nature reviews drug discovery

https://doi.org/10.1038/s41573-026-01509-0

Perspective

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Towards precision psychiatry: initial foundations and future directions

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Abstract

Psychiatric disorders carry a major public health burden, yet advances in treatment have been slow to emerge, partly owing to reliance on traditional symptom-based diagnostic frameworks. In this Perspective, we explore the emerging paradigm of precision psychiatry, which seeks to align therapeutic development with underlying neural biology dysfunctions using biomarkers. Drawing lessons from the success of precision oncology and neurology, precision psychiatry utilizes patient-specific biological measures of brain function — such as electroencephalography, objective behavioural assessments, functional magnetic resonance imaging and peripheral biomarkers — to understand drugs' effects on the brain, define indications and stratify patient populations for targeted intervention development. We discuss mechanistic approaches that focus on excitation–inhibition balance, reward and aversion circuits, hippocampal–prefrontal neuroplasticity, and processing of social cues, highlighting how these frameworks can elucidate drug mechanisms and predict treatment responses. Proof-of-concept examples, including predictors of response to standard-of-care treatments, and patient subgroup-driven successes in postpartum depression and schizophrenia, underscore the potential of stratified trials to reduce development risks and improve clinical outcomes. We address ongoing and future regulatory, commercial and clinical considerations for integrating scalable and reproducible biomarkers into drug development. Precision psychiatry thus represents a new strategy to refine clinical trial design and develop biology-defined treatments, which may help to overcome longstanding challenges in psychiatric drug discovery.

Sections

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Introduction

Psychiatric disorders affect a substantial portion of the population, yet treatment options are limited, with progress in drug development stagnating for decades. Although conditions such as major depression have multiple treatment options, these are often variations of the same mechanisms and do not provide benefits to a large portion of the patients. By contrast, conditions such as cognitive impairment associated with schizophrenia lack effective treatments, despite substantial research investment. This issue is compounded by the retreat of Big Pharma from psychiatry 10–15 years ago, citing limited progress in psychiatric neuroscience.

To overcome some of these limitations, the field is increasingly embracing a precision psychiatry approach, inspired by the successes of precision medicine in oncology and neurology. Here, we address how precision medicine can be applied to drug development for psychiatric indications, discussing recent approaches based on symptom domains or subsets of patients sharing common biology, and looking forward to implementation of brain circuit-based and other biological measures for patient selection. We explore some specific examples of circuit alterations and potential measures for use as pharmacodynamic (PD) and predictive biomarkers, highlighting promising efforts as well as missed opportunities.

This emerging approach contrasts with the traditional trial-and-error method of diagnosing and treating psychiatric disorders, which has shown limited progress over the years. Importantly, even a partial understanding of neurobiology, including one borne primarily out of empirical observations, without a deep mechanistic understanding, may substantively advance outcomes over the current state of affairs. Although we would not expect all biomarkers and drugs outlined in this article to successfully play out if developed through a precision approach, even limited success or modest enrichment of drug response would represent a substantial change in how drugs are developed and deployed in psychiatry. In other words, successes and failures to date should be considered the initial steps of a larger precision-medicine thesis. Much more work will be needed before the role of a precision approach is established in psychiatry drug development, as it now is in other areas of medicine.

Defining precision psychiatry

We define the concept of precision psychiatry similarly to precision medicine, in which patient-specific information (such as biology assessed at any of various levels, clinical characteristics and psychosocial factors) is used to divide a broader clinical population into subgroups whose disease has a shared underlying pathophysiology and/or are more likely to respond to specific treatments. This segmentation may be based on either mechanistic causal relationships or empirical associations that are later understood. Biological measures that help to define target populations are often referred to as stratification or enrichment markers, and intermediate PD biological measures linking disease processes to treatment effects are known as surrogate biomarkers or intermediate phenotypes[1].

Precision psychiatry offers a potential breakthrough by focusing on the biological underpinnings of psychiatric illnesses and tailoring treatments to individual patients or specific subpopulations (Fig. 1). This new direction uses advances in neuroscience to identify and measure specific brain biology dysfunctions in both humans and animal models. The key principles of precision psychiatry include the following points.

1. Mechanistic connections: drugs are designed to target specific disease mechanisms that affect brain function, which should be measurable in humans (and translatable from experimental animals). An important element in a precision approach is to identify measures that index the state of key brain systems and consequently a drug's effects on those systems. These PD effects may inform about actions of the drug (such as dose–response) but may also serve as surrogate markers of ultimate clinical effect.
2. Patient selection biomarkers: identifying biomarkers that predict treatment response helps to define responsive patient populations and strengthens the drug–disease link, reducing development risks along with sample sizes required to show drug effects. Ideally, patient selection biomarkers should align with PD markers, as targeted therapeutics aim to remediate pathophysiology characterized by abnormalities in the target process. Precision is possible, however, even if PD and patient selection markers are different, in part because of as-yet-emerging understanding of pathophysiology.
3. Transdiagnostic biologically defined treatments: because precision approaches target treatments for biologically defined patient subgroups, this may facilitate therapeutic development that transcends boundaries between traditional clinically defined diagnoses by focusing on biological processes that may underlie different symptom clusters.

Lessons from precision oncology and neurology

Historically, cancers were classified based on characteristics like tissue type and cellular structure. However, as research advanced, tumours became classified according to underlying mechanisms, leading to targeted treatments. The key shift was from descriptive categories to those defined by the biological drivers of a given tumour, particularly somatic genomic alterations and their downstream disease consequences. This shift is reflected by the growing body of precision oncology research (Fig. 2a), with important milestones such as the approval of trastuzumab and gefitinib for patients with overexpression or genetic mutations of the targeted receptor, and later, immuno-oncology treatments such as pembrolizumab that target specific characteristics of diverse types of cancer in a tumour-agnostic manner. Therefore, the operative source of 'precision' in oncology has become the tumour's genomics-driven landscape, which provides mechanistic stratifiers such as HER2 amplification, EGFR mutations and MSI-H/TMB-high status, which in turn directly inform treatment selection independent of tissue of origin. Even within oncology, there have been debates about whether biomarker-based drug development or broader, all-comer approaches are more effective — debates that have only recently been resolved with the adoption of precision medicine across many oncology indications owing to compelling clinical outcomes[2].

Further support for a precision approach comes from neurology, in which recent drug approvals have been driven by patient selection or PD effects on biomarkers. For example, treatment with anti-amyloid strategies in Alzheimer disease requires evidence of amyloid pathology (for example, by positron emission tomography (PET) imaging), whereas approval of tofersen for ALS (amyotrophic lateral sclerosis) was based on its ability to reduce neurofilament light chain levels as a measure of neuronal damage[3–5]. In neurodegenerative conditions, the integrative level at which pathophysiology is understood is that of protein function, leading to the use of molecular pathology biomarkers, whether captured centrally or peripherally[6].

By contrast, precision psychiatry research is at an earlier stage, comparable citation-wise to oncology 15 years ago. In psychiatry, in which clear genetic or genomic disease drivers remain elusive and

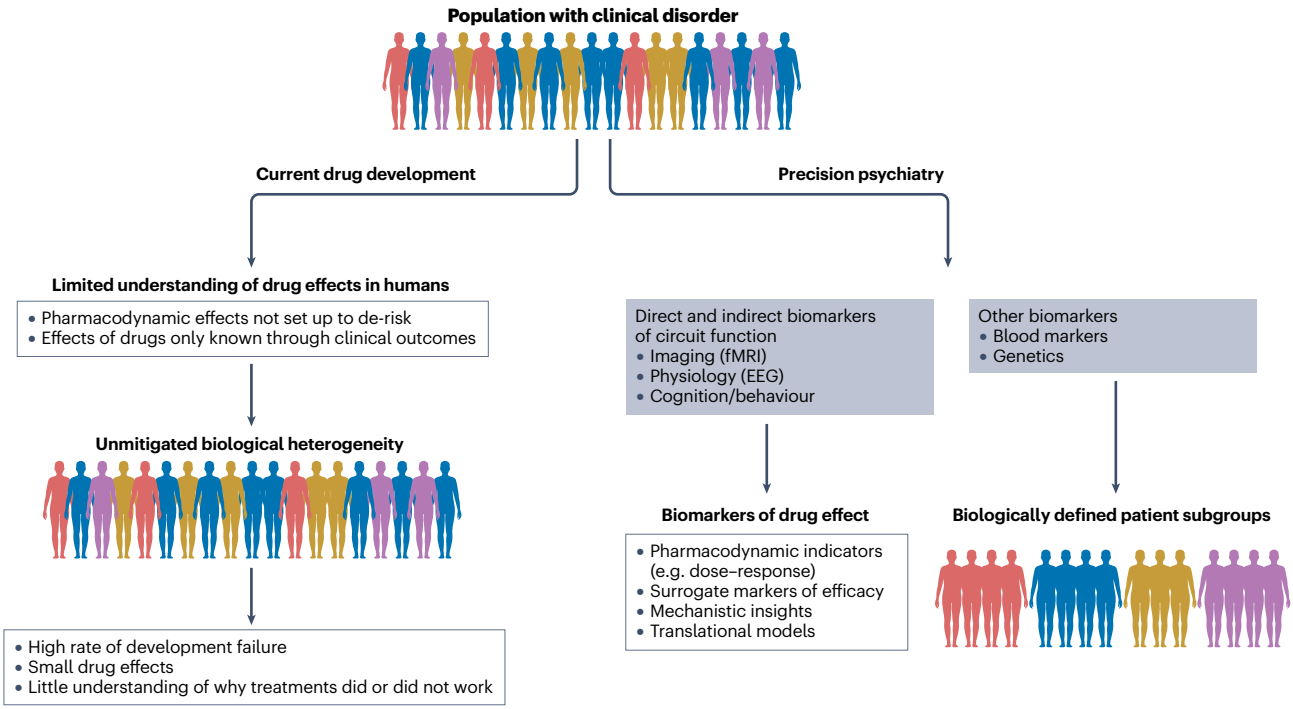

Fig. 1 | The opportunity for a precision framework in psychiatric drug development. Psychiatric disorders (depression and schizophrenia as examples) can be characterized along multiple dimensions or domains of dysfunction, which can map to distinct brain circuits or other biological features, and serve as separate therapeutic targets, guided by objective biological measures of those circuits. The current 'all-comer' approach often mitigates little of the development risk until the ultimate readout of phase III studies, resulting in a higher risk of failure and smaller clinical effects owing to reliance on unselected populations. Because the biology of a drug's treatment effects in humans is often not measured, nor are biological predictors of clinical response used during development, the opportunity for a feedback loop is missed in terms of explaining why a trial failed and what can be improved next time. A precision psychiatry approach to drug development seeks to intervene at each of these 'failure points' to increase the odds of success and inform other programmes through the extracted learnings. EEG, electroencephalography; fMRI, functional magnetic resonance imaging.

