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Towards a consensus roadmap for a new diagnostic framework for mental disorders

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ABSTRACT

Current nosology claims to separate mental disorders into distinct categories that do not overlap with each other. This nosological separation is not based on underlying pathophysiology but on convention-based clustering of qualitative symptoms of disorders which are typically measured subjectively. Yet, clinical heterogeneity and diagnostic overlap in disease symptoms and dimensions within and across different diagnostic categories of mental disorders is huge. While diagnostic categories provide the basis for general clinical management, they do not describe the underlying neurobiology that gives rise to individual symptomatic presentations. The ability to incorporate neurobiology into the diagnostic framework and to stratify patients accordingly will be a critical step forward for the development of new treatments for mental disorders. Furthermore, it will also allow physicians to provide patients with a better understanding of their illness's complexities and management. To realize this ambition, a paradigm shift is needed to build an understanding of how neuropsychiatric conditions can be defined more precisely using quantitative (multimodal) biological processes and markers and thus to significantly improve treatment success. The ECNP New Frontiers Meeting 2024 set out to develop a consensus roadmap for building a new diagnostic framework for mental disorders by discussing its rationale, outlook, and consequences with all stakeholders involved. This framework would instantiate a set of principles and procedures by which research could continuously improve precision diagnostics while moving away from traditional nosology. In this meeting report, the speakers' summaries from their presentations are combined to address three key elements for generating such a roadmap, namely, the application of innovative technologies, understanding the biology of mental illness, and translating biological understanding into new approaches. In general, the

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meeting indicated a crucial need for a biology-informed framework to establish more precise diagnosis and treatment for mental disorders to facilitate bringing the right treatment to the right patient at the right time.

1. Introduction

The European College of Neuropsychopharmacology (ECNP) New Frontiers meeting 2024 set out to develop a consensus roadmap for building a new diagnostic framework for mental disorders by discussing its rationale, outlook, and consequences with all stakeholders involved. The meeting program overview can be found in Box 1.

The program started with two opening lectures that highlighted the current status and future outlook with respect to the diagnosis and treatments for mental disorders.

2. Steven Hyman: psychiatric disorders: grounded in human biology but not natural kinds

Steven Hyman kicked-off the meeting and indicated that we should forget the current Diagnostic and Statistical Manual of Mental Disorders (DSM) system. It is a lost cause. Trying to improve it will be like arguing with religious fundamentalists about details of their scriptural stories. There is no reason to believe that next generation DSM-6 will be more than a small iterative change, given the wide adoption of the current DSM-5 and lucrative sales. The fundamental structure of DSM is irretrievably flawed, based on (1) limitation to phenomenology, (2) discontinuous categories rather than dimensions, (3) rigid and arbitrary thresholds, and arbitrary splitting of psychopathology into thin slices. DSM-5 contains approximately 300 diagnostic categories (based on remarkably little evidence), leading to a plague of comorbidity and unstable diagnostic trajectories (Hyman, 2010). Full reliance on phenomenology is a fatal flaw. Across all of medicine, surface- level clinical syndromes represent a collection of mechanistically heterogeneous underlying conditions that affect prognosis and treatment response. The resulting variability in treatment response has led to a call for precision medicine in which biomarkers would inform selection of the right treatment for the right patient at the right time (Krainc et al., 2023). Cancer medicine has demonstrated early success in doing so (Lynch et al., 2004).

Steven also indicated ways on how to proceed. The process should be multisector, multistakeholder, and global including not only academics but also individuals with lived experience, regulators, and industry. He recommended that we 'retreat' from individual DSM disorders to large spectra, such as the psychosis, neurodevelopmental, internalizing, and compulsive spectra defined by family studies, genetics, and comorbidity (Andrews et al., 2009; Grotzinger et al., 2022a). An alternative is to use the chapter heads in DSM-5 table of contents and the first digit clusters in the ICD-11 numeric notation. (Bipolar disorder is currently 'hanging' but should be in the cluster with the schizophrenia spectrum based on shared genetic risk and the large number of individuals with symptoms of both.)

Having selected a starting point, large spectra or alternatively the current chapter headings (or ICD first digits), the task is to re-analyze these clusters into clinically relevant, and as the science progresses, neurobiologically homogeneous components defined dimensionally (beyond severity alone). To do this we will need some old and some new quantitative instruments. We will need to motivate outcome studies of genotyped and well phenotyped affected individuals to inform threshold setting that is also sensitive to age and context (Hyman, 2021; Whelton et al., 2018). Importantly we will need to encourage biomarker discovery and then apply biomarkers along with circumspect use of polygenic scores (PGS) to a new dissection of these clusters (Krainc et al., 2023). While probabilistic, PGS use may be warranted, at least until some future in which we might have fully adequate biomarkers. (Every individual has an admixture of genetic risk factors associated with diverse disorders that probabilistically influence course and likely therapeutic response.)

Text box 1. Overview of topics and presenters of the ECNP New Frontiers meeting 2024

Opening lectures

1. Steven Hyman: Psychiatric disorders: grounded in human biology but not natural kinds
2. Leanne Williams: Towards a precision neuroscience approach for application in psychiatry

Session 1: Applying innovative technologies to measure the patient

3. Diego Hidalgo-Mazzei: Digital phenotyping in psychiatry to measure the patient and to intervene
4. Quentin Huys: Computational understanding of mental illness
5. Matthew Hotopf: Predicting relapse using multimodal biomarkers and longitudinal assessments

Session 2: Understanding the biology of the patient

6. Bruce Cuthbert: The research domain criteria (RDoC) project as a biological framework for research on mental disorders
7. Cathryn Lewis: Genetics of psychiatric disorders; transcending the diagnostic boundaries
8. Martien Kas: The quantitative biology of social dysfunction: a transdiagnostic and translational approach
9. Paris Alexandros Lalousis: Using machine learning to extract new transdiagnostic categories predicting disease progression from MRI data
10. Livia De Picker: The neuroinflammatory hypothesis in psychiatry

Session 3:Translating biological understanding into new approaches

11. Amit Etkin: Redefining psychiatry with AI-driven brain biomarkers that align the right patient with the right drug
12. Gemma Modinos: Backtranslation of human findings to rodents; testing for causality using a multi-modal approach
13. Hugh Marston: Translating biological knowledge into drug development

We must also encourage large studies of psychiatric genetics and biobanking associated with well phenotyped longitudinal cohorts from diverse global populations.

