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Neuropsychiatric drug development: Perspectives on the current landscape, opportunities and potential future directions

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Mental health represents a major challenge to our societies. One key difficulty associated with neuropsychiatric drug development is the lack of connection between the underlying biology and the disease. Nevertheless, there is growing optimism in this field with recent drug approvals (the first in decades) and renewed interest from pharmaceutical companies and investors. Here we review some of the most promising drug discovery and development endeavors currently deployed by industry. We also present elements illustrating the renewed interest from key stakeholders in neuropsychiatric drug development and provide potential future directions in this field.

The need for new therapies in mental disorders

Psychiatric diseases are a leading cause of the global health-related burden.^{(p1),(p2)} Currently, half of the world's population experiences a mental disorder by age 75,^(p3) and mental health problems are growing, notably due in part to the COVID-19 crisis.^{(p1),(p4),(p5),(p6)} In addition to the terrible impact on patients' lives, mental disorders place an enormous economic burden on our societies. In Europe alone, this cost is estimated at more than €600 billion [4% of gross domestic product (GDP)].^(p7)

Although currently available treatment options may support acceptable patient management, they are often associated with poor effect sizes,^(p8) and 20–60% of patients do not respond at all.^(p9) One potential explanation for this is the fact that mental health conditions are still classified, diagnosed, and prescribed

for solely based on patients' symptomatology, not on their underlying etiology.^{(p10),(p11)} This lack of biology-based patient clustering prevents the use of objective/quantitative biomarkers and raises significant challenges in clinical practice when it comes to defining, diagnosing, and managing therapeutic strategies. For instance, in obsessive-compulsive disorder (OCD), depression, and schizophrenia, patients can receive multiple treatments via a trial-and-error approach before being stabilized with an acceptable therapeutic.^{(p8),(p12),(p13),(p14)} During this iterative process, the psychiatrist might test different molecules/dosages over several months, which requires several weeks of washout between treatment types until an acceptable response is observed, if indeed a response occurs while side effects certainly occur. With this treatment algorithm, the psychiatrist

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has no tools to predict treatment response although patients are likely to experience functional impairment.

In light of the above, it is clear that urgent action is needed to deliver innovative and more efficacious treatment options for those living with mental disorders. ^{(p2),(p10),(p11),(p15),(p16)}

Neuropsychiatric drug development: some of the challenges ahead

Historically, drug discovery for central nervous system (CNS) disorders in general has been associated with higher attrition rates, longer development times, and higher costs than other areas of drug discovery, which has led many pharmaceutical companies to leave this domain. ^{(p8),(p16)} This particularly applies to mental disorders; indeed, most drugs currently used to treat mental disorders are decades old, and psychiatry (together with cardiology) is the only medical field where the innovation index has decreased since the beginning of the millennium. ^(p11) Over the last few decades, the drug failure rate has been high, ^{(p10),(p11)} which contributes to neuropsychiatry's reputation as a particularly challenging therapeutic area. Most of the key challenges are due to the fact that mental disorders are highly heterogeneous and solely defined based on an observed cluster of symptoms that nevertheless transcend the current Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 diagnostic boundaries. ^{(p10),(p11)} In fact, psychiatric symptoms often even transcend the strict dichotomous distinction between health and disease. ^(p17) This symptom-driven paradigm is not underpinned by the underlying biology associated with individual symptoms. Hence, it does not optimally foster the discovery and development of biology-based novel treatments.

One possible solution to this problem is precision medicine, whose goal is to select the best treatment based on biology-driven markers, as with antibiogram for infectious diseases. The idea that clustering patients based on biology (potentially regardless of specific symptoms/diagnosis) could help develop or identify improved treatments is now well established. ^{(p8),(p10),(p11),(p17),(p18),(p19)} Precision medicine supports patient stratification, which would greatly de-risk clinical trials by preselecting subpopulations more likely to respond to a particular treatment, thus offering an opportunity to achieve larger effect sizes. ^(p20) This approach might also improve clinical management by giving the psychiatrist a biomarker that can be used to better guide the therapeutic strategy.

Nevertheless, successful implementation of precision medicine in psychiatry will require addressing a few challenges. First, the ideal marker(s) should be easy to insert into the clinical workflow and easily usable for guiding an actionable therapeutic strategy; for instance, a marker that relies on existing or new treatments. Second, most neuropsychiatric diseases are evolutive (often with prodromal, remission, and relapse phases), ^{(p11),(p17)} and their causes (although not well known) are multifactorial. ^{(p16),(p17)} Thus identifying relevant stratification biomarkers will likely require processing a huge amount of data that will need to be cross-referenced in innovative ways, leveraging a multidisciplinary approach. ^{(p8),(p17),(p19)} Third, regulatory aspects must also be anticipated, given that novel markers are unlikely to always align with the current DSM-5-based system used by regu-

latory agencies and payers ^{(p8),(p11)} (Box 1). Solid evidence will be needed to convince health authorities of the rationale and need to focus on particular symptoms, endophenotypes, patient subpopulations, and endpoints.

