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Harnessing the potential of cellular, animal and computational neuroscience models for mental health

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Executive Summary

Context and objectives of the report

Neuroscience has made impressive progress in advancing our understanding of the brain by leveraging cellular, animal and computational models. However, while these scientific advances have increased our understanding of anxiety, depression and psychosis, little benefit in terms of modernising treatment has yet accrued. This is a troubling disconnection. Mental health conditions account for 13% of all disease burdens globally and affect hundreds of millions of people's lives and wellbeing.

The main objective of this landscaping report is to explore the potential for cellular, animal and computational neuroscience models, individually and in combination, to make meaningful contributions to our understanding and early intervention of anxiety, depression, and psychosis. To prepare this report, we conducted interviews with 43 key opinion leaders across academia, industry and healthcare, in addition to systematic literature reviews.

Key findings

Cellular and animal models have made important advances in our understanding of the neurobiology of genes and psychological processes relevant to depression, anxiety and psychosis. These models allow precise investigation of how genetic, biological and environmental factors linked to these mental health illnesses affect cellular and behavioural endophenotypes, which can suggest targets for early identification and therapeutic intervention. However, these approaches have often prioritised simple-readout and high throughput assays in highly standardised environments that are disconnected from the complex manifestation of clinical problems, which has resulted in limited translatability back to human patients.

Computational models are increasingly used for understanding both basic brain mechanisms and psychiatric symptoms. Techniques such as reinforcement learning, Bayesian inference and biophysical modelling have revealed important mechanisms of human behaviour and brain function, and machine learning models have facilitated patient stratification and biomarker discovery. Yet, these models often have a narrow focus on behaviour (e.g. reward processing) and lack interpretability or reliability.

Based on these advances and gaps, we identify three major challenges, and advance a set of recommendations across all model systems to overcome these. A common strand is our advocacy of aligning and/or combining theoretical and experimental approaches as the best route to catalyse neuroscience to deliver mechanistic understanding of anxiety, depression and psychosis, which can more rapidly translate to patient benefit. To facilitate this process, stakeholders from academia, industry and healthcare systems as well as funders must develop structures and funding models that prioritise imaginative and bold ideas that embrace the complexity of depression, anxiety and psychosis and take a long-term perspective aimed at ambitious goals.

A. How can we better combine cellular, animal and computational models to further our understanding of anxiety, depression and psychosis?

- We need to bridge the translational gap between neuroscience models and the clinic, through (1) prioritising symptom-focused back translation and (2) ensuring peoples' experienced symptoms and needs inform neuroscience studies. To achieve this, laboratory research should be conducted in a collaborative, cross-disciplinary fashion, with direct clinical and/or lived experience input as standard.
- We need to develop richer, more ecologically- and clinically-valid measures and paradigms that are tractable to neuroscientific investigation. This can be expedited by (1) identifying innovative behavioural and cellular readouts that recapitulate the complex cognitive, emotional, physiological, pathological and autonomic alterations observed in anxiety, depression and psychosis; (2) accelerating adoption of automated, neuroethological measures; and (3) seeking implicit "modellable" behavioural, cellular and computational metrics beyond standard experimental readouts.
- We need to identify better and more harmonised brain and body readouts such as electrophysiological biomarkers, heart rate variability and/or facial expressions across multiple scales and species to facilitate translation between models and the clinic.

B. How can cellular, animal and computational models improve ways to predict, identify and intervene early in anxiety, depression and psychosis?

- We need to recognise and leverage variation in our models to better reflect patient heterogeneity and facilitate identification of risk factors. This can be achieved by ensuring our models better capture: (1) genetic diversity; (2) biological diversity (e.g. sex, ancestry); and (3) the

impact of social environment on brain function and mental health; and also by (4) accelerating research using models to improve the stratification of patients based on individual differences in their neurobiology and environment.

- We need to extend the timescale of investigation in cellular, animal and computational models to unravel how cumulative experience across the lifespan shapes mental health trajectories, the development of behavioural phenotypes and their neural correlates.

C. How can we create a sustainable and standardised scientific environment to ensure work in cellular, animal and computational models can fulfil their potential and be as widely used as possible?

- We need to establish community standards for models and their outputs to ensure the models are appropriately designed to meet their need, to maximise reliability and to encourage replication, data sharing and transparency.
- We need to ensure datasets are accessible and diverse, and that state-of-the-art methods are as widely available as possible, by (1) increasing the findability, accessibility, interoperability, reusability and inclusivity of neuroscience datasets; and (2) advancing the development and deployment of lower cost, more accessible and inclusive measurement tools.

In summary, to accelerate progress toward better understanding and improved care for anxiety, depression and psychosis, experimental and theoretical neuroscientists must be incentivised to embrace the biological diversity and complexity inherent in these conditions through their models (a 'messy science' approach) and to pursue interdisciplinary integrative science that spans scales, species and from bench-to-bedside.

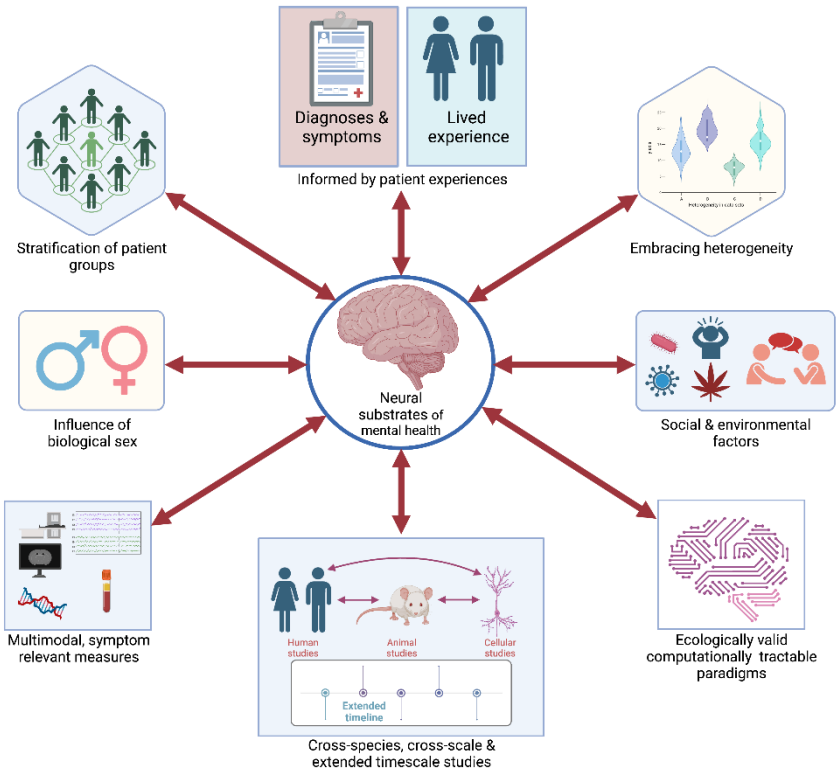

Figure 1: Schematic summary of the report. To harness the power of neuroscience for mental health, we need to embrace the biological diversity and complexity inherent in mental health conditions through experimental and theoretical neuroscience models (a 'messy science' approach) and pursue interdisciplinary integrative science that spans scales, species and from bench-to-bedside. Parts of the above image were created with Biorender.com

Table of abbreviations

ABCD	adolescent brain cognitive development
CNV	copy number variants
DBS	deep brain stimulation
EEG	electroencephalogram
GDPR	General Data Protection Regulation
GWAS	genome-wide association studies
HALIP	hallucinatory-like percepts
ICD	International Classification of Diseases
IPSC	induced pluripotent stem cell
LMIC	low- and middle-income countries
MEG	magnetoencephalography
PTSD	post-traumatic stress disorder
RDoC	Research Domain Criteria
SSRI	selective serotonin reuptake inhibitors
WEIRD	western, educated, industrialised, rich, and democratic

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Introduction

Mental health illnesses impose a significant global burden, affecting individuals, economies and societies at large. Collectively, they account for 13% of the global burden of disease and are a leading cause of disability worldwide (GBD 2019 Mental Disorders Collaborators, 2022; Holmes et al., 2018; Steel et al., 2014; Whiteford et al., 2013). Among these, anxiety, depression and psychosis represent some of the most prevalent and debilitating conditions, affecting hundreds of millions of people worldwide, many of whom struggle from a young age. Despite the profound impact of these conditions, there is a substantial unmet need in terms of their care and treatment. While current therapeutic options, such as antipsychotics and antidepressants, have improved the lives of many people, a significant proportion of individuals with these conditions do not fully benefit from these interventions, experiencing relapse or persistent symptoms due to treatment resistance (Jaffe et al., 2019). For example, it is estimated that one third of patients with major depression do not respond within two years of their first prescription of antidepressants (Zhdanava et al., 2021). The major obstacle to effective therapeutic strategies is our limited understanding of the neurobiology underlying mental health illnesses.

A fundamental factor contributing to unmet mental health needs is that, by nature, anxiety, depression and psychosis are highly complex and heterogeneous conditions that often exhibit comorbidities we do not fully understand. The aetiology and pathogenesis of these illnesses also remain largely unknown. Large consortium-led studies, such as ENIGMA (Alex et al., 2023; Thompson et al., 2022; X. Wang et al., 2021) and the Psychiatric Genomics Consortium (Breen et al., 2016; Smeland et al., 2019; Sullivan et al., 2018), have made significant strides in unravelling the underlying pathogenesis of psychiatric disorders such as schizophrenia. These efforts, in combination with behavioural and clinical studies, investigations of post-mortem tissue and epidemiological analysis, have provided insights into the multifactorial nature of these disorders, highlighting the contributions of both environmental and genetic factors to their development (Sullivan et al., 2012). Moreover, macroscopic and microscopic changes within the brain have been observed in association with anxiety, depression and psychosis. These changes encompass alterations in behaviour and system and circuit-level functioning, as well as abnormal cellular and molecular processes.

However, to comprehensively dissect and elucidate the mechanisms underlying anxiety, depression and psychosis, it is crucial to leverage existing neuroscience knowledge and employ a variety of model systems. These models aid in identifying biomarkers, understanding disease progression and exploring potential therapeutic strategies. One factor that has impeded progress in these areas is the use of categorical (nosological) diagnostic criteria. While these criteria are essential for clinical practice, they do not adequately guide neurobiological investigations into the foundations of anxiety, depression and psychosis, particularly due to the lack of reliable biomarkers that can be used in clinical practice. Model systems have been employed to study the neurobiological underpinnings of anxiety, depression and psychosis, including animal models, cellular models, computational neuroscience and computational psychiatry. Each model system is designed as an imperfect and incomplete facsimile of the real illness, but the advantage is that each system isolates a particular set of features, making them simplified probes for the analysis of these complex problems.

In this report, we describe the role of cellular models, animal models and computational modelling approaches in neuroscience (section 1.4) for understanding and treating anxiety, depression and psychosis.

Cellular models, specifically induced pluripotent stem cell (iPSC)-based models, have emerged as a promising tool for studying the neurobiology of anxiety, depression and psychosis. iPSCs are generated by reprogramming somatic cells into a pluripotent state, capable of differentiating into various cell types, including neurons and glial cells. This technology allows researchers to derive patient-specific iPSC lines and differentiate them into neural cell types relevant to psychiatric illnesses (Falk et al., 2016; Gordon & Geschwind, 2020; Levy & Pasca, 2023; Seah et al., 2023; Whiteley et al., 2022). These cellular models provide a unique opportunity to study disease-specific cellular phenotypes, investigate the impact of genetic and environmental factors and explore potential therapeutic targets (Levy & Pasca, 2023; Seah et al., 2023; Whiteley et al., 2022).

Animal models have played a pivotal role in advancing our understanding of anxiety, depression and psychosis. By manipulating genes or inducing specific environmental conditions, researchers have been able to investigate the molecular and cellular mechanisms underlying these disorders. Animal models have provided valuable insights into the neural circuits,

neurochemical imbalances and behavioural manifestations associated with these mental health illnesses (Nestler & Hyman, 2010). While animal models have contributed significantly to our knowledge, their translational relevance to human conditions is inherently limited due to species differences in brain anatomy, cognitive capabilities and genetic makeup (Nestler & Hyman, 2010).

Computational models play another distinct yet increasingly important role in understanding anxiety, depression and psychosis. Researchers can simulate (Fagerholm et al., 2021; Huys et al., 2012; Murray et al., 2018) and analyse complex neural systems with mathematical tools (Ji et al., 2021; Kafadar et al., 2020), allowing them to gain insights into the underlying mechanisms of these disorders while also formalising symptoms as aberrant computational processes. These approaches not only help make predictions for treatment response and symptom progression (e.g. by leveraging machine learning (Lanillos et al., 2020)), but also reveal the dynamics of the brain, identifying aberrant patterns and exploring how alterations in brain function contribute to the behaviour and clinical symptoms observed in mental health conditions (Dzafic et al., 2021). By integrating computational modelling with advanced analysis of clinical, neuroimaging and behavioural data, researchers can identify biomarkers, understand disease progression and develop personalised treatment strategies (Friston et al., 2017). Computational models provide a quantitative framework for studying mental health disorders, enabling the investigation of complex interactions between genetic, environmental and neural factors and aiding in the development of innovative interventions for these conditions.

In section 1, we provide an overview of each model system before delving into the gaps and opportunities within each approach. In section 2, we highlight needs and recommendations for advancing the ways in which a combination of these model systems can be employed to further our understanding of anxiety, depression and psychosis. By integrating findings from multiple model systems, we can enhance our knowledge of these disorders, explore new early intervention strategies and ultimately facilitate the development of novel therapeutic approaches for mood and psychotic disorders.

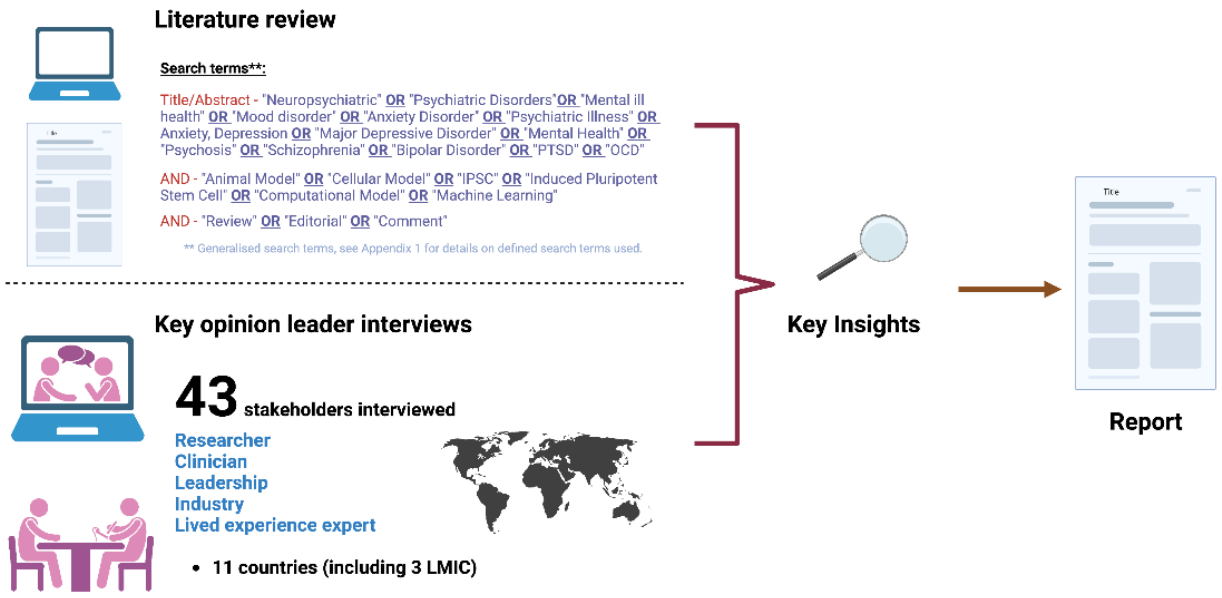

Figure 2: Methodology for writing. We conducted a thorough literature review of research using cellular, animal, and computational models at the intersection of neuroscience and mental health. We also interviewed a total of 43 stakeholders and key opinion leaders across sectors. Key insights from these processes were synthesized and integrated by the authors of this report. Parts of the above image were created with Biorender.com

The current landscape

1.1 Cellular models for mental health

1.1.1 Background

Since Ross Granville Harrison demonstrated the ability to culture neural explants from frogs in the early 1900s, multiple approaches and technologies have been developed to generate *in vitro* neuronal cultures (Gordon et al., 2013). This has enabled the study of fundamental characteristics, such as functional properties, cellular mechanisms, signalling pathways and molecular processes, that occur in neuronal and glial cell types. In the context of mental health illnesses, cellular models have been used to study how genetic and environmental factors, posited to be central to the underlying pathophysiology, drive alterations in the development and/or physiology of the brain. Additionally, cellular models have been used as a platform to investigate the mechanisms of action of drugs and to conduct drug discovery studies to identify and validate potential novel therapeutic compounds. Broadly, three methodological approaches have been used to study mental health illnesses: immortalised cell lines, primary neuronal cultures and induced pluripotent stem cell (iPSC) lines.

Immortalised cell lines such as SH SY5Y and NT2 have been widely used due to their easy culture, scalability and genetic manipulation (Kovalevich & Langford, 2013). However, they lack authentic nervous system development ontogeny as they come from non-neuronal or tumour-derived tissues. Though efforts have been made to differentiate them to display neuronal-like properties, they do not fully acquire these in a representative way (Kovalevich & Langford, 2013). Another approach involves generating immortalised human neural stem cell lines derived from post-mortem fetal tissues using factors such as v/c-myc or SV40 large T antigen. Multiple clonal immortalised human neural stem cell lines have been established from first-trimester human fetal tissues originating from distinct brain regions (Pollock et al., 2006). These cell lines have been employed in the study of factors associated with mental health illnesses (Anderson et al., 2015). However, challenges in reproducibility, expansion and differentiation, as well as ethical concerns relating to their derivation from human fetal tissue, have limited their widespread application in mental health research.

Primary neuronal cultures offer a valuable model for studying the neurodevelopment and neuronal function of cells from different brain regions. They can be derived from both human and animal tissue. Human primary cultures closely model neurodevelopment (Gordon & Geschwind, 2020), but have limited application for the study of mental health illnesses due to tissue availability and donor variability. Conversely, primary rodent neuronal cultures have contributed significantly to our mechanistic understanding of brain physiology and the pathophysiology relevant to mental health illnesses (Banker & Goslin, 1988; Verstraelen et al., 2018). However, primary rodent cultures do not capture the complex genetic architecture associated with mental health illnesses. Differences in neurodevelopment, neuronal cell type expression, neurogenesis and aspects of gene regulation, including epigenetic regulation, are unique to human physiology and cannot be fully replicated in primary rodent cultures (Gordon & Geschwind, 2020). This inability to fully recapitulate the human cellular context (i.e. human physiology and pathophysiology) limits the utility of this cellular model.

The ground-breaking work of Takahashi and Yamanaka (Takahashi et al., 2007; Takahashi & Yamanaka, 2016) demonstrated that it is possible to reprogramme adult somatic cells into iPSC, paving the way to the development of a cellular system that recapitulates the human cellular context. IPSC retain the genetic information of the donor, are self-renewing and have the potential to generate any cell type within the human body. In the context of the brain, this technology offers an unprecedented opportunity to unravel the complexities of human neurodevelopment, investigate the underpinnings of various conditions and diseases, and facilitate drug discovery efforts (Falk et al., 2016; Kleiman & Engle, 2021; Seah et al., 2023; Silva & Haggarty, 2020; Whiteley et al., 2022).

1.1.2 State of the field

Despite the relative infancy of the field, remarkable progress has been made in the past decade in establishing iPSC-based cellular models specifically tailored for the study of mental health illnesses including psychosis (e.g. schizophrenia, bipolar

disorder), depression and, to a lesser extent, anxiety (Bassil et al., 2022; Levy & Pasca, 2023; Silva & Haggarty, 2020; Whiteley et al., 2022). These models have also been instrumental in investigating the influence of extrinsic environmental factors associated with these disorders, such as stress and immune-related mechanisms (Bassil et al., 2022; Seah et al., 2023).