there has largely not been a focus on specific molecular pathologies, the emphasis has shifted towards phenotypic approaches, particularly using brain circuit-based frameworks. Rather than focusing on symptoms, behaviours, genetics or neurotransmitters, this approach views neural circuits as key drivers of distinct behaviours, offering a more integrated and contextually relevant understanding of disease. In this framework, brain circuits represent the level of the biological system at which psychiatric symptoms are generated, risk is mediated, and effects of drugs can be observed, making measures of circuit function the closest analogue to genomic drivers in oncology.

Primary indices of brain circuit function used in the literature include imaging modalities such as electroencephalography (EEG; a direct measure of neurophysiology at high temporal but low spatial resolution, which can index inter-regional connectivity and cortical microcircuit function) and functional magnetic resonance imaging (fMRI; a low-spatial-and-temporal-resolution indirect measure of activity or connectivity more sensitive to deep brain structures), as well as cognitive/affective tasks (which probe the behavioural output of circuits)[7]. EEG is currently clinically used for a wide range of purposes across various conditions, including management of seizures and epilepsy; polysomnography; diagnosis of encephalopathy; monitoring of anaesthesia; testing of evoked responses in the visual, auditory and somatosensory system; and diagnosis of brain death and disorders of consciousness. Although fMRI has seen little clinical use outside of certain presurgical planning contexts, MRI more generally is a widespread clinical tool. Behavioural testing is a mainstay of neuropsychological assessments across a wide range of conditions.

Although there are other potential levels of measurement that could inform aspects of precision psychiatry, such as genetic risk, common psychiatric disorders have proved highly polygenic, with any single polymorphism explaining very little variance (and not able to index drug-related changes). Other peripheral blood biomarkers potentially serve both enrichment and PD needs, but are often removed from the function of the brain itself. Although it could be argued that psychiatry is personalized by its clinical nature, it is hardly precise, and attempts at a clinical-based precision approach have not yet been successful[8]. Anchoring patient selection in objective, biology-linked features such as circuitry assessments offers a stronger path for precision psychiatry. A brain circuit-based approach could also offer greater translational potential for drug development than symptom-based strategies, given that rodent models have often failed to translate directly to human outcomes.

Proofs of concept in psychiatry

Precision psychiatry studies, which have multiplied over the past 5–10 years, have largely taken two forms: 1) a prediction of a known outcome of interest (such as treatment response, conversion to disease from a high-risk state), or 2) 'biotype' identification based on a

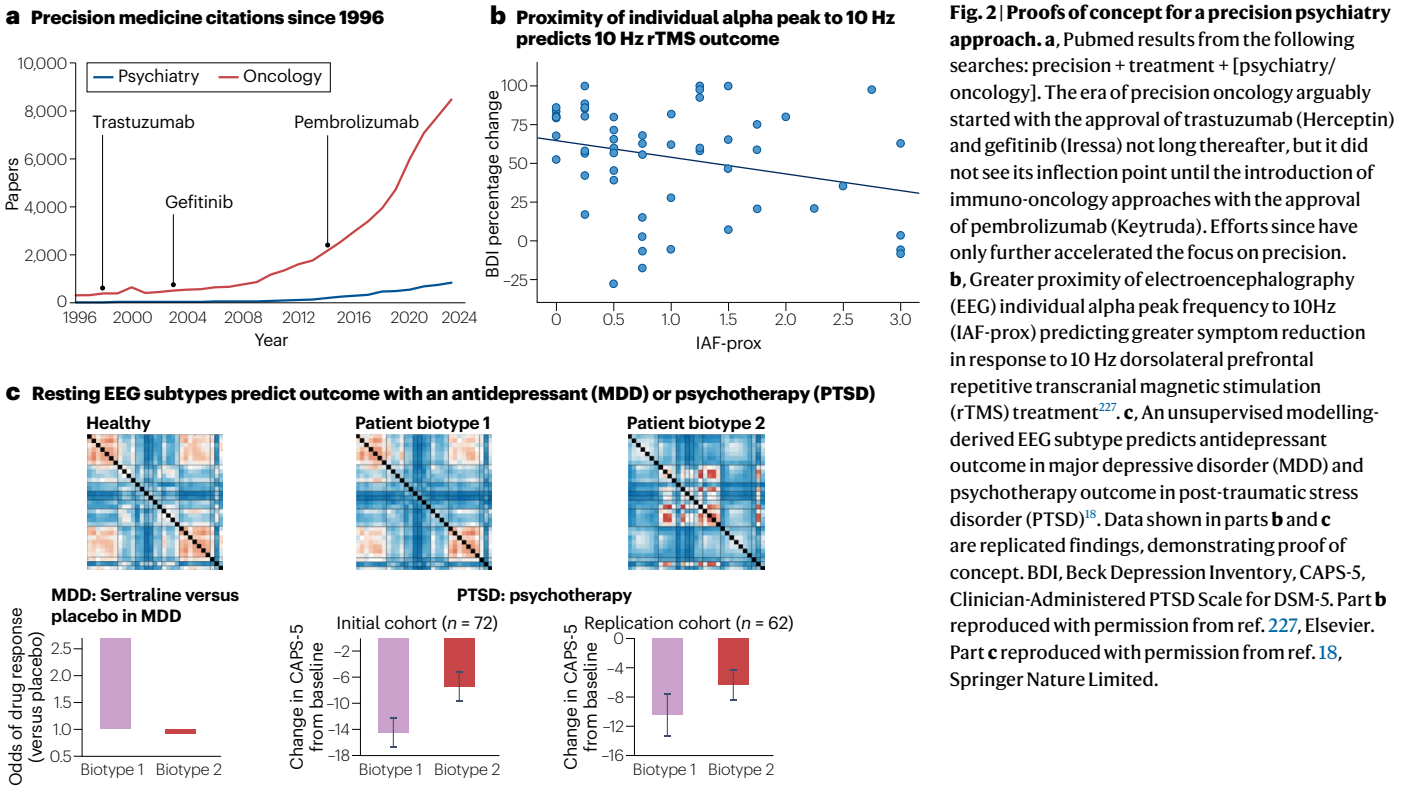

Fig. 2 | Proofs of concept for a precision psychiatry approach. a, Pubmed results from the following searches: precision + treatment + [psychiatry/oncology]. The era of precision oncology arguably started with the approval of trastuzumab (Herceptin) and gefitinib (Iressa) not long thereafter, but it did not see its inflection point until the introduction of immuno-oncology approaches with the approval of pembrolizumab (Keytruda). Efforts since have only further accelerated the focus on precision. **b**, Greater proximity of electroencephalography (EEG) individual alpha peak frequency to 10Hz (IAF-prox) predicting greater symptom reduction in response to 10 Hz dorsolateral prefrontal repetitive transcranial magnetic stimulation (rTMS) treatment[227]. **c**, An unsupervised modelling-derived EEG subtype predicts antidepressant outcome in major depressive disorder (MDD) and psychotherapy outcome in post-traumatic stress disorder (PTSD)[18]. Data shown in parts **b** and **c** are replicated findings, demonstrating proof of concept. BDI, Beck Depression Inventory, CAPS-5, Clinician-Administered PTSD Scale for DSM-5. Part **b** reproduced with permission from ref. 227, Elsevier. Part **c** reproduced with permission from ref. 18, Springer Nature Limited.

clustering of biological features, with the goal of achieving greater biological homogeneity. The specific biological features vary widely, but they have often been captured by neuroimaging with fMRI or EEG. In both cases, and especially by virtue of the high dimensionality of the data, supervised and unsupervised machine learning for fMRI and EEG, respectively, have become critical components of the analytical approach. This raises important issues both around the need for prospective replication of any finding, given the high likelihood of false positives or over-fitting when using machine learning[9], and around the clinical relevance of a correlation.

Current psychiatric interventions often show modest average effects relative to placebo but substantial variability in individual responses. For a precision psychiatry approach to succeed, whether through supervised or unsupervised means, biologically linked variability in treatment outcome must be predictable and reproducible. Already, data on existing interventions demonstrate that individual differences in treatment response are predictable and reproducible, and that this can inform precision development of novel therapeutics. Importantly, biomarkers predictive of treatment outcomes are typically unrelated to overall symptom severity or traditional clinical constructs. This argues that discovery and validation of such biomarkers will reflect a process that is different from how heterogeneity has traditionally been viewed in the primarily clinical psychiatric literature.

To date, the published literature on biomarkers of brain circuit function that can predict treatment response has focused on standard-of-care or approved treatments such as antidepressants, psychotherapy or repetitive transcranial magnetic stimulation (rTMS). We consider proof of concept as being achieved when the observed effects are replicated in a separate patient sample, given that this reflects initial precision psychiatry efforts on often inadequately sized samples of convenience (that is, those that happen to be available for a given biological measure). We further discuss below the clinical relevance of the level of predictive capacity (that is, percent of outcome variance explained) to put these effects in context. Data supporting these biomarkers are drawn primarily from structured clinical trials, but also from observational data on naturalistic treatment courses.