Box 1 Overview of market access challenges anticipated in neuropsychiatric drug development

- Realizing the potential value of new therapies depends on the successful completion of a series of steps: from initial economic evaluations based on clinical trial data, to reimbursement decisions based on these evaluations, to implementation of these decisions in clinical practice. Achieving market access for a new product involves understanding the current evidence requirements for reimbursement, recognizing the challenges these hurdles pose for drug developers, and identifying tactics to address them. These challenges can be better anticipated through early interactions between industry players and health technology assessment agencies during the development process. ^{(p144),(p145)} This could improve both the quality and credibility of the studies, which would become more useful in guiding reimbursement decisions. ^(p144)
- Payers are also increasingly focusing on products that can be seen as 'innovative'. Although the operable definition of innovation might be unclear or inconsistent across laws, regulations, and policies, demonstrating the innovation of the product is necessary to secure market access. 'Innovation' can generally be defined as improvement in relative efficacy and/or efficiency compared with the current standard of care. A 'valuable innovation' is defined as something that truly fills an unmet need. The National Institute for Health and Care Excellence in the UK suggests that an innovative product is one that also provides 'a step-change in terms of outcomes for patients'. Clarification of the definitions of innovation as they relate to market access, investment in the development of products that meet those requirements, and subsequent positioning of the differentiating features associated with innovation are crucial to justify premium pricing. ^(p145)
- Economic evaluations and coverage decisions are based on less-than-perfect data, and the impact of both on actual outcomes in clinical practice is uncertain. ^(p144) It is therefore important to collect data on actual use and outcomes in clinical practice. Because outcomes depend on multiple factors, individual patient data are essential. Analyses based on such data can also help inform decisions in clinical practice that are not, and often cannot be, guided by clinical trial data, such as the costs and outcomes of using drugs in particular combinations and/or sequences. These data must include not only drug therapies, but also all relevant diagnostic and therapeutic interventions; these are important to optimize and increase the value of new drugs in clinical practice. ^(p144)

The lack of a biological basis for defining psychiatric disease and/or symptoms, in addition to their multifactorial roots, also constitutes a major hurdle for identifying novel drug targets. Strong target linkage to disease is one of the pillars of the risk mitigation strategy in drug development. ^(p21) However, in psychiatry, the causal link between single targets and disease states is often weaker, and biological systems can show a high degree

of redundancy that blunts the efficacy of highly targeted drugs.^(p22) Modulating complex behaviors often relies on fine tuning brain activity, which could be difficult to achieve by selectively modulating brain targets that might be expressed across various brain regions/circuits potentially involved in ‘antagonistic’ activities. This echoes previous considerations around ‘dirty’ drugs characterized by complex pharmacology that does not solely modulate a single brain receptor^{(p23),(p24)} and the need for more holistic approaches (‘zooming out’).^(p17) Furthermore, engaging the complex neural networks that underlie psychiatric symptoms is difficult following modulation of single targets. Ideal (novel) targets would be linkable to clear neural networks with ‘disease relevance’ that can be assessed in an objective, quantitative, and translational manner.

Another well-known major challenge in neuropsychiatric drug development is the poor translation of nonclinical findings to clinical outcomes.^{(p24),(p25),(p26),(p27),(p28),(p29)} As with the identification of novel targets, a lack of understanding of the neurobiology and endophenotypes (a measurable characteristic that exists somewhere along the biological pathway from gene risk to the overall phenotype or categorical diagnosis) associated with psychiatric disorders has complicated the development of animal models. Of note, the key question concerns ‘how to model cross-species, clinically relevant quantitative phenotypes’.^(p11) Current animal models (which mostly rely on behavioral assessment) have been instrumental in advancing our understanding of psychiatric diseases and in developing new treatments. However, it is also clear that animal behavior does not precisely replicate or reflect the complex syndrome or symptoms present in humans. One obvious limitation relies on excessive anthropomorphism in interpreting animal behavioral outcomes.^(p30) Another limitation is that these animal models have mostly been ‘validated’ with drugs that predominately work via similar modes of action; as a result, they might be suitable for the discovery of ‘me too’ iterations of existing agents but not for developing truly innovative therapies.^(p30) Ideal nonclinical testing would therefore rely on more appropriate use of these behavioral models, for example to inform the recruitment of brain circuits rather than modulate symptoms, and incorporate biomarkers that rely on evolutionarily preserved neurobiological and neuropharmacological systems.^(p11) This challenge underscores the need to carefully select and develop animal models with pathophysiology-relevant and circuit-specific alterations.