How do we maximize the likelihood that we are on the right track?

§ Multilevel scientific approaches (genetic, molecular, cellular, synaptic, circuit, cognitive, behavioral, and social approaches to individuals and attention to exposomes). We must then follow causation in a disciplined manner across levels.

§ Avoid circular reasoning and folk psychological explanations- always ask what grounds a clinical observation in biology (ranging from genetics to computational and cognitive neuroscience).

3. Leanne Williams: towards a precision neuroscience approach for application in psychiatry

In the follow-up opening lecture, Leanne Williams indicated that principles of precision medicine are already at work in fields such as cardiology, oncology, and infectious disease—where the unique biology of a patient's disease is combined with clinical information to tailor treatment choices. It's Psychiatry's turn. In a series of studies direct brain circuit measures were used to stratify the heterogeneity of major depression and compare circuit biomarkers across different treatment modalities. Circuit measures are obtained from functional magnetic resonance imaging and standardized protocols are used across studies to enable direct comparisons. The choice of circuits and imaging protocols is grounded in accumulated knowledge about circuits implicated in both the neurobiology of depression and the mechanisms of treatment. These circuits include the default mode, salience and frontoparietal attention networks, assessed in task-free states, and the negative affect, positive affect and cognitive control circuits assessed during tasks in which cognitive and emotional stimuli are presented. Dysfunction in each of these circuits characterizes different forms of depression (Williams et al., 2016) and arguably may be conflated when we consider major depression as an overarching diagnostic category. Focusing on these six circuits provides a tractable set of inputs for biomarker testing. Williams has developed and validated a standardized fMRI technology for quantifying activation and functional connectivity within these six circuits in standard deviations for each individual patient compared to a healthy reference dataset (Goldstein-Piekarski et al., 2022). These circuit metrics show predictive associations with individual symptom and behavioral profiles. The utility of these circuit metrics as predictive and response biomarkers of treatment has been demonstrated for commonly used SSRIs and SNRIs in the iSPOT-D trial, a problem-solving behavioral therapy in the ENGAGE trial, a selective mediation in the BIG trial, transcranial magnetic stimulation (TMS) in the B-SMART-f trial, and an exploratory therapeutic, MDMA in the mechanistic RBRAIN study. To illustrate this approach, findings for the negative affect and cognitive control circuit were presented.

Within the negative affect circuit amygdala activity is a differential predictor of treatment response in major depression. Hyper-activation of the amygdala evoked by sad stimuli predicts poor response to venlafaxine with 81 % leave-one-out cross-validated accuracy in receiver operating characteristic (ROC) analyses (Williams et al., 2015) while relatively lower amygdala activation to fear predicts a better response to SSRIs with 75 % accuracy (Williams et al., 2015). Predictive accuracy is further increased when the impact of early life trauma on amygdala activity is considered (Goldstein-Piekarski et al., 2016). In the ENGAGE trial, excessive amygdala activity is attenuated with problem solving therapy compared to treatment as usual, associated with a two-fold increase in symptom improvement (Goldstein-Piekarski et al., 2021). Amygdala activity shows promise as a biomarker for the acute impact of MDMA. In the RBRAIN study of individuals with sub-clinical symptoms, MDMA reduced amygdala activity and a behavioral threat bias compared to placebo after 40–60 min post-dosing. Within the cognitive control circuit, in the iSPOT-D trial dLPFC activity and connectivity distinguished remission from non-remission to SSRIs and SNRIs (Gyurak et al., 2016). We have identified a specific cognitive biotype defined by low dLPFC activity together with impaired performance on cognitive control tests, poorer psychosocial function and low response and remission rates (Hack et al., 2023). In the prospective BIG study we enriched for the cognitive biotype by stratifying patients at pre-treatment screening. We targeted cognitive control circuit function with a mechanistically selective medication, yielding a significant improvement in circuit function, cognitive performance and function as well as a two-fold increase in remission rate. In the TMS study, stimulation was applied to the dLPFC in clinical settings (Williams et al., 2021). TMS induced specific improvements in both cognitive control circuit function and behavioral performance that were pronounced after 5 days of stimulation and maintained after 30 days.

Patients report that 'knowing about their brain' helps reduce stigma and increase engagement in treatment. The findings highlight the promise of actionable circuit metrics for aiding in the choice of conventional treatments for selecting which patents might benefit most by more expedited access to new and emerging treatments.

Applying innovative technologies to measure the patient

In the first session after the opening, three speakers addressed innovative technologies to measure the patients with a focus on digital phenotyping and computational methods.

4. Diego Hidalgo-Mazzei: Digital phenotyping in psychiatry to measure the patient and to intervene

Diego Hidalgo-Mazzei indicated that symptoms, diagnosis and treatment response in mood disorders are still assessed with clinical interviews and standardized scales, which are fundamentally based on retrospective and subjective information provided by the patient. This entails limitations such as recall and confirmation bias, and lack of insight from the patient (Hidalgo-Mazzei and Young, 2019). Despite the extensive research in biological biomarkers during the last decades, there are no available objective tools in clinical settings for diagnosing, monitoring illness activity or response to treatment assessment in mood disorders (Kennis et al., 2020). Digital biomarkers, collected by smartphones and wearables sensors, might address the need for more objective tools, as they capture physiological changes associated with mood changes non-invasively. Moreover, they could also provide a cost-effective method to deliver psychological interventions to people suffering from these illnesses, particularly through smartphone apps. In fact, recent meta-analyses have demonstrated the efficacy of smartphone apps' interventions at reducing moderate and severe depressive symptoms (Bae et al., 2023) while their efficacy in bipolar disorder is still unconclusive, despite their feasibility and acceptability (Anmella et al., 2022).