Among brain-circuit-function-biomarker modalities, resting-state EEG has the most evidence for reproducibly predicting treatment outcomes based simply on number of replicated associations[1]. For example, anterior cingulate theta power predicts responses to a range of antidepressant treatment modalities (medications, rTMS and electro-convulsive therapy), as well as the antidepressant response to placebo[10,11]. Although anterior cingulate theta power is a nonspecific response predictor, it is noteworthy that the degree of specificity of other biomarkers remains largely unknown as most biomarkers have been defined from open-label single-arm trials and not tested on placebo-controlled intervention data. Other studies have found that a resting EEG-based vigilance measure predicts response to antidepressant medication[12], whereas individual alpha peak frequency predicts response to 10 Hz rTMS[13] (Fig. 2b). Interestingly, one study noted that the difference between 10 Hz and an individual's alpha peak frequency predicts better response to 10 Hz rTMS but worse response to 18 Hz rTMS[14], suggesting an element of intervention-specific outcome prediction that may tie to distinct biological effects associated with rTMS at different frequencies. Individual alpha peak frequency also predicts response to stimulants in attention-deficit/hyperactivity disorder[15],

suggesting that its relevance is not restricted to rTMS. Machine learning has been used to identify multivariate resting EEG biomarkers predictive of response to antidepressants[16,17], as well as separate EEG patterns that predict psychotherapy response in post-traumatic stress disorder[18,19] (PTSD; Fig. 2c).

fMRI, although historically challenged by lower test–retest reliability, which limits predictive power, has also demonstrated promise as a biomarker of treatment response. Subgenual cingulate–lateral prefrontal cortex connectivity predicts response to 10 Hz rTMS in depression[20–22]. A salience network topology index derived from fMRI reliably indexes depression diagnosis[23], though its treatment predictive value remains unknown.

Cognitive task performance, a behavioural indicator of cognitive circuit function, also predicts treatment outcomes. For instance, poor verbal memory predicts worse responses to antidepressants in major depressive disorder[24] (MDD) as well as psychotherapy in PTSD[25]. Collectively, however, these findings establish that reproducible prediction of treatment outcomes by various biomarkers is possible, setting the stage for applying this lens to novel drug development.

It is noteworthy that although predictions are modest (typically explaining ~5–15% of variance in outcomes in independent data), reproducible predictors can inform a biological understanding of disease and treatment while also still providing meaningful clinical benefit given the small placebo-adjusted clinical outcome effect sizes seen in psychiatry. We argue that the goal of precision psychiatry in drug development at this point should be twofold: achieve a greater degree of enrichment of drug response and enable approval of novel treatments that might otherwise fail in trials in unselected populations. The kind of biomarker test performance required for a screening or diagnostic test is unnecessary for positively affecting clinical outcomes, is not the goal of precision medicine approaches in other areas of biomedicine and may not be achievable given our poorly operationalized treatment outcome measures.

Consider two clinical contexts: as a first example, in depression, some of the most prescribed antidepressants have Cohen's d effect sizes below 0.3, which is considered a small effect. A predictor that explains only 5% of variance in response to treatment (that is, r = 0.22), if positive in half of the population, would result in a d > 0.5 in patients who are predictor positive (and d = 0.1 in patients who are predictor negative). As such, even modest enrichment could be clinically meaningful for patients who respond positively and would avoid unnecessarily exposing patients who respond negatively to the drug. As a second example, consider the cognitive impairment aspect of schizophrenia, which is the strongest determinant of dysfunction in these patients, but currently has no approved treatment. The difference between nothing and a drug with even modest benefit in a subpopulation could be substantial.

Seen with the lens above, we expect that the initial focus for precision psychiatry efforts will be on cases for which treatments in development can achieve greater efficacy in enriched populations. With time and refinement, it could be possible to take a more radical 'biology-first' approach to discovering and validating entirely new mechanisms of action. The case studies below provide a roadmap for both paths.

Clinical examples supporting precision psychiatry

Beyond circuit biomarker-based predictions, clinical trial evidence already exists for differential drug efficacy in biologically distinct subgroups, even if those distinctions are identified through clinical characteristics rather than direct measures of the relevant biology. The neurosteroid analogue zuranolone, for example, consistently demonstrated efficacy in postpartum depression[26], a condition characterized by parturition-related reductions in allopregnanolone levels. This resulted in zuranolone receiving US Food and Drug Administration (FDA) approval for postpartum depression. By contrast, multiple large and similarly designed phase III trials in MDD failed to show sustained efficacy of zuranolone[27–30]. Furthermore, the biological rationale for neurosteroid efficacy is stronger in postpartum depression than in the highly heterogeneous broader MDD population[31].

A genetics-based precision approach was also recently published. A single nucleotide polymorphism in the neuronal intracellular structure gene *ANK3* was found to predict response to liafensine, a triple monoamine reuptake inhibitor, in patients with MDD[32]. Placebo-controlled efficacy was subsequently shown in patients with MDD carrying this polymorphism[33], albeit no results were reported in patients lacking this biomarker, and it is unknown how this gene links to liafensine's mechanism of action. Although this is exciting as the first genetically driven precision approach in depression, it should be viewed with caution as common genetic variations typically explain far less variance (by at least 1–2 orders of magnitude) than is implied by the study for the single *ANK3* polymorphism.

There is also evidence that the orexin-2 antagonist seltorexant is more effective as an antidepressant for patients with depression with higher levels of insomnia[34,35], which has led to the use of the presence of insomnia symptoms as an enrichment strategy for its phase III programme[36,37].

These results further underscore the potential of a precision psychiatry framework to identify clearer drug effects within biologically relevant subgroups. Additionally, they emphasize that although discovery of new drug mechanisms will be important in the long term, taking a precision approach may produce important outcomes in the near to intermediate term with already known but clinically novel mechanisms.

Replicated clinical predictors of response to lithium treatment have also been found[38]; biological predictors of lithium response have been widely sought, but more work is needed to ascertain their reliability[39].

Precision psychiatry case studies, organized by neural circuits

We focus below on four areas in which first steps towards precision psychiatric drug development have already been taken, to varying degrees, and are primed for expansion. Because an important principle behind precision psychiatry is the explicit tying together of biological measures of pathophysiology, PD effects of drugs and markers for patient selection, our perspective grounds the discussion in the most well-supported, but also clinically scalable, biomarkers within each area. The issue of scalability is an important consideration, especially in psychiatry, to avoid access barriers and fragmentation. To the degree possible, these measures should also be translationally relevant.

These results demonstrate that success of precision psychiatry is more about systematically capturing key biomarker variables in patients across all phases of drug development, rather than needing ideal candidate biomarkers or sufficient patient-level biological knowledge. Arguably, the only limitation to widespread adoption is not having sufficient proof-of-concept outcomes from precision approaches to catalyse this reorientation, although these may be coming in the near future through ongoing drug development efforts. Some of these approaches make use of measures of brain circuit functioning (such as EEG or behavioural tests), whereas others use less direct approaches

such as symptom-based enrichment. Nonetheless, they all share a common development, regulatory and commercial mindset (discussed further after the case studies). In each section below, we provide a framing of relevant components of each circuit domain with respect to how it can be measured with biomarkers (whether currently used for patient selection or not) and current drug candidates targeting that circuit (noting which programmes already utilize a precision framing). Table 1 summarizes a selection of potential and current precision programmes that provide examples for posing and testing precision hypotheses.

Case study: E/I balance, early sensory processing and cognition

The balance between excitatory and inhibitory (E/I) processes is essential for maintaining cognitive function, particularly in brain regions such as the prefrontal cortex and hippocampus[40–42]. This balance depends primarily on the interplay between glutamatergic and GABAergic neurons in cortical circuits, and it is a core mechanism being investigated in several neuropsychiatric conditions, including schizophrenia, autism and neurodegenerative diseases. The canonical neocortical circuit underlying E/I balance consists of excitatory glutamatergic pyramidal neurons and a variety of inhibitory interneurons that shape pyramidal cell activity within a cortical column (Fig. 3). Parvalbumin (PV)-positive and somatostatin (SST)-positive interneurons stand out as setting up temporal and spatial control necessary for adequate performance of cortical ensembles. Despite advances in our understanding of how these neurons interact and their effect on cognition, there have not been new drug approvals based on the targeting of this mechanism.

In schizophrenia, for example, the prevalent hypothesis on the neurobiology of cognitive impairment posits that an altered E/I balance may stem from loss of inhibitory interneuron function[43,44], which can be seen in post-mortem studies of the dorsolateral prefrontal cortex[45]. Emerging evidence also argues for a pathophysiological role of altered inhibition in neurodegenerative cognitive deficits[46] and autism spectrum disorders[47]. The canonical circuitry responsible for E/I balance is consistent across cortical regions, and its key features and cellular components are remarkably conserved across species[48].

The conserved nature of these circuits across species also enables a reasonable translational approach, providing an opportunity to test relevant physiological readouts in rodents prior to bringing compounds into the clinic. For example, auditory evoked potentials such as mismatch negativity (MMN) — frequently impaired in schizophrenia[49] — can be also assessed in rodents[50]. Cortical regions reach adult-like maturation at different developmental stages, typically through refinement of E/I balance in critical periods[51]. Circuits involved in cognitive functions exhibit late critical periods, primarily during adolescence[52], and aberrant maturation during such critical periods might trigger the onset of abnormal glutamatergic–GABAergic interactions that drive altered E/I balance and impaired function[53]. By objectively evaluating physiological and behavioural measures related to E/I balance, we should be able to both select a subset of patients with altered E/I, and therefore more likely to respond to interventions that address such deficits, and to use a PD biomarker to evaluate the effect of novel agents on such deficits.