Overall, the elements discussed above suggest that improvement of neuropsychiatric drug development requires the implementation of a strategic approach aiming to select biomarkers that target specific biological dysfunctions or symptom domains (rather than diagnosis).^(p31) This is expected to enhance precision, treatment sensitivity, and cost-effectiveness throughout the drug development process (and beyond), notably by improving three key aspects:

- Target validation and clinical translation through the implementation of readouts usable in similar modalities across non-clinical species and humans.

- Clinical trials derisking through implementation of precision medicine and biology-driven patient stratification strategies, which is expected to lead to larger effect sizes in target patient populations.
- Selection of appropriate therapeutic strategies in clinical practice through more rational identification of symptom domains and/or treatment response prediction.

Disruptive innovations will rely on a paradigm shift

In large part as a reaction to the challenges raised by the lack of a biological rationale for the definition of mental disorders, in 2009 the National Institute of Mental Health (NIMH) proposed a new research classification system: the Research Domain Criteria (RDoC).^(p32) The RDoC framework is centered around dimensional psychological constructs and methods used to investigate and understand constructs (termed ‘units of analysis’), including molecular, genetic, neurocircuitry, and behavioral assessments.^(p32) The RDoC come from a large governmental agency acknowledging the need for novel approaches and providing support to reach a turning point. This is an illustration of the consensus on the need to accelerate the paradigm shift to support the development of novel pharmacotherapies in psychiatry.^{(p8),(p10),(p11),(p16),(p17)} The subsections below describe and exemplify, though in a non-exhaustive manner, a few promising avenues and ongoing endeavors.

Precision psychiatry

A growing number of initiatives aiming to accelerate the application of precision medicine to psychiatry (also referred to as ‘precision psychiatry’) have emerged. These include research consortia involving industry players, such as the Innovative Medicine Initiative PRISM project (<https://prism-project.eu/en/prism-study/>), as well as efforts from biotech and pharma companies^{(p17),(p33)} including Boehringer Ingelheim^(p34) and Johnson & Johnson.^(p35) This growing interest has been notably fueled by recent progress in data science and computational approaches, which offer new opportunities for the identification of endophenotypes.^{(p8),(p17),(p36),(p37),(p38)} Through analytical tools including artificial intelligence/machine learning, it is now possible to process large [e.g. genomics, proteomics, electroencephalogram (EEG), imaging, digital, clinical measures] datasets and carry out multimodal and multi-timescale evaluations (e.g. the *2021 Neuropsychopharmacology Reviews: Big Data in Psychiatry* <https://www.nature.com/collections/jcc-jabadbf>). As an example, three different psychosis biotypes were highlighted following evaluation of cross-dimensional characteristics including genetic measures, brain structure, electrophysiology, clinical assessment, symptom complexes, and psychosocial functions,^{(p39),(p40)} thereby providing opportunities for patient stratification in schizophrenia drug development^(p41). Other precision medicine strategies also relying on multimodal computational approaches are currently being deployed by biotech companies such as Neumora Therapeutics (see corporate presentation^(p42)).

Big data-driven multimodal computational analyses notably foster the development of circuit-based approaches whereby

endophenotypes can be associated with neural network functioning/brain connectivity patterns. As a result, therapies relying on circuit-based biomarkers have recently emerged.^(p8) This approach is notably being pursued by the clinical-stage company Alto Neuroscience. The company website (<https://www.altoneuroscience.com/>) contains publications reporting interesting data supporting the identification of subtypes of connectivity patterns in post-traumatic stress disorder (PTSD) and depression using a machine learning approach leveraging functional magnetic resonance imaging (fMRI) and EEG data.^{(p43),(p44),(p45)} Other reports highlight fMRI/EEG connectivity subtypes in PTSD and EEG-measured network functional connectivity patterns in depression that could help predict treatment response.^{(p46),(p47),(p48),(p49),(p50)}

The development of digital biomarkers corresponds to another growing area offering opportunities for the implementation of precision psychiatry.^(p51) Digital biomarkers are collected from devices in everyday use such as computers (e.g. via keyboard keystrokes/social media), mobile phones, or wearables that measure individuals' physiology and behavior as they go about their daily lives.^(p51) As an example, a recent study from the PRISM consortium reported digital behavioral signatures reflecting transdiagnostic clusters within patients with schizophrenia and Alzheimer's disease.^(p52) Some biotech companies, such as Monument Therapeutics, are progressing digital biomarker-based therapies.^(p53) It is also worth mentioning the development of 'digital precision medicine' companies, such as Feel Therapeutics, offering FDA-approved tools allowing active and passive collection of multimodal data 24/7/365 (via wearables) that can notably support better identification of biomarkers and endpoints (<https://www.feeltherapeutics.com/>).