Recent advances in wearables technologies, allows nowadays to collect continuous, granular and unobtrusive physiological and behavioural signals such as actigraphy, heart rate (HR), temperature, blood pressure, and electrodermal activity (EDA) in ecological settings. Over the last decade, there has been increasing interest on exploring the association of physiological digital data with behavioural alterations in psychiatric disorders. In the TIMEBASE-INTREPIBD study (https://intrepibd.github.io/) we have employed research-grade wearables to identify patterns of illness activity across mood disorders episodes and healthy controls. Through machine learning (ML) analyses, we determined actigraphic and stress-related physiological data (EDA and HR) models predicting mania and depression (5). We also found differences in EDA tonic and phasic components between manic and depressive states (Anmella et al., 2024). Moreover, using ML we were able to predict with high accuracy mood assessment scalés items just based on wearables data models (Corponi et al., 2024).

Despite these promising advancements, most digital tools have not yet penetrated clinical practice due to multiple barriers hindering their

implementation. One significant obstacle is the lack of consensus on designing studies for the proper validation of smartphone apps. Furthermore, even when an app proves effective, it must navigate costly and lengthy regulatory approval pathways before clinical implementation can occur. This process is further complicated by the absence of formally established reimbursement frameworks in many countries, which is essential for the adoption and sustainability of such digital health tools (Berardi et al., 2024).

5. Quentin Huys: computational understanding of mental illness

In the subsequent lecture, Quentin Huys addressed the application of computational psychiatry which is a rapidly growing field attempting to translate advances in computational neuroscience and machine learning into improved outcomes for patients suffering from mental illness (Huys et al., 2016, 2021). It encompasses both data-driven and theory-driven efforts. Focusing on the latter, QH first discussed the fundamental motivation for applying quantitative mathematical methods to phenomena in mental health. Briefly, because the brain's distinctive function is to compute, computational tools are indispensable to understanding symptoms arising from brain malfunction. Computational methods are also the only path to link across Marr's levels of description (Murray et al., 2014; Schmack et al., 2021), and particularly to link between objective neurobiology and subjective phenomena.

The presentation then turned to recent research using computational methods to develop novel clinical tools. This started with a novel computational approach to understanding anhedonia (Hall et al., 2024). Briefly, this showed that the state value in reinforcement-learning accounts of proximity to goals is able to capture multiple aspects of anhedonia in depression, both in terms of aetiology and the effects of stressors, but also in terms of effective psychotherapeutic approaches. The second example concerned the identification of mechanisms for psychotherapeutic interventions. Despite extensive research, which specific mechanisms mediate the effect of specific interventions has remained difficult to ascertain (Kazdin, 2007). However, the combination of computational modelling with psychometrically optimized behavioural tasks has recently shown promise in this setting (Huys et al., 2022; Norbury et al., 2024; Reiter et al., 2021). The third example considered a very specific problem, namely the development of decision-support tools to help identify relapse risk prior to antidepressant discontinuation. QH presented results from a study where computational (Berwian et al., 2020) and neuroimaging (Berwian et al., 2023; Erdmann, n.d.) outperform standard clinical measures (Berwian et al., 2022). Overall, the presentation outlined how computational tools can be developed to better understand symptoms of mental illness; how they can be used to identify the mechanisms of psychotherapeutic interventions, and to predict the outcome of pharmacological interventions. As such, computational characterisations of brain function are likely to be important to a meaningful redevelopment of diagnostic nosology.

6. Matthew Hotopf: predicting relapse using multimodal biomarkers and longitudinal assessments

In the third lecture, Matthew Hotopf addressed digital methodologies to help predicting relapse using multimodal biomarkers and longitudinal assessments. He indicated that mobile technologies – including smartphones and wearable devices – have considerable potential to provide real-time sensing of a range of CNS functions, including sleep, physical activity, speech, physiology (including heart rate, heart rate variability and galvanic skin response), cognition, sociability, symptoms and stressors. These technologies, variously referred to as remote sensing, digital phenotyping (Mohr et al., 2020), have a range of potential uses in improving understanding of psychiatric disorders, including – providing insights into current clinical state for monitoring purposes, predicting future changes in clinical state, and for stratification. As such they have been proposed as an important tool to deliver "precision psychiatry".

The state of the art in most psychiatric disorders has been for small short-term studies, often in non-clinical samples, purporting to provide information on differences in sensor data between healthy controls and people with disorders (De Angel et al., 2022). These studies are often poorly reported and do not attend to inevitable challenges in the field including data loss, drop out and participant acceptability, but have provided evidence that, for example, depression is associated with objectively measured home-stay (from GPS data), sleep disturbance and changes in physical activity. Large-scale decentralised studies on remote sensing across multiple health disorders have found retention of participants to be highly challenging, with many showing a half-life of study retention of only two weeks (Pratap et al., 2020).

The RADAR-CNS programme, an IMI2 funded public private partnership sought to address some of these challenges, by building a flexible platform capable of ingesting, storing, analysing and visualising data from participants in real time (Ranjan et al., 2019). The RADAR-MDD study (Matcham et al., 2019) recruited over 600 participants with major depressive disorder, followed over 2 years. The project paid considerable attention to user experience and identified and mitigated barriers to participation including concerns about privacy and wearable device selection. The programme identified excellent recruitment and retention, with variable data completeness according to whether data were passively or actively collected, the latter having considerably better completeness (Matcham et al., 2022).

The data from RADAR-CNS indicated numerous signals were associated with depression severity, including measures of homestay (Laiou et al., 2022), sociability (Zhang, Folarin, Sun, Cummins, Ranjan, et al., 2021), sleep (Zhang, Folarin, Sun, Cummins, Bendayan, et al., 2021), and speech (Cummins et al., 2023) . Preliminary analyses indicate promising results for changes in the variability of sleep duration may be associated with depressive relapse and future analyses will test for multimodal predictors of depression symptoms and relapse, and identify whether digital markers can provide insights into subgroups of depression based on physiological, cognitive, behavioural and environmental markers.