Collaborative efforts by large consortia and scientific organisations have established guidelines and standardised protocols for iPSC generation and biobanking, leading to significant advancements in standardisation (Dutan-Polit, 2023; Engle et al., 2018; International Society for Stem Cell Research, 2023; Steeg et al., 2021). Furthermore, several biobank repositories, including the CIRM Human Pluripotent Stem Cell Repository, NIMH Stem Cell Center, NYSCF Research Institute Stem Cell Repository, European Bank for induced Pluripotent Stem Cells (EBiSC) and HipSci Consortium, provide researchers with access to well-established, extensively characterised and thoroughly annotated iPSC lines (Dutan-Polit, 2023; Engle et al., 2018). These repositories, which include lines derived from deeply phenotyped patient cohorts, increase accessibility and raise quality standards.

1.1.2.1 Progress in developing iPSC-based neural differentiation models

Fundamental technological advancements have enabled the generation of diverse neuronal and glial cell types from induced pluripotent stem cells in both 2D and 3D formats. Well-established protocols exist for differentiating iPSCs into glutamatergic, GABAergic, dopaminergic and serotonergic neurons and various glial cell types representing different brain regions (Falk et al., 2016; Mertens et al., 2016; Silva & Haggarty, 2020; Whiteley et al., 2022). Deterministic forward programming methods, utilising specific transcription factors, offer a rapid and scalable approach to generating functional neuronal and glial cell types from either iPSCs or somatic cells such as fibroblasts and peripheral blood mononuclear cells (Flitsch et al., 2020; Mertens et al., 2016). Direct conversion (transdifferentiation) of somatic cells to neural cell types captures unique epigenetic signatures, unlike iPSC reprogramming (Mertens et al., 2016). These forward programming approaches exhibit faster neuronal development but produce only a single cell type, bypassing early neurodevelopmental stages, which is a consideration when studying mental health illnesses. However, limited availability of the tissue of origin and of somatic cells that do not self-renew pose challenges for studies using transdifferentiated cells. Another approach developed has been to pool iPSCs from multiple donors in a single dish. These ‘cell village’ model systems enable the scaling of experiments using iPSC-based models to sample sizes close to those required for population-scale studies (Jerber et al., 2021; Tegtmeyer & Nehme, 2022).

A key challenge in the study of brain function, especially in the context of mental health illnesses, is to investigate the interaction between multiple neural cell types. This includes understanding excitatory and inhibitory cell or neuron–glia interactions. To this end, new protocols and approaches for the co-culturing of multiple cell types in 2D are being developed and refined but are yet to be standardised across the field. A significant development in the iPSC field has been the development of multiple protocols to facilitate the intrinsic ability of iPSCs-derived neural cells to self-organise in 3D structures (Arlotta & Gage, 2023; Levy & Pasca, 2023; Pasca et al., 2022). These 3D cultures, known as brain organoids, exhibit remarkable capabilities in recapitulating key aspects of *in vivo* human neurodevelopment and faithfully representing the diverse cell types found in the brain (Chiaradia & Lancaster, 2020; Di Lullo & Kriegstein, 2017). The term brain organoid encompasses various strategies for generating 3D cultures, broadly categorised as guided or unguided approaches (Pasca et al., 2022). Recent advancements include the fusion of organoids from distinct brain regions (assembloids and i-assembloids (Levy & Pasca, 2023)), xenografting into animal models and the integration of neuronal and non-neuronal tissue organoids (Pasca et al., 2022; Wang et al., 2023). Collectively, co-culturing techniques and brain organoids represent promising advances in modelling the intricate interactions between multiple cell types, key for studying mental health illnesses.

1.1.2.2 Modelling mental health conditions using iPSCs

Broadly speaking, iPSC cells have been used in a ‘diagnosis-first’ approach, where iPSC lines are generated from patients selected based on their diagnosis, or a ‘gene-first’ approach, based on the study of specific genes and/or copy number variants (CNVs). Both approaches have been used to recapitulate known phenotypes and for the discovery of new phenotypes, which often require validation in patients.

Early studies using patient-derived iPSCs in a diagnosis-first approach exemplified how iPSC-derived neural cells could recapitulate phenotypes observed or predicted from genetic screens, human and post-mortem studies and animal models (Brennand et al., 2011). To date, patient-derived iPSCs have been used to study a wide range of diagnoses including schizophrenia, bipolar disorder, depression and post-traumatic stress disorder (PTSD), to name only a few (Bardy, 2019; De Los Angeles et al., 2021; Falk et al., 2016; Levy & Pasca, 2023; McNeill et al., 2020; Seah et al., 2023; Whiteley et al., 2022), furthering our understanding of potential causal mechanisms relevant for these complex disorders. As iPSCs capture the complex genetic landscape associated with mental health illnesses, they are often used to also assess genotype–phenotype relationships. This has been done in the context of genome-wide association studies (GWAS) and other large-scale genetic studies (Arlotta & Gage, 2023; Bardy, 2019; Brennand et al., 2012; Seah et al., 2023; Whiteley et al., 2022). For example, GWAS-based polygenic

scores have been proposed to help generate greater insight into the neurobiology of specific mental health conditions (Dobrindt et al., 2021; Muhtaseb & Duan, 2022; Page et al., 2022).

However, a challenge of such studies is that the heterogeneity of genotypes associated with mental health illnesses often produces weak or variable phenotypes (De Los Angeles et al., 2021; Dutan-Polit, 2023; Falk et al., 2016; Silva & Haggarty, 2020). To address this heterogeneity, some studies have begun to prioritise generating iPSCs from patients with a known genetic background, i.e. patients with a known genetic mutation or who carry specific CNVs. This makes it easier to assess genotype–phenotype relationships (Flaherty & Brennand, 2017; Muhtaseb & Duan, 2022; Rutkowski et al., 2017). However, as many genetic factors have been associated with multiple conditions, it can be hard to discern which phenotypes or mechanisms are causal for a specific diagnosis.

Human chromosome 22q11.2 illustrates the challenges of establishing causal genotype–phenotype relations. Deletions in this chromosome are the strongest genetic risk factor for schizophrenia (Sullivan et al., 2012) but individuals with 22q11.2 deletions can present with a variety of psychiatric outcomes (Fiksinski et al., 2023). While several studies have generated iPSCs from individuals with deletions in the 22q11.2 chromosomal region (Khan et al., 2020; Li et al., 2021; Nehme et al., 2022; Reid et al., 2022), these individuals had a range of diagnoses. Thus, one question is how deletions in this region drive specific mechanisms that contribute to specific mental health outcomes. Indeed, there is a growing appreciation of the complex interplay between penetrant rare variants, such as 22q11.2 deletions, and genetic background that may account for the diversity in observed clinical outcomes (Cleynen et al., 2021; Nehme & Barrett, 2020). It is also of note that deletions within the 22q11.2 region are not homogenous, and can differ between individuals, adding further complexities to such studies (Fiksinski et al., 2023).

To improve the predictive ability of diagnosis-first approaches, several studies have begun to consider mechanisms specific to subpopulations of patients. This includes the generation of iPSCs from patients who have been stratified based on their ability to respond to specific therapeutic compounds. Two examples employed iPSCs generated from bipolar disorder patients who are responders or non-responders to the mood stabiliser lithium (Mertens et al., 2015; Stern, Santos et al., 2018) – see also the case study on combining cellular and computational models to predict treatment responses – and from major depressive patients with divergent responses to selective serotonin reuptake inhibitors (Vadodaria et al., 2019). Such studies have begun to identify intrinsic differences between subgroups of patient populations (for an example, see the case study in section 1.5.1). Another strategy has been to stratify patient cohorts based on genetic background (polygenic score, calculated based on GWASs (Dobrindt et al., 2021)) for a specific mental health condition to study the impact of genetic background on disorder-related phenotypes (Page et al., 2022). Stratifying patients based on measurable *in vivo* physiological phenotypes (such as neuroimaging phenotypes) to identify from whom to generate iPSCs has also been done (Reid et al., 2022). However, to date, few studies have employed this strategy in the context of mental health illnesses.

Gene-first approaches, combining iPSC technology and gene-editing approaches, have significantly improved our understanding of how specific mutations or CNVs contribute to molecular and cellular phenotypes in human neural cell types (De Los Angeles et al., 2021; Flaherty & Brennand, 2017; Seah et al., 2023). By introducing specific gene mutations or CNVs into wild-type/healthy-donor lines, or correcting mutations or CNVs in patient lines, studies have facilitated a more robust linking of genotypes to molecular and cellular phenotypes (De Los Angeles et al., 2021; Flaherty & Brennand, 2017; Seah et al., 2023). However, as discussed above, genetic variations can be associated with multiple conditions. Therefore, while gene-first approaches enable a robust linking of genotypes to molecular and cellular phenotypes, it is not always clear how this relates to a specific diagnosis. For example, reciprocal rearrangements in the 16p11.2 chromosome region have been modelled in both isogenic cell lines and patient-derived cell lines (Parnell et al., 2022; Sundberg et al., 2021; Tai et al., 2022; Urresti et al., 2021). However, rearrangements of this chromosomal region have been linked with a range of mental health and neurodevelopmental outcomes. Interestingly, patient-derived iPSCs from individuals carrying 16p11.2 chromosomal duplications display subtle phenotypic differences with isogenic iPSC lines engineered to carry 16p11.2 chromosomal duplications (Parnell et al., 2022). Furthermore, phenotypic differences can be observed between iPSC lines generated from 16p11.2 duplication carriers who have distinct diagnoses (Parnell et al., 2022; Sundberg et al., 2021; Tai et al., 2022; Urresti et al., 2021; Yasvoina & Srivastava, 2023). These differences could be driven by additional variants within the genome, particularly disorder-relevant mutations (Yasvoina & Srivastava, 2023). Indeed, there is evidence from genetic studies that polygenic burden is associated with psychiatric outcome in patient cohorts (Bergen et al., 2019; Cleynen et al., 2021; Mariani et al., 2021).

1.1.2.3 Studying gene-environment interactions and drug discovery in iPSC models

IPSC-based models have also been used to model how gene × environment interactions contribute to mental health illnesses. The study of how pro-inflammatory cytokines such as IFNγ or IL-6 impact neurodevelopment, using iPSCs, has begun

to uncover potential mechanisms by which maternal infections could increase the likelihood of mental health illnesses. These studies have taken advantage of both the generation of specific cell types (thus giving insight into cell-specific mechanisms (Couch et al., 2023; Warre-Cornish et al., 2020)) and brain organoids (Sarieva et al., 2023) to better understand the effects of cytokines in a more complex cellular system. Similar studies have been conducted using brain organoids to understand how glucocorticoid influences physiological and pathophysiological brain development (Cruceanu et al., 2022). Use of patient-derived iPSCs has begun to further reveal how the genetic background associated with schizophrenia can alter the response of cells to cytokines, providing a nuanced insight into how genetic factors could influence the impact of pro-inflammatory cytokines on the development of neurons (Bhat et al., 2022). Similar studies have also been conducted using iPSCs derived from combat veterans with PTSD to model gene × environment interactions (Seah et al., 2022).

Drug discovery studies increasingly employ iPSC-based cellular models. This is an area of intense biopharmaceutical industry investment (e.g. Roche and pRED; a:head; bit.bio (Kleiman & Engle, 2021; Silva & Haggarty, 2020)). Specifically, iPSC-based models have been used in high-throughput screening platforms and have demonstrated translational potential (Haggarty et al., 2016; Silva & Haggarty, 2020; Stern, Linker et al., 2018). Patient-derived iPSCs have also been effectively used in expression-based drug-screening studies to identify candidate compounds for testing (Readhead et al., 2018). Additionally, the mode of action of drugs in a human cellular context can be studied using iPSC-based models (e.g. ketamine – (Cavalleri et al., 2018)). However, to date few studies have utilised patient-derived iPSC lines to investigate whether the mode of action differs in a neuron that harbours a genetic background associated with specific disorders.

1.1.3 Gaps and opportunities

While the use of iPSC-based models has shown great promise in the investigation of (causal) mechanisms for mental health illnesses, there are several key challenges that are yet to be fully met. A major challenge is how to disentangle the causes of observed phenotypes and understand the underlying mechanisms. Variability and weak phenotypes have necessitated the use of multiple patient and healthy iPSC lines to identify robust phenotypes. Sources of variability include technical factors such as iPSC quality and differentiation protocols, as well as biological factors driven by the donor's genetic background (Anderson et al., 2021; De Los Angeles et al., 2021; Dutan-Polit, 2023; Engle et al., 2018; Rivetti di Val Cervo et al., 2021). The importance of considering additional factors such as biological sex or ancestry is emerging in iPSC study designs (Dutan-Polit, 2023; Engle et al., 2018; Steeg et al., 2021; Tegtmeyer & Nehme, 2022).

It is also crucial to consider the most relevant and disorder-specific phenotypes. Moreover, developing standardised phenotypic pipelines for biochemical, imaging and physiological measurements in iPSC-based models is important. This will enable a better understanding of how to link cellular based observations with those seen in humans. In a similar regard, it is important to consider the relevance of drug concentration, pharmacological dynamics, therapeutic doses and treatment intervals in drug discovery studies using iPSC-based models. Understanding the concentration of the drug within the brain and its effects over time is essential, as beneficial effects may require multiple doses.

Overall, further advancements in iPSC research require refining study design, standardising protocols, considering disorder-specific phenotypes, integrating biological diversity, investigating gene–environment interactions and exploring temporal dynamics of phenotypes. These efforts will enhance our understanding of mental health illnesses and contribute to the development of effective treatments.

1.2 Animal models for mental health

1.2.1 Background

Since the serendipitous discoveries of pharmacological agents that were shown to be clinically effective in mental disorders in the mid-20th century, animal models have played a central role in attempts to understand the underlying biology and develop new treatments for these conditions. Subsequent laboratory work elucidated the mechanisms of these psychoactive drugs and set the stage for advancements in our understanding of the brain mechanisms underpinning psychological processes and affective states. In recent years, there have been dazzling advances in the precision with which we are able to probe and intervene in brain function.

Nevertheless, despite a huge investment of resources in preclinical animal models over the past 70 years, a dearth of conceptually new treatments is widely acknowledged. Moreover, despite the notable advances in our knowledge of the genetic, molecular, cellular and circuit function and dysfunction implicated in anxiety, depression and psychosis, the biological basis of these disorders is far from clear and even our understanding of how efficacious treatments work to alleviate symptoms is not

resolved. The difficulty in translating our rapidly expanding scientific knowledge into new and effective therapeutic strategies resulted in many pharmaceutical companies retreating entirely from psychiatric drug discovery.

This lack of progress is not for lack of endeavour. A PubMed search for articles referring to animal models and mental health conditions returned over 16,600 results, approximately 75 percent published since 2007. This striking disconnection between the volume of research and tangible advancement of new treatments has led some to question the foundational rationale for trying to use animals to develop treatments for complex human conditions. As pointed out by Garner (2014), every drug entering human trials has, by definition, “worked” in an animal model in terms of both safety and efficacy, yet a large majority (>90%: Hay et al., 2014) fail to make it to market.

However, given the wide consensus that mental health conditions result from specific changes in underlying brain biology, and the challenges of investigating human brain function with high precision, a more widespread perspective is that we must improve the quality of our animal models (e.g. Bale et al., 2019; Belzung & Lemoine, 2011; Kas et al., 2019; Monteggia, 2016; Monteggia et al., 2018; Phillips et al., 2018; Pratt et al., 2022). In this spirit, sections 1.2.2 and 1.2.3 will examine how animal models have been used to further our understanding of mental health conditions, concentrating on anxiety, depression and psychosis, describing how they have been employed and evaluated to date, and highlighting key advances as well as areas that require further development.

1.2.2 State of the field

While the ultimate goal of any research using animals is to facilitate the fundamental understanding of human mental health conditions and to spur the development of new treatment approaches for humans, the ways animal models are used to navigate towards this goal can be distinct. The following sections will outline some of the most widely used approaches.

1.2.2.1 How animal models are used in mental health research

Preclinical animal models have been used to focus on understanding key features of psychological processes and neural systems relevant to a given condition or conditions, leveraging genetic tools and new technologies that enable researchers to monitor and manipulate brain activity with high precision from genes to cells and circuits during complex behavioural tasks (see also section 1.4). Animal models also allow researchers to test hypotheses about the causal role of genetic and environmental factors linked to disorders. This can involve examining how interfering with specific genes and molecules implicated in anxiety, depression or psychosis affects disease-related outcomes in highly controlled environments (e.g. Barkus et al., 2014; Baud & Flint, 2017; Farsi & Sheng, 2023; Harrison et al., 2012; Johnson et al., 2006; Planchez et al., 2019), or investigating whether environmental challenges such as stressors, known in a subset of individuals to trigger or exacerbate mental health conditions, can prompt presentation of disease-like phenotypes (e.g. Arnsten et al., 2023; Bale et al., 2019; McEwen & Akil, 2020; Richter-Levin et al., 2019; Schmidt et al., 2011).

Preclinical animal models have also been utilised to try to unravel and refine treatment mechanisms such as those of promising and innovative rapid-acting antidepressants (e.g. ketamine (Lopez et al., 2022) and psychedelic compounds (Meccia et al., 2023)). A second critical role for animal models is in screening novel pharmacological agents. A third use is to investigate how to close the gap between technologies that allow exquisite control over brain function in animal models, usually through invasive procedures, and the comparatively imprecise tools available to clinicians (Bansal et al., 2023; Dandekar et al., 2018; Marton & Sohal, 2016; Rao et al., 2019; Spix et al., 2021).

Although a range of species has been used, from vertebrates such as zebrafish to non-human primates, most research has utilised rodents, particularly mice. This is in part because it is straightforward to manipulate their DNA and generate genetic models, allowing detailed study of the effects of candidate genetic substrates on biology and phenotypes. There is wide-ranging evidence that genetic risk factors, shared between mice and humans, play an important role in the aetiology and pathogenesis of mental health conditions, most clearly in psychosis, although evidence is also emerging in depression and anxiety (Flint, 2023; Griebel & Holmes, 2013; Koskinen & Hovatta, 2023; Schizophrenia Working Group of the Psychiatric Genomics, 2014; Trubetskoy et al., 2022). There are also clear structural and functional equivalents between rodent and human brains, particularly across limbic circuits that regulate motivation, emotion and autonomic processes. An analysis by Howe and colleagues found that all the top-selling neuropsychiatric drugs indicated for treatment in humans by the Food and Drug Administration in the USA were efficacious in at least one standard mouse model behavioural assay (Howe et al., 2018). Nonetheless, brain anatomy differs in important ways between rodents and primates, particularly in prefrontal and cingulate regions (Ma et al., 2022; Wise, 2008). Given the wealth of evidence for abnormal activity patterns in cortical-centred circuits in a variety of neuropsychiatric conditions, cross-species studies including non-human primates have made and will continue to make a crucial contribution in facilitating a translational pathway from animal models to humans.

1.2.2.2 Using behaviour as a window onto mental health conditions

Behavioural phenotyping has been a core component of modelling anxiety, depression and psychosis in animals for many decades. A wide variety of behavioural assays have been developed in animals to help screen novel drugs (e.g. the forced swim test to test antidepressant potential for monoaminergic compounds) and to model particular underlying symptoms associated with these conditions in humans. For pragmatic reasons, many of these bioassays were designed to be simple to administer, to require little if any training of the animals and to provide easily interpretable readouts, and therefore to be high throughput. However, there is concern that this has promoted drug development to treat specific clinical symptoms over remedying underlying mechanistic causes of conditions or tackling debilitating symptoms that are harder to model using such tests (Gururajan et al., 2019; Robinson, 2018). The apparent simplicity of the behavioural readouts in these assays is also a potential pitfall. First, this renders them prone to be influenced by small differences in experimental protocol or laboratory conditions (Ennaceur & Chazot, 2016; Fisher & Bannerman, 2019; Headley et al., 2019). Second, it makes it challenging to determine whether the observed behaviour accurately models the targeted cognitive process or emotional state in humans and therefore whether a change in the observed behaviour following an intervention might be clinically relevant (Fisher & Bannerman, 2019; Jackson & Robinson, 2022).