Other approaches considering the intricate interactions between the immune system and the brain^{(p54),(p55),(p56),(p57),(p58)} are increasingly seen as particularly promising for the development of new treatments in psychiatry (Box 2). Immunocentric approaches have real potential to contribute precision therapeutics in psychiatry, as suggested by accumulating evidence pointing to immune-related markers/signatures across various psychiatric patient populations^{(p59),(p60),(p61),(p62),(p63),(p64),(p65),(p66),(p67),(p68),(p69),(p70),(p71),(p72),(p73),(p74),(p75),(p76),(p77),(p78)} suggesting an immune component of some endophenotypes, thereby opening the door to patient stratification strategies. As an example, studies have reported the presence of autoantibodies against N-methyl D-aspartate (NMDA) receptors in subgroups of patients with psychosis.^{(p63),(p69),(p79)} These NMDA receptor autoantibodies are targeted by ART5803, a biologic developed by a recently launched precision psychiatry company^(p80) now entering phase I (NCT06575153). Another study recently highlighted the anxiogenic potential of a protein, *Imood*, expressed in and released from T cells as well as its differentiated expression profile in peripheral blood mononuclear cells (PBMCs) from patients with OCD compared with healthy controls,^(p75) which opens the door to potential *Imood*-based stratification strategies.^(p81) As biology transcends diagnostic boundaries, the development of precision medicine approaches based on immune biomarkers might connect a medication to biological deficits and/or psychological dimensions that span multiple DSM-5 categories.^(p82)

The interest in developing transdiagnostic approaches to further accelerate the implementation of precision psychiatry has

Box 2 The bilateral crosstalk between the brain and the immune systemA wealth of supporting literature describes the communication between the immune system and the brain,^{(p54),(p55),(p56),(p57),(p58),(p146)} and consideration of the neuroimmune axis is increasingly capturing interest from the scientific community [this is notably illustrated by the 2022 *Neuron's* 2022 Special Issue (Volume 110, Issue 21, pp. 3407–3644), which is fully dedicated to the topic].

The nervous and immune systems share various similar functions and properties (notably plasticity),^(p81) and over the past few decades it has become apparent that not only do the two systems interact and influence each other, but also that such crosstalk takes place under homeostatic conditions.^{(p58),(p147)} This led to the proposal of the existence of a 'continuum' between the brain and the immune system.^(p81) In normal physiological conditions, the brain and the immune system 'balance' each other. However, in pathological conditions, when one of the two becomes dysfunctional or weak, the other one becomes hyperactive and loses control. The most common examples^(p81) of this homeostatic system of balance and bilateral communication are the increased emergence of mental disorders in patients suffering from autoimmune diseases and, conversely, the immunological dysfunctions of patients suffering from mental disorders.

The role of adaptive immune cells, and especially T cells, is of particular interest, notably because, like neural cells, T cells are plastic and can respond to external stimuli (antigens or infections) by changing their functions.^(p148) Furthermore, among immune cells, T cells are considered the 'cellular bridge' to the CNS because of their presence in the cerebrospinal fluid and ability to home in on the CNS and produce factors that modulate neuronal cell functions.^{(p54),(p58),(p149)} Accumulating evidence demonstrates the capabilities of T cells to modulate brain functions, including memory, learning, and emotional behavior, in both healthy and disease state/models.^{(p54),(p106),(p150),(p151),(p152),(p153),(p154),(p155),(p156),(p157),(p158),(p159)} Thus it is reasonable to hypothesize that impaired T cell-mediated regulation of brain functions can lead to neuropsychiatric disorders. Supporting this concept, when looking at the clinical manifestations and development of both autoimmune disorders and psychiatric diseases, there is an unresolved problem at the cellular and molecular levels that is periodically activated and shut down. These flares or rounds of relapse/remissions emerge for reasons that are not yet clear. However, as discussed elsewhere, it is known that in some mental disorders like OCD and PANDAS (pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection), the flares might coincide with an infection and/or might be linked to autoimmunity.^{(p66),(p81)} Furthermore, recent work showed the capability of a factor, *Imood*, expressed and released from T cells to modulate anxiety-like behavior in mice while being dysregulated in PBMCs from patients with OCD.^(p75) This protein might play a key role in T cell-mediated

regulation of brain activity, was proposed as a novel drug target,^(p81) and is of interest to Karla Therapeutics.