Understanding the biology of the patient

In the second session, five consecutive speakers addressed novel concepts and findings to highlight the importance of including biology in the diagnosis of mental disorders.

7. Bruce Cuthbert: the research domain criteria (RDoC) project as a biological framework for research on mental disorders

First, Bruce Cuthbert addressed the Research Domain Criteria (RDoC) project which was initiated by NIMH in 2009. The RDoC project was set out to develop new approaches to research on mental disorders, as a result of increasing concerns that current diagnostic classes do not align very well with advancing data from such sources as neuroimaging, genetics, and behavioral tasks. RDoC was intended to address these issues by creating a research framework based on normal dimensions of functioning that may be implicated in psychopathology when disrupted, thus connecting specific symptoms with particular aspects of behavior and neural circuits.

The RDoC research framework is organized around psychophysiological constructs of observable behavior and neurobiological measures, i.e., to investigate functional behavior that is quantitatively related to implementing neural circuits or systems. The framework incorporated four primary components for this purpose. These are six domains of functioning (Negative Valence, Positive Valence, Cognition, Social Processes, Arousal/Regulation, and Sensorimotor [each with several dimensional constructs]), various types of data, lifespan development, and environmental influences.

Five primary aspects represent the RDoC research principles. First, a translational perspective emphasizes normative neurobehavioral processes, including conserved circuits with animal-to-human continuity. Second, investigators are encouraged to study fundamental constructs (e.g., response to threat, attention, social processes) observed across multiple disorders. Third, the dimensional approach covers a full range of variation from normal to abnormal in order to understand shifts toward psychopathology. Fourth, a significant goal is to combine different data types in a given study (genetic, neurobiological, behavioral, self-report, etc.) in order to understand how the various measures relate. Finally, development and environment in study designs are encouraged in order to observe how these influences affect changes, in positive or negative directions, that affect risk for psychopathology.

Finally, another set of ideas is intended to advance the conduct of RDoC experimentation. First, studies with patients are encouraged to be grouped in terms of specific symptoms that represent deviations from normal processes. Next, improving functional assessments necessitates new behavioral tasks that provide reliable and valid measures of constructs. Third, computational neuroscience is a large and growing part of RDoC research for seeking clinical phenotypes as well as models to develop functional constructs. Finally, an important process for RDoC studies involves new study designs, such as transdiagnostic samples that are lumped into a single group and analyzed for unexpected new phenotypes and novel patterns of data.

RDoC is not intended to be a nosology, but rather to inform future versions of psychiatric manuals. The RDoC approach of studying could help shape a refined diagnostic framework as studies demonstrate the parsing of heterogeneous syndromes (Belleau, 2022). The number and types of studies consistent with the RDoC framework have continued to grow, which have recently included developmental studies, widespread computational analyses, and RDoC-oriented clinical trials. The latter has included a proof-of-mechanism trial funded by an NIMH RDoC contract, demonstrating that a kappa-opioid blocker increased ventral striatum activity during a task in which rewards were anticipated if reaction times were fast enough (Krystal et al., 2020). Multiple articles have noted the potential for RDoC to facilitate clinical trials with similar approaches of selected brain circuits (Nicholson and Sommer, 2018), as well as the facilitation of targets from the homologies that result from RDoC emphasizing specific symptoms and circuits rather than heterogenerous syndromes (Tricklebank et al., 2021). This is a small sample of the studies reporting the RDoC's utility for dissecting various circuits in broad syndromes and contributing to new approaches to trial designs.

8. Cathryn Lewis: genetics of psychiatric disorders; transcending the diagnostic boundaries

In the next lecture, Cathryn Lewis highlighted the importance of large genetic studies in the understanding of disease etiology and to address patient heterogeneity. Genetics forms a widely available and powerful source of information to identify the biological component within and across mental disorders. Genome-wide association studies have identified hundreds of genetic variants contributing to disorder risk, with many shared across traits. The Psychiatric Genomics Consortium (PGC) has spearheaded international collaborations enabling researchers to share studies, and study results, to perform the largest genetic studies. This collaboration has been an essential component of identifying the genetic component of psychiatric disorders, highlighting specific variants (single nueclotide polymorphisms, SNPs), genes and pathways contributing to disorder risk. The PGC openly shares summary statistics, enabling researchers worldwide to perform downstream analysis of genomic contributions (Sullivan et al., 2018). Despite this progress, much further work is needed in population of diverse ancestries to ensure that genetic contributions are captured worldwide (Peterson et al., 2019).

The genetic architecture of psychiatric disorders is polygenic, comprising thousands of genetic variants, each with a very small effect on risk. Summary statistics from genome wide association studies allow researchers to estimate the genetic contribution to a single disorder (SNP-based heritability), and genetic correlations between two traits. For example, SNP-based heritability for depression is 8.7 % and for schizophrenia is 24 % (Trubetskoy et al., 2022; Wray et al., 2018). The genetic correlation between depression and schizophrenia of 0.3 indicates substantial shared genetic variation for these disorders, a pattern seen across psychiatric traits (Lee et al., 2019). Multi-trait methods such as Genomic SEM show multi-trait relationships inferred from genetic information. A recent analysis of 11 traits estimated four factors for internalising, thought, compulsive and neurodevelopmental disorders (Grotzinger et al., 2022b).