In humans, E/I balance has often been assessed via EEG. As the overall activity in cortical columns is entrained by the fast-spiking

Table 1 | Selected psychiatric drug development programmes implementing a precision approach

Mechanism of action	Agent(s)	Indication	Status	Patient selection measure
Depression				
Orexin-2 antagonist	Seltorexant (JNJ-42847922)	Adjunctive depression	Phase III	Insomnia
Dopamine/noradrenaline reuptake inhibitor	Solriamfetol (Sunosi)	Monotherapy depression	Phase III	Excessive daytime sleepiness
Triple reuptake inhibitor	Liafensine (DB104)	Treatment-resistant depression	Phase III	*ANK3* SNP
Vasopressin 1b antagonist	Nelivaptan (Nelivabon)	Monotherapy depression	Phase III	SNP panel
$MT_{1/2}$ agonist, 5-HT_{2C} antagonist	Agomelatine (ALTO-300)	Adjunctive depression	Phase IIb	EEG entropy
Bipolar disorder				
Pro-neuroplasticity (undisclosed mechanism)	ALTO-100	Bipolar depression	Phase IIb	Poor verbal memory
Schizophrenia				
mAChR1/4 positive allosteric modulator	Xanomeline/trospium chloride (Cobenfy)	Psychosis	Approved	Poor baseline cognition
Nicotinic agonists	Varenicline–tropisetron (MT1988)	Psychosis high risk	Phase II	Attentional test
mGluR2/3 agonist	Pomaglumetad (DB103)	Psychosis	Phase II	Planned (details not disclosed)
PDE4 inhibitor	ALTO-101	CIAS	Phase II	EEG/cognition
Autism				
PDE4 inhibitor/NKCC inhibitor	Ibudilast–bumetanide (STP1)	ASDs	Phase II	Metabolomic subtype

ASDs, autism spectrum disorders; CIAS, cognitive impairment associated with schizophrenia; EEG, electroencephalography; 5-HT_{2C}, 5-hydroxytryptamine receptor $_{2C}$; mAChR1/4, muscarinic acetylcholine receptor 1/4; mGluR2/3, metabolomic glutamate receptor 2/3; $MT_{1/2}$, melatonin receptor 1/2; NKCC, Na–K–Cl cotransporter; PDE4, phosphodiesterase 4; SNP, single-nucleotide polymorphism.

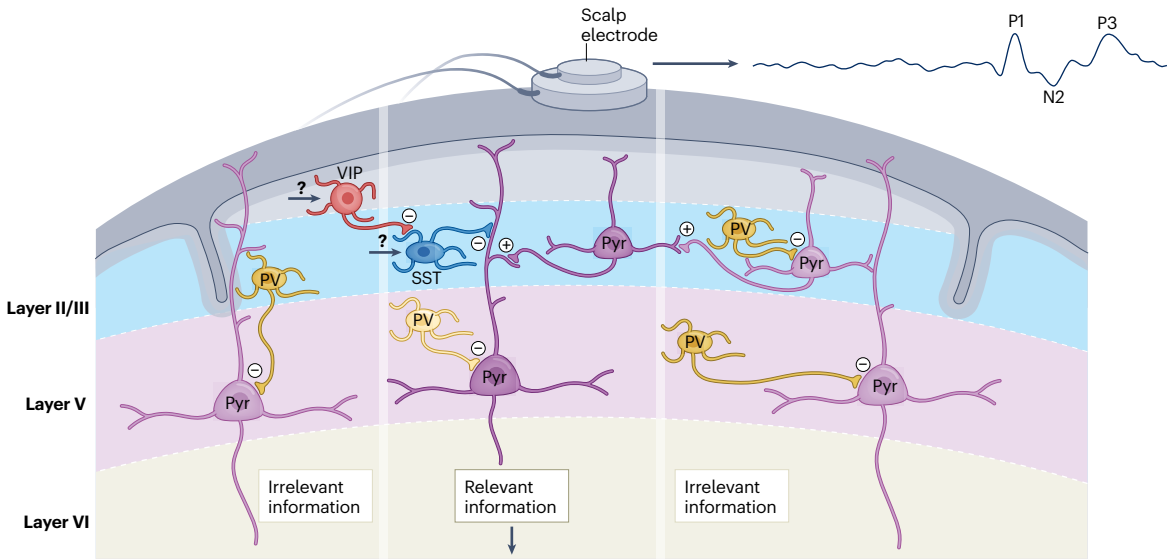

Fig. 3 | Capturing excitation–inhibition balance with objective measures. Canonical cortical circuity features the interplay among excitatory pyramidal neurons (Pyr) and diverse subsets of inhibitory interneurons, with the resulting outcome being the selection of the appropriate information-encoding outputs from that cortical region[228]. Biomarkers that reflect the state of cortical circuits can be obtained through electroencephalography assessments with millisecond resolution, with gamma band power assumed to reflect the state of parvalbumin-positive interneurons (PV) and overall excitation–inhibition balance and evoked potentials capturing the effect of excitation–inhibition balance on circuit output. SST, somatostatin; VIP, vasoactive intestinal peptide.

nature of PV and SST interneurons, adequate E/I balance is reflected in the strength and regularity of high-frequency EEG oscillations, primarily in the beta and gamma range[54,55]. There is also growing interest in slower oscillations[54,56] as a reflection of abnormal cortical circuitry function, with the theta range showing alterations in patients with schizophrenia[57].

Although EEG oscillations can be captured during resting conditions, activation of cortical regions may improve the ability to detect E/I imbalance. In schizophrenia, auditory-evoked MMN and auditory steady state response are commonly used to ascertain the state of cortical circuitry function[58]. Those responses are also affected by the *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine[56], supporting the hypothesis that NMDA receptors are critical for E/I balance. Interestingly, the event-related potential (ERP) response to ketamine varies depending on the baseline state of the circuit. In participants with a 'healthy', large MMN signal, ketamine reduces MMN, whereas in participants with a small, impaired MMN signal at baseline, ketamine enhances it[59]. This discrepancy can be interpreted as the same pharmacological manipulation having a beneficial effect on an imbalanced circuit and a deleterious one or no effect on a balanced circuit (that is, having a homeostatic effect). Similarly, identifying patients with schizophrenia who do exhibit an E/I imbalance is a necessary step in developing treatments addressing this mechanism.

Many new analytical approaches are emerging, unveiling complex elements in EEG signals that may also be related to E/I imbalance. For example, the 'background' EEG signal, which shows a 1/f relationship to frequency and can be characterized by a measure termed the aperiodic exponent, is related to E/I imbalance and changes during adolescence as the brain (and E/I balance) matures[60,61]. The aperiodic exponent is also associated with working memory[62]. Steeper 1/f indicates dominance of inhibitory activity, and flatter exponents indicate a trend towards stronger excitatory activity[63].

Another way to evaluate activated circuitry is by objectively assessing its functional effect. In psychiatry, cognitive domains can be objectively assessed, and these end points also reflect E/I balance in the relevant cortical networks.

Scalability is an important consideration for potential biomarkers to be used in clinical trials and ultimately in clinical practice. Although novel EEG systems, such as dry wearable EEG, enable their use outside of an electrophysiology lab, there is still the need for a device and training on how to use it. Some investigators are seeking a plasma biomarker that reflects E/I balance. A promising example is the use of extracellular vesicles to ascertain expression of interneuron-driven markers, such as mir137, which correlates with gamma-band EEG assessments[64]. Identifying a blood-based biomarker will certainly help to move the field forward, but existing EEG-based signals are excellent tools to quantify circuit state driven by E/I imbalance.

One novel approval for schizophrenia is the combination of the muscarinic M1/M4 acetylcholine receptor (AChR) agonist xanomeline with a peripheral blocker of those receptors (trospium) to mitigate xanomeline's systemic side effects. This combination, called 'Kar-XT', showed a good antipsychotic profile without the side effects associated with dopamine blockade, resulting in its FDA approval in 2024. There are also some potential cognitive benefits with Kar-XT treatment, but those are only evident in patients with poor baseline cognition. This was observed in a post hoc analysis of a Kar-XT phase II study[65], and replicated prospectively[66], which can be considered an attempt at a precision approach. Enhancing M1 and M4 muscarinic output offers a way to improve fast-spiking interneuron function, potentially driving the cognitive benefits in patients with abnormal E/I balance but causing no change in patients with a presumably balanced circuit.

Very few new schizophrenia drugs are being developed with stratification in mind, and indeed only rarely do clinical trials even select patients with schizophrenia based on the presence and nature

of their cognitive deficits in trials of putative pro-cognitive agents[67]. Notably, only half of the patients in the Kar-XT study met the cognitive impairment threshold (>1 standard deviation impairment in global cognition) even though all had schizophrenia. Although some agents that showed promise in phase II studies but failed in larger, all-comer phase III studies are being revisited with a biomarker lens, the field has not yet adopted a precision approach (Table 1).

EEG measures related to E/I imbalance, by contrast, have been used as PD biomarkers in recent trials of novel mechanisms for cognitive impairment associated with schizophrenia, but those efforts were not carried into clinical trials as patient selection markers, which may explain the late-stage failures across these programmes. These include the α7 nicotinic receptor agonist encenicline[68], the mGluR2/3 agonist pomaglumetad[69,70], the D-amino oxidase inhibitor luvadaxistat[71] and the GlyT1 inhibitor iclepertin[72,73], all of which showed some PD EEG signal in early-stage studies but failed in all-comer phase III or IIb studies[58,68,69,71,73–75]. In such studies, any potential benefit of having used the PD signals identified in phase I studies was lost through lack of patient selection. Therefore, the question of whether E/I PD biomarkers can predict clinical response in a subset of patients remains outstanding.