Overall, this field of research, known as psychoneuroimmunology or immunopsychiatry, is booming as it is thought to offer opportunities for new mechanistic understanding and insights for novel therapies in psychiatric disorders.^{(p66),(p68),(p81),(p82),(p106),(p146),(p147),(p160),(p161)}

been already highlighted.^{(p10),(p11),(p17)} Transdiagnostic approaches were proposed to support the identification of bio-clinical dimensions relying on quantitative biological parameters to be implemented in future preclinical/clinical trials.^(p83) The interest in these approaches is notably supported by recent evidence showing six different profiles of functional connectivity within the default mode network (DMN) in a large transdiagnostic sample of patients with mood disorder and anxiety disorder.^(p84) Another important study carried out by the PRISM consortium reported a transdiagnostic association of social dysfunction with DMN functioning in schizophrenia and Alzheimer's disease.^(p85) The same group published another study this year showing transdiagnostic digital signatures associated with social dysfunction in schizophrenia and Alzheimer's disease.^(p52) It is worth noting here that, as for the PRISM studies, transdiagnostic approaches might also include neurodegenerative (e.g. Alzheimer's, Parkinson's) or neuroimmunological conditions (e.g. multiple sclerosis) sharing similar psychiatric symptoms^{(p86),(p87),(p88)} (which could suggest common biological pathways, as previously pointed out^(p17)).

To summarize, a growing body of evidence supports the existence of different (transdiagnostic) biotypes within DSM-5-defined psychiatric patient populations.^(p89) This is certainly encouraging and will probably continue to drive the transition to precision psychiatry. The industry is already engaged in this transition with multiple precision therapeutics being under development and with NMRA-335140, ALTO-300; ALTO-100, KYN-5356, and ART5803 now being in the clinic (<https://clinicaltrials.gov/>). Nevertheless, endeavors aiming to further validate biomarkers/endophenotypes/stratification strategies should be continued to support their acceptance by regulatory agencies and payers. From this perspective, it will be critical to work in a collaborative and transdisciplinary manner to define methodological standards and improve replicability. Processing multimodal data, including genetic, EEG, fMRI, cognitive function task, immune marker, clinical, and patient history data, through computational approaches will certainly be key to fully capture the heterogeneity of symptom clusters and identify subgroups for which a pragmatic therapeutic strategy can be deployed.^(p8)

Novel targets and emerging therapies in the pipeline

Most recent updates on the current development pipeline in neuropsychiatry highlight a myriad of targets under exploration, illustrating the need and desire for new mechanisms of action.^{(p8),(p16),(p90),(p91),(p92),(p93),(p94)}

Investigation of new avenues has been recently rewarded with the approval by the US FDA of esketamine (Spravato) and brex-

anolone (Zulresso), modulators of NMDA and gamma-aminobutyric acid (GABA) receptors, respectively, in 2019. These two approvals (representing the first newly approved mechanisms of action in decades) are expected to stimulate the development of novel, rapidly acting therapies relying on glutamatergic or GABAergic modulation, with a few compounds already in the clinic.^{(p94),(p95),(p96)}

Other approaches relying on the recently renewed wave of interest in psychedelics and exciting research have led to the clinical testing of multiple psychedelic agents for various psychiatric conditions. This topic is already well covered by excellent reviews^{(p93),(p97),(p98)} and will not be further developed here. It is worth noting, however, that most of these emerging therapies (like those referred to in the previous paragraph) lack predictive response and mechanistic biomarkers.^(p8) Furthermore, the FDA rejection of 3, 4-methylenedioxy-methamphetamine (MDMA) for PTSD earlier this year^(p99) might have an impact on future psychedelic developments.

It is exciting to see some of the most advanced/promising molecules with novel mechanisms of action entering late-stage clinical trials. This includes modulators of the M1/M4 receptor KarXT, CVL-231 (M4 selective), and NBI-1117568 for schizophrenia (NCT05145413, NCT05443724, and NCT05545111, respectively) as well as the kappa opioid receptor NMRA-335140 for depression (NCT06058013). Notably, KarXT just received FDA approval, generating considerable excitement as a non-dopaminergic treatment for schizophrenia.^(p100) Suggestions that it might have greater efficacy against cognitive and negative symptoms of schizophrenia require further investigation. Other earlier programs include KYN-5356 (NCT06225115), a KAT-II inhibitor modulating the kynurenine pathway^(p101) that was announced this year as entering phase I.^(p102) If successful, these first-in-class candidates could not only increase the number of therapeutic options for psychiatric patients but also further fuel the ongoing momentum in psychiatry research (see also the section below discussing opportunities).