One response to this has been to explore more ethologically relevant measures of complex behaviours, for example, utilising advances in home-cage monitoring to enable behavioural and physiological measurements of group-housed animals to be collected over extended time periods without experimenter intervention (Bains et al., 2016; Chaumont et al., 2019; Forkosh et al., 2019; Shemesh et al., 2013; Ziegler et al., 2021). Another approach has been to focus on using richer behavioural paradigms, grounded in an increasingly sophisticated understanding of psychological processes and the control of behaviour, which can be applied both in animal models and in clinical populations (Corlett & Schoenbaum, 2021; Headley et al., 2019; Jean-Richard-Dit-Bressel et al., 2018; Oikonomidis et al., 2017; Redish et al., 2022; Robbins, 2015; Robinson, 2014; Rutherford & Milton, 2022). While both require greater investments in resources and involve a step-change in complexity, there is increasing consensus that such methods are advancing our understanding and can ultimately greatly improve the translation to human conditions.

1.2.2.3 Perspectives on progress through use of animal models

To date, animal models have played a pivotal role in increasing our understanding of the biology of disease-relevant genes and predisposing factors such as stress, and of the neural mechanisms implicated in aspects of motivation, cognition and arousal, which can be altered in anxiety, depression and psychosis. For example, there has been a rich seam of research into how the brain and body react during aversive conditioning and situations that engender approach-avoidance conflict in animals as a window onto mechanisms of anxiety- and fear-related disorders (Ball & Gunaydin, 2022; Jean-Richard-Dit-Bressel et al., 2018; Kenwood et al., 2022; Mitchell et al., 2000; Pittig et al., 2018; Ressler, 2020; Roberts, 2019). This work builds on decades of fundamental experimental and theoretical research into hippocampus function (Barkus et al., 2014; Behrens et al., 2018; Eichenbaum, 2017; Moser et al., 2008; O'Keefe & Nadel, 1978), translated to humans (Bach et al., 2014; Y. Liu et al., 2021; Schuck & Niv, 2019), which is now being used to probe altered processing in mental health conditions (McFadyen et al., 2023; Nourizonoz et al., 2020).

Important insights have been gained into how different psychological processes relevant to anxiety, depression and psychosis are supported by distinct brain networks, sometimes even originating from within the same region. For example, disrupting pathways from the subcallosal cingulate cortex, a region of interest as a target for deep brain stimulation in depression (Holtzheimer & Mayberg, 2011; Ressler & Mayberg, 2007), to either the nucleus accumbens or the amygdala in marmosets had dissociable effects on measures relevant to anhedonia or anxiety, respectively (Wood et al., 2023). Strikingly, activation of pathways from the rat medial frontal cortex to either the dorsal raphe nucleus, which contains a substantial proportion of the brain's serotonin cells, or to the lateral habenula, a potential mediator of the rapid antidepressant effects of ketamine (Yang et al., 2018), has opposite effects on behavioural activation in the forced swim test (Warden et al., 2012).

While the development of behavioural assays of psychosis-relevant symptoms has lagged behind those for anxiety and depression (though see section 1.5.2 for an example of how computationally-inspired cross-species approaches are opening up new avenues for research), mouse models with disrupted schizophrenia-risk genes, such as those encoding specific NMDA and AMPA receptor subunits, have greatly enhanced our understanding of how these influence underlying neurobiology and psychological processes relevant to psychosis (Barkus et al., 2014; Farsi & Sheng, 2023). Animal models have also enabled the mechanisms of action of efficacious drugs to be determined and new drugs with improved side-effect and safety profiles to be developed (Brown & Wobst, 2022; Casarotto et al., 2021; Hillhouse & Porter, 2015; Lieberman et al., 2008; Scangos et al., 2023).

Nonetheless, there is widespread acknowledgement that work in animal models has not often succeeded in advancing new treatments. As described by Monteggia (2016), "we have cured depression endless times in rodents without clear advances

in diagnosis or patient treatment". Our understanding of how the biochemical actions of clinically effective drugs work to alleviate neuropsychiatric symptoms remains rudimentary.

One perspective is that it is perhaps unrealistic to expect animal models to have met this criterion for successful translation. Anxiety, depression and psychosis are hugely complex, heterogeneous conditions, with diverse causes and symptoms, that are still not well understood in humans. As Bale and colleagues (2019) highlight, it has taken over four decades of painstaking research to advance precision medicine in cancer and immunology, where the underlying biology is much more tractable to research in animals than human mental health conditions and the mammalian brain. It is easy to overlook that when the first mainstream psychiatric drugs emerged in the early 1950s, not only did we not understand their biological mechanisms, but also many key neurotransmitters such as dopamine had yet to be discovered.

However, many within the field actively question whether the current utilisation of animal models may be stymieing progress towards developing disease-relevant interventions and whether a shift in approach is therefore needed.

1.2.3 Gaps and opportunities

The rapid revolution in technologies over the past decade in neuroscience, allied with computational approaches to dissect underlying processes in healthy and dysfunctional states (see section 1.3), is propelling an increasingly sophisticated, mechanistic understanding of how widespread circuits in the brain support cognition and emotion. As mental health conditions result from specific changes in underlying brain biology and it is unlikely in the foreseeable future that the resolution of non-invasive methods for manipulations and measurements of human brain activity will match the precision achieved using invasive methods, a need remains for research in animal models to develop a molecular-, cellular- and circuit-level understanding of the biology of human conditions and mechanisms of efficacious treatments. There is optimism that, in time, this can be foundational to new, precision approaches to allow early detection, prevention and individually tailored treatment for psychiatric conditions.

However, alongside this viewpoint, there is a widespread belief in a pressing need to improve how we employ preclinical animal models if we want to advance our understanding of mental health conditions and foster improved translation from the laboratory to the clinic. Though the evolutionary distance between animal model systems and humans is raised as a potential fundamental hurdle to progress (some of which may be circumvented through use of cellular models, as described in section 1.1), a more prevalent position is that, while current animal models have some critical shortcomings in how they recapitulate key features of anxiety, depression and psychosis, tangible opportunities to advance translatability exist (Bale et al., 2019; Garner, 2014; Pratt et al., 2022; Redish et al., 2022; Spanagel, 2022).

As will be described in detail in section 2, one common theme is the need to ensure animal models better capture aspects of the complexity, variability and time course of symptoms observed in anxiety, depression and psychosis. For example, most preclinical research has been done in male animals to avoid potential variability introduced by the hormonal cycle. This has led to a lack of in-depth consideration of how sex differences and sex hormones might affect and be implicated in disease mechanisms (Eid et al., 2019), which, given that conditions such as anxiety and depression disproportionately affect women, has significant ramifications. To do this will require stepping back from long-held practices that have aimed to minimise individual differences; to do this successfully will therefore potentially necessitate standards for how to validate, report, run and replicate studies using animal models. This will be facilitated by consideration of the barriers that currently hinder productive cross-species work, to enable smoother transitions between experienced symptomology in human patients and fine-scale work in animals to understand the underlying biology. Crucially, there will need to be sharper focus on richer, high-quality behavioural and physiological phenotyping. Together, this can facilitate the development of better explanatory frameworks, opening the door to improved biomarkers of risk and successful clinical target engagement.

1.3 Computational models for mental health

1.3.1 Background

Computational models are increasingly being used to study the brain and mental health. These models primarily come from the field of computational neuroscience. A long-standing field, computational neuroscience has existed since the work of William James in the late nineteenth century, propelled by Donald Hebb in the 1940s and was well-ensconced as an intersectional discipline with the establishment of the International Neural Network Society in 1987. The general issues addressed by the field are how neurobiological elements process information and how computational models can simulate mechanisms that underpin observed data (Corlett et al., 2019; Horne et al., 2022; Huang et al., 2019). An often-rehearsed taxonomy that captures

the breadth of study considered is the spatial scale at which the model is aimed, from synaptic, neuronal, circuit- or map-based to system-level information processing (Churchland & Sejnowski, 1992; Maia & Frank, 2011).

Computational psychiatry, as a younger, decade-old endeavour, attempts to harness the formal descriptions provided by computational neuroscience to probe the algorithmic and neurobiological alterations that manifest in psychiatric disorders (Friston et al., 2014; Montague et al., 2012; Wang & Krystal, 2014). It is also concerned with aberrant information processing at each of these scales. The field of computational psychiatry has gone through exponential growth in the past decade. Still considered a nascent field, computational psychiatry has two main objectives: (1) understanding mental function and dysfunction at the algorithmic level; and (2) predicting clinically relevant variables (e.g. antidepressant response) by leveraging large-scale data mining and tools such as machine learning. Despite its relatively short history, computational psychiatry is now its own dedicated field, with a sizeable community, dedicated workshops and conferences, and increased amounts of funding across many agencies. Across the board, computational psychiatry has greatly enhanced and fostered the cross-talk between computational scientists, clinicians, cognitive scientists and neuroscientists. At the scientific level, more updated and newer understandings of the brain in health and disease have emerged largely due to the power and clarity of computational models. Clinically, although computational psychiatry has yet to generate new treatments or therapies, model-driven approaches are now expediting our understanding of how existing treatments work.

Arguably, the psychiatry focus of the type of computational models discussed here will eventually call for more concrete definitions of the observable symptoms of psychosis, depression and anxiety. To date, the levels of human behaviour, neural system and, in some instances, circuit, have emerged as the predominant scale of analysis, using computational cognitive models allied with human brain imaging data (Braun et al., 2021; Clementz et al., 2020; Shen et al., 2023). However, computational psychiatry is also attempting to co-opt research all the way from synaptic-level models to the systems level (Datta & Arnsten, 2018; Elibol & Şengör, 2021; Friston, 2023; Wang & Krystal, 2014) to address the roadblocks that exist in progressing mental health research, including issues around the lack of new and optimised pharmacological and non-pharmacological therapies, and issues around diagnostic labelling and patient heterogeneity, or ‘precision psychiatry’.

If the pinnacle of this research were to provide a complete, patient-based brain model from the cellular scale to emergent behaviour, the outcome could be a personalised intervention test platform where the simulation of distinct therapies could be performed and selected to treat a particular set of symptoms. This effort is ongoing, however; even this framework may suffer from key omissions around the social and environmental impact on brain processes impacted by the disorder, by virtue of how we organise our tests of aberrant behaviour and their link to symptomologies. Nevertheless, compelling advances that have begun to link human brain imaging data (macroscopic functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG) and electroencephalography (EEG)) from people with mental health illnesses to behavioural abnormalities formalised by a model suggest that the direction of travel can unlock a new era in clinical psychiatric practice.

1.3.2 State of the field

Computational psychiatry primarily entails two major classes of computational model. The first is theory-driven and is considered a ‘top-down’ approach for hypothesis testing. Its models rely heavily on Marr’s tri-level of analysis framework (Marr & Poggio, 1976). According to this framework, understanding intelligent systems such as the human brain requires considering multiple levels of explanation: the system’s goal (“why”), the algorithmic level (“how”), and the physical implementation (neural substrates, “where”). This influential idea provides a blueprint for mapping the relationship between computations, behaviour and neural substrates, shaping the landscape of computational psychiatry today. Theory-driven models involve explicit theory-based hypothesis testing and require neurobehavioral data collected under controlled experimental paradigms. There are three major types of theory-driven models – reinforcement learning, Bayesian, and biophysical models – which we will briefly discuss in sections 1.3.2.1–1.3.2.3.

The second major class of model frequently used in computational psychiatry is machine learning (section 1.3.2.4). Its models are used in a data-driven, ‘bottom-up’ fashion to identify features or patterns that might be indicative of psychiatrically relevant variables (e.g. treatment response). There are two main types of machine learning approach: unsupervised and supervised learning. Unsupervised learning uncovers hidden structures in unlabelled data and can be used to identify subtypes of participants (e.g. melancholic vs. anxious vs. anhedonic patients with depression). Supervised learning requires a training dataset to learn patterns and make predictions on unseen data. For example, algorithms such as support vector machines and neural networks can predict treatment responders vs. non-responders.

Theory-driven and data-driven approaches are complementary and the integration of both would lead to important new insights into the mechanisms of addiction. Both approaches have already yielded fruitful findings, which we review below.

1.3.2.1 Reinforcement learning approaches

Reinforcement learning, often used to study reward- and punishment-based decision-making processes, has been one of the most popular types of models in computational psychiatry research. In a nutshell, reinforcement learning models are constructed based on the idea that agents – such as humans – learn the values of stimuli, update these values based on the mismatch between observed outcomes and their expectations (prediction error), and adjust their choices in the future to optimise behaviour (Sutton & Barto, 1998). In model-free reinforcement learning, we assume that people learn based on trial and error and use cached values of their choices for value updating. In a more sophisticated type of reinforcement learning – model-based learning – learning is no longer based on reward prediction errors alone; instead, people form a mental simulation of future states, predict the transition probabilities between states and calculate state prediction errors to optimise future decisions (Botvinick, 2012; Daw et al., 2011).

Collectively, these reinforcement learning models represent a substantial body of work within computational psychiatry that focuses on learning and decision-making dysfunction across many psychiatric disorders (Maia & Frank, 2011). There are several key computational parameters that can be readily interpreted. Learning rate, for example, represents how fast a person updates predictions based on prediction errors and is often used as the computational proxy for sensitivity to positive and negative stimuli. The connection between reinforcement learning, key neurotransmitters such as dopamine and serotonin, and mesolimbic structures such as the ventral tegmental area, striatum and ventromedial prefrontal cortex (Daw et al., 2002; Dayan & Huys, 2009; Niv et al., 2005; Rushworth et al., 2012), makes learning rate suitable for translational work across rodents, non-human primates, and humans.

Reinforcement learning models are frequently used to study conditions with aberrant valence processing, such as mood disorders. Depression has been the condition most frequently associated with reinforcement learning alterations, because reduced sensitivity to reward (i.e. anhedonia (Husain & Roiser, 2018; Treadway & Zald, 2011)) is one of its key symptoms. Using computational modelling, previous work has shown that the reward learning rate has also been shown to correlate with the severity of anhedonia (Brown et al., 2021; Chase et al., 2010). A recent meta-analysis of 27 studies that provided computational estimates suggests that people with mood disorders (depression and anxiety) showed an enhanced punishment learning rate but an only modestly reduced reward learning rate (Pike & Robinson, 2022). Research has also started to examine the impact of depression on model-based reinforcement learning and reported initial evidence that impaired model-based computation might be associated with depression (Blanco et al., 2013; Heller et al., 2018; Heo et al., 2021). These models are now also being used in research on schizophrenia (Strauss et al., 2011; Waltz et al., 2007), obsessive-compulsive disorder (Gillan et al., 2016), addiction (Gueguen et al., 2021; Redish, 2004) and personality disorders (Gregory et al., 2015). We are yet to see how reinforcement learning might help delineate the different choice behaviours across psychiatric conditions.

1.3.2.2 Bayesian approaches

Bayesian models represent another major approach for quantifying cognition and behaviour in computational psychiatry. Briefly, Bayesian models assume that individuals try to infer the underlying causes of their perceptions and update their beliefs based on both prior expectations (known as a Bayesian prior) and the incoming sensory evidence (likelihood) in a Bayes-optimal way (Doya, 2007; Knill & Pouget, 2004). An enactive form of Bayesian inference, called active inference, further suggests that an agent could act on the world in order to minimise the mismatch between its predictions and sensory evidence (Adams,Shipp et al., 2013; Friston et al., 2011; Pezzulo, Barca et al., 2015). The Bayesian framework is frequently used in accounting for how people form perception and beliefs under uncertainty, as Bayes' theorem takes into account the uncertain nature of the world by constructing sensory evidence and subjective estimates of them as probabilistic distributions. Importantly, Bayesian approaches also provide a natural candidate accounting for subjective states (Gu et al., 2019). As such, Bayesian models offer an important complementary view to reinforcement learning in computational psychiatry, as altered perception and beliefs are key to many psychiatric disorders (Brown et al., 2013; Edwards et al., 2012; Lawson et al., 2017; Lawson et al., 2014; Van de Cruys et al., 2014).

Psychosis represents one of the most fruitful areas of research for the Bayesian framework (see also the case study on hallucination-like percepts below*)*. Common across all psychotic disorders (including schizophrenia), psychosis refers to a condition in which individuals feel disconnected from reality and experience symptoms such as hallucinations, delusions and disorganised thinking. Bayesian inference becomes a natural candidate that can account for the aberrant percepts and beliefs found in psychosis (Adams, Stephan et al., 2013; Brown et al., 2013; Edwards et al., 2012; Friston et al., 2012). Specifically, it has been hypothesised that faulty inference leads to false concepts (delusions) and percepts (hallucinations) in psychosis. This faulty inference is hypothesised to be caused by reduced precision (increased uncertainty) in an individual's prior beliefs, which results in misattribution of sensory data and inaccurate posterior beliefs. At the neural level, this precision dysfunction has been linked to post-synaptic gain of neurons encoding prediction errors, which might be attributed to hyper dopamine tone and

hypofunctioning of NMDA receptors (Adams, Stephanet al., 2013; Sterzer et al., 2018). Despite its explanatory power, this framework does not work well with all the symptoms in psychosis. Negative symptoms (e.g. flat affect) and cognitive symptoms, for example, are not yet readily explained by the Bayesian account. Furthermore, the highly variable treatment response and prognosis are not well understood (Dempster et al., 2020; Fond et al., 2015; Levine & Rabinowitz, 2008).

1.3.2.3 Biophysical models

Crossing scales of brain function using biophysical models is a task that has been undertaken for the last 20 years in animal and human studies (Brunel & Wang, 2001). Such models serve as a template of how to study behaviour (e.g. executive function) in animals and humans with the goals of understanding the behavioural and cognitive outputs while measuring – through the model – their neural substrates (Bianciardi & Uhlhaas, 2021). The objective of these models is, in other words, to link cognition and behaviour to mechanisms within the circuits and cell types involved. These biophysical models have been recently updated to become generative models for task-based fMRI and incorporate distributed large-scale networks commensurate with activity patterns on the whole cortex (Torres-Gomez et al., 2020). These models include important circuit features such as recurrent connectivity and differences between feedforward and feedback projections to reproduce empirical patterns of activations (Mejías & Wang, 2022), with new work even incorporating second order level neurotransmitters such as dopaminergic receptor densities (Froudist-Walsh et al., 2021). Thus, these models are moving closer to unravelling the complex network pathologies involved in mental health conditions (e.g. identifying putative fault lines in the combined circuits of the neocortex and subcortical dopamine).

Biophysical models can be refined by focusing on cognitive tasks, which limits the regions involved in the processing (Huang et al., 2019; Mejías & Wang, 2022). In this task-based context, modulation of local activity can be combined with region-to-region connections and include parameters that code for local cell processing within an assembly (e.g. specific interneurons). A key challenge in the study of brain function in the context of mental health illnesses is to investigate the interaction between multiple neural cell types. These models provide that need and add a layer of local neurobiology to the node-to-node models more prominent in resting state fMRI. Moving down in scale to microcircuit models, studies have dissected the functional consequence of particular cell vulnerability and have been important in the understanding of the developmental aspects of schizophrenia (Krystal et al., 2017). A critical advantage of these models is the prescription of local wiring, e.g. of how distinct interneurons signalling to principal neurons break down in schizophrenia. These local models thus show how cell sensitivity may make circuits vulnerable to disease and provide testable hypotheses for empirical study in animal or cellular models.

At a more compact (spatially small) circuit scale, biophysical models of electrophysiology have proven useful in dissecting interactions between distinct brain regions. One prototypical pair of regions and their coupling involves prefrontal–hippocampal interactions. Synchrony between these two structures during exploration and goal-directed tasks emerges in local field potentials in certain frequency bands. Importantly, these frequency features can be measured in both animals and humans (Koshiyama et al., 2020, 2021) and also, potentially, in organoids. Deploying biophysical models of this data has helped to unpack how disruptions of timed oscillations lead to features that occur in disorganised cognition. For example, nested oscillations are disrupted with mutations of the schizophrenia-risk gene Gria1. In animal mutants, theta coherence appears enhanced compared with wild-type animals, indicative of a failure to regulate selective attention (Bygrave et al., 2019). The importance of these electrophysiological oscillations is that they relate to other computational models more generally, such as those related to planning in the hippocampus (Kurth-Nelson et al., 2023; Yunzhe Liu et al., 2021). They thus help to understand how disorganised thoughts in schizophrenia may emerge, in part, as a failure of region-to-region temporal organisation (Speers & Bilkey, 2021, 2023).