Despite these setbacks, the field is close to being able to use biomarker-based stratification, given how commonly EEG and cognitive biomarkers are now used as PD outcomes, and, most importantly, the fact that these biomarkers derive from patient characterizations rooted in biology and pathophysiology. This is critical as new mechanisms are being tested in the clinic. E/I imbalance can be addressed, for example by enhancing NMDA receptor function, by reducing glutamate release, or by targeting nicotinic AChR or GPCR modulation of fast-spiking interneurons to enhance their activity[76]. Enhancement of cAMP signalling through inhibition of the phosphodiesterase 4 (PDE4) enzyme[77,78] and alleviation of PV interneuron oxidative stress[79] have also shown improvements in measures of E/I balance. An ongoing study of ALTO-101, a PDE4 inhibitor, uses poor performance on a measure of processing speed for patient selection, building on the results above with Kar-XT as well as PD effects of the drug itself[78].

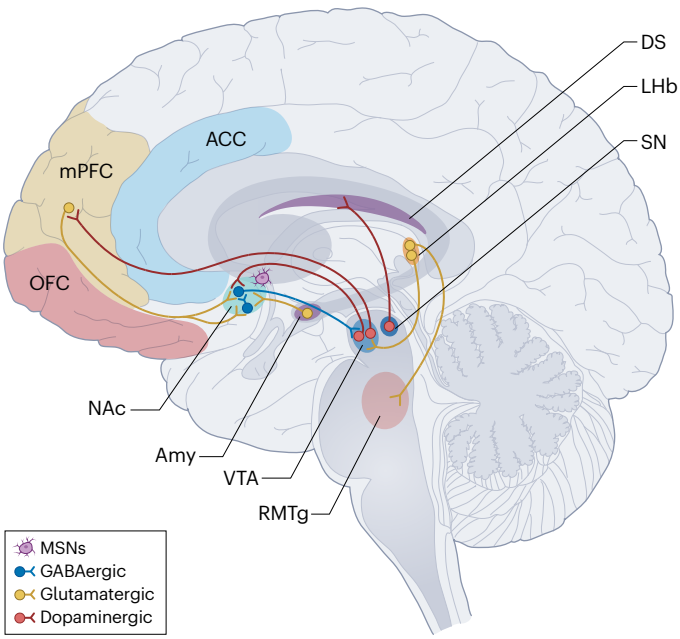

Fig. 4 | Brain circuits involved in anhedonia and aversion. The circuitry involved in reward interacts with the circuitry involved in aversion to drive anhedonia and stress-disordered states. The mesocorticolimbic pathway, which originates in the ventral tegmental area (VTA), plays a key role in reward processing and motivation, projecting to areas like the ventral striatum (including the nucleus accumbens (NAc)), dorsal striatum and prefrontal cortex. Dysregulation of dopamine signalling, particularly blunted dopaminergic transmission in the ventral striatum and anterior cingulate cortex (ACC), has been linked to anhedonia[229]. In rodents, decreased phasic bursting of VTA dopaminergic neurons correlated with anhedonic behaviours that could be reversed by antidepressant treatment[83]. Optogenetic manipulation of VTA dopaminergic neurons modulated depressive phenotypes[230,231]. Brain aversion circuits, responsible for the brain's response to harmful stimuli, involve regions such as the lateral habenula (LHb), medial prefrontal cortex (mPFC), VTA and insula. The LHb is considered an 'anti-reward' centre, modulating dopamine and serotonin during aversive events. Dysfunction in these circuits has been linked to anhedonia and social aversion in mood disorders[23,81,83]. Amy, amygdala; DS, dorsal striatum; MSNs, medium spiny neurons; OFC, orbitofrontal cortex; RMTg, rostromedial tegmental nucleus; SN, substantia nigra. Figure reproduced with permission from ref. 232, Wiley.

Case study: anhedonia and reward-related and aversion-related circuits

Progress has recently been made in understanding anhedonia and abnormal reward processing, which are core components of depression[80–84]. Anhedonia covers a spectrum of reward-processing deficits that include difficulty anticipating pleasure from future events and lack of pleasure during previously enjoyable activities[85]. Notably, it also occurs across a range of other psychiatric and neurodegenerative disorders and is a notable risk factor for suicidality[81,86,87]. Assessing anhedonia is challenging owing to its subjective nature, pointing to a need for quantitative biological metrics of reward-system dysfunction.

Brain reward circuits (Fig. 4) are crucial for reward responsiveness (anticipation/consumption), reward learning (positive prediction errors) and reward valuation (effort for rewards). Anhedonia — which is associated with deficits in reward liking, wanting and learning — has been linked to abnormal dopaminergic and glutamatergic activity, especially in the ventral tegmental area (VTA) and nucleus accumbens[81,88,89]. In addition, dysfunction in brain aversion circuits including the lateral habenula has been linked to anhedonia and social aversion in mood disorders[23,81,83].

Human neuroimaging studies have found reduced grey matter in areas like the orbitofrontal cortex and caudate nucleus[90], and increased functional connectivity in some networks (for example, frontostriatal) and hypoactivity in others (for example, ventral striatum) during reward anticipation, reflecting impaired reward processing and learning[23,81,88,91]. Studies have also found increased lateral habenula activation and volume correlated with more severe symptoms[23,81,88,91]. Despite all of these associations, findings are often of small magnitude or replicate poorly, indicating that self-reported anhedonia and behavioural or neural indices or reward processing abnormalities are still largely separate constructs, even if somewhat correlated.

Common antidepressants have shown limited effectiveness in treating anhedonia clinically (reviewed elsewhere[92–95]). Because of their ability to cause emotional detachment, selective serotonin reuptake inhibitors may also worsen anhedonia. Studies suggest that agents with more dopaminergic activity, such as agomelatine[96,97], bupropion[98], and its combination with dextromethorphan[92,94,95], may better treat anhedonia. Several targets, however, have been recently suggested to

represent novel anti-anhedonia treatments and are in late-stage trials, including anti-inflammatory modulation, NMDA receptor antagonism, kappa opioid receptor (KOR) antagonism, dopamine agonists and potassium channel (KCNQ) modulation. Earlier-stage clinical efforts focused on dopaminergic modulation through blockage of the histamine H3 receptor are also ongoing[99].

Treating anhedonia with a precision approach has also been made difficult by the limited set of circuit-based biomarkers beyond fMRI measures. In recent years, however, some attention has been placed on EEG alpha asymmetry with respect to anhedonia[100,101]. Interestingly, despite EEG detecting primarily surface cortical electrical signals, it is nonetheless sensitive to deep brain structure activity, as evidenced by use of EEG in an FDA-cleared neurofeedback paradigm and similar approaches for the EEG-based accumbens neurofeedback[102,103]. Because of the relative immaturity of neuroimaging measures of reward system function, precision approaches currently primarily use anhedonia symptoms or performance in dopamine-sensitive reinforcement learning or effort-based motivated behaviour tasks to enrich samples. Reward learning has been reported to predict the antidepressant effect of pramipexole in one small study[104].

Blood-based measures of biological processes associated with anhedonia are also candidate biomarkers. Factors such as inflammation, cytokine dysregulation and chronic stress can impair neural activity in brain regions affected in depression, further reducing motivation and reward processing[23,81,88,91]. Elevated levels of inflammatory cytokines (such as interleukin (IL)-1β, IL-6 and interferon-α (IFNα)) have been associated with depression for decades[105,106], as well as reduced dopamine release in reward-related brain regions[107–114]. Approximately 30% of patients with MDD exhibit heightened inflammation, possibly representing an 'inflammatory subtype' of depression, for which targeted treatments like dopaminergic agents or anti-inflammatory drugs may be beneficial[108,109]. In line with a potential role for an inflammatory subtype, the tumour necrosis factor (TNF) inhibitor infliximab improved patients' motivation to exert effort for rewards compared with placebo. Although the treatment had only a modest effect on self-reported anhedonia, neuroimaging revealed that infliximab modulated brain regions involved in effort-based decision-making, such as the dorsomedial prefrontal cortex and ventral striatum, through decreased TNF signalling[115]. The anti-IL-6 monoclonal antibody sirukumab has also shown potential in treating depression and anhedonia, particularly in patients with elevated C-reactive protein (CRP) levels[116].

Ketamine, an NMDA receptor antagonist, has gained attention for its rapid antidepressant and anti-anhedonic effects[117–122]. Preclinical studies found that ketamine's antidepressant effects are mediated at least in part by the preferential inhibition of inhibitory GABA-ergic interneurons in the prefrontal cortex. This leads to increased synaptic glutamate release, which potentiates AMPA receptor activation and induces synaptic plasticity via the mammalian target of rapamycin (mTOR) pathway[123,124]. These processes are thought to enhance dopaminergic activity in the mesocorticolimbic pathways, contributing to improved reward processing and reduced anhedonia. Whether the success of ketamine/esketamine (esketamine is the *S*(+) enantiomer of ketamine) can be translated to the development of other NMDA receptor antagonists is unknown, however, as many of them have failed in late-stage clinical trials[125]. It is worth noting that none of those trials used a precision approach to identify patients with prominent reward-processing abnormalities or reward-related circuit assessments, nor has the anti-anhedonic activity of ketamine been translated into an anhedonia-based enrichment approach in related development programmes. Nonetheless, several small studies have shown that increased fronto-striatal connectivity and decreased amygdala–striatal connectivity predicted better response to ketamine[126,127], suggesting that biomarkers of reward and aversion/stress-related processes may help guide development of future NMDA receptor antagonists such as ketamine.