Genetic liability at for any individual can be estimated using polygenic scores, which aggregate information at risk loci, genomewide, into a single measure. Polygenic scores provide only modest trait *prediction* for an individual, limiting population level applications. In a clinical setting, polygenic scores may have potential for predicting recurrence, progression or prognosis (Lewis and Vassos, 2022). For example, polygenic scores from schizophrenia, bipolar disorder and depression can indicate diagnosis after a first episode of psychosis (Rodriguez et al., 2023) or progression from first episode of depression to bipolar disorder. Integrating population level assessments of transdiagnostic features such as cognitive measures and molecular biomarkers from biobank studies gives an assessment of cross-cutting factors that may be relevant across diagnoses. Genetics is an easily acquired data modality that can give insights into the molecular mechanisms behind multiple diagnoses and may be used to validate transdiagnostic features. The common biological pathways across disorders or traits may indicate important biological mechanisms and drug repurposing opportunities.

9. Martien Kas: the quantitative biology of social dysfunction: a transdiagnostic and translational approach

In the next lecture, Martien Kas addressed the transdiagnostic and translational approach of the EU funded PRISM project. The overall aim of the PRISM project was to develop a quantitative, transdiagnostic neurobiological approach to the understanding of neuropsychiatric disorders to accelerate the discovery and development of better treatments for patients with those disorders (Kas et al., 2019). Elucidation of common underlying pathologies across conditions could facilitate development of therapeutics that address those symptoms directly, outside of the constraints of treating the diseases as a whole. The development and implementation of such an innovative transdiagnostic framework required a multi-staged approach. First, homologous transdiagnostic and translational quantitative biomarkers were identified and implemented in clinical and pre-clinical domains. Second, proof-of-concept was provided for identified biomarkers, showing that they allow for stratification of patients on the basis of quantitative biological measures. To this end, the PRISM consortium carried out a range of tests on patients diagnosed with Schizophrenia or Alzheimer's disease (Bilderbeck et al., 2019) to determine which biological parameters can be matched with specific clinical symptoms like social dysfunction (Porcelli et al., 2019). The PRISM consortium identified quantitative biological parameters that allowed the grouping of patients into clusters based on symptoms and underlying causes. For example, PRISM found that social dysfunction is transdiagnostically associated with default mode network disconnectivity in schizophrenia and Alzheimer's disease (Saris et al., 2022). PRISM also developed new behavioral readouts using passive remote smartphone monitoring with the aim of identifying novel digital biomarkers (Jagesar et al., 2021; Jongs et al., 2020; Kas et al., 2024) and has a digital endpoint for social functioning under review as part of a qualification procedure at the European Medicine Agency (EMA). Finally, a preclinical testing battery with parameters homologous to those studied in patients was implemented to allow for back-translation of human findings and deliver predictive model systems to accelerate the drug discovery process (Ike

et al., 2023; Peleh et al., 2019). These findings support the notion that there is more etiological overlap between psychiatric and neurodegenerative disorders than previously thought, and that they may better be described as domains of cross-disorder-related functions rather than separable categories (Insel and Cuthbert, 2015; Kas et al., 2007). Furthermore, they provide a framework to build an understanding of how neuropsychiatric diagnoses can be based on quantitative biological parameters and aim to contribute to the development of more precise diagnostic tools and treatment strategies. The ability to precisely link transdiagnostic symptoms to underlying neurobiology will not only facilitate the development of better treatments, it will also allow physicians to provide patients with a better understanding of the complexities and management of their illness.

10. Paris alexandros Lalousis: using machine learning to extract new transdiagnostic categories predicting disease progression from MRI data

Subsequently, Paris Alexandros Lalousis addressed new insights into the use of machine learning approaches to extract new transdiagnostic categories predicting disease progression from MRI data. Current nosological categories are not reflective of underlying brain pathology. Patients whose symptoms are potentially caused by different biological processes being placed in the same category and patients whose symptoms are potentially caused by same biological processes being placed in different categories with detrimental effects to disease and treatment course prediction. This lack of biological validity is thought to be one of the major reasons for the lack of biomedical translation in psychiatry (Cuthbert, 2014; Linden, 2012; Stephan, Bach, et al., 2016; Stephan, Binder, et al., 2016). Depression and psychosis specifically share hippocampal grey matter volume (GMV) reductions and they have both been found to be pro-inflammatory states with certain cytokines such as IL-6 and CRP detected at elevated levels. Recent studies have identified the presence of an impaired neuroanatomical cluster which is characterized by overall poorer outcomes and functioning in schizophrenia (Chand et al., 2020) and in youth with internalizing symptoms (Kaczkurkin et al., 2020) but there has not yet been a transdiagnostic investigation of neuroanatomy in depression and psychosis. Herein, we aimed to identify replicable neuroanatomical clusters across patients with recent onset depression (ROD) and recent onset psychosis (ROP) using semi-supervised machine learning. We hypothesised that neuroanatomically derived clusters would be transdiagnostic, and related to distinct phenotypes drawn from symptom, neurocognitive, and inflammatory data across both disorders. We further aimed to explore the predictive validity of neuroanatomically identified clusters and externally validated our neuroanatomically based clusters in chronic depression and chronic schizophrenia. We also developed supervised machine learning models to predict symptom remission in ROP and ROD and our neuroanatomically based transdiagnostic clusters. We hypothesised that models developed in neuroanatomically based transdiagnostic clusters will show greater predictive accuracy compared to those in traditional diagnostic groups. HYDRA (Heterogeneity through Discriminant Analysis) was trained on whole-brain volumetric measures from 577 participants from the discovery sample of the multisite PRONIA study to identify neurobiologically driven clusters, which were then externally validated in the PRONIA replication sample (n = 404) and three datasets of chronic samples (Centre for Biomedical Research Excellence, n = 146; Mind Clinical Imaging Consortium, n = 202; Munich, n = 470). The optimal clustering solution was two transdiagnostic clusters (cluster 1: n = 153, 67 ROP, 86 ROD; cluster 2: n = 149, 88 ROP, 61 ROD; adjusted Rand index = 0.618). The two clusters contained both patients with ROP and patients with ROD. One cluster had widespread gray matter volume deficits and more positive, negative, and functional deficits (impaired cluster), and one cluster revealed a more preserved neuroanatomical signature and more core depressive symptomatology (preserved cluster). The clustering solution was internally and externally validated and assessed for clinical utility in predicting 9-month symptomatic remission, outperforming traditional diagnostic structures. We identified two transdiagnostic neuroanatomically informed clusters that are clinically and biologically distinct, challenging current diagnostic boundaries in recent-onset mental health disorders. These results may aid understanding of the etiology of poor outcome patients transdiagnostically and improve development of stratified treatments. Whilst such challenge to current diagnostic structures will need significant further replication and longer follow-up, identifying a transdiagnostic signature of poor prognosis has the potential to aid new and targeted treatment strategies across early stages of mental disorder.