Biomarkers can be emergent features of biophysical models and enable linking of a disorder's 'signature' (the biomarker) to a mechanism (a cellular or circuit component). For example, gamma band (high frequency) electrophysiological activity has a long, albeit complex literature in the study of schizophrenia (Bianciardi & Uhlhaas, 2021; Hirano & Uhlhaas, 2021; Shaw et al., 2020). Depending on the stage of the disorder, it can appear in patients as a hyperactive or hypoactive signature of aberrant brain activity. Using a biophysical model, Sherif et al. (2020) tried to understand what the cellular constituents of this aberrant activity may be. Using a high-dimensional neuronal model of a hippocampal subfield, their microcircuit model tested whether aberrant gamma emerges from three potential pathological mechanisms (modelling the effects of NMDA, HCN1 and GABA receptors). All three had impacts on the gamma activity in the hippocampus in distinct ways, suggesting that the model may serve as a test of appropriate pharmacotherapies, i.e. for precision medicine in schizophrenia. This neuron-level model highlights the early potential of using biophysical simulation to predict patient-specific pharmacotherapies.

Biophysical models offer great potential in linking animal and cellular models with human research. Using this 'virtuous triangle' of models, we may better understand and treat mental health conditions in humans. What is lacking is more high-

resolution data from humans to validate these models against. Connecting this research or 'back translating' to cellular and animal investigations will improve impact and accelerate application.

1.3.2.4 Machine learning (statistical) models

The field of computational psychiatry has been regarded as a 'two cultures' field – with one set of experiments around the process and necessitating explanatory models (as discussed in sections 1.3.2.1–1.3.2.3) and another based more on machine learning that can be black-box and data-driven, for example, to predict a particular treatment outcome (Bennett et al., 2019). Although formal theories and particularly those of computational processing are, in the long run, how we will refine and interpret purely data-based approaches (Maia et al., 2017), machine learning, in the short term, can help achieve pragmatic goals for clinical psychiatry (Steele & Paulus, 2019). Studies using machine learning in the context of computational psychiatry typically aim to subtype patients (Drysdale et al., 2017) or identify biomarkers that are predictive of a certain clinical variable (Sajjadian et al., 2021), instead of discovering new mechanisms of behaviours and disorders. To date, treatment outcome might be the most clinically relevant and most frequently examined clinical variable in machine learning studies in psychiatry. Among these studies, depression is again the most frequently examined due to its high prevalence and data availability as a result of several large clinical trials (see (Sajjadian et al., 2021) for a systematic review and meta-analysis).

Many of these studies have relied on purely demographic and clinical data to predict antidepressant response (Chekroud et al., 2016; Webb et al., 2020), primarily due to the easy access to such data. However, these models are usually difficult to interpret, as the number of input variables is usually very large and the resulting output features can still be of high dimensionality (e.g. similar to GWAS). Furthermore, as the selection of input features can drastically influence the output of predictive features, it is thus very difficult to compare results from different machine learning studies even when predicting the same outcome variable.

Large-scale machine learning studies using neural measures have started to emerge as a result of the adaptation of these methods in clinical patient studies. The literature shows that even in the absence of formal models that link the brain to symptoms, models of a data-driven sort – e.g. imaging data that uses advanced computational or machine learning approaches – have a key role to play (Bennett et al., 2019). Among these, EEG has been one of the most commonly used neural measures and has shown added utility for machine learning, compared with using demographics and clinical variables alone (Rajpurkar et al., 2020), and has also displayed increased predictive accuracy (Zhdanov et al., 2020). Functional MRI (fMRI) time series, combined with machine learning, have revealed that brain-based indices such as regional sample entropy (Shen et al., 2023) and functional connectivity (Kulkarni et al., 2022) could provide decent sensitivity for clinical predictions. Moreover, brain imaging studies that track longitudinal change in patient data is another application of machine learning methods. These studies seek to address the cascade of pathology and use unsupervised machine learning to identify clusters based on certain brain imaging metrics. For example, Shen et al. (2023) showed that using functional imaging data transformed using computational models was most sensitive to early disease identification. This model-based analysis was more sensitive than more typical anatomical metrics which could only identify patients from controls many years after diagnosis. This sort of analysis shows that computationally advanced machine learning methods may enhance the sensitivity of imaging-based methods to assess trajectories of mental health conditions (Schwarzer et al., 2022).

1.3.3 Gaps and opportunities

Despite its relatively short history, computational models have shown impressive success in terms of expediting our understanding of psychiatric mechanisms and treatment responses. Reinforcement learning has provided a foundational framework for cross-species investigations into learning and decision-making and how these are differentially altered in anxiety, depression and psychosis; Bayesian approaches have advanced our understanding of perception, beliefs and subjective states and lent new insight into a core symptom of psychosis; biophysical models provide a bridge from mental health conditions to changes in neural circuit function; and machine learning has provided insight into potential biomarkers for treatment stratification, such as antidepressant responses.

However, the challenges facing computational neuroscience and psychiatry are also evident. As a starter, theory-driven research often focuses too much on reinforcement learning and monetary reward-based tasks, ignoring the potential mismatch between these highly abstracted laboratory paradigms and complex real-life behaviours in humans with mental health illnesses. This might explain – at least partially – why empirical findings on depression have reported either no difference in reward learning rate (Gradin et al., 2011), reduced reward and punishment learning rates (Chase et al., 2010) or intact reward but reduced punishment learning rates (Dombrovski et al., 2010) in people with depression compared with controls (see (Chen et al., 2015) for an in-depth review). At the neural level, findings are even more mixed, with both decreased and increased activations related to prediction errors in different parts of the brain even in the same study (see (Chen et al., 2015) for a review).

Bayesian models that aim to examine perception and beliefs are often difficult to falsify and are not examined against participants' actual, self-reported beliefs (i.e. are not necessarily designed to assess their actual individual delusions or hallucinations). Despite its explanatory power – even in the context of psychosis, the Bayesian framework does not work well with all symptoms of psychotic disorders. Negative symptoms or cognitive features, which are crucial to remedy for the improved everyday lives of patients, have not been fully addressed within the Bayesian framework. Furthermore, the highly variable treatment response and prognosis are not well understood (Dempster et al., 2020; Fond et al., 2015; Levine & Rabinowitz, 2008).

In addition, many machine-learning-based studies lack interpretability or mechanistic explanations, such as those primarily relying on electronic medical records. For treatment response prediction, the overall predictive accuracy remains moderate (e.g. ranging from 56%–69% for studies with adequate power and methods, depending on the exact outcome measure chosen (Sajjadian et al., 2021)). This calls for larger sample sizes, more diverse datasets and the harmonisation of brain and cognitive measures in future machine learning studies.

Finally, computational paradigms, models and theories in clinical trials remain scarce, impeding the translation of research findings to mental healthcare. Looking ahead, computational models of the brain and behaviour urgently need to address these issues to reach their full potential.

1.4 Building a common understanding: What is a model?

In research into mental health illnesses, a model – whether it be cellular, animal or computational – is a simplified representation of the true complexity inherent to mental health conditions and their underlying neurobiology. Designed to isolate key features and uncover new meaning about these conditions, models also prompt researchers to make foundational assumptions about the terminology they are using, the form those terms take and the relationships between them (Levenstein et al., 2023). Amid the vast complexity that is a human with depression, anxiety or psychosis, each distinct modelling approach confer its own representational benefits.

A major theme of this report is how, in combining these distinct modelling approaches, greater progress in both the scientific understanding of how brain, body and environment interact in the trajectory and resolution of anxiety, depression and psychosis and how new and improved ways to predict, identify and intervene as early as possible may be forthcoming. To ensure parity of understanding across different research fields, it is important that the concept of 'what is a model' for each approach is clearly defined.

1.4.1 Cellular and animal models

Cellular and animal models serve as valuable tools for researchers to isolate and control specific features of interest, making the investigation of complex syndromes such as anxiety, depression and psychosis more manageable. Models are inevitably simplifications, and consequently the terminology has shifted from considering models *of* anxiety/depression/psychosis to models *useful for* (or homologues of) the conditions, indicating their ability to recapitulate condition-related features. In fact, many cellular and animal models do not aim to recapitulate clinical conditions, but instead focus on modelling mechanisms relevant for risk and vulnerability factors, such as stress or genetic alterations, associated with developing specific conditions (Brennand et al., 2012; Falk et al., 2016; Richter-Levin et al., 2019; Söderlund & Lindskog, 2018).

Over the past decades, numerous approaches have been utilised to model anxiety, depression and psychosis in cellular and animal models (Arlotta & Gage, 2023; Bardy, 2019; Brennand et al., 2012; Whiteley et al., 2022). The utility of these models is typically evaluated based on validity criteria such as predictive validity (whether a model's response to treatments predicts human response), and construct validity (whether a model captures aetiology and pathophysiological mechanisms) (Belzung & Lemoine, 2011; Willner, 1984). For animal models, face validity (whether a disorder replicates key features of the condition) can also be an important consideration. However, there is active debate about whether additional or distinct criteria should be adopted to ensure models are reliable and clinically useful. For example, to improve the translational value of animal models, increasing attention is being paid to ethological validity (whether a task models an organism's natural environment and thus natural or pathological behaviour in such settings) and computational validity (whether the strategies used in behavioural tasks rely on similar information processing across species) (Belzung & Lemoine, 2011; Drude et al., 2021; Lyons et al., 2023; Mücke-Heim et al., 2023; Redish et al., 2022; Robinson, 2014).

A fundamental challenge for cellular and animal models lies in striking a balance between experimental control and the generalizability of conclusions to heterogeneous human conditions. For example, cellular models aim to enhance our understanding of the cellular, molecular and (electro)physiological properties of the brain under controlled experimental conditions. They not only help study normal physiological function but also elucidate cellular and molecular phenotypes

associated with mental health conditions, establishing connections with clinical, behavioural and genetic studies (Bardy et al., 2019; Brennand et al., 2012; Hoffman et al., 2019; Rasanen et al., 2022). As iPSC-based neuronal models best represent cells found during mid-gestation of brain development, they are therefore particularly effective in studying causative mechanisms and identifying risk factors that contribute to the development of complex mental health illnesses during prodromal or premorbid phases (Brennand et al., 2012; Seah et al., 2023). However, cellular models alone have limitations in advancing the development of interventions, identifying early intervention points or creating novel biomarkers or therapeutic agents. These limitations arise from the inherent constraints of *in vitro* systems, which restrict investigations to the cellular, molecular and (electro)physiological levels without establishing causality at a behavioural or systems level (Kleiman & Engle, 2021; Silva & Haggarty, 2020).

Conversely, preclinical animal models are an ideal platform for probing the correlative and causal relationships between neural circuits and behaviour relevant to mental health conditions (Nestler & Hyman, 2010). However, they are limited by the significant biological differences between humans and other animals, encompassing cellular and circuit characteristics as well as cognitive abilities and, obviously, language. Hence, a recurring issue for animal models pertains to how to effectively capture core dysfunctional aspects of reasoning and emotional characteristics associated with human mental health conditions and how to infer an animal's internal state from its observable behaviour and/or physiological readouts.

1.4.2 Computational models

A computational model is a mathematical representation of specific mental or neural processes. These models can simulate or explain how the brain processes information and generates mental constructs and behaviours. A useful taxonomy introduced in computational psychiatry distinguishes normative models from process models (First et al., 2022). Normative models would refer to the software level of implementation asking what the brain is seeking to do, while process models refer to the implementation layer asking how the brain would perform such an operation. Some frameworks provide both normative and process models. Models can thus formalise and simplify complex algorithmic content of mental health problems and potentially identify their neural representation – for instance, treating aspects of depression as a learning bias toward negative reinforcers via aberrant neuromodulation or value encoding (Huys et al., 2015; Price & Duman, 2020; Stephan et al., 2016). Model comparison is often conducted to allow researchers to assess different hypotheses about the studied cognitive or neural processes. By constructing theory-driven computational models, we can test hypotheses, generate predictions and gain a deeper understanding of how the brain processes information and gives rise to complex behaviours (Frässle et al., 2021). Importantly, we can examine how the structure of the model or the model parameters representing different subcomponents of a mental process might differ between a certain psychiatric sample and healthy controls. We can even create virtual 'lesions' of the model and see if the output behaviour might match that of people who have the condition being studied, thus making (at least partially) causal inferences of what might be going awry (An et al., 2022). These models have provided a valuable framework for integrating experimental data, theoretical concepts and computational simulations, advancing our knowledge of the brain and its functions.

A second type of computational model frequently used in computational psychiatry is machine learning. These models are used in a data-driven, 'bottom-up' fashion to identify features or patterns that might be indicative of certain psychiatrically relevant variables (e.g. treatment outcome (Galioulline et al., 2023)). There are two main types of machine learning approaches: unsupervised and supervised learning. Unsupervised learning uncovers hidden structures in unlabelled data, such as cluster analysis identifying similar subgroups among patients in computational psychiatry research (Ji et al., 2021). This approach can be used to classify subtypes of participants (e.g. with distinct symptom profiles or response responses). Supervised learning uses a labelled training dataset to teach a particular model (e.g. a neural network (Lanillos et al., 2020)) patterns that separate groups and make predictions on unseen data. For example, these might be utilised to predict responders from non-responders to treatments based on training data.

1.5 Case studies

When assessing the state of the field and the progress made to date in how each model has advanced our understanding or treatment of mental health illnesses, it is instructive to highlight some examples. Here, we discuss two, with a focus on a specific model, but at times also demonstrating integration between multiple models.

1.5.1 Combining cellular and computational models to predict treatment responses

Early intervention and timely administration of appropriate therapeutic interventions play a crucial role in determining the overall outcome for patients suffering from mental health disorders. However, it is important to acknowledge that therapeutic drugs may have undesirable side effects, and treatment responses can vary among individuals. Prescribing ineffective medications not only prolongs the duration of symptoms experienced by patients but can also result in long-term harm.

Consequently, there is a pressing need to identify potential phenotypes or biomarkers that can enhance treatment response, aligning with the principles of personalised or precision medicine. In this regard, iPSCs hold promise as they offer an opportunity to not only elucidate causal mechanisms but also to identify potential phenotypes or biomarkers that can predict treatment response (Bardy, 2019; Haggarty et al., 2016; Silva & Haggarty, 2020; Stern, Linker et al., 2018). A notable example where iPSC-based models have provided such insights is the research conducted to understand the mechanism of action of lithium in patients with bipolar disorder.

Currently, lithium stands as the primary treatment option for managing mood episodes in individuals with bipolar disorder. However, only approximately 30% of bipolar disorder patients respond positively to lithium treatment (Haggarty et al., 2021; Hoffmann et al., 2018). Other options, such as alternative mood stabilisers, antipsychotics, combinations of antidepressants and antipsychotics, and anticonvulsants are available. Hence, being able to predict whether a patient with bipolar disorder will respond to lithium would greatly aid in selecting the most suitable treatment option. In 2015, Mertens and colleagues generated iPSCs from six patients with bipolar disorder type one and unaffected individuals (2015). They observed distinct differences in synaptic function and hyperactive synaptic activity in bipolar-disorder-specific iPSC-derived hippocampal neurons not present in control iPSC-derived neurons. Of the patients investigated, three were known to be responsive to lithium treatment, while the remaining three were non-responsive. Stratifying by treatment response, Mertens et al. demonstrated that the hyperactive phenotype in iPSC-derived hippocampal neurons could only be normalised through chronic lithium treatment in neurons obtained from lithium-responsive patients. Furthermore, transcriptome analysis revealed a greater response to lithium in iPSC-derived hippocampal neurons from lithium-responsive individuals compared with those derived from non-responsive patients. A subsequent study replicated the finding of hyperexcitability in iPSC-derived hippocampal neurons from a second patient cohort, further reinforcing the observation that this hyperexcitability may serve as a distinctive characteristic of lithium responders that could be attenuated by chronic lithium exposure (Stern, Santos et al., 2018).

Moreover, the electrophysiological data obtained was utilised to develop an effective naïve Bayes classifier that could predict the response of test iPSC-derived hippocampal neurons to lithium treatment (Stern, Santos et al., 2018). With an accuracy exceeding 92%, this classifier made it possible to determine if iPSCs derived from a bipolar disorder patient with unknown responsiveness to lithium would exhibit positive treatment response. It should be noted, however, that these results include samples from only five individuals for training and a single test. More recently, the inclusion of information theory-derived features has been reported to enhance the success of prediction (Tripathi et al., 2023). Additionally, these studies, alongside others, have contributed to a better understanding of the neurobiology underlying lithium response, potentially paving the way for the development of novel therapeutic compounds and a deeper comprehension of bipolar disorder itself (Niemsiri et al., 2023; Paul et al., 2020; Santos et al., 2021; Tobe et al., 2017; Osete et al., 2021; 2023). Similar approaches utilising iPSCs derived from patients with depression have been employed to investigate mechanisms underlying the response to selective serotonin reuptake inhibitors (SSRIs) (Vadodaria et al., 2019; Vadodaria et al., 2020) or bupropion (Avior et al., 2021), or to study response to clozapine or olanzapine in iPSC-derived neural cells generated from schizophrenic patients with divergent response to either treatment (Akkouh et al., 2022; Hribkova et al., 2022; Sun et al., 2022). A challenge now is to understand if such findings can be replicated in larger cohorts and for other mental health disorders. Moreover, how such an approach could contribute to clinical practice is currently unclear. Nevertheless, collectively, these studies exemplify how iPSCs can be employed to understand the mechanisms of actions of specific drugs in the context of responding and non-responding patients, and thus predict drug responsiveness in iPSC-based models (Bardy, 2019; Stern, Linker et al., 2018).

1.5.2 Combining computational and animal models to unravel the neurobiology of hallucination-like percepts

The experience of hallucination-like percepts (HALIPs) illustrates how advances in understanding both the underlying neurobiology and associated psychological processes can arise from combining computational approaches with cross-species models. Hallucinations are a core, debilitating feature of psychotic disorders, yet despite their complexity and subjective nature, they are nonetheless proving amenable to neurobiological study.

The Bayesian computational framework suggests that ‘top-down’ prior beliefs can influence ‘bottom-up’ sensory data processing (combining into a posterior belief), such that priors can outweigh the veridical sensory experience. An idea that has gained widespread interest is that hallucinations and other symptoms of psychosis may arise from disruptions in the balance between prior beliefs and sensory evidence (e.g. Corlett et al., 2009; Fletcher & Frith, 2009; Sterzer et al., 2018). Importantly, this computational framework allows key assumptions about how false percepts might arise to be formally tested and their neural correlates to be investigated. For example, by manipulating sensory expectations (i.e., the likelihood that a particular visual or auditory cue will be presented at any point in time), it is possible to induce false percepts or hallucinations in both humans and

non-human animals – specifically, subjects indicate the presence of a sound when it did not exist (a ‘conditioned hallucinations’ task). Combining this approach with computational modelling and neuroimaging methods in people with and without a diagnosis of schizophrenia has revealed a network of brain regions that are activated during conditioned hallucinations (Cassidy et al., 2018; Powers et al., 2017). Testing model-derived predictions in mice has allowed these to be compared against moment-by-moment striatal dopamine levels (Schmack et al., 2021), an excess in which has long been implicated in mediating the positive symptoms in schizophrenia (Howes & Kapur, 2009). In line with theoretical predictions around the enhanced precision of beliefs (higher weighted priors (Adams et al., 2013)), higher striatal dopamine levels were present prior to false percepts than before correct rejections (Schmack et al., 2021).