The approaches outlined above have real game-changing potential but rely on relatively traditional brain-targeting small molecule drug discovery endeavors, which is probably not the only way to treat mental disorders.^(p30) In fact, the capability of the periphery to regulate brain activity is increasingly seen as critical in psychiatric disorders and emotional/affective status.^{(p81),(p103),(p104),(p105)} In particular, approaches taking into consideration the capabilities of the immune system to modulate brain functions, also referred to as immunopsychiatry (Box 2), are thought to bring interesting opportunities for novel target identification in psychiatry.^{(p16),(p82),(p106)} By contrast, with selective modulation of brain targets ('zooming in'), modulation of brain-regulating immune targets might allow fine tuning of brain activity/circuits, thereby supporting a more holistic approach (zooming out). The other interesting aspect of immunocentric approaches is the possibility to connect a medication to immune markers that might be peripherally available, thereby supporting patient stratification (see 'Precision psychiatry' section above). Several trials reviewed elsewhere^{(p8),(p82)} have been testing immunotherapies aiming to modulate the inflammatory pathway, which has captured a lot of attention in

psychiatry.^{(p107),(p108),(p109)} However, most of these attempts were not clearly a success,^{(p8),(p17)} for reasons potentially linked to weak stratification strategies,^(p8) and approaches focused on other immune-related mechanisms are now emerging. For instance, a new biological entity targeting autoantibodies against NMDA receptors, ART5803, has recently entered phase I (NCT06575153; see also the 'Precision psychiatry' section above). Other more early-stage approaches more specifically take the capabilities of T cells to modulate brain functions into consideration (Box 2). As an example, Karla Therapeutics' approach notably relies on data highlighting the angiogenic potential of *Imood*, a protein expressed in and released from T cells found to be dysregulated in PBMCs from patients with OCD.^(p75) Altogether, immunocentric approaches emerge as a rapidly developing research field, also referred to as immunopsychiatry, which is thought to provide new perspectives and opportunities for new therapeutic targets in neuropsychiatric disorders.^{(p81),(p82),(p106),(p110)} In a recent paper sharing perspectives on neuropsychiatric drug development, Paul and Potter^(p30) highlight the need to embrace disruptive concepts, reminding us that, over decades, '...very targeted approaches to treating cancer based on well accepted somatic driver mutations (e.g. gain of function receptor tyrosine kinase mutations) were dominant but in many cases have now been superseded by the advent of immuno-oncology which has been shown to be very effective for certain cancers'. The parallel with immunopsychiatry is interesting.

Clinical translation

An integrated experimental medicine approach leveraging both preclinical and clinical data is thought to be key to advance the field of neuropsychiatric drug development, with preclinical research providing insight about the potential mechanisms underlying neuronal dysfunction and clinical research having relevance to humans.^(p11) Such an integrated approach should notably support reverse translation from clinical to preclinical research, to work with relevant models. Reverse translation implies that homologous human and animal endpoints, which should be highly quantitative and neutral, are being defined to facilitate the translation from humans to animals and vice versa.^(p11) To maximize their translational value, reverse translational approaches should focus on evolutionarily preserved neurobiological and neuropharmacological systems.^{(p10),(p11)} This includes circuit-based approaches allowing cross-species mapping of neural network activity.^{(p8),(p17),(p111),(p112)} Existing/future behavioral models have a translational value that might rely more on their capability to be informative regarding the engagement of specific brain circuit(s) rather than symptom modulation.^{(p16),(p30)} The engagement of a particular circuit, as suggested (notably) by behavioral studies, can be further assessed quantitatively/objectively through implementation of readouts that can be used in similar modalities across nonclinical and clinical settings (e.g. EEG or fMRI).^(p10) In such a paradigm, the question to be addressed in nonclinical testing becomes 'what do current/future nonclinical models tell us about the neurobiological/brain-circuit effects of a compound, and to what extent this can support clinical efficacy/clinical trial design?'. Reverse translation approaches integrating experimental medi-

cine and clinical data are thought to support the selection/development of animal models having circuit-specific alterations that can be involved in human pathophysiology.

