg, Germany
- ²³ Center for Behavioral Brain Sciences, Otto von Guericke University, Magdeburg, Germany
- ²⁴ German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany
- ²⁵ Department of Translational Brain Research, Central Institute of Mental Health (ZI), University of Heidelberg/Medical Faculty Mannheim, Mannheim, Germany
- ²⁶ Hector Institute for Translational Brain Research (HITBR gGmbH), Mannheim, Germany
- ²⁷ German Cancer Research Center (DKFZ), Heidelberg, Germany
- ²⁸ Department of Behavioural and Cognitive Sciences, University of Luxembourg, Esch-sur-Alzette, Luxembourg
- ²⁹ Neuropsychiatry and Laboratory of Molecular Psychiatry, Charité, Universitätsmedizin Berlin, Berlin, Germany
- ³⁰ University of Edinburgh and UK DRI, Edinburgh, UK