11. Livia De Picker: the neuroinflammatory hypothesis in psychiatry

In the next presentation, Livia De Picker advocated for a paradigm shift in psychiatric treatment, the focus was placed on the underutilized potential of precision psychiatry, particularly through the lens of immunopsychiatry, to fundamentally transform mental health care.

Despite the significant strides made in neuroscience and a deeper understanding of the genetic and environmental foundations of mental health disorders, the transition of these discoveries into tangible improvements in patient care has been disappointingly slow. For over a decade, the concept of precision psychiatry has promised a revolutionary approach to mental health care by tailoring treatment to the individual. This approach could leverage the vast amounts of genetic, molecular, and immunological data now at our disposal to inform treatment decisions in a manner far superior to the current trial-and-error method. Yet, the practical application of precision psychiatry in clinical settings remains minimal, highlighting a translational gap between research advancements and their implementation in patient care. Building upon our advanced understanding about the bidirectional interactions between the immune system and the CNS, the relatively new research field of immunopsychiatry strives to harness the immune system to bring benefit to patients with mental health disorders (De Picker, 2021). Immunopsychiatry holds the promise of identifying transdiagnostic subtypes of psychiatric disorders, such as depression, that are linked to immune system dysregulation.

Dr De Picker's presentation outlined the Precision Psychiatry approach for immune-mediated depression:

1. Immune dysregulation is both a feature and a cause of depressive disorders, and up to 30 % of MDD patients display an immune-mediated subtype of depression. (Capuron et al., 2000, 2004; Langley et al., 2010; Tyring et al., 2006; Udina et al., 2012)(Milaneschi et al., 2021; Osimo et al., 2019).
2. Immune-mediated MDD is associated with poor response to treatment as usual and needs targeted intervention.
3. Existing anti-inflammatory compounds can be repurposed as first-line immune-targeted augmentation for immune-mediated MDD
4. Cases of immune-mediated MDD can be identified both through (blood-based) biomarkers as well as through their atypical clinical symptom profile, which includes more prominent symptoms of fatigue, anhedonia, hypersomnia, and increased appetite (Arteaga-Henríquez et al., 2019; Carvalho et al., 2013).
5. CRP has been identified as a trait marker of immune-mediated MDD, and can easily be measured in routine clinical settings (Foley et al., 2021; Köhler-Forsberg et al., 2017; Nettis et al., 2021). The choice of hsCRP as a stratification tool to predict response to immune-targeted augmentation is validated by Proof of Concept studies (Nettis et al., 2021; Porcu et al., 2018; Raison et al., 2013) and its high utilisation potential in clinical practice, representing the first scalable Precision Psychiatry solution.

The lessons learned from immunopsychiatry teach us that to move

the needle on targeted therapies, we need to develop innovative strategies for clinical research in close collaboration with stakeholders, including representatives or patients and carers, clinicians, policymakers, regulatory bodies and industry. These should include strategies to (1) select the right patient population, such as enriched (e.g. INFLAMED; https://immunometaboledepressie.nl/; (Zwiep et al., 2023)) or stratified (e.g. INSTA-MD; https://www.sinapsduffel.com/insta-md) trial designs; (2) identify novel outcome measures which are better able to capture symptom changes specific to inflammation compared to standard compound depression scales (e.g. scales of anhedonia or atypical depression), and (3) develop novel diagnostic entities that better represent disease mechanisms or treatment targets (e.g. major depression with increased inflammation) (Fig. 1).

The scalability of the precision psychiatry approach is crucial for its success and widespread adoption. Primary care practitioners are often the first point of contact for individuals experiencing mental health issues such as depression, making them an essential component in the early identification and management of psychiatric disorders. By equipping these healthcare providers with the tools and knowledge to implement precision psychiatry approaches, we can significantly enhance the effectiveness of mental health care. In the Wellcome Trust-funded ASPIRE project, we will study and validate this approach based on stratified and individual-participant meta-analyses of up to 175 previous trials on immune interventions in patients with depression. The project will deliver a personalized decision tool to tailor anti-inflammatories to individual patients' needs, as well as data on feasibility and acceptability which take into account the views of people with lived experience and clinicians.

Translating biological understanding into new approaches

In the third session, three lectures provided novel insights on how biological understanding of the patient can lead to new approaches for biomarker development, translational research and drug discovery.

12. Amit Etkin: redefining psychiatry with AI-driven brain biomarkers that align the right patient with the right drug

First, Amit Etkin put forward new findings to illustrate how to redefine psychiatry with AI-driven brain biomarkers that align the right patient with the right drug. Selection of antidepressants rely on trial-and-error because they were developed through all-comer studies. A precision psychiatry approach that prospectively identifies drug-responsive patients could yield greater efficacy and increase the likelihood of drug development success. For biomarker-based patient selection to be robust, measures must be reliable and scalable, and the enrichment produced on clinical outcomes must be reproducible and clinically meaningful. Alto Neuroscience has developed a biomarker platform for systematically testing novel drugs that it is developing in a precision psychiatry approach, beginning with two drugs for major depressive disorder (MDD), the results of which were presented.