Note, however, there is still much we do not understand. For instance, while these dopaminergic-driven ‘strong prior’ accounts are compelling (Corlett et al., 2019), they do not yet fully explain the mechanisms driving the ignoring of sensory data (Sheldon et al., 2022; D. Wang et al., 2021). Incorporating developmental aspects, such as models of synaptic pruning in sensory systems and longitudinal investigations may further deepen our understanding of the aetiology of this phenomenon. Furthermore, a key area for future research is to understand the mechanistic aetiology of the excessive striatal dopamine characteristic of psychosis and how this might be predicted and remediated before a psychotic episode presents.

Thus, HALIPs show the potential for using computational and psychological models to form a cross-species bridge, allowing researchers to directly test mechanistic links from a computational processing model to dopamine activity to provide new insight into a core symptom of psychosis. Continuing the story of HALIPs to its longitudinal and developmental conclusion therefore may provide new and improved ways to predict, identify and intervene as early as possible for psychosis.

How can neuroscience propel transformative changes for mental health?

Since the mid-2000s, there have been revolutionary advances in the experimental and theoretical tools used across neuroscience. However, this has not yet led to an equivalent step-change in our understanding or treatment of anxiety, depression and psychosis. As we have outlined earlier, key gaps between how cellular, animal and computational models are commonly being used as experimental tools on the one hand, and the clinical experience of mental health conditions on the other, are slowing the speed of progress.

In the following section, we will outline a series of steps that can bridge these gaps. Specifically, we must address three major challenges:

A. How can we better combine cellular, animal and computational models to further our understanding of anxiety, depression and psychosis?
B. How can cellular, animal and computational models improve ways to predict, identify and intervene early in anxiety, depression and psychosis?
C. How can we a create sustainable and standardised scientific environment to ensure work in cellular, animal and computational models can fulfil their potential and be as widely used as possible?

By doing so, we can unlock the transformational potential for neuroscience to deliver an improved understanding of the aetiology and trajectory of anxiety, depression and psychosis and help develop new and improved ways to predict, identify and intervene as early as possible.

How can neuroscience propel transformative changes for mental health?

	A. How can we better combine cellular, animal and computational models to further our understanding of anxiety, depression and psychosis?	**B. How can cellular, animal and computational models improve ways to predict, identify and intervene early in anxiety, depression and psychosis?**	**C. How can we create a sustainable and standardised scientific environment to ensure work in cellular, animal and computational models can fulfil their potential and be as widely used as possible?**
CHALLENGES			
NEEDS	• Bridge translational gap between neuroscience models and the clinic • Develop richer, more ecologically valid behavioural measures and paradigms • Employ better and more harmonised neural readouts across multiple scales and species	• Recognise and leverage variation within our models to better predict and identify biological risk factors and individual differences • Unravel how cumulative experience across the lifespan shapes mental health trajectories and their neural correlates	• Establish community standards for models and their outputs • Ensuring datasets are accessible and diverse, facilitated by scalable measurement tools

Table 1. How can neuroscience propel transformative changes for mental health: challenges and needs.

A. How can we better combine cellular, animal and computational models to further our understanding of anxiety, depression and psychosis?

A.1. We need to ensure that theoretical and experimental neuroscience models consider clinical relevance

A.1.1 Summary

A fundamental challenge concerns how to better translate clinical questions to neuroscientific studies using cellular, animal and computational models. To accelerate progress towards early interventions and better understanding of mental health conditions, it is imperative to close the gap between the categorical diagnoses of anxiety, depression and psychosis used in the clinic, the lived experience of patients diagnosed with these conditions, and laboratory studies of phenotypes and neural substrates in cellular, animal and computational models. To achieve this, there needs to be a more pointed focus back towards symptoms and symptom alleviation.

Clinical diagnosis, codified through the Diagnostic and Statistical Manual of Mental Disorders (DSM) and International Classification of Diseases (ICD), is grounded in clinical observations and subjective reporting of symptoms using questionnaires. These diagnostic criteria emphasise reliability and utility, to allow differentiation between disorders and consistency between clinicians. However, current nosological psychiatric classifications do not fully account for the heterogeneity seen in mental health illnesses or the subtyping of patients within a specific illness. It is very unlikely that there is a single mechanism underlying any condition; instead, there are likely multiple different and distinct biological mechanisms or distinct patient subtypes seen in diagnosis outcomes (Sawa et al., 2022). Moreover, it is challenging to bridge the categorical responses in a questionnaire and criteria that can be validated within a model.

To address this concern, the National Institute of Mental Health developed the Research Domain Criteria (RDoC) framework, which defines five domains or constructs of observable behaviour and neurobiological measures with common underlying neurobiological circuits affected in mental health illnesses (Cuthbert, 2022; Cuthbert & Kozak, 2013). This dimensional approach was designed to facilitate research from animal models to clinical studies that aim to investigate how behavioural abnormalities might result from changes in neural activity. However, while this has encouraged research to identify potential biomarkers and provided focus for cross-scale investigations into biological mechanisms, it has come at the expense of diverging from clinical diagnoses, which may limit its ability to generate targets for treatment strategies.

Below, we highlight back-translation and stratification as key areas to help build bridges between our refined and specific models and the core clinical goal of alleviating suffering.

A.1.2 Prioritising symptom-focused back-translation over bench-to-bedside approaches

There is increasing consensus in both academia and industry that back-translation – using insights and evidence from clinical research to shape and refine the questions asked in cellular and preclinical animal models – will play a crucial role in speeding our understanding of the causal, mechanistic factors underlying mental health problems. This approach also has the important benefit of allowing direct patient involvement in identifying where there is greatest need for research. For example, if resources focus on new treatments for the positive symptoms of psychosis, when it is the cognitive features that prevent a person from engaging in their lives more fully, then the cognitive features should become the priority.

In iPSC models, the selection of which patient to generate iPSCs from, or which existing patient-iPSC lines to use in a study, should extend beyond selection criteria based on diagnosis or genetics (e.g. patients with a specific diagnosis and/or carriers of rare mutations/CNVs). Rather, more integrative selection criteria in which a combination of multi-omic data aids in identifying patients to generate iPSCs from will help to break down the heterogeneity of mental health conditions. Such multi-omic approaches are being used effectively to stratify patients in oncology into homogenous populations (Boufraqech & Nilubol, 2019). In the context of mental health conditions, using patient cohorts with detailed molecular (genetic, epigenetic, proteomic, metabolomic), biomarker and neuroimaging analysis will guide researchers in their selection of individuals from whom to generate iPSCs (Bardy et al., 2019; Engle et al., 2018; Hoffman et al., 2019; Rivetti di Val Cervo et al., 2021). This approach would facilitate back-translation by providing a more informative basis from which to link cellular and molecular phenotypes derived from iPSC-based models, with specific symptoms or phenotypes in patient subgroups. For studies using gene-editing techniques with the aim to study the function of disorder-related genetic variants, the choice of which iPSC line to use is also critical (Dobrindt et al., 2021; Muhtaseb & Duan, 2022; Rivetti di Val Cervo et al., 2021; Volpato & Webber, 2020; Wen et al., 2016).

Animal models relevant to anxiety, depression or psychosis should align both with aspects of the disease criteria and symptomatology expounded by the DSM classification and an objective dimensional approach of the RDoC. This will require the field to determine how to objectively classify anxiety-, depressive- or psychosis-like states, potentially based on correlations between behavioural endophenotypes, physiological measurement and cellular transcriptomic analyses (Dzirasa & Covington, 2012; Mücke-Heim et al., 2023). It will be important to reach consensus over what types of readouts in different species can be considered pathological versus simply adaptive. For example, it is adaptive to show anxiety and avoidance behaviour in a situation that is or was threatening; this can only be considered pathological if this generalises to or persists in safe contexts (Ayash et al., 2023; Duits et al., 2015). Consideration should also be given to the minimum duration of symptom presence that is required for diagnosis, as defined in the DSM, taking into account age-related differences between humans and model species (Mücke-Heim et al., 2023). Different strands of information could be combined in an algorithm to provide a simple readout of whether a condition-like syndrome in an animal model has been achieved (Guilloux et al., 2011; Mücke-Heim et al., 2023). The overarching aim would not be to determine a single best model, but to provide a set of foundational criteria to align different animal models that have been developed to capture different sets of potential causes and symptoms across different conditions.

Furthermore, since behaviour serves as the key interface between brain activity and the environment, we should also ensure that there is back-translation from the neuropsychological deficits found in people with anxiety, depression and psychosis into the behavioural paradigms chosen for use in preclinical animal models. For example, there has been a focus, particularly in rodents, on how evolutionarily conserved subcortical circuits might be involved in mediating emotional states and motivational drives, but much less consideration given to the consequences of perturbations in the different cortical networks known to play a major role in the pathophysiology and symptomatology of anxiety, depression and psychosis and how these might alter processes affected in mental health conditions. Renewed focus on the neural mechanisms of cognitive features and cortical regulation of emotion and motivation will be important to bridge symptoms from cellular and rodent models.

A.1.3 Ensuring neuroscience studies are informed by the symptoms and needs people have

There is a need to ensure that what is studied in the laboratory aligns with the requirements of people with anxiety, depression and psychosis. Research priorities for neuroscience should be informed by the symptoms people experience and the degree to which these impede their day-to-day functioning. For example, if the side effects of a clinically efficacious treatment are impeding its take-up or sustained use, research should be focused on developing alternative compounds that do not have similar side-effect profiles. For example, second generation antipsychotics may cause birth defects, which means this medication should not be taken during pregnancy, while in adolescents, weight gain is the major side-effect of these medications and is reported to cause non-adherence to prescribed medication therapies. Moreover, in multifaceted conditions such as psychosis, renewed consideration should be given to whether it is the positive, negative or cognitive disruptions that most disable a person from engaging in their lives more fully.

Moreover, it will also be important to align markers of success between models and the clinic, with a key factor being a consideration of a relevant change in people's symptoms as a core marker of success. For example, while researchers might consider a meaningful effect being a statistically-reliable reduction in maladaptive behaviour or emotional state or a change in cellular or molecular phenotype, following a particular treatment in the model, clinically this might only affect a subset of symptoms experienced, or may result in the person no longer meeting DSM criteria for a particular categorisation (Milton & Holmes, 2018; Shumake et al., 2018).

The fact that the majority of laboratory neuroscience research has not prioritised the needs and subjective experience of the people with the condition it is studying is clearly problematic for the field and contributes to the translational gap between neuroscientific models and the clinic.

A.1.4 Recommendations

To bridge the gap between modelling approaches and clinical reality, prioritising symptom level features turns the lens first to the patient and then to the science. Furthermore, we may proceed with symptom and scale-crossing analyses only with better and more consistent stratification of patients.

- We need to ensure laboratory studies of phenotypes and neural substrates in cellular, animal and computational models are directly informed by the clinical reality – including both diagnostic criteria used by clinicians and the lived experience of individuals with these conditions.

- We recommend prioritising cross-scale research collaborations, bringing together experimental and theoretical neuroscientists and clinicians, with a common objective related to specific, clinically relevant questions.

A.2. We need to develop rich, ecologically-valid behavioural measures and paradigms tractable to neuroscientific investigation

A.2.1 Summary

No condition or symptom is a single process phenomenon; instead, multiplexed mechanisms involving cognitive, biological, environmental and other layers contribute to almost all mental health conditions. To dissect and understand this complexity calls for a move away from relying on a small number of simple, species-specific behavioural assays to richer and more ecologically-valid paradigms for humans and non-human animals that encapsulate some of the key challenges faced by people in modern life.

To date, most laboratory and theoretical neuroscience research uses highly operationalised paradigms that aim to obtain 'clean' measures of cognition and behaviour. This is deeply rooted in the tradition of cognitive neuroscience of operationalising high-dimensional real-life behaviour into low dimensional behaviours that can be measured in a lab (Posner and DiGirolamo, 2000). In computational studies, highly abstracted tasks are used to reflect the simple elegance of established theories.

While this approach has been very successful in providing basic mechanistic understanding, there is increasing evidence to suggest that current laboratory paradigms, which are highly regularised and 'clean', might be missing important features of real human behaviours and environmental factors. Depression and a well-established mechanism such as mesolimbic circuitry-mediated reinforcement learning processes are one example. A recent meta-analysis showed only moderately different value learning rates between patients and healthy controls (Pike & Robinson, 2022). The association between the beads task and psychosis is a similar case. Despite the elegance of the theory, a meta-analysis revealed large between-study and between-subject variability (Ross et al., 2015).

Below, we outline promising approaches to dissect real-world problems in laboratory settings that still allow for research into underlying neural correlates.

A.2.2 Identifying complex cognition and behaviours that can be measured across species

It is important to adopt behavioural tasks and readouts with sufficient complexity that allow for the fractionation of overlapping but distinct features observed in different mental health conditions.

An emotional state or behaviour can arise from multiple psychological and/or algorithmic processes. For example, although disrupting distinct neural circuits in an animal model can result in the emergence of comparable anxious phenotypes in which threat responses appear heightened, the underlying reasons for each phenotype can be distinct and therefore respond to different treatment approaches (Roberts, 2019). Moreover, many spurious factors can change a behavioural readout. For example, in tests of fear and anxiety using fear conditioning, the standard measure of freezing is strongly influenced by overall locomotor activity, which is frequently altered in rodent models (Fisher & Bannerman, 2019). Single snapshot readouts therefore cannot provide the psychological resolution to reliably bridge to the human condition.

Fortunately, there is an increasing body of work demonstrating the possibility of measuring behavioural analogues of complex cognitive and emotional states, such as deliberation, confidence and regret, in both non-human primates and rodents (Redish et al., 2022; Robbins, 2015; Sapolsky, 2016; Tricklebank et al., 2021). While most of this work has been focused on understanding the neural basis of these cognitive processes in the healthy animal, we recommend using this foundation to dissect dysfunctional cognitive processes in models relevant to anxiety, depression and psychosis (see section 1.5.2). Moreover, the field should be encouraged by the promise shown so far to develop new, computationally tractable behavioural paradigms that engage overlapping psychological processes in animal models and humans. We should aim to move away from being rigidly prescriptive about what assays should be used and instead form a consensus about best practice for behavioural phenotyping and cross-species translation.

In human data, we should attempt to identify a relatable readout to those available from well-characterised animal and cellular circuits. Currently, relatively simple cognitive functions have appealed to computational models across scales and species. For example, working memory (Bygrave et al., 2019; Froudist-Walsh et al., 2021; Mejías & Wang, 2022) is a core building block of executive function and has been analysed with biophysical models for some decades (Wang et al., 2013). Models of detailed biophysical mechanisms describing 'attractor basins' are well-accepted concepts that could be extended further to pinpoint precise deficiencies in patient samples (Arnsten et al., 2022). Identifying analogous processes in rodent models or iPSC-based models may be made possible by translating more abstract concepts, such as that of an 'attractor basin', to these preparations. Thus, a computational concept – that may have slightly different substrates in the animal, iPSC and human patient (Torres-Gomez et al., 2020) – may nevertheless bridge to the core symptom problem. In other words, we could consider that by

abstracting away some basic features (such as the exact items in working memory or exact cause of negative affect) into more abstract constructs, complex high level 'cognition' could be bridged, even between patient and cellular models.

A.2.3 Accelerating automated, neuroethological readouts

One priority area should be to leverage advances in methods for the automated collection of large data sets from cellular and animal models with machine learning approaches to advance our understanding of anxiety, depression and psychosis in relevant models.

For example, machine learning approaches are being applied to data generated from iPSC-based models. Automated high content microscopy combined with increasingly sophisticated computational methods for image analysis allow for the assessment of a wide range of cellular phenotypes (Chandrasekaran et al., 2021; Rivetti di Val Cervo et al., 2021; Silva & Haggarty, 2020), which, in the context of mental health conditions, enable the quantification of genotype–phenotype relationships and the identification of common biological phenotypes (Rivetti di Val Cervo et al., 2021; Silva & Haggarty, 2020). Such approaches have been applied to iPSC models for autism and used to link cellular phenotypes with genetic or clinical data (Adhya et al., 2021; Cederquist et al., 2020). Multi-electrode arrays offer a parallel approach to assessing synaptic/neural network activity and can capture genotype-associated changes or monitor pharmacological effects on electrophysiological readouts. Machine learning approaches are being applied to multi-electrode array datasets to predict and provide mechanistic insights (Doorn et al., 2023; Trujillo et al., 2021; Wen et al., 2022). While both approaches lend themselves to unbiased hierarchical clustering and machine learning approaches, a key challenge is to understand how best to integrate such high content approaches to link observable phenotypes with data from other models, such as animal models or patient data.

In non-human animal models, it is now possible to generate rich data sets through home-cage monitoring. Home-cage monitoring offers several potential advantages over alternative methods for phenotyping. First, it avoids the need for animal handling and out-of-cage testing that inevitably cause arousal changes, which might mask or even fundamentally change more subtle or intermittent individual phenotypes. All animals – and mice in particular – are sensitive to environmental factors that can drive changes in their arousal levels, and these have long been known to have non-linear effects on cognitive performance (Yerkes & Dodson, 1908). This can have important implications for the identification of treatment targets. For example, there is evidence that group II metabotropic receptors, implicated as a potential treatment target in a range of psychiatric conditions including psychosis and anxiety, can have distinct effects on learning and behavioural output depending on stress levels (Lyon et al., 2011; Sandi, 2011).

Second, new supervised and unsupervised machine learning approaches are becoming widely available that enable the automatic tracking of multiple animals and segmenting their behaviours into different behavioural fingerprints or "syllables" (Markowitz et al., 2018; Mathis et al., 2018). These hold promise to deliver new insights into the emergence of individual traits and their underlying neural substrates, some of which have already been shown in mice to predict performance across classic behavioural assays of cognition and emotion used in depression- and anxiety-related research (e.g. forced swim test, elevated plus maze) (Forkosh et al., 2019). Such automatically-derived behavioural fingerprints have been shown to be able to successfully categorise types and doses of administered psychoactive drugs (Wiltschko et al., 2020). A key next test will be to understand if and how these could be used to classify potential treatment targets in animal models and behavioural situations relevant to anxiety, depression and psychosis.

It is important to keep in mind that these approaches are in their infancy and there is much still to understand how to interpret the vast array of variables that are produced, how these relate to unrestricted natural behaviours in humans and how they might be used to identify and cluster pathological features of mental health conditions. However, this is an accelerating area of high promise, ripe for further development.

A.2.4 Seeking modellable behaviours beyond forced choices

In order to dissect the psychological processes that guide everyday behaviour, it is important to look beyond explicit behavioural metrics and also include implicit measures.

For example, the majority of studies in humans and non-human animals using reinforcement learning and reward-guided decision-making as a foundation use task designs where subjects make choices between two options and their pattern of choices is the main readout. However, behaviours can be expressed in a much wider range of forms beyond forced choices and may allow a window onto dissociable psychological processes that may be differentially affected in mental health conditions.

Eye movement has a long history in basic research (Adams et al., 2020; Pierrot-Deseilligny et al., 1995; Van der Stigchel et al., 2006) and provides rich information for inferring cognitive and motivational processes (Grogan et al., 2020; König & Buffalo, 2016; Korbisch et al., 2022; Muhammed et al., 2021) including individual differences (Muhammed et al., 2021), but is under-utilised in computational psychiatry research beyond very specific topics such as psychosis (Adams et al. 2012, Hutton et

al. 1998). Whole-body movements, which can be measured by specialised cameras and sensors and are commonly used in areas such as sports psychology and robotics, can be a potentially useful tool for measuring individual differences in healthy (Rodrigues et al., 2020) and psychiatric populations (Alcaniz Raya et al., 2020). A related measure is GPS location, which has been adopted in cognitive neuroscience research as an indicator of real-life movement trajectory (Heller et al., 2020) but is as yet rarely used in clinical research. Comparable measures ("roaming entropy") can also be tracked in animal models (Kempermann et al., 2022). Even reaction time, for example, has well-established computational models that are widely used in psychology and economics research (e.g. drift diffusion model (Pedersen et al., 2017; Ratcliff & McKoon, 2008)) and can be recorded across species; however, it is rarely examined in computational psychiatry research. In humans, computer mouse tracking has emerged as a novel and highly informative metric for the human decision process (Maldonado et al., 2019; Stillman et al., 2018), yet its application in computational psychiatry is almost non-existent.