Attempts have been made to enhance reward processing by targeting KORs, based on preclinical data implicating KORs in negative regulation of reward processing, stress response and dopamine release, particularly in regions like the nucleus accumbens[128–134]. KOR antagonists act by blocking the effects of dynorphin, a neuropeptide that, under stress, inhibits dopamine release in the mesolimbic system, which is implicated in reward processing[135,136]. Doing so may restore normal dopaminergic activity and ameliorate anhedonic symptoms[128,130–134]. The KOR antagonist aticaprant had beneficial effects on striatal response during reward anticipation in individuals with anhedonia[131] and on reinforcement learning[137]. However, clinical studies of the KOR antagonist combination of buprenorphine–samidorphan have obtained mixed results[138], leading to its rejection by the FDA in 2019. A phase II study of aticaprant demonstrated efficacy as an adjunctive treatment in MDD, with greater separation from placebo seen in patients with greater levels of anhedonia[134]. However, in a phase III programme in patients with MDD with elevated levels of anhedonia, aticaprant failed to separate from placebo[139,140], and development was discontinued[141]. Another KOR antagonist, navacaprant (NMRA-140), had shown efficacy on secondary analyses of anhedonia symptoms[142], but a recent phase III study in all-comer MDD populations without a precision approach yielded negative results[143], including on both depressive and anhedonia symptoms.

These findings thus point to two 'false positive' results that were obtained despite the goal to de-risk development. On the biomarker side, one possible explanation for this lack of replication is that the fMRI task is not itself a validated marker of antidepressant effect. On the anhedonia enrichment side, a possible explanation is that symptom domains such as anhedonia do not support reliable prediction given their distal and multifactorial relationship to the biological processes that the drug more directly targets, leading to inconsistency.

More direct stimulation of the dopamine D2/D3 receptor using the D3-preferring agonist pramipexole has also been found in multiple controlled trials to be effective for the treatment of depression[144,145]. This includes a large recent trial of pramipexole in treatment-resistant depression, which showed a strikingly large effect on depressive as well as anhedonia symptoms[146]. Another study in patients with high level of anhedonia (using a design similar to the aticaprant fMRI study), also demonstrated large effects on anhedonia symptoms as well as increased nucleus accumbens activation and daytime activity levels[147]. Given the discordant clinical effects across pramipexole (consistently large responses) and KOR antagonists (consistently null effects), the similarity of their effects on reward-based fMRI activation and reward learning[147] cast doubt on these as PD markers relevant to clinical antidepressant effects.

A separate reward circuitry-targeting approach comes from data in mice exposed to chronic social defeat, in which resilient animals were characterized by upregulation of KCNQ2/3 potassium channels in the VTA and with that normative phasic firing of the VTA and protection against anhedonic-like behaviour[148]. The anticonvulsant ezogabine — a positive allosteric modulator and selective KCNQ2/3 channel opener — restored VTA homeostasis and reversed anhedonic and pro-depressive

behaviours in these animals[149]. Inspired by these preclinical findings, a controlled trial of ezogabine in 45 patients with MDD with prominent anhedonia[150–152] showed a substantial clinical antidepressant effect and evidence suggestive of increased VTA responsiveness to reward[150–152] as well as increased accumbens–cortical connectivity[153]. Ezogabine, however, has since been removed from the market owing to concerns about retinal effects. Newer KCNQ2/3 activators such as azetukalner (XEN1101) and opakalim (BHV-7000) are in phase II or phase III trials in patients with MDD and bipolar depression[154–156], even though these appear to be all-comer trials, a potential missed opportunity given the initial large ezogabine signal in patients with high anhedonia.

Positive valence systems are also opposed by negative valence processes associated with stress. Psychosocial stress has been linked to neuroinflammatory processes, as well as the onset and maintenance of a number of psychiatric conditions, including MDD and post-traumatic stress disorder (PTSD). 'Stress' is most classically defined by activation of the hypothalamic–pituitary–adrenal (HPA) axis. 'Classic' MDD tends to be associated with non-suppression (or reduced feedback) of the cortisol response following dexamethasone-mediated HPA suppression; conversely, 'classic' PTSD (with limited depression symptoms) has been associated with super-suppression of the HPA axis[157], suggesting distinct biological regulation of the HPA axis in these clinically overlapping syndromes. Notably, a recent trial of nelivaptan, a vasopressin V1b antagonist that aims to target stress axis activation, demonstrated efficacy in an all-comer population in depression but failed to show the predicted enrichment in a genetic biomarker-defined subpopulation relevant to stress processing[158].

Case study: neuroplasticity, cognition and mood

Neuroplasticity, defined as the brain's capacity to modify synaptic strength and connectivity, is likely involved in pathophysiological mechanisms of psychiatric conditions and in some therapeutic approaches[159]. Neuroplasticity-related assessments may offer an opportunity for a precision approach and represent an area in which explicit biomarker-based patient selection is happening in late-stage trials. Extensive human and preclinical research supports a neuroplasticity deficit framework for affective disorders, emphasizing the roles of hippocampal and prefrontal plasticity in mood and cognition[160]. Reduced neuroplasticity is thought to reinforce dysfunctional thought patterns in depression and other affective disorders, sustaining pathological mood states. The hippocampus and prefrontal cortex are central anatomical hubs for mental functions, particularly learning, memory, mood and cognition.

Human data supporting this framework come from studies of neurophysiology, learning and memory, neuroimaging, genetics, and post-mortem analyses of neuronal morphology and gene expression. Post-mortem analyses of brains from patients with MDD and bipolar disorder (BPD) have shown reduced hippocampal and prefrontal cell numbers and sizes[161,162], along with decreased expression of synaptic signalling and plasticity-related genes, including glutamatergic and brain-derived neurotrophic factor (BDNF)-related components[163–166]. These gene expression changes are accompanied by synaptic loss in the brains of patients with MDD[167]. At the cellular level, reductions in hippocampal and prefrontal neuronal numbers and abnormalities in plasticity-related molecular machinery have been observed. Consistent with dysfunctional hippocampal neuroplasticity, structural brain imaging studies conducted in patients with MDD and BPD repeatedly show smaller hippocampal volumes[168]. These reductions are associated with episode recurrence, treatment resistance[169] and childhood maltreatment history, and it correlates with deficits in visual and verbal memory performance[168,170,171].

Behavioural tests of learning and memory provide direct assessments of neuroplasticity and reflect impairments in hippocampal function[172]. Tests like word-list learning and verbal memory recall tasks specifically reflect NMDA receptor-dependent hippocampal neuroplasticity[173,174]. Verbal memory recall is strongly associated with hippocampal integrity, with poorer recall reflecting smaller, more dysfunctional hippocampi[172]. Numerous neuropsychological studies demonstrate learning and memory recall deficits in MDD and BPD[175]. Genetic risk for MDD is also associated with poor verbal memory[176]. Memory impairments in patients with MDD are at least equivalent to deficits in other domains, such as executive functioning and processing speed[177]. Cognitive impairment is evident even in first-episode patients[178] and children[179], suggesting it is neither age related nor attributable to neurodegeneration and therefore likely the outcome of brain circuit state that could be captured with appropriate predictive biomarkers. There is also growing recognition of MDD with cognitive impairment as an important subtype requiring new treatments[180]. Strikingly, the magnitude of cognitive impairment in patients with MDD with cognitive impairment is similar to that in patients with schizophrenia[181], a disorder in which cognition is considered a primary driver. Cognitive dysfunction is likewise a strong predictor of occupational and social functional impairment in adults with MDD[182–184], serving as a principal mediator of psychosocial and workplace dysfunction[185], and driver of hospitalizations[186].

Cognitive and memory deficits affect approximately 25–50% of patients with MDD and BPD[187]. In other words, if a pro-plasticity intervention were to work better for those patients with impaired hippocampal plasticity (for example, as identified through impairments in memory), a precision approach may enrich responses 2–4 times relative to that seen in all-comer populations. For the development of drugs that enhance plasticity, selecting patients based on deficits in cognition, and in particular memory (as well its EEG correlates), is a rational way to implement precision psychiatry. Use of hippocampal volume on structural MRI may be another alternative but may lack the sensitivity and dynamic range of cognitive measures.

Various other tools can also quantify plasticity-relevant processes, offering differing levels of scalability relative to memory and cognition. Direct imaging of synaptic vesicle density with a PET ligand for SV2A has demonstrated reductions in MDD and correlations with memory and cognition[188]. Similarly, transcranial magnetic stimulation combined with EEG or fMRI can quantify stimulation-evoked neuroplastic changes, showing reduced plasticity in MDD[189]. EEG measures such as the aperiodic exponent and gamma power have also been proposed as indices of neuroplasticity, although they are more broadly considered markers of E/I balance[190].

Drugs aimed at enhancing synaptic transmission by acting as positive allosteric modulators of either the AMPA or NMDA receptors are similarly being developed for MDD, although they are taking an all-comer approach. This includes the AMPA positive allosteric modulator osavampator (NBI-1065845), on which positive phase II data were recently reported[191], and the NMDA receptor positive allosteric modulator zelquistinel (GATE-251)[192], which builds on positive phase II data[193] but negative phase III data in MDD from the related compound rapastinel[194]. SPN-820/NV-5138 aimed to activate mechanistic target of rapamycin complex 1 (mTORC1)[195,196], but top-line data from a phase II study in treatment-resistant depression was negative. Activation of mTORC1 is thought to enhance neuroplasticity by increasing

plasticity-related protein synthesis and synaptic remodelling, as well as release of BDNF and an increase in neurogenesis[1].

Neurostimulation approaches such as repetitive transcranial magnetic stimulation (rTMS) may also enhance neuroplasticity. rTMS for MDD is generally understood to exert its antidepressant effects via activity-dependent neuroplasticity — at synaptic, circuit and systems levels — rather than by simply stimulating the cortex transiently. Mechanistic work shows that standard rTMS protocols induce long-term potentiation-like and long-term depression-like synaptic plasticity and reconfigure functional connectivity, whereas longitudinal imaging studies in patients with depression demonstrate rTMS-associated changes in grey matter structure and large-scale networks that correlate with clinical improvement[197]. Precision approaches to identify predictors of rTMS response are continuously being sought. Functional connectivity with fMRI and E/I measures using transcranial magnetic stimulation and EEG hold some promise[198], but they require further validation.