The first drug to which a patient selection approach was taken was ALTO-100, a first-in-class pro-plasticity compound identified through a functional assay for compounds that enhance hippocampal neurogenesis. In analyzing data from a large MDD Phase 2a study, patients with poor verbal memory (an important component of the cognitive impairment phenotype present in 30–50 % of MDD patients) responded substantially better with respect to depression symptoms relative to those with intact verbal memory. This biomarker was then prospectively replicated in an independent cohort of MDD patients, and furthermore found to be specific to ALTO-100 as it did not predict better response to placebo. Thus, patients characterized by a behavioral metric indicative of reduced hippocampal neuroplasticity were found to benefit most from a drug that enhances hippocampal neuroplasticity. A conceptually similar approach was taken in MDD for ALTO-300 (also known as agomelatine), for which a machine learning-derived EEG biomarker was found to predict better response. This biomarker was found to prospectively replicate with respect to ALTO-300 response, and not predict response to either placebo or standard-of-care treatments. Phase 2b studies are ongoing for both drugs ($n = 266$ for ALTO-100, $N = 200$ for ALTO-300) wherein patients are prospectively selected based on their respective biomarkers and randomized to receive drug versus placebo to determine efficacy in biomarker-identified patients.

In addition to patient selection, behavioral and EEG biomarkers can be used as pharmacodynamic outcomes to understand drug effects, dose, and indication selection. This approach was taken for ALTO-101, a brain-penetrant phosphodiesterase 4 (PDE4) inhibitor. Given the central role of cyclic adenosine monophosphate (cAMP) signaling in plasticity and cognition, a PDE4 inhibitor would be expected to improve cognitive processing. In a well-powered Phase 1 study, ALTO-101 was found to have dose-related beneficial effects on multiple EEG measures of cognitive processing as well as aspects of cognitive task performance. Together, these data identify a likely indication (cognitive impairment associated with schizophrenia; CIAS), dose/blood level to target in

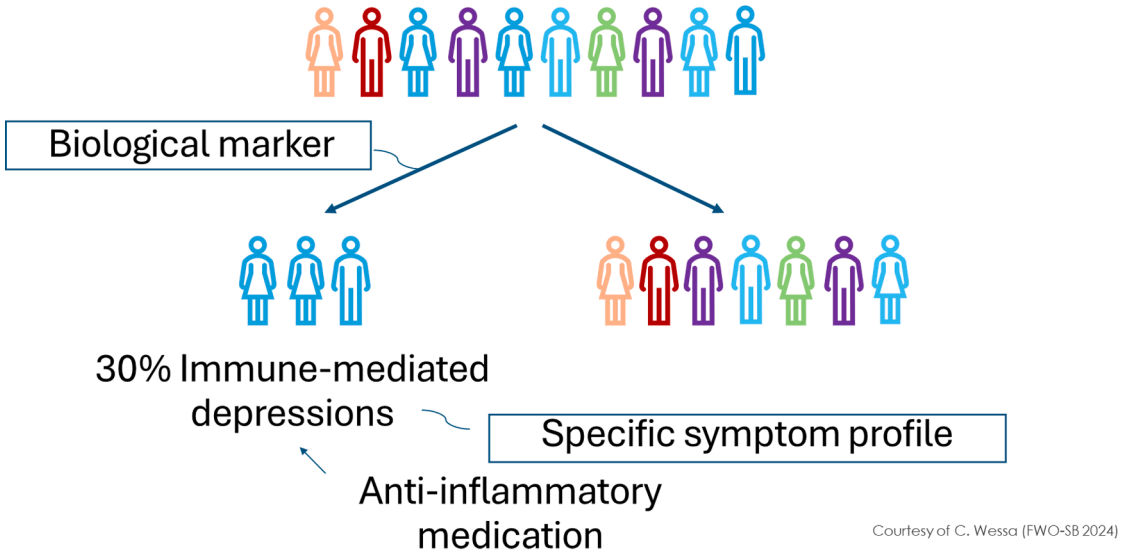

Fig. 1. The precision psychiatry approach for immune-mediated depression.

patients, and pharmacodynamic effects to track during the course of therapy. These findings are expected to drive a Phase 2 proof of concept study of ALTO-101 in a biomarker-defined subgroup of patients with CIAS.

13. Gemma Modinos: backtranslation of human findings to rodents; testing for causality using a multi-modal approach

Subsequently, Gemma Modinos showed innovative preclinical ways for backtranslating of human findings to rodents with the aim of testing for causality using a multi-modal approach. A major obstacle to developing better treatments is our limited understanding of disease mechanisms underlying mental illness. In this context, animal models have provided valuable insights into neural circuits, neurochemistry and behaviours associated with mental illness. Seeking to model schizophrenia spectrum disorders (SSD), three general types of rodent models have been used: (1) acute pharmacological modulation (e.g., ketamine), (2) genetic models (e.g., D2-R over-expression), and (3) developmental disruption models (e.g., Methylazoxy-Methanol Acetate (MAM))(Oliver et al., 2020). For example, research using the MAM model revealed a key SSD-relevant phenotype, dopamine system hyperfunction, is driven by hyperactivity of the ventral hippocampus, and that this hyperactivity is due to a dysfunction of parvalbumin-expressing GABAergic inhibitory interneurons (PV+)(Lodge and Grace, 2009). Using a translational imaging approach, we previously showed a decreased density of GABAA alpha5 receptors in the hippocampus of MAM-treated rats compared to saline-treated rats (Kiemes et al., 2022). By applying the same radioligand by in vivo PET in individuals at clinical high-risk for psychosis and people with first-episode psychosis, this research may inform novel targets for drug development aimed to reduce hippocampal hyperactivity in psychosis. Despite the progress made by such animal model studies, there are inherent difficulties in using DSM criteria to construct an animal model of mental illness, due in part to the heterogeneity in symptomatology among individuals receiving the same DSM diagnosis. An alternative approach has involved modelling intermediate phenotypes, such as behavioural (e.g., a cross-species computational measure of hallucinations (Schmack et al., 2021) or neuroimaging readouts. As an example of the latter approach, we recently showed that selective disruption of PV+ interneuron function in mice (Erbb4 conditional mouse mutants)(Kiemes et al., 2023) recapitulates key in vivo neuroimaging findings early psychosis, including elevated resting cerebral blood flow and levels of glutamatergic metabolites, as well as lower synaptic density, in the hippocampus (Arnatkeviciute et al., 2023). Such cross-species neuroimaging approaches represent a useful strategy to unravel the cellular and molecular mechanisms underlying disease-relevant neuroimaging phenotypes, and which may be amenable to treatment. Furthermore, newer strategies involving the use of bioinformatic approaches to bridge knowledge across scales (from genes to cells/molecules to whole-brain neuroimaging to behaviour, such as imaging transcriptomics and neuroreceptor mapping (Hansen et al., 2022; Knight et al., 2024; Revah et al., 2022), and those combining cellular and animal modelling (e.g., organoid grafting in rodents), offer great promise to uncover mechanisms and unlock the discovery of new druggable targets in psychiatry (Revah et al., 2022). Finally, the session concluded with future recommendations based on a recent expert review commissioned by the Wellcome Trust, by (1) prioritising symptom-focussed back-translation, (2) being informed by people with lived experience, (3) using common readouts across species, (4) leveraging genetic, biological and environmental variation, (5) using larger timescales of investigation, (6) establishing community standards and (7) ensuring datasets are open, and diverse (Xiaosi Gu, 2023).