With the rapid development of language models, narrative data – such as text from electronic health records (Mukherjee et al., 2020; Rumshisky et al., 2016), monologues from people with mental health illnesses (Bartal et al., 2023; He et al., 2017), or dialogues between clinicians and their patients (Althoff et al., 2016; Ryu et al., 2023) – could become an extremely important measure in human mental health research. While well developed for AI, such models – especially large language models enhanced by deep learning – have yet to be explored extensively in computational psychiatry (Rezaii et al., 2022; Ryu et al., 2021), despite a few initial efforts in applying them to psychosis (Chandran et al., 2019), bipolar disorder (Harvey et al., 2022), PTSD (Bartal et al., 2023) and depression (DeSouza et al., 2021; Nanomi Arachchige et al., 2021). In relation to talking therapies, novel language models could reveal how a patient's behaviour or inference style are impacted by self-narratives (Ryu et al., 2023). This is a missed opportunity as we already have a rich literature on the relationship between human language and the brain (Armeni et al., 2017; Kemmerer, 2014; Poeppel et al., 2012).

A.2.5 Recommendations

In a move to understand the complex layering of neural, biological and environmental interactions that lead to mental health problems, the field needs to advance its repertoire of experimental tasks. Incorporating more behavioural measures from eye movements to home-cage tracking with novel neuroethological discovery analyses could enable this transition.

- A priority is to develop new, computationally tractable paradigms that recapitulate the complex cognitive, emotional and autonomic alterations observed in anxiety, depression and psychosis better than the simple, snapshot behavioural readouts often used in laboratory experiments.
- There are opportunities to leverage computational analyses to uncover changes in naturalistic behaviours and emotional states in both patients with anxiety, depression and psychosis and animal models relevant to these conditions.

A.3 We need harmonised neural readouts across multiple scales and species

A.3.1 Summary

In order to remove silos of scientific work and speed up engagement in developing better predictive markers and markers for early intervention, a common or translatable set of empirical measures among cellular, animal and computational models is required. While harmonising every metric is unrealistic, several areas around electrophysiology and imaging, bodily measures and transcriptomics offer avenues to improve translation.

To contemplate harmonisation, it may be useful to consider a range of empirical results, from direct homologues (e.g. genetic) to more common quantities of brain and behaviour across species. Below we highlight potential roadmaps that could enhance cross-scale and cross-species interpretations of mental health problems.

A.3.2 Advancing cross-species neural readouts

One important way to help reduce the translational gap between human and animal or cellular studies will be to focus efforts on cross-species studies using common readouts and common interventions.

For example, aligned electrophysiological and neuroimaging experimental work in humans and animals has suggested that disruptions in neural coherence between and within brain regions might reflect dysfunctional psychological processes (Bygrave et al., 2019; Uhlhaas & Singer, 2015). Biophysical modelling has then suggested how these changes might reflect alterations in microcircuit function, which in turn can be tested in animal and cellular models to better understand the aetiology, functional relevance and treatment possibilities (Sherif et al., 2020). Based on this template, we now need to encourage more joined-up cross-species studies using common readouts to build on these promising foundations.

This is particularly important in conditions such as psychosis when many different neurotransmitter systems have been hypothesised to break down. For example, although a hyper-dopaminergic state is believed to underlie the positive psychotic

symptoms of schizophrenia, and all antipsychotic medications target D2-type dopamine receptors, we know from animal models that such hyper-dopaminergic states can arise from several different causes (e.g. Harrison & Weinberger, 2005; Laruelle et al., 2003; Panayi et al., 2023; Weinberger, 1987). Validated condition-relevant cross-species neural signatures should be leveraged to probe the order and sequence of pathological breakdown, allowing for a rich test bed for evaluating alternative sequences of disease as well as effects of early interventions.

E/I balance (summarising the ratio of excitation to inhibition in groups of neurons) represents a cross-scale and cross-species neural assay that has been applied across different experimental preparations. Again, the challenge is now to better conjoin approaches across model systems. E/I balance is readily measurable in iPSC-based models (Mossink et al., 2022; Jianbin Wen et al., 2022) and human biophysical models and can even be manipulated in animal models (Yizhar et al., 2011). E/I imbalance has been marked as a key phenotype associated with neuropsychiatric pathologies (Dehorter et al., 2017; Exposito-Alonso & Rico, 2022; Lam et al., 2022) and in schizophrenia has served as a prominent anchor for developmental cascades, with Krystal et al. (2017), hypothesising a developmental trajectory that begins, *in utero*, with a reduction in 'E', and later cascades into a compensatory reduction in 'I'. These alterations from normal developmental trajectories are difficult to study in human patients given both the long developmental timescales and impoverished and indirect measures such as magnetic resonance spectroscopy or event related potentials. Thus, animal and cellular models could serve as direct assays of the E/I circuit summary (Murray & Wang, 2018; Shi et al., 2021) and help refine the timing and regional specificity of these tests in human patients while also allowing for tests of early interventions in model systems.

Neuroimaging readouts in combination with computational approaches can also be used to guide cellular and animal studies to investigate mechanisms that are directly associated with these patient-led observations. To capitalise on such an approach, it would be important to prioritise studies to find common molecular and cellular readouts that can be used across models. For example, the PET radioligand UCB-J binds to synaptic vesicle 2A (SV2A), and has been used as a proxy measure to assess synaptic density in patients with mental health illnesses (Holmes et al., 2022; Holmes et al., 2019; Onwordi et al., 2020). However, this work leaves the question of causality unanswered, and it is also not possible to dissect underlying mechanisms using neuroimaging; both can be directly investigated using cellular and animal models (Halff et al., 2021; Onwordi et al., 2020).

Common readouts from animal models and human patients could accelerate successful neurostimulation approaches as a treatment for mental health conditions. For example, deep brain stimulation (DBS) is currently being trialled for the treatment of several mental health conditions including treatment-resistant depression, anxiety and schizophrenia (Corripio et al., 2020; Mayberg et al., 2005; Saez & Gu, 2023; Sturm et al., 2003). A more recent development, focused ultrasound, is also showing promise both as a minimally- or non-invasive way of modulating brain activity in deep brain structures (Darmani et al., 2022; Folloni et al., 2019), and might help to increase the precision of drug delivery by targeted opening of the blood-brain barrier (Abrahao et al., 2019). However, to improve the success of these therapies, we need improved data around the correct anatomical target, optimal stimulation settings and likelihood of an individual's responsivity. To understand the required circuit disruption, the field first needs to establish the pathology of the circuit itself (cf. Parkinson's disease, where DBS is commonplace and where a clear target and abnormal neural signature was identified). Such clear signatures of pathology that neurostimulation methods should aim to disrupt have not yet been discovered for depression or obsessive-compulsive disorder and likely will not present as clearly as Parkinson's disease in neural recordings. Thus, animal and computational models may help to identify more subtle and more integrated brain patterns that are promoting pathological circuit behaviours and may be targeted with neurostimulation. Hence, testing neurostimulation strategies in animal models, where high-resolution data is available, could improve their clinical reliability where the models imbue a virtuous cycle of improved classification and refined disease classes.

A.3.3 Advancing neurally relevant readouts beyond the brain

A major limitation in current experimental and theoretical research is the limited types of readouts or behaviours being measured. Therefore, there should be more research focusing on the development and integration of parallel, implicit measures, including of the autonomic system, to provide an important cross-species tool to align experienced symptoms in the clinic with emotional states in animals (Bliss-Moreau & Rudebeck, 2021).

There is increasing attention on interactions between brain and body in health and disease. Poor physical health is a common feature of anxiety, depression and psychosis (Tian et al., 2023), and stress and arousal do not only affect brain function but also the body (e.g. blood pressure, inflammatory responses, gastric function). Parts of medial prefrontal, cingulate and insula cortex dysfunctions which are linked with anxiety, depression and psychosis are not only involved in cognitive processes but also can regulate cardiac function and breathing (Barrett & Simmons, 2015; Dum et al., 2016; Harrison et al., 2021; Khalsa et al., 2018; Roberts, 2019). Importantly, measures such as heart rate variability, recorded through wearable sensors, have been suggested as a transdiagnostic marker of emotional dysregulation in clinical populations (Beauchaine & Thayer, 2015; Thayer et al., 2012). Changes in pupil size can also index aspects of arousal and cognitive factors, which in turn can help provide insights

into how individuals suffering from mental health conditions respond to their environment (Browning et al., 2015). Machine learning approaches have shown promise at automatically dissecting and quantifying facial expressions as individuals watch video, which can then be used to classify depressed and non-depressed individuals (Jeganathan et al., 2022). Theory-driven models have also started to formally account for how bodily signals may contribute to cognition and mental health (Allen, 2020; Gu et al., 2019; Pezzulo, Rigoli et al., 2015; Seth & Critchley, 2013).

While taking autonomic measures during behavioural tasks in animal models is still infrequent, particularly in rodents, there is emerging evidence that it may provide a lens to explore the negative emotional states observed in anxiety, depression and the negative symptoms of psychosis in a precise and translational manner. In restrained animals, it may even be possible to monitor facial expressions to facilitate identification and fluctuations in affective states (Morozov et al., 2021), aligning with the aforementioned work in humans. Therefore, an area of promise is to use animal models to unravel the causal links between psychological states, changes in neural activity and fluctuations in bodily physiology (Fujimoto et al., 2021; Hsueh et al., 2023; Klein et al., 2021; Signoret-Genest et al., 2023; Wallis et al., 2017). This work will again be facilitated through integration with new theory-driven computational frameworks for how bodily signals might contribute to affect (Bach & Dayan, 2017; Roelofs & Dayan, 2022) and cognition (Gu & FitzGerald, 2014; Pezzulo, Rigoli et al., 2015; Seth et al., 2011), and extended to understand how these might become dysregulated in depression, anxiety and psychosis (Cameron, 2001; Gu et al., 2019; Paulus & Stein, 2010).

A.3.4 Harmonising transcriptional & proteomic datasets with human patient data

There are opportunities to build biologically grounded bridges from cellular and animal models to clinical conditions through better harmonisation and integration of transcriptional and proteomic datasets from animal and iPSC models with human/patient datasets. While technically challenging and resource intensive, advances in both transcriptomics and proteomics can now enable organisational principles, connectivity and activity in molecularly defined circuits reflecting behavioural traits to be monitored in animal models (e.g. Ayash et al., 2023; Bagot et al., 2016; Forkosh et al., 2019; Lui et al., 2021; Bulovaite et al., 2022; Yim & Nestler, 2023). Transcriptional and proteomic datasets derived from iPSCs also offer valuable insights into mental health conditions, enabling the elucidation of disease mechanisms, investigation of disease heterogeneity, drug discovery and identification of potential biomarkers (Hoffman et al., 2017; Hoffman et al., 2019; Melliou et al., 2022; Murtaza et al., 2020). While data sharing among researchers is important, additional strategies can be employed to improve harmonisation and integration.

One strategy involves the utilisation of common tools (e.g. bulk vs single-cell RNA sequencing) and consistent analysis pipelines across animal models, cellular models and human studies. This approach facilitates direct comparisons of gene expression patterns, mitigating technical biases and promoting data harmonisation. Another consideration is the careful selection of disorder-relevant brain regions and cell types for transcriptional profiling and comparison. When considering translating genetic risk into a neurobiological understanding of mental health conditions, it is also important to map in which cell types and neural circuits and at which (developmental) timepoint(s) specific genes and their corresponding proteins, are expressed (Di Lullo & Kriegstein, 2017; Hoffman et al., 2017; Willsey et al., 2018). Here, referencing expression patterns in iPSC or animal models with *in vivo* human transcriptomic or proteomic datasets will aid in understanding the pleiotropic effects of disorder-related genetic variants. Focusing on these specific datasets enables the capture of disorder-specific transcriptional changes and enhances meaningful comparisons across model systems.

To align gene and protein expression data between species, cross-species orthologous gene mapping is of the utmost importance. This approach allows for direct comparisons of gene and protein expression patterns, highlighting conserved molecular pathways relevant to mental health conditions. Integration of transcriptional data with other omics datasets, such as proteomics, metabolomics and neuroimaging, further enhances our understanding of mental health disorders. Multi-omics integration enables the identification of key molecular pathways and networks shared across species, shedding light on the underlying biological mechanisms.

Finally, validation of findings from animal and cellular models using human samples and/or datasets is essential to ensure translational relevance. Targeted experiments on human brain tissues or leveraging publicly available human transcriptomic and proteomic datasets serve to validate key findings, confirming the biological significance and clinical relevance of identified gene and protein expression patterns.

A.3.5 Recommendations

Common readouts have helped to unite disparate fields of study around mental health problems. For example, studies around E/I balance permeate the animal model and computational modelling literatures. However, the field has more to do to unite around a patient focus and around a common question. We should do more to harmonise our outputs across fields and potentially support joint research groups who seek a mirrored output and analysis across species.

- To advance our mechanistic understanding of causes and treatments of anxiety, depression and psychosis, it will be valuable to promote multi-scale, cross-species research employing analogous, relevant and, where appropriate, common translational measurements and manipulations of neural activity.
- It should be a priority to develop integrative approaches that investigate the relationships between body, brain and environment in model systems and how these become dysregulated in anxiety, depression and psychosis.

B. How can cellular, animal and computational models improve ways to predict, identify and intervene early in anxiety, depression and psychosis?

B.1. We need to recognise and leverage variation to better predict and identify biological risk factors and individual differences

B.1.1 Summary

A key challenge for theoretical and experimental neuroscience is to adopt approaches that recognise and use variation ("systemised heterogenisation") as an opportunity to derive more reliable data and gain new insights.

Clinical populations are highly heterogeneous in terms of their genetic and biological background, environment and life history. Hundreds of genes seem to cause or contribute to anxiety, depression and psychosis, all of which interact with other genetic and non-genetic factors (Burrows & Hannan, 2016; Brainstorm Consortium et al., 2018; Flint, 2023; Kaiser et al., 2017; Koskinen & Hovatta, 2023). There is also evidence that social determinants have a profound impact on mental health and treatment responses. For instance, socioeconomic status shapes patients' response to antidepressant drugs (Viglione et al., 2019) and family environment and even cultural milieu can shape the emergence of psychosis (Vinogradov et al., 2022).

By contrast, laboratory work predominantly aims to minimise variation in order to increase the contrast between groups and therefore maximise the chances of detecting reliable differences between experimental/treatment and control conditions while minimising individual differences within a group and, in animal studies, reducing animal numbers. Thus, there is a profound disconnection between the highly controlled approach of the laboratory and the complex trajectory of a patient's experience and the manifestation of clinical problems, which may be a key reason why laboratory work to date has such poor translational success.

Below we highlight some new approaches that instead aim to embrace this diversity. Exploring risks and individuality will not only facilitate increases in the robustness of results across model systems but will also allow researchers to ask new questions about how risk factors can propel the development or remission of symptoms of anxiety, depression and psychosis.

B.1.2 Considering genetic diversity and its interaction with the environment as it relates to neural activity and mental health

There is a need to embrace greater complexity in our models in order to capture the multitudinous impact of genetic diversity – with the consideration of gene–environment interaction – on mental health conditions such as depression, anxiety and psychosis.

It needs to be acknowledged that mental health conditions are inherently polygenic, and differences in phenotypes are observed even within patient groups segregated by genetics or symptoms. We should therefore now endeavour to determine how genetic background, and specifically disorder-related variations within the genome, may influence observed differences within phenotypes in human and iPSC studies. We need deeply phenotyped patient cohorts which include information on genetic background to account for additional factors influencing observed phenotypes (Dutan-Polit, 2023; Nehme & Barrett, 2020).

Another consideration for iPSC studies is how the genetic background of an iPSC line may shape the magnitude of a phenotype (Dobrindt et al., 2021; Dutan-Polit, 2023; Volpato & Webber, 2020). Careful consideration and inclusion of the genetic background of donor iPSC lines, in combination with gene-editing approaches, would aid in this regard. For example, we need to use cell lines from healthy individuals with either extreme polygenic scores for a particular condition or correct genetic variants in patient-iPSC lines (Dobrindt et al., 2021). IPSCs are an ideal platform to study the polygenicity of mental disorders and to link specific genetic variations, mutations or CNVs to molecular and cellular phenotypes. However, there is also a need to design studies to understand how multiple genetic variations may interact to influence molecular and cellular phenotypes. Such multiplexed studies could be iPSC-based, and could reveal how multiple genetic factors interact in a cell-type-specific manner. Thus, to further our understanding, future studies should consider how combinations of genetic variations or mutations/CNVs influence observable phenotypes (Flaherty & Brennand, 2017; Hoffman et al., 2019; Nehme & Barrett, 2020; Seah et al., 2023). Embracing genetic heterogeneity and complexity may therefore give greater insight into disorder-specific phenotypes.

Similarly, genetic background should be considered, and where appropriate, genetic models used when attempting to understand the impact of extrinsic (environmental) factors on the emergence and trajectories of mental health illnesses. Many animal and iPSC studies examining environmental factors use in-bred wild-type animals or iPSC lines from apparently healthy

donors. As such, the possibility that a (poly)genic background may alter how environmental factors impact observable phenotypes needs to be accounted for (Bhat et al., 2022). Therefore, it is crucial to consider the use of appropriate genetic animal models or patient cohorts with known diagnoses and genetic backgrounds from which to generate patient-iPSC lines or use isogenic iPSC lines with known genetic backgrounds to investigate and understand complex gene–environment interactions.

B.1.3 Embracing biological diversity across cellular, animal and computational models

How biological variables such as sex, age and ancestry shape the neurobiology of anxiety, depression, and psychosis needs to be given more detailed consideration.

While sex differences in the prevalence, onset and symptomatology of and treatment responses in mental health illnesses are well described in human studies (Dalla, 2023; Galea & Parekh, 2023), they have too infrequently been the focus of laboratory neuroscience research (Fernando et al., 2020; Hodes & Kropp, 2023; Rechlin et al., 2022). Sex differences are more complex than the dichotomous idea that a difference between sex presents as one phenotype in males and another in females. Sex differences can manifest as a continuum (the phenotype is the same in both sexes with a different magnitude of effects in one sex versus the other), as a latent or hidden sex difference (the end phenotype is the same in both sexes, but distinct mechanisms underlie the phenotype) or as a variable that manifests following a genetic or environmental perturbation (Becker & Koob, 2016; McCarthy et al., 2012; Woolley, 2021). Much greater attention to such details will further our understanding of how sex differences in psychiatric illnesses occur, potentially aiding the identification of sex-specific biomarkers and treatment avenues and deepening our understanding of differences in treatment responses.

Several challenges are associated with studying the influence of sex. In iPSC research, to what extent X inactivation erosion occurs in female iPSC lines is still a matter of debate, but needs to be carefully assessed when using such lines (Dutan-Polit, 2023; Nehme & Barrett, 2020). To date, however, the majority of iPSCs have been generated from male individuals. While consideration of sex as a biological variable is becoming more common in animal models, the norm for decades was to use young adult male animals (McCarthy et al., 2012; Shansky & Murphy, 2021). Therefore, many of the standard protocols for looking at key factors in anxiety and depression, such as the social defeat stress model, are male (and adult) biased (Lopez & Bagot, 2021; Lyons et al., 2023). Moreover, across iPSC, animal and human clinical research, even when both sexes are included in a study, limited research has specifically focused on sex differences. To improve translation, it will be important to investigate how these biological variables influence risk factors for mental health conditions such as genetic variation, stress responsivity and treatment.

In terms of ancestry, less is known about how genetic variants associated with European ancestry may differ in individuals with other ancestries (Atkinson et al., 2022; Duncan et al., 2019; Fatumo et al., 2022; Martin et al., 2017; Moreno-De-Luca & Martin, 2021). Therefore, considering the ancestral originals of patients from whom iPSCs have been derived may unlock deeper insights into how this biological variable influences cellular and molecular phenotypes (Dobrindt et al., 2021; Tegtmeyer & Nehme, 2022). Similarly, human neuroscience study participants have predominantly had European ancestry (see section C.2.2. for a more thorough discussion) and it remains to be seen how brain–behaviour relationships might differ between individuals from different ancestral groups in the context of depression, anxiety and psychosis.