Recent examples of ongoing endeavors in this space includes a study investigating mismatch negativity (MMN) in patients with schizophrenia and Alzheimer's, as well as in rodent models of these diseases.^(p113) The authors applied EEG-recorded stimulation protocols adapted from those used in patients to evaluate MMN in rodents and back-translated their clinical findings in the animal models, suggesting their translational value. Accumulating evidence highlights the value of MMN as a translational EEG biomarker^{(p114),(p115)} and, not unexpectedly, it is increasingly being implemented by industry in early clinical trials to inform target engagement, as exemplified by CNV058, for instance.^(p116)

Other examples illustrate how cross-species evaluation of EEG can guide neuropsychiatric drug discovery and development. Notably, convergent clinical literature indicates abnormalities in the synchronization of EEG gamma oscillation as an endophenotype in patients with schizophrenia, whereas acute NMDA receptor blockade in rodent produces schizophrenia-like behavior and cognitive deficits associated with increased cortical network excitability and impaired gamma oscillation synchrony.^{(p117),(p118)} It has been shown that modulation of EEG gamma oscillations might reflect antipsychotic activity.^(p117) Thus studies aiming to detect drug-induced gamma oscillations are increasingly observed in industry.^{(p119),(p120)}

EEG endpoints have been established as important translational biomarkers in neuropsychiatric drug development,^{(p121),(p122),(p123)} and there are multiple examples of industry studies (not all published) reporting similar drug-induced EEG signatures between preclinical species and humans^(p124) Hence, industry is making efforts to standardize reliable and scalable EEG biomarkers to enable wider use of these measures in drug discovery and development.^(p125)

Concluding remarks and opportunities in the neuropsychiatric drug development space

After a period of reluctance to invest in neuroscience, the pharmaceutical industry is beginning to reinvest in this area, as highlighted in various business reports^{(p34),(p35),(p126),(p127),(p128),(p129),(p130),(p131),(p132)} and in takeaways from the 2024 JP Morgan Healthcare Conference.^(p133) Neuropsychiatry contributes significantly to this renewed interest, as reflected by a number of recent deals,^{(p34),(p35),(p126),(p127),(p128),(p129),(p131),(p132)} most notably the \$14 billion deal between Bristol Myers Squibb and Karuna Therapeutics, as well as AbbVie's deals with Cerevel (\$9 billion) and Gilgamesh Pharmaceuticals (\$2 billion), all of which were completed this year.^{(p127),(p134)} Other deals from 2024 include the partnership between Neurocrine Biosciences and Nxera Pharma.^(p135)

This interest from pharmaceutical companies has come with increased funding from investors (Box 3 and Figure 1). Although oncology continues to be the therapeutic area in which there is most investment, neuroscience is capturing a significant and growing portion of the venture capital (VC) money, with psychiatry