14. Hugh Marston: translating biological knowledge into drug development

In the final lecture of the meeting, Hugh Marston addressed innovative ways of translating biological knowledge into drug development. He indicated that innovative drug discovery in the mental health space had a golden period in the 1950′s and 60′s with the introduction of the first neuroleptics, antidepressants and anxiolytics (Abuzzahab, 1970; Ban, 2007; Hillhouse and Porter, 2015). The following 30 years saw significant refinement but no major breakthroughs neither in mechanism nor in the ability to tackle the many unresponsive symptomatic domains. In the last 10 to 15 years though significant thought and effort has gone into trying to reverse this trend (Cuthbert and Insel, 2013). The point of convergence of these efforts has been a growing acknowledgement that a better biological understanding of the disorders is both needed and potentially possible. In addition, it can be argued that we also need different and improved assessment tools and endpoints that mirror and quantify the clinical presentation of groups of individuals that share a common biological perturbation. The systems of clinical assessment available have been developed to allocate individuals within the DSM (Anon., American Psychiatric Association, 1952, Anon, 2013) framework that in turn has come, quite sensibly, to align with the available therapeutics. But as this system is not based on homologous biologies it may miss classify. The consequence is that this will blur the results of clinical trials and tend to sustain the status quo. As such this now provides a barrier to innovation. The increasing availability of better techniques to both probe the human condition but also back-translate into the pre-clinical space are making this a reality. Electroencephalogram (EEG) techniques, positron emission tomography (PET), functional imaging, complex behavioural analysis and many others now offer homologous methods of assessment in man and animal. This now allows drug discovery to start from well understood human circuits and systems and back-translate to homologous constructs rather than rely on poorly understood “disease models”. In this way the circuits controlling cognition, impulsivity, reward and motivational valence amongst others to be used as target constructs. Drug targets within these systems can then be tested not just for target engagement but also for circuit engagement. If successful, the techniques for assessing circuit engagement can then be forward translated to proof of principal studies in patients. If schizophrenia is taken as an example, we probably now have sufficiently refined tools to effectively develop therapeutics to address not just the positive symptoms but also the cognate. Similarly, the third area of unmet need, the negative symptoms, can also be addressed. Our understand of both the pharmacology but also the manner through which behavioural therapies work has allowed a range of novel therapeutics, both pharmacological and digital, to enter late-stage clinical development. The next near horizon is to then be better able to assess, preferably in the “real-world”, the progression and constant change that is unique to mental state. Taken together there is real hope that soon it will be possible to assess an individual’s needs and, because of a clear biological understanding, prescribe the right package of therapeutics at the right time. Though the emerging transdiagnostic science is exciting it must though be acknowledged that there are other challenges. This approach needs not just clever novel therapeutics but the support and the courage to adapt from clinicians, payers, regulators as well as the patients and their carers. If this can be achieved, then may be a new era is close that will increase the likelihood of success in mental health therapeutic development allowing innovative treatments to be brought to patients.

15. Conclusions

Based on the presentations and discussions at the ECNP New Frontiers meeting 2024, it was concluded that time has come to start developing a roadmap for implementation of a biology-informed framework for mental disorders. While the current diagnostic systems provide a global language for defining neurological and psychiatric disorders, it stands in the way to address the current failures of treatments due to a mismatch between the existing symptom-based diagnosis and the need for mechanism-based treatments that should be based on

biological understanding beyond the current diagnostic boundaries. Following the event, the steering committee of the New Frontiers meeting mapped out a Roadmap for global alignment to start implementing a biology-informed framework for mental disorders which is planned to be published this year.

Declaration of competing interest

MJHK, DHM, MH, and BC declare no conflict of interest. SH is member of the scientific advisory boards for Johnson and Johnson (formerly Janssen) and F-Prime Capital, and he is member of the Boards of Directors for Voyager Therapeutics, Cyclerion Therapeutics, and Vesalius Therapeutics. LMW discloses the following patents in which she contributed, namely, US Patent App. 16/921,388, 16/368,774, 10,702,232 B2, 15/997,631, 10,285,658, 15/830,338, 10,034,645. LJdP declared consultancy and paid presentations for Boeringer-Ingelheim, paid presentation for Viatris – all outside the current work. LJdP is also the Co-chair of the ECNP Immuno-NeuroPsychiatry Network. CML is SAB for Myriad Neuroscience. Speaker & Consultancy fees from UCB and SYNLAB. AE receives salary and equity from Alto Neuroscience, and equity from Akili Interactive. PAL has received honoraria for talks presented at educational meetings organised by Boehringer-Ingelheim outside of the presented work. QJMH has obtained fees and options for consultancies for Aya Technologies and Alto Neuroscience. HM is a full-time employee of Boehringer Ingelheim Pharma GmbH.

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