To better understand how pathogenetic differences that underpin biological diversity in anxiety, depression and psychosis impact neural mechanisms, it should be a priority to ensure studies are sufficiently powered to enable factors such as sex and ancestry to be included as an independent variable (Miller et al., 2017; Shansky, 2019; Shansky & Murphy, 2021; Tegtmeyer & Nehme, 2022).

B.1.4 Recognising and systematically examining the impact of social environment on brain function and mental health

Neuroscience experiments across our model systems regularly fail to consider the social environment of patients. While epidemiological studies account for the social environment, when we get to the brain, we often ignore or negate the social influences that may be impacting behaviours or symptoms or treatment efficacy. Often neuroscientists simply assume that these features will emerge within their prescribed experimental protocols. Actively assessing social factors and their neural correlates while we probe our mechanism of interest may be challenging but is vitally important.

In animal models, movement tracking and pose estimation algorithms can now be used to monitor the behaviour of multiple individuals in naturalistic settings (Chaumont et al., 2019; Nourizonoz et al., 2020; Shemesh et al., 2013). This sets the stage for detailed neurobiological investigations into whether changes in an individual's pattern of social interactions might be a sensitive and translatable endophenotype for changes in emotional state. This is highly relevant to anxiety, depression and psychosis, given that social withdrawal is a transdiagnostic symptom evinced in all of these conditions. Moreover, given the role

that psychosocial stress and socioeconomic status play in shaping individuals' mental health trajectories, resilience to stressors and responsiveness to treatment (Farah, 2017; Tost et al., 2015; Viglione et al., 2019), this type of approach can be used in animal models to systematically test factors such as how social rank and/or prosociality affect neural mechanisms underpinning individual animals' abilities to cope with environmental stress and how these influence pharmacological treatment efficacy (Alboni et al., 2017; Larrieu et al., 2017; LeClair & Russo, 2021). As highlighted in section B1.3 above, to be of reliable and translatable value, this work will need to pay close attention to how social behaviours are normally expressed as there are distinct patterns in males and females across different species.

The importance of interpersonal dynamics to mental health illnesses is well appreciated in the clinical community (Corrigan & Nelson, 1998; Couture et al., 2006; Segrin, 2000) but challenging to measure in laboratory studies. With the advances made in social neuroscience (Adolphs, 2010; Blakemore, 2008; Frith & Frith, 2007; Na et al., 2023; Rilling et al., 2008; Sanfey et al., 2014; Saxe, 2006; Schafer & Schiller, 2018; Seo & Lee, 2012), computational models of social interactions have begun to emerge for conditions such as personality disorders (King-Casas et al., 2008), addiction (Reiter et al., 2017), delusion (Na et al., 2022) and paranoia (Barnby et al., 2020; Barnby et al., 2022), obsession and compulsion (Banker et al., 2022) and social anxiety (Beltzer et al., 2023; Hopkins et al., 2021; Hunter et al., 2022; Koban et al., 2017). These studies have examined elements such as social inference – about self- and other-relevant beliefs – (Hopkins et al., 2021; Moutoussis et al., 2014; Sui & Gu, 2017), preference (Chung et al., 2020), learning (Barnby et al., 2020; Beltzer et al., 2023; Hunter et al., 2022), controllability (Na et al., 2023), and power and affiliation (Tavares et al., 2015).

Beyond these laboratory paradigms, models of social networks such as agent-based models (Goldstone & Janssen, 2005) and graph theory models (Baek et al., 2021; Jiang et al., 2023) have started to shed light into the architecture of the real-life social environment of an individual and how it might affect his or her mental health (Fiori et al., 2006). Furthermore, there is now a better understanding of how socioeconomic status affects the brain and its development at a mechanistic level (Hackman et al., 2010; Yaple & Yu, 2020). Together, these emerging literatures provide an important foundation to better understand how adverse social experiences such as trauma (Mauritz et al., 2013; McKay et al., 2021), poverty (Lund et al., 2011; Ridley et al., 2020) and social isolation (Blazer, 2020; Brandt et al., 2022) might be detrimental to well-being, as well as how protective factors such as social support (Cohen & McKay, 2020; Taylor, 2011) and enrichment (Tost et al., 2015) may support mental health. Supporting these sorts of studies to account for social factors over the course of some treatment will be vitally important to extend our understanding of tipping points to wellness and the role of social networks, given that social support is a critical ingredient in the treatment and recovery of all mental health conditions including anxiety, depression and psychosis.

B.1.5 Leveraging computational models and neuroscientific data mining to better stratify individual patients based on their neurobiology and environment

Given the complex interactions between biology and environment, one area where experimental and theoretical neuroscience has great potential to advance our understanding of anxiety, depression and psychosis is in terms of subtyping and stratifying neuropsychiatric disorders and in identifying condition-relevant biomarkers and biotypes.

The advancements in guidelines and standardised protocols for iPSC generation and biobanking described in section 1.1.2 need to continue, if not increase (Engle et al., 2018; Kleiman & Engle, 2021; International Society for Stem Cell Research, 2023). Larger repositories of patient-derived iPSC line with multimodal clinical and non-clinical datasets are required (Dutan-Polit, 2023; Hoffman et al., 2019; Nehme & Barrett, 2020; Reid et al., 2022). Furthermore, better integration with computational approaches is needed to combine datasets from clinical and non-clinical measures more effectively. As described above, this will help identify robust phenotypic signatures between patient subgroups and build predictive algorithms and classifiers to help understand how iPSCs can be used to help stratify patients in terms of diagnosis or treatment response (Rivetti di Val Cervo et al., 2021; Stern, Linker et al., 2018).

Animal models can also help with this endeavour by dissecting how distinct networks, some of which might originate from the same brain region, can support different psychological processes that are implicated in and are treatment targets for anxiety, depression and psychosis (cf. Groman et al., 2019; Warden et al., 2012; Wood et al., 2023). Furthermore, they can facilitate translational pipelines by searching for targets that are selectively expressed in these defined circuits (cf., how transient receptor potential channels 4 and 5, through being densely expressed in cortico-limbic circuits but not in striatum, are now a target for treating depression and PTSD (Bohringer Ingelheim, 2023).

By combining neural readouts with machine learning techniques in human clinical research, several groups have shown it is possible to identify patient subtypes that map onto global brain connectivity and identify biomarkers that are predictive of treatment outcome in depression and psychosis (Clementz et al., 2020; Drysdale et al., 2017; Ji et al., 2021). Few attempts, however, have been made to replicate, compare and contrast biotypes across different studies, not even in those using

overlapping datasets. Therefore, there is an urgent need to better understand what a subtype is and whether these stratifications have clinical utility. This can be aided both by larger and better characterised datasets with multimodal data and by improved machine learning algorithms with standardised outcomes.

B.1.6 Recommendations

Embracing heterogeneity in patient and animal samples transgresses our current norms in experimental settings. Obviously, to be useful for treatment prediction and planning, in the long term, people with mental health illnesses should collate around distinguishable phenotypes. Introducing comprehensive heterogenous accounts of genetic, social and biological, and social environmental variability, we believe, will accelerate more precise characterisations.

- There is a need to embrace genetic and biological diversity (e.g. sex, ancestry) in the pathophysiology of anxiety, depression and psychosis; this is a key gap given the substantial influence of sex on the prevalence and presentation of these conditions.
- We need to better understand how the brain processes social information and how social environmental factors affect the brain in the context of anxiety, depression and psychosis.
- There is potential for neuroscience research to harness an improved understanding of heterogeneity within clinical populations to improve the stratification of patients through identification of multimodal, condition-relevant neurobiological biomarkers.

B.2 We need to unravel how cumulative experience across the lifespan shapes mental health trajectories and their neural correlates

B.2.1 Summary

There is a clear need to examine longitudinal trajectories of behaviour and their neural correlates in experimental settings, as well as symptom progression and treatment effects in humans with anxiety, depression and psychosis, over longer timescales. This would reveal how life events shape the development of pathological behaviour and brain function over time, and also how treatment works during acute and chronic phases. The latter is especially critical in young people during a period of rapid neurodevelopmental changes.

In human clinical settings, patients' symptoms fluctuate dynamically over time, shaped by their real-life experiences and treatments. It is also widely acknowledged that patients with anxiety, depression and psychosis show both fast and slow responses to treatments (Crowell et al., 2019; Kotan et al., 2011; Saveanu et al., 2015; Scangos et al., 2021; Shilyansky et al., 2016), often exhibiting distinct patterns and subserved by very different underlying neural mechanisms (Fava & Offidani, 2011; Zanos et al., 2018). However, to date, few cellular, animal or human clinical studies have systematically probed how cumulative life history (e.g. repeated bouts of stress or previous treatments) affects how phenotypes and underlying biology change over time (Akil et al., 2018; Hitchcock et al., 2022). This may be a missed opportunity. A key advantage of investigating such questions using cellular, animal and computational models is that there can be experimental control of the timing of potential triggering events, allowing the evolution of phenotypic and neurobiological readouts to be monitored before, during and after each event.

Below we foreground new approaches using cellular, animal and computational models to track the development of behavioural and neural signatures associated with anxiety, depression and psychosis and how they respond to treatment.

B.2.2 Expanding the timescale of investigation using cellular, animal and computational models

Temporal aspects of phenotypes are currently too often overlooked. It will therefore be valuable to promote investigations into the emergence and evolution of phenotypes over time, particularly during early developmental stages, which is characterised by multiple, often overlapping, processes.

Many iPSC studies examine single or selected time points without consideration of when a phenotype may emerge or whether it may resolve or change over time. Many genes associated with anxiety, depression and psychosis are expressed during early neurodevelopment (Falk et al., 2016; Muhtaseb & Duan, 2022; Rivetti di Val Cervo et al., 2021). Thus, assessing the impact of variations in these genes at multiple stages of development may reveal insights into the mechanisms of risk for a condition or help identify at which stage in development variation in a specific gene most increases the likelihood of a mental health illness. Exposure to environmental factors, such as severe infections or stress, during early development is also associated with increased likelihood for mental health illnesses (Kepinska et al., 2020; Massrali et al., 2022; Suri & Vaidya, 2015). However, such insults are often short-lived, thus raising the key unanswered question of how transient exposure to these environmental risk factors potentially causes lifelong change at the cellular and molecular level (Cattane et al., 2022; Warre-Cornish et al., 2020). One profitable approach using cellular models would be to assess phenotypic readouts either at multiple

time points or in a longitudinal manner to unravel the temporal dynamics of disorder-related mechanisms (Rivetti di Val Cervo et al., 2021; Warre-Cornish et al., 2020). Ultimately, understanding how genetic and environmental factors impact cellular and molecular processes longitudinally can provide insights into the underlying mechanisms of illnesses that manifest later in life.

It should also be a priority across approaches to develop assays that can be administered reliably in the same individual at multiple timepoints. For example, many of the canonical behavioural assays in animal studies were designed to deliver a quick and simple-to-administer snapshot at a single point in time, and often do not have the necessary test-retest reliability needed for longitudinal work (Ennaceur & Chazot, 2016; Fonio et al., 2012; Shoji & Miyakawa, 2021). Similarly, many patient studies take snapshots (e.g. using cross-sectional designs for assessing treatment effects). This impedes our ability to chart the trajectory of brain and behavioural alterations over extended time periods and thus learn more about what factors tip individuals into experiencing a pathological illness or cause a relapse.

One potential area of opportunity for animal models comes again from advances in home-cage monitoring as this provides an opportunity to monitor animals over long time periods (across the circadian cycle and over many weeks) without experimenter intervention (Bains et al., 2016; Castelhano-Carlos et al., 2014; Kempermann et al., 2022; Mingrone et al., 2020; Ziegler et al., 2021). Together with targeted manipulations of environmental or genetic factors, and machine learning approaches to parse out behavioural changes, this could allow new, detailed information to better understand those risk factors that can propel the development of symptoms of anxiety, depression or psychosis in individual animals and whether there are phenotypic, physiological and/or molecular correlates that can predict which animals are most susceptible to these and how they might respond to treatments (Mücke-Heim et al., 2023; Shemesh & Chen, 2023).

Machine learning models have shown some promise in developing prognostic markers using amalgamated clinical and wearable data for extended timescales. However, these studies are largely small in sample and with limited follow-up duration (De Angel et al., 2022). While many clinical trial studies do follow patients over time (e.g. (Barlow et al., 2017; Köhler et al., 2014; Newport et al., 2015; Warden et al., 2007; Wunderink et al., 2013)), the time window is usually months – some up to a few years – and may not be sufficient to capture the complexity of symptom changes over decades in real life. Some longitudinal cohort studies are being conducted at the moment, including the Adolescent Brain Cognitive Development (ABCD) project, which is the largest cohort study on mental health with neuroscience measures in the USA. Assessing longer timescales during neurodevelopment as in the ABCD study will also facilitate our understanding of causal relationships between biology and environment and mental health outcomes (Karcher & Barch, 2021). Importantly, such an effort would be critical for optimising early intervention strategies in young people with anxiety, depression and psychosis. Greater efforts towards standardised reporting measures will help to consolidate these early attempts (see section C).

B.2.3 Recommendations

Anxiety, depression and psychosis can each be considered trajectories: from the development of pathology through to the response to treatment. By embracing experimental approaches that allow for behavioural and/or physiological changes over extended timescales, we can propel new insights that could be invaluable to determine the neurobiological signatures of risk, triggering factors and resilience, potentially in the process revealing refined targets for early intervention.

- Increased attention should be given to using models as a platform to systematically probe and predict how phenotypes and underlying neurobiological measures change over time and following interventions.

C. How can we create a sustainable and standardised scientific environment to ensure work in cellular, animal and computational models can fulfil their potential and be as widely used as possible?

C.1. We need to establish community standards for models and their outputs

C.1.1 Summary

As the use of cellular, animal and computational models in mental health research continues to increase, the need for clearer gold standards for reporting and methodological practices has become more urgent than ever. This need includes establishing appropriate standards for cellular phenotypes that consider mechanistic or drug discovery needs and ensuring common standards for task design and computational modelling. The reasons for this are twofold.

First, if we are to embrace true underlying heterogeneity in our brain and behavioural samples, we need to ensure that noise or errors introduced through differing approaches are minimised. 'Good' heterogeneity – that which we wish to consider and probe, as described in section B – occurs both due to a spectrum disorder with differing symptoms and due to individuals' diverse genetic and environmental backgrounds. To embrace and understand the role this obligatory diversity plays in shaping mental health trajectories, we need to eliminate 'bad' heterogeneity arising from differing experimental designs or methodologies.

Second, a lack of standards could hinder efforts towards rigour and reproducibility. Indeed, most scientific communities have consensus on key methods used across individual laboratories, such as a standard operating procedure, so that experimental procedures and results can be compared. Yet, in many areas of neuroscience and psychiatry research, standardised procedures in data collection and analysis are still lacking, preventing cellular, animal and computational models from reaching their full potential.

Together, these issues highlight the need to establish methodological consensus across modelling fields. We will further discuss each need in these sections.

C.1.2 Ensuring appropriate standards for cellular phenotypes that consider the disorder-relevant mechanism or drug discovery need

In cellular models, there is a critical need to consider what is the most appropriate (disorder-relevant) phenotype to assess.

A wide range of end point assays is easily applied to iPSC models, but we need to carefully consider what is the most relevant phenotype for different purposes – i.e. for elucidating causal mechanisms for mental health illnesses versus drug-screening studies. Developing standardised recommendations for phenotypic pipelines (biochemical, imaging and physiological) for mechanistic and drug discovery studies will be necessary (Kleiman & Engle, 2021; Silva & Haggarty, 2020). For example, it is important to understand what readouts or measures are specific to symptom domains, diagnoses or specific phenotypes (observed in the patient, such as cognitive measures, neuroimaging, or genetics) (Dutan-Polit, 2023; Falk et al., 2016). In order to better link animal and human scales, it is also critical to identify and develop phenotypic measures that are cross-species or cross-scale and relevant in multiple models (Dutan-Polit, 2023; Halff et al., 2021; Onwordi et al., 2020; Silva & Haggarty, 2020). This need may be particularly acute for drug screening.

There is also still a need to assess how different technical approaches to generating specific neuronal or glial cell types induce variability between batch differentiations and lines and between studies and centres (Engle et al., 2018; Hanger et al., 2020; Muhtaseb & Duan, 2022; Volpato & Webber, 2020). It is crucial to identify and validate (using datasets generated from human tissue, from both typically developing and those with diagnosis mental health conditions) robust identifiers of desired cell types – at genetic, epigenetic, proteomic, cellular and functional levels (Engle et al., 2018; Rivetti di Val Cervo et al., 2021). To achieve this endpoint, more effective data sharing and multicentred efforts, particularly those involving multiple key stakeholders including academia and industry, are required. This will enable a deeper understanding of the major drivers of technical variability when using iPSC-based models. Another key element will be to bring groups from academia, biotechnology, pharmaceutical companies and manufacturers of key reagents together in order to develop high-quality products essential for the differentiation of iPSCs into specific cellular models.

Recent efforts have gone into identifying publicly available cell lines that could be used as a standard across studies and centres (Pantazis et al., 2022; Volpato & Webber, 2020); with defined polygenic scores (Dobrindt et al., 2021). Consortia, such as the iPSC Neurodegenerative Disease Initiative in partnership with Jax lab, are using a single line (Ramos et al., 2021) to generate

CRISPR-knockout lines of genes associated with neurodegenerative diseases. This offers researchers access to highly characterised cell lines where the onus of iPSC maintenance and assessing quality of iPSCs is divided between the end user and Jax lab. Despite this progress, there is a need to better define differentiation protocols, which can often differ minimally at the surface but result in substantive differences in phenotypes. Here again, multicentred studies will aid in determining the bases of technical variability. Collectively, a greater emphasis on multicentre, replication studies and use of highly characterised and even consensus iPSC lines, a better understanding of how different differentiation approaches produce variability in observed phenotypes and recommendations on standard operating procedures will aid in separating technical and biological variation in iPSC studies.

C.1.3 Ensuring common standards for task design and data collection to enhance reliability

In animal and human studies, there is a critical need to ensure behavioural tasks have satisfactory reliability (e.g. test-retest reliability) and are well documented to allow protocols and data to be easily shared.

This need is particularly important in treatment studies, which aim to demonstrate changes in neural activities, behaviour or clinical symptoms due to an intervention (e.g. response to cognitive behavioural therapy or an antidepressant over time) instead of practice effects. Similarly, in animal research, rather than being rigidly prescriptive about which specific assays and models relevant to anxiety, depression and psychosis should be adopted, reproducible advances are most likely to be made if there is foundational consensus on best practice for behavioural phenotyping and cross-species translation. Careful thought will be required to choose appropriate batteries of tests or control conditions to ensure that factors such as baseline changes in locomotor activity do not contaminate results (Fisher & Bannerman, 2019; Robinson, 2014; Slattery & Cryan, 2012). Particularly for new models and paradigms, it will be highly important to support replication within and across research teams, and across strains and species, allied to rigorous reporting of experimental conditions (Drude et al., 2021). Given the increasing range of hardware, approaches and machine learning algorithms being implemented to enrich the profiling of animal behaviour, it would be timely and profitable to consider how to benchmark datasets across groups to ensure reliability and facilitate data sharing (Ziegler et al., 2021).

The need for examining task reliability is highlighted by several recent discussions on this topic (Hedge et al., 2020; Karvelis et al., 2023; Paredes et al., 2021; Zorowitz & Niv, 2023). For example, a recent analysis suggests that in a community adult sample, the mean between-session test-retest reliability of the key computational parameters of the Pavlovian instrumental transfer task – a popular behavioural task used in computational psychiatry studies – is as low as 0.19 (Paredes et al., 2021). If used in a treatment or interventional study, a task with low reliability could affect the interpretation of findings in several different ways, from masking true treatment effects (false negatives) to artificially inflating small or null effects (false positives). As such, quantification of task reliability must be addressed in future work.