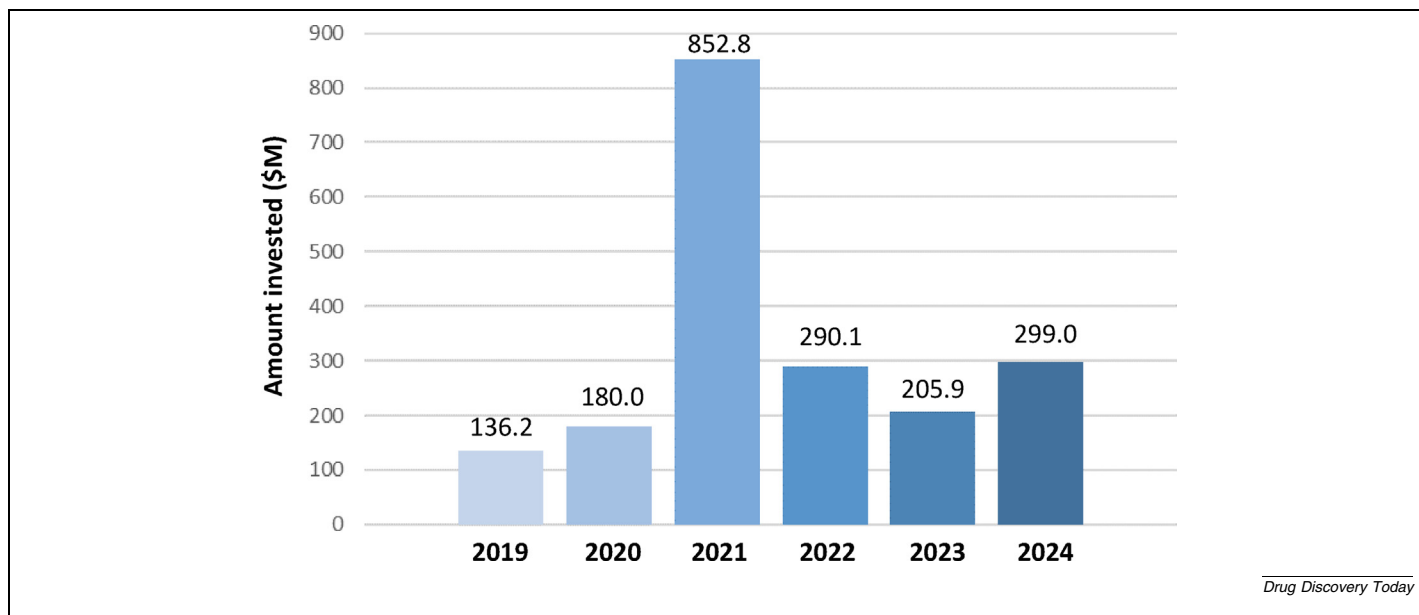


FIGURE 1

Evolution of global VC investment in neuropsychiatric drug development companies over the last 5 years (excluding IPOs and acquisitions). Source: Byte51 database (<https://www.byte51.com/>).

receiving a generous share of potential investment funds.^{(p33),(p131),(p132),(p133),(p136),(p137)} As an example, two clinical-stage precision psychiatry companies raised series A financing above \$50 million in 2023,^{(p41),(p80)} while Seaport Therapeutics and Lykos Therapeutics both received \$100 million funding this year.^{(p132),(p138)} Furthermore, Neumora Therapeutics, Rapport Therapeutics (launched in 2023 with \$100 million from major venture capitalists^(p139)) and Alto Neurosciences, as three CNS biotech companies with lead candidates in psychiatry, raised \$250 million, \$174 million, and \$148 million, respectively, through their recent initial public offerings (IPOs).^{(p140),(p141),(p142)} Interestingly, all of these finances were raised in the context of a challenging financial environment for biotech and the IPO market,^(p132) which likely reflects growing optimism about the neuropsychiatry market at the moment. It is worth noting that precision medicine approaches seem to be key to this renewed interest.^(p33)

Several indicators give us reasons to believe that the field is witnessing a revolution in mental health care.^(p143) The favorable developments outlined in this section certainly afford opportunities for those involved in neuropsychiatric drug discovery and development to explore the paradigm shift that will ultimately deliver new treatments for mental disorders.

Box 3 Insight into investors' interest and expectations
Market data clearly show that investors have an increasing interest in, and willingness to finance, novel approaches in neuropsychiatric drug development (Figure 1), with the level of venture capital investment into biotech companies rising from \$136 million in 2019 to \$299 million in 2023 (excluding IPOs and acquisitions) according to the database Byte51

(<https://www.byte51.com/>, accessed on 26 September 2024). The investment trends indicate an increased interest from specialized venture capitalists, with 80 active investors in the space (Byte51) and conversations with investors suggesting increasing enthusiasm.

However, the investor's perspective seems to further highlight the need to address challenges (consistent with those outlined above in this article), as suggested by a statement from Manuel Lopez-Figueroa, Managing Partner at Bay City Capital and Scientific Liaison for the Pritzker Neuropsychiatric Disorders Research Consortium:

'There is a mix of enthusiasm and hesitation. The transformative potential of leveraging big data, artificial intelligence/machine learning, and neurobiology promises personalized and precise treatments, with rapid advancements in technology boosting investor confidence. However, challenges remain, particularly in clinical validation, regulatory pathways, reimbursement, and the complexity of multimodal data integration and patient stratification. Additionally, high development costs, lengthy timelines, and the need for multidisciplinary expertise could contribute to some reluctance in the space. In many cases, investors are looking for well-designed clinical trials, validated biomarkers, and clearer commercial and regulatory pathways to boost confidence and drive investment.'

Declarations of interest

SL and FDA are shareholders of Karla Therapeutics. PML has been a consultant and/or advisor to, or has received honoraria from, AbbVie, Boehringer-Ingelheim, Eisai, Ethypharm, HAC, Janssen, Karla Therapeutics, Lilly, Lundbeck, MSD, Neuraxpharm, Newron, Novartis, Otsuka, Roche, Sanofi, and Teva. He also provided expert testimony for Janssen and Otsuka. HKM is former R&D Head of Neuroscience at Janssen/J&J

and is currently on the board of directors (BOD) of Alto Neuroscience. He has consulted for Boehringer-Ingelheim, Sanofi, and Lundbeck. The other authors declare no conflicts of interest.

CRediT authorship contribution statement

Simon Loiodice: Writing – original draft, Supervision, Conceptualization. **Fulvio D'Acquisto:** Writing – review & editing.

Pim Drinkenburg: Writing – review & editing. **Christian Suojanen:** Writing – review & editing. **Pierre-Michel Llorca:** Writing – review & editing. **Husseini K. Manji:** Writing – review & editing.

Data availability

Data will be made available on request.

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