Enhancement of neuroplasticity has also been argued to be an important component of the potential antidepressant effect of psychedelic drugs such as psilocybin[199]. At present, however, it is unknown whether efficacy shown in phase II trials is related simply to the unblinding that occurs with its psychedelic effects and the relative contribution of the experiential changes relative to pro-neuroplastic cellular effects. A new class of non-psychedelic derivatives, such as DLX-001 (ref. 200), are poised to test whether activation of the 5-HT_{2A} serotonin receptor as seen with psychedelics, but without triggering associated perceptual/experiential effects, can therapeutically engage related neuroplasticity-enhancing effects in MDD. For all these novel agents that intend to enhance plasticity and synaptic function, it will be essential to implement a stratifying approach selecting patients with evidence of altered neuroplasticity, such as through deficits in verbal learning and memory.

An emerging category of compounds aims to enhance neuroplasticity in mood disorders, targeting different aspects of the cellular and molecular processes shown in Fig. 5. ALTO-100 is a novel agent identified based on a phenotypic assay for neurogenesis, and subsequently found to enhance synaptic and cellular plasticity, at least in part by

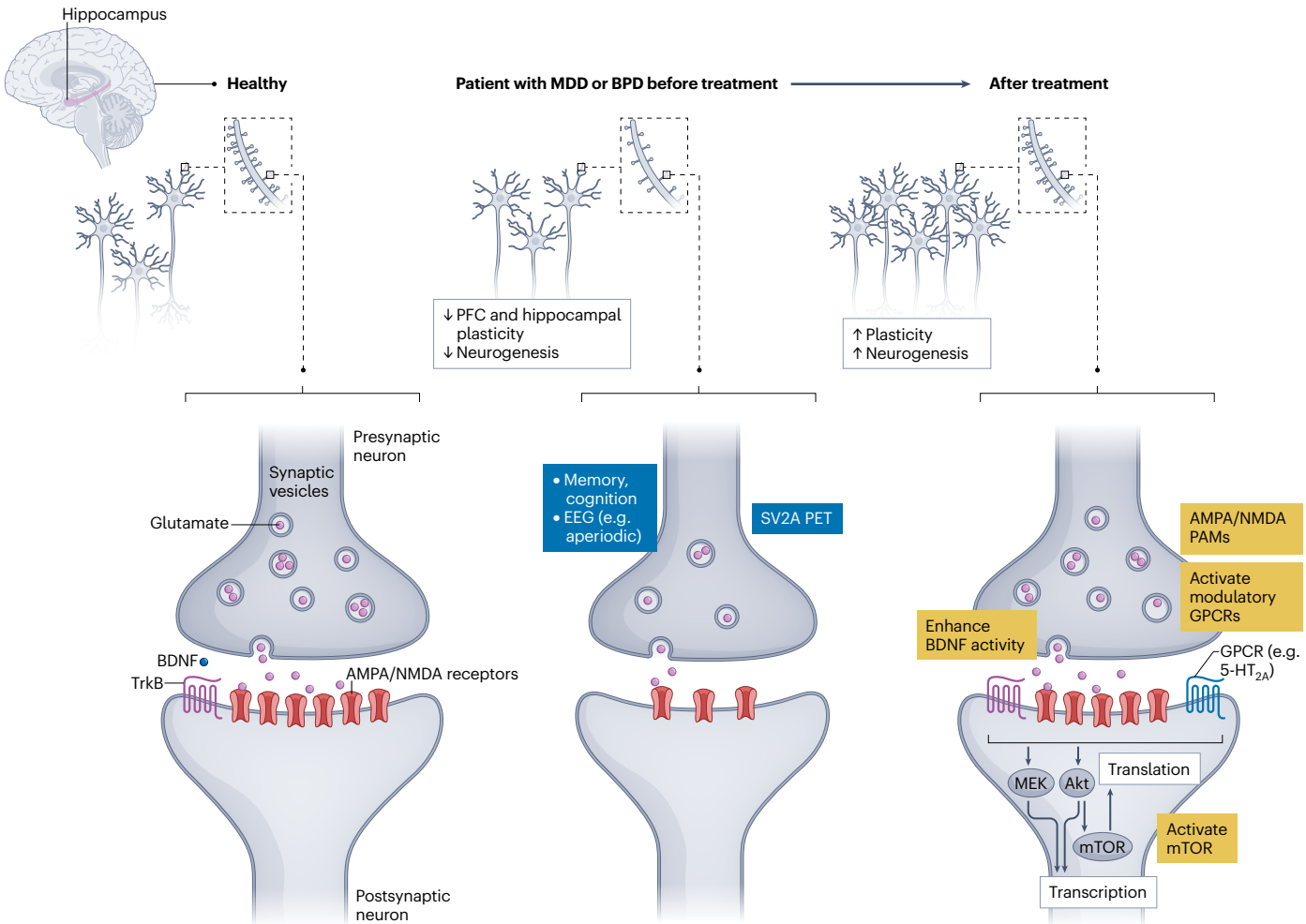

Fig. 5 | Targeting neuroplasticity-related pathways in affective disorders. Schematic showing decreased structural and functional neuroplasticity and synaptic efficacy in affective disorders, biomarkers of these impairments (blue boxes), and molecular pathways that may be targeted to remediate these deficits (yellow boxes). BDNF, brain-derived neurotrophic factor; BPD, bipolar disorder; EEG, electroencephalography; GPCR, G protein-coupled receptor; 5-HT_{2A}, 5-hydroxytryptamine receptor 2A; MDD; major depressive disorder; PAM, positive allosteric modulator; PET, positron emission tomography; PFC, prefrontal cortex; SV2A, synaptic vesicle glycoprotein 2A; TrkB, tropomyosin receptor kinase B.

increasing signalling via BDNF and downstream Akt and MEK pathways post-synaptically[201,202]. ALTO-100 is being investigated in a phase II study of bipolar depression that takes a precision approach by specifically targeting patients with evidence of a hippocampal neuroplasticity deficit based on impaired verbal memory[203]. It had been shown earlier that clinical response to ALTO-100 in MDD is greater in patients with impaired verbal memory than in those with intact memory, supporting a precision framework for its development[204]. A phase IIb study in patients with MDD with impaired verbal memory showed mixed results, driven primarily by lack of drug adherence in subsets of patients owing to non-drug factors, with evidence of enrichment of drug effect versus placebo in patient subsets with higher drug adherence[205]. Another phase IIb study using the same patient selection approach is ongoing in bipolar depression.

Case study: face processing and autism

As in psychotic disorders, in autism spectrum disorders (ASDs) there is evidence of an altered E/I balance, but this seems to be centred in cortical regions related to sensory processing. Sensory alterations are a hallmark of ASD pathophysiology, and patients can present with increased or decreased sensitivity to stimuli[206,207]. Processing of sensory cues related to social interactions is particularly affected, yielding potentially useful PD or predictive EEG biomarkers. E/I-related biomarkers such as those outlined above may be relevant in ASDs, along with biomarkers related to socially relevant cues such as face identification[208] and social communication assessments[209].

Although sensory processing readouts have been extensively used as PD biomarkers, there are some caveats and inconsistencies in their implementation. Responses to auditory stimuli show differences in individuals with autism compared with typically developing people, but those effects are small and variable[210]. Traditional pre-attentive ERPs such as passive MMN have also provided variable results[211]. As attention deficits may be at play in ASDs, it is notable that attention-requiring tasks have yielded more consistent results[212,213].

EEG biomarkers relevant to social interactions are perhaps the most promising for use in a precision framework in ASDs, in particular for patient selection. Processing of human faces elicits consistent responses in specific ERP components (P100 and N170)[214], with their latencies and amplitudes varying in response to real upright faces and distorted, cartoonish or inverted faces[215], indicating processing of social cues. Some patients with ASDs show slower N170 responses[208], which has been related to a number of social function measures, although altered responses are not universal in ASDs[216]. Several studies have attempted stratification based on the N170 ERP, which has also been used as a PD biomarker for a behavioural intervention. Age-corrected evaluations have identified subsets of patients with clear face-processing deficits[216], enabling use of face-response ERPs for patient selection.

Recent development of EEG systems that can be remotely used may enable future trials to widely adopt this readout for stratification. However, challenges remain, including the lack of standardized methods for capturing ERPs, sensory sensitivity issues with head-worn devices in patients with ASDs and age-dependent variability in results. To ensure reliable and reproducible outcomes, global standards for EEG acquisition and analysis are needed[208].

Drug development in ASDs in general has been challenging, with few trials of novel agents ongoing. Promising data, however, have been reported with the PDE4 inhibitor zatolmilast (BPN-14770)[217], which is currently in phase III trials for fragile X syndrome. Taking a precision approach, the combination of ibudilast and bumetanide is in an early-stage trial for a multi-omic pattern-defined ASD subtype[218] that includes several EEG features and molecular markers with data expected by the end of 2025 (ref. 219). The N170 response is also currently being evaluated by the FDA as a stratification marker for ASD through its drug development tools qualification programme[220]. The Autism Biomarkers Consortium for Clinical Trials (ABC-CT) has led those efforts[221,222], revealing mixed results in the use of N170, which, although related to clinical measures, was also affected by other factors such as age and IQ, complicating its potential implementation in clinical trials. However, a critical ongoing effort for future ASD drug development is the HEALthy Brain and Child Development (HBCD) study, which includes participants with ASDs and focuses on EEG readouts during development[223]. Addressing patient heterogeneity in ASDs with EEG tools in clinical trials represents a rational circuit-based approach to increase probability of success in this high-unmet-need population. Lastly, if and when EEG tools provide compelling reasons for a precision approach in ASDs, it will be critical to scale up those measures to clinical practice or at least make them accessible to practitioners for their implementation in the clinic.