Several factors might lead to the unsatisfactory task design in existing research. In human studies, the laboratory testing environment could be perceived as unpleasant by participants. For instance, the confining environment of MRI scanners, combined with scanner noise, may limit the duration of each session to one hour and each cognitive task to 30 minutes or less; and clinical groups could have even less tolerance to such testing environments than non-clinical participants. Certain features associated with a mental health condition, such as lack of motivation or fatigue as common symptoms of depression, could further limit the window for assessment in patients. In extreme cases, such as behavioural testing and intracranial recording during a neurosurgery (e.g. in DBS patients), each task or measurement might be limited to a duration as brief as a few minutes.

This calls for the need for designing highly efficient yet robust paradigms for human clinical research so that data collected under such conditions are still optimised for computational modelling purposes. For instance, tasks should ensure a sufficient number of trials so that they can generate stable computational estimates. To address this, simulations must be implemented for task design to ensure optimal trial numbers, durations and sequences (see section C.1.4 for a more detailed discussion on this topic).

C.1.4 Establishing standard practice for computational modelling

The need for establishing common standards for conducting computational modelling is no less important than ensuring high task reliability. While each model has its own specifics, the aforementioned models (reinforcement learning, Bayesian, biophysical models and machine learning) also share commonalities in their procedures. For instance, researchers should clearly document and provide justification for the chosen model setups (e.g. why a reinforcement learning model should include a “memory decay” parameter but not two separate learning rates). For theory-driven models (reinforcement learning, Bayesian and biophysical models), pre-experimental simulation can help with hypothesis formation, robust experimental design (e.g. to determine the minimum number of trials needed or optimal sequence of stimuli for the task) and identification of potential noise

arising from parameter estimation and approximation processes (Daw, 2011; Wilson & Collins, 2019). Procedures such as parameter recovery are crucial for ensuring the identifiability and robustness of computational estimates. Finally, comparing a set of models ("model comparison") is almost always preferred over using a single model. Several tutorials already provide examples of how computational modelling should be standardised (Daw, 2011; Wilson & Collins, 2019) and can be updated as the field of modelling continues to grow and improve.

The role of standards for neuroimaging-based biophysical models also derives from the need to separate empirical noise from true patient variability. Currently, the field uses a variety of different mathematical equations to model a patient's brain data, from simple kuramoto oscillators to spatially extended neural field equations. Whether one type or another is most relevant for understanding or prognosing mental health symptoms is an area of active research. However, the key point here is that to address this question, the community needs a standardised output (e.g. prognostic ability at 3, 6 or 24 months after treatment X) rather than a prescribed technique. Promoting parameter sharing and reproducible modelling will be key to this and will help to address which model is most stable, robust and informative. Supporting transparent and efficient code for neuroimaging models is important because the degrees of freedom available are high and choices on parameter-estimability must be considered carefully, as in behavioural models. Developing techniques around brain imaging that allow clinicians to answer very specific questions in their workflow may take a piecemeal effort. Painstakingly small steps in very specific areas can lead to a neuroimaging application that is robust, has validity and improves the practice by which patients are diagnosed and treated.

Finally, as reviewed in previous sections (e.g. 1.3.2.4), machine learning models have emerged as a powerful tool for mental health research. They have generated insights from identifying patient heterogeneity and subtypes to identify biomarkers that are predictive of treatment outcome (Pintelas et al., 2018; Sajjadian et al., 2021; Vieira et al., 2020). Nevertheless, there is a need to establish gold standards for such studies to fully harness the power of big data. For example, cross-validation steps are important for ensuring predictions are accurate and reliable. Whenever feasible, out-of-sample predictions should be provided. Machine learning studies in the mental health field can additionally benefit from established standards of machine learning in other areas (Pereira et al., 2009; Turgeon & Lanovaz, 2020; Vercio et al., 2020). With the increase in large datasets involving mental health data across multiple sites (e.g. UK Biobank, the ABCD study), better practice of machine learning models for anxiety, depression and psychosis-related prediction will become increasingly feasible and common in the years to come.

C.1.5 Recommendations

We should attempt to establish gold standards that squash technical noise and retain true biological variability while providing robust and reliable findings. These needs exist particularly for behavioural modelling, where currently this mission is implicit in the literature but not necessarily or explicitly implemented or agreed upon. Each level of analysis has its own challenges, but behavioural studies could learn from cellular approaches, where standardisation is more pervasive. In cellular studies, standardised phenotypes can now go further to the point where they are specific for either a mechanistic, symptom-derived or drug-screening purpose.

- To maximise the promise, reliability and reach of cellular, animal and computational models, it will be valuable to reach a consensus over foundational criteria against which the models can be assessed and to encourage replication, data sharing and transparency.
- It will be important to continue to support educational efforts centred around good modelling practice, which will facilitate the adoption of established modelling standards.

C.2 We need to ensure datasets are accessible and diverse, facilitated by scalable measurement tools

C.2.1 Summary

To maximise the potential of all mental health research data, and in particular big data, researchers must be able to access diverse datasets with ease. Despite many funders' explicit mandate for data sharing, there is still a lack of infrastructure to support these efforts and of universal standards for how to share data in an accessible yet secured way. As a result, many researchers often view data sharing as an administrative burden instead of a meaningful task contributing to scientific goals.

A more critical issue concerns the diversity of available datasets in neuroscience and mental health research. At the moment, the majority of data are collected in highly developed countries and research participants often come from WEIRD (western, educated, industrialised, rich and democratic) societies (Henrich et al., 2010). This issue prevents us from understanding anxiety, depression and psychosis in non-WEIRD societies and severely dampens the generalizability of research findings. A notable example addressing this challenge is the Accelerator Program for Discovery in Brain Disorders using Stem Cells (Research, 2023a), initiated by three distinguished Indian institutions – the National Centre for Biological Sciences, the

Institute for Stem Cell Science and Regenerative Medicine and the National Institute for Mental Health and Neurosciences. This programme has a focused mission of comprehensively studying mental health conditions in India through a prospective, longitudinal cohort comprising patients with individuals with mental health conditions, including at-risk individuals with genetic predisposition, along with asymptomatic controls. A combination of a standardised battery of clinical assessments as well as genetic and molecular and cellular analyses, facilitated by a biorepository of biological material, including patient-derived iPSCs, genetic and patient data has been established (National Centre for Biological Science, 2023b) This endeavour aims to enhance the mechanistic understanding of mental health conditions in a way that is specifically tailored to individuals in the Indian subcontinent (Mahadevan et al., 2021; Sreeraj et al., 2021; Viswanath et al., 2018).

Finally, it is important to consider the scalability and inclusivity of measurement tools in mental health research, which would create possibilities for studying anxiety, depression and psychosis outside labs in WEIRD settings. Progress has been made (see section C.2.4. for a detailed discussion) in terms of portable MRI scanners, wearable EEG systems and optically pumped magnetometers (OPM-MEG). The continuation of such efforts calls for collaborations across academic and industrial entities.

C.2.2 Increasing the accessibility and diversity of neuroscience datasets

FAIR principles (FAIR, 2023; Wilkinson et al., 2016)), an acronym which refers to the findability, accessibility, interoperability and reuse of digital assets, is a set of principles that were established in 2016 to enhance the management and harmonisation of scientific data. Despite many funders' efforts regarding data and resource sharing, in practice, FAIRness is lacking across cellular, animal and computational models (Akil et al., 2011; Martone et al., 2004; White et al., 2022). Beyond well-known consortium studies, it is often difficult for researchers to identify neuroscience and mental health datasets that are relevant to their research interest (Ferguson et al., 2014). Even with usable datasets to analyse, it is often still difficult and burdensome to access this data and researchers often need to navigate unfamiliar administrative and sometimes legal issues. Furthermore, neuroscientific data collected by one research group is often not readily analysable by another group who might use a very different analysis pipeline or programming language. Finally, neuroscientific data usage and re-usage rates are generally low compared with the richness of data being collected, which has led to certain secondary analysis funding initiatives. It is thus important to reach community standards for best data sharing practice, with both accessibility and privacy issues in mind (see (Markiewicz et al., 2021; Pernet et al., 2020) for initial efforts).

A more critical issue concerns the diversity and accessibility of research data being collected in existing research on anxiety, depression and psychosis. In order to fully appreciate the impact of ancestry, biological sex and genetic background on mental health conditions, the need for iPSCs with accompanying detailed genetic, ancestral and clinical information was highlighted above (see sections B1.2 and B1.3). However, there is also a need to ensure FAIRness in data accessibility and sustainability in resource sharing (Nehme & Barrett, 2020; Steeg et al., 2021). This needs to be applied at multiple levels: from ensuring sustainability in ethics, informed patient consent (including the General Data Protection Regulation (GDPR) in the EU and other local legal requirements) and use of unique cell line names to enable traceability and discrimination of cell lines and sharing of (anonymised) clinical and genetic data as well as of the actual lines, to ensuring that data generated from iPSC models (from molecular to cellular datasets) are openly available and accessible (Dutan-Polit, 2023; Nehme & Barrett, 2020; Steeg et al., 2021). Two relevant examples of key recommendations for these approaches or of applications of these principles are from EBiSC (Steeg et al., 2021) and the Library of Integrated Network-Based Cellular Signatures (LINCS) consortium (Keenan et al., 2018).

In human clinical studies, there is a critical need to include research participants from diverse biological and cultural backgrounds across all levels of investigations (as discussed in section B.1.3). Unfortunately, current computational studies in humans are often based on non-representative samples of research participants, limiting their generalisability to wider, non-WEIRD contexts (Henrich et al., 2010). Even for studies using out-of-sample validation procedures, the independent dataset often still suffers the same issues as the main dataset (no diversity, small *n*) and thus does not completely address the generalizability issue.

The lack of larger, diverse datasets of neural, cognitive, and clinical measures relevant to mental health is partially due to the relatively short history of using machine learning in neuropsychiatry research as opposed to in other areas (e.g. computer version). Another contributing factor is the complexity of data in most neuropsychiatry studies compared with other areas, which often rely on data that are static images (for image recognition models) or text (for language models). In contrast, input data in neuroscience studies – such as fMRI time series – often have much higher dimensionality, more complex dynamics and greater noise introduced by various factors (e.g. differences in image acquisition protocol). Nevertheless, technical challenges can be addressed if we reach the same level of awareness of the lack of diversity issue and willingness to address it. For example,

efforts such as the ABCD study mentioned above (Garavan et al., 2018) and the All of Us Research Program ("The “All of Us” Research Program," 2019) have started to address data diversity issues. To conclude, the field needs to continue with inclusivity and diversity efforts in participant recruitment and data collection across cellular, animal and computational models.

C.2.3 Advancing the development and deployment of lower cost, more accessible and inclusive measurement tools

Finally, there is a need to advance the development of low-cost, accessible measurement tools for mental health and neuroscience research.

One of the biggest bottlenecks preventing neuroscience research from establishing large, diverse datasets is the high cost and low accessibility of many measurement tools. Such an issue becomes particularly salient when considering conducting neuroscience and mental health research in low- and middle-income countries (LMICs). For instance, it is estimated that in a sub-region of Western Africa (comprising Benin, Burkina Faso, Cape Verde, Ivory Coast, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Mali, Mauritania, Niger, Nigeria, Senegal, Sierra Leone and Togo), there are only 84 MRI scanners – and the vast majority are non-research scanners – for a total population of 370 million (Anazodo et al., 2023; Hilabi et al., 2023; Ogbole et al., 2018). EEG systems are generally much cheaper than MRI, yet their availability is still lower in LMICs – with roughly only 60–70% of people having access to EEG (McLane et al., 2015). Furthermore, traditional MRI, EEG and MEG systems often have strict exclusion criteria, which can prevent individuals from certain racial backgrounds (e.g. the majority of Black people have EEG-incompatible hair textures) from participating in research. This calls for the need to develop novel neural recording systems.

Addressing this need requires close collaborations between academia and industry – the former often makes theoretical and experimental advances and the latter has the infrastructure and incentive to commercialise and mass produce the developed tools. In recent years, advances in neurotechnology have started to show great potential as scalable tools, with the goal of collecting neural readouts outside laboratory settings. For example, lower cost, more portable MRI systems have started to emerge (e.g. (Deoni et al., 2021; Sheth et al., 2021)), which promise to increase the availability of MRI as a brain measurement in LMICs. Novel EEG systems – often wearable – represent another area where industry–academia collaborations have led to the invention of more inclusive and cheaper systems. These systems have been used to measure cognition and behaviour in field-study-like settings (e.g. (De Vos, 2014; Ladouce et al., 2019)); some even use dry electrodes (Gargiulo et al., 2008), which can remove the limitations related to subject’s hair texture and style. Similar breakthroughs have also been made in terms of OPM-MEG (Boto et al., 2018), which allow subjects to move more freely during recording and can significantly increase the tolerance of clinical patients to research protocols. A revamp of the old functional near-infrared spectroscopy (fNIRS) technique has also generated newer generations of the device that are wearable and have improved precision and interpretability (Pinti et al., 2020).

These neurotechnological advances, combined with novel behavioural and cognitive measures such as eye tracking, mouse tracking, GPS data and other mobile-based data collection (e.g. as discussed in section A.2.4.), will lay important foundations for neuroscience and mental health research across contexts and geographical locations.

Likewise, there is also a need to ensure that the tools needed to conduct neuroscientific research in cellular and animal models are as made as widely available as possible and do not become the preserve of a handful of well-resourced institutions (Maia Chagas, 2018; Marder, 2013). Many of the methodological advances in neuroscience in the past decade have come with a concomitant increase in setup and running costs and a level of technical complexity that can be a barrier to widespread adoption. In response to this, there has been a burgeoning interest in the development and dissemination of low-cost, open-source analogues of these tools within the community (Akam et al., 2022; Lopes et al., 2015; Luxem et al., 2023; White et al., 2019). It is important that the field incentivises developments of particular relevance to mental health research to follow these examples. This will create opportunities for diverse communities of researchers to conduct experiments to characterise brain–behaviour relationships in model systems at scale, which will accelerate progress and innovation in mental health research globally.

C.2.4 Recommendations

While implementing good practice around data, code documentation, sharing and the use of existing open-source platforms (e.g. GitHub, National Data Archive (NDA), NeuroVault), it is vital that the field make every effort to increase diversity and representativeness in large samples. Carefully considering hurdles that might prevent inclusivity, such as cost, and potentially using research methods that are more inclusive (e.g. behavioural research, wearables, EEG) rather than less inclusive (e.g. MRI) should be championed. Incentives should be put in place to promote accessibility of open-source analogues of key neuroscience tools most relevant to mental health research in model systems to ensure they are as widely accessible as possible.

- Data repositories need to include diverse samples derived from, and available to, a range of communities across the globe.
- Accessibility and inclusivity need to be considered when choosing or developing measurement tools.

Conclusions

Cellular, animal and computational models have made important strides in advancing our understanding of the brain. Nevertheless, key knowledge gaps still exist across all levels of investigations, preventing laboratory findings from improving the understanding and treatment of mental health conditions. The main objective of this landscaping report is to explore the potential of how integrating cellular, animal and computational models can advance knowledge of and early intervention in anxiety, depression, and psychosis. After engaging with key opinion leaders and the relevant literature, several overarching themes have emerged (see Table 2).

First, to improve our understanding of these mental health illnesses, there is an urgent need to bridge the translational gap between theoretical and experimental neuroscience models and the clinic. To address this, laboratory research needs to be informed by clinical reality; to achieve this, it should be conducted in a collaborative, cross-disciplinary fashion, with direct clinical and/or lived experience input as standard. We also need to ensure our behavioural measures and paradigms are rich, ecologically grounded *and* computationally and neurobiologically tractable. To this end, models must endeavour to capture complex, high-order cognition and behaviours, ideally aided by automated, neuroethological platforms and using measurements that go beyond standard forced choice tasks. Translation between models and the clinic will be facilitated through continued development of better and more harmonised cross-species and cross-scale neural and autonomic readouts.

Second, to better predict, stratify and intervene early in conditions such as depression, anxiety and psychosis, we must recognise and embrace heterogeneity and diversity across conditions, leveraging variation within our models to identify neurobiological risk factors aligned with individual differences. This calls for studies that dissect how social factors, biological diversity such as sex and race or ethnicity, and gene–environment interactions shape brain function and phenotypic variation. Furthermore, there is a critical need to unravel how cumulative experience across the lifespan shapes mental health trajectories and their neural correlates. Addressing both longer scales and earlier experiences during neurodevelopment in cellular, animal and computational models will help better determine the neurobiological signatures of risk or triggering factors or resilience, potentially in the process revealing refined targets for early intervention.

Finally, to ensure that we maximise the potential of neuroscience models for mental health, it is imperative that a healthy and diverse research culture is prioritised. To this end, we must establish community standards for models and their outputs across cellular, animal and computational studies. We also need to enhance the accessibility, diversity and inclusivity of neuroscience datasets, facilitated by scalable measurement tools. Innovation and progress in anxiety, depression and psychosis research will be expedited by ensuring that state-of-the-art neuroscience methods are as widely accessible as possible. To paraphrase Eve Marder (Marder, 2013), the new explorers into the unknowns of mental health conditions require sponsors who realise that sending multiple ships into the unknown is more likely to succeed than sending a small number of lone voyagers.

Building on this latter point, we end this report by noting an issue that is far from unique to neuroscience or mental health research, but is a particular hinderance to transformative progress through the meeting of these areas. Much of what we are advocating for requires a move away from what have been common approaches in the field over many years. To achieve this requires an understanding of the factors that have worked against the widespread adoption of these practices before now. For neuroscience to deliver on its promise for mental health research, it is imperative for the field to develop structures and funding models that incentivise creativity allied to scientific rigour, and taking a long-term perspective aimed at ambitious goals.

In summary, the promise of neuroscience to deliver novel interventions for depression, anxiety and psychosis requires the research community to prioritise imaginative and bold ideas that embrace the complexity of these conditions. Throughout these endeavours, research must actively integrate the lived experience of individuals afflicted with such conditions for laboratory models to stay close to reality. By embracing diversity, adopting a ‘messy science’ approach, promoting interdisciplinary integrative science, we can accelerate our progress toward a better understanding and improved care of these mental health illnesses.

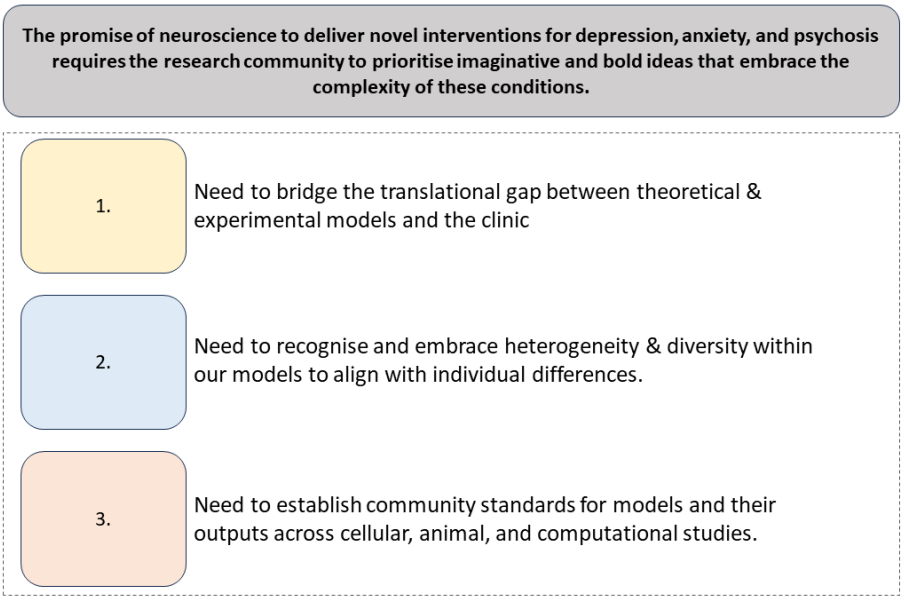

Table 2. The promise of neuroscience to deliver novel interventions for depression, anxiety, and psychosis requires us to prioritise imaginative and bold ideas that embrace the complexity of these conditions.

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Conflict of interest statement

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XG has been a speaker and/or consultant and/or has currently or previously received funding support for academic collaborations and/or contract research from Essence Global and has previously received research support from Wellcome.

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