Broader considerations

Regulatory framework for a precision approach

In oncology, genetic tumour drivers often serve as treatment selection biomarkers, but in precision psychiatry, the FDA's 2019 enrichment strategy guidance[224] outlines a framework for phenotypic markers. The guidance covers different ways in which biomarkers can be used to define patient subpopulations that are either more responsive to an intervention or tolerate it better, as well as the level of evidence and type of trial design needed to demonstrate the argument with respect to drug labelling. Key considerations for biomarkers in psychiatry include their predictive value for treatment response, effect on the drug's benefit–risk profile and relevance to the drug's mechanism of action.

When following the enrichment guidance and drawing conclusions about biomarker-defined subgroups, trials must be powered to account for patients who are biomarker positive, with the degree to which patients who are biomarker negative are included depending on the drug's risk–benefit profile and potential response in these individuals. Additionally, given the often weaker mechanistic relationships of biomarkers to drugs' therapeutic actions in psychiatry compared with those in other fields like Alzheimer disease, phase III trials will likely need to include enough participants who are biomarker negative to show that enrichment was achieved (that is, studies only of patients positive for a biomarker are unlikely to suffice). Moreover, although initial efforts can be expected to target subsets of established indications, because drug effects are likely better tied to biology than to arbitrary clinical diagnostic categories, future efforts may seek approvals that cut across traditional diagnoses (potentially through multiple, separate approvals in different indications).

The guidance also affects drug labelling, which could specify that the drug is effective in all patients but primarily in individuals who are biomarker positive (an enrichment marker) or label the drug exclusively for patients who are biomarker positive (a companion diagnostic). Regulatory considerations may also extend to the biomarker itself, which may require clearance as a diagnostic tool, potentially involving hardware or software, and the FDA's experience with machine learning-derived markers could support advances in neurobiological biomarkers for psychiatry.

Commercial and clinical implementation considerations

In the late twentieth century and early 2000s, drugs targeting large populations, like statins and antidepressants, dominated, but the focus has since shifted towards drugs for niche populations. For example, oncology now accounts for over 25% of drug approvals in the 2010s, up from just 4% in the 1980s (ref. 225). Although these drugs serve smaller groups, their higher pricing owing to their effectiveness in treating rare or hard-to-treat conditions has compensated for the reduced patient numbers.

Revenues from oncology drugs surged 70% between 2010 and 2019, while non-oncology drug revenues declined[226]. Precision oncology's commercial success shows the potential of biomarker-driven treatments Precision medicine reduces development risks by targeting subpopulations who are more likely to respond, allowing drugs to be approved for smaller subgroups (even if represented within multiple traditional diagnoses), and offering quicker insights into a programme's viability, which could be especially valuable in psychiatry, in which failures often occur late in development.

In psychiatry, biomarkers could help to validate multiple therapeutic targets, but their clinical adoption faces challenges. Psychiatric practice is slow to incorporate new technologies. However, clinician surveys suggest dissatisfaction with the current state, potentially signalling openness to biomarker-based tools. To be widely adopted, these biomarkers must be scalable and easy to interpret. Preferred options include EEG, behavioural tests and blood tests, as opposed to more complex methods like fMRI or PET that need specialized testing centres and costly equipment.

To work at scale, EEG would likely need to be done with fewer electrodes and in a manner that does not require training or technical expertise. This would be analogous to the Alzheimer disease's β-amyloid space, in which the only available tool initially was PET, but cerebrospinal fluid and ultimately blood markers have since been developed that can perform at similar fidelity but at greater scale and lower cost.

Cost of biomarker testing is another critical factor. Given the high prevalence of psychiatric conditions, the cost of biomarker testing must also be factored into the development and commercialization strategy. Biomarker testing costs are not only for those who test positive for the marker and eventually receive the drug, but also those negative for the marker. Biomarker tests for which positive results are infrequent would likewise be associated with greater overall costs, as more patients would need to be tested in order to find those for whom the drug is indicated.

Oncology's development approach, in which diagnostics and therapeutics are often separated into different organizations or companies, also offers lessons for psychiatry. Psychiatry lacks established reimbursement pathways for biomarkers but could explore models like low-cost, scalable screening tools or integrating diagnostics and therapeutics under a unified business model. This could minimize costs for biomarker tests while generating revenue through therapeutics, not relying on development of a standalone psychiatric diagnostics market.

A precision psychiatry framework would also strengthen intellectual property protections. Method-of-treatment patents, covering biomarker-defined on-label populations, can extend intellectual property lifespans beyond the original composition of matter patents. This approach is already common in psychiatry, in which development timelines are lengthy. Blockbuster drugs like esketamine, xanomeline–trospium chloride and bupropion–dexamethasone rely entirely on method-of-treatment-based protections.

Lessons learned and future application

The insights outlined above highlight several steps to advance precision psychiatry (Fig. 6). First, the field requires more systematic collection of

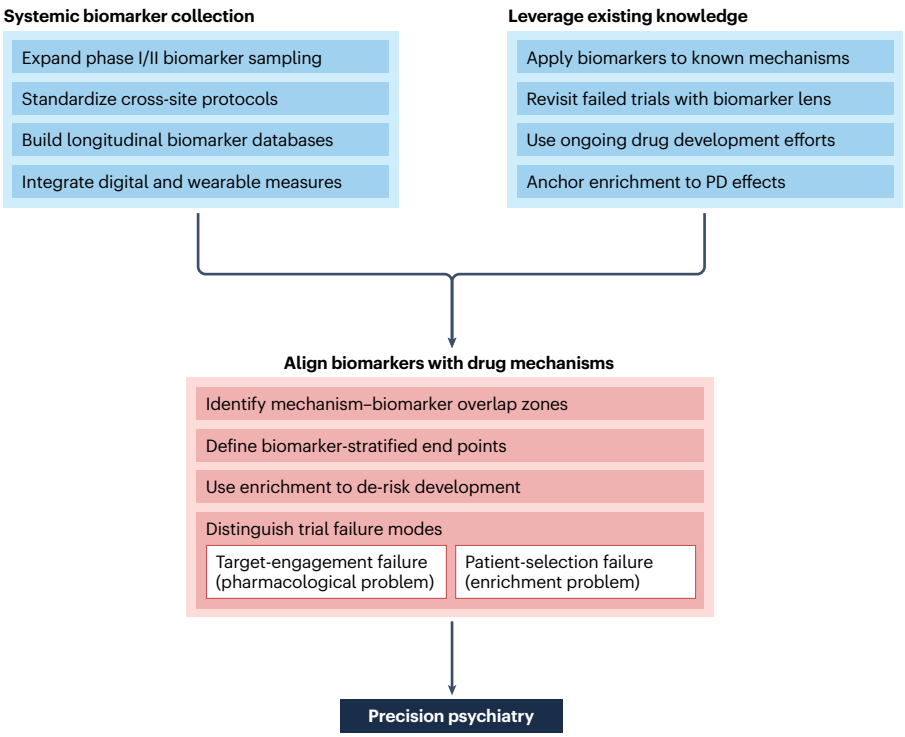

Fig. 6 | A framework for implementation of a precision-psychiatry drug development approach. Much of the foundation needed to bring precision into drug development already exists, but it should be pursued more systematically. This includes systematic collection and harmonization of standard biomarker modalities at scale and across development phases. Considerable progress can already be made by anchoring to known mechanisms and those in development (that is, there is no need for a new, wholesale 'bottom-up' science to support precision). Through iteration and application to clinical trials, sources of failure and their solution can be identified and anticipated. PD, pharmacodynamic.

biomarkers from human studies, which are currently limited by underpowered phase I trials and phase II trials with little biomarker collection. Second, existing knowledge should be leveraged. There is a wealth of novel drug mechanisms and drugs in development that can benefit from biomarkers. Innovation should not solely focus on new targets but also make better use of known drug mechanisms, as demonstrated by the long development journey of xanomeline–trospium. Third, biomarkers should be aligned with drug mechanisms. Identifying specific areas within disorders in which biomarkers and drug mechanisms align can help to guide and de-risk development, regulatory and commercial strategies. Careful distinction should be made between trials failing owing to not identifying responsive subpopulations versus those that fail despite well-defined biomarker populations.

Overall, precision psychiatry's future depends on better use of biomarkers to guide therapeutic development and refine clinical trials. Although our focus here is on brain circuit-based measures, as they are the most advanced and coherently organized, we hope that continued evolution of the field will broaden the range of useful biomarkers. Ultimately, precision psychiatry is an approach to knowledge generation in therapeutic development, and, as such, it is agnostic to the type of biomarkermodality. Moreover, as different biomarker tools show their utility, the economic implications of large-scale testing will become an important area to consider alongside drug development.

Published online: 24 August 2026

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Author contributions

The authors contributed equally to all aspects of the article.

Competing interests

A.E. and P.O. receive salary from Alto Neuroscience. A.E., P.O. and H.M. hold equity in Alto Neuroscience. H.M. holds equity in Johnson & Johnson. He is Scientific Advisory Board member, Board member, strategic adviser and/or consultant (past 5 years) for: Stanley Center, Dana Foundation, Healthy Brains Global Initiative, McLean Hospital, Foundation for OCD, Dolby Family Ventures, Vanna Health, Alto Neuroscience, Noema, Otsuka, Boehringer-Ingelheim, Sanofi, Apollo Therapeutics, Freedom Biosciences, Empyrean, Lundbeck, Psychogenics and Rapport Therapeutics. K.J.R. has performed scientific consultation for Bioxcel, Bionomics, Acer and Jazz Pharma; serves on Scientific Advisory Boards for Sage, Boehringer Ingelheim, Senseye and the Brain Research Foundation; and has received sponsored research support from Alto Neuroscience.

Additional information

Peer review information *Nature Reviews Drug Discovery* thanks Mirko Manchia, Seth Hopkins and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.