



University of Groningen

New approaches in psychiatric drug development

van der Doef, Thalia F.; Domingo, Silvia Zaragoza; Jacobs, Gabriel E.; Drevets, Wayne C.; Marston, Hugh M.; Nathan, Pradeep J.; Tome, Maria B.; Tamminga, Carol A.; van Gerven, Joop M. A.; Kas, Martien J. H.

Published in:
European Neuropsychopharmacology

DOI:
[10.1016/j.euroneuro.2018.06.006](https://doi.org/10.1016/j.euroneuro.2018.06.006)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2018

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

van der Doef, T. F., Domingo, S. Z., Jacobs, G. E., Drevets, W. C., Marston, H. M., Nathan, P. J., ... Kas, M. J. H. (2018). New approaches in psychiatric drug development. *European Neuropsychopharmacology*, 28(9), 983-993. <https://doi.org/10.1016/j.euroneuro.2018.06.006>

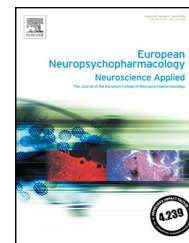
Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.



REVIEW

New approaches in psychiatric drug development



Thalia F. van der Doef^a, Silvia Zaragoza Domingo^b,
Gabriel E. Jacobs^{a,c}, Wayne C. Drevets^d, Hugh M. Marston^e,
Pradeep J. Nathan^{f,g}, Maria B. Tome^h, Carol A. Tammingaⁱ,
Joop M.A. van Gerven^{a,c,1}, Martien J.H. Kas^{j,1,*}

^aCentre for Human Drug Research, Leiden, The Netherlands

^bResearch and Development Department, H. Lundbeck A/S, Valby, Denmark

^cLeiden University Medical Centre, Leiden, The Netherlands

^dJanssen Research & Development, LLC, Johnson & Johnson, United States

^eLilly Research Laboratories, Eli Lilly and Co, Windlesham, UK

^fHeptares Therapeutics Ltd, Cambridge, UK

^gDepartment of Psychiatry, University of Cambridge, Cambridge, UK

^hEuropean Medicines Agency (EMA), 30 Churchill Place, Canary Wharf, London, UK

ⁱDepartment of Psychiatry, University of Texas, Southwestern Medical School, Dallas, TX, United States

^jFaculty of Science and Engineering, Groningen Institute for Evolutionary Life Sciences, University of Groningen, Nijenborgh 7, 9747 AG Groningen, The Netherlands

Received 17 March 2018; received in revised form 18 June 2018; accepted 25 June 2018

KEYWORDS

Drug discovery;
Neuroimaging;
Translational research;
Psychiatry;
Precision medicine

Abstract

Numerous novel neuroscience-based drug targets have been identified in recent years. However, it remains unclear how these targets relate to the expression of symptoms in central nervous system (CNS) disorders in general and psychiatric disorders in particular. To discuss this issue, a New Frontiers Meetings of European College of Neuropsychopharmacology (ECNP) was organized to address the challenges in translational neuroscience research that are impeding the effective development of new treatments.

The main aim of this meeting was to discuss scientific insights, concepts and methodologies in order to improve drug development for psychiatric disorders. The meeting was designed to bring together stakeholders from academia, pharmaceutical industry, and regulatory agencies.

* Corresponding author.

E-mail addresses: m.j.h.kas@rug.nl, tvddoef@chdr.nl (M.J.H. Kas).

¹Both authors shared last authorship.

Here we provide a synopsis of the proceedings from the meeting entitled 'New approaches to psychiatric drug development'. New views on psychiatric drug development were presented to address the challenges and pitfalls as identified by the different stakeholders. The general conclusion of the meeting was that drug discovery could be stimulated by designing new classification and sensitive assessment tools for psychiatric disorders, which bear closer relationships to neuropharmacological and neuroscientific developments. This is in line with the vision of precision psychiatry in which patients are clustered, not merely on symptoms, but primarily on biological phenotypes that represent pathophysiological relevant and 'druggable' processes. To achieve these goals, a closer collaboration between all stakeholders in early stages of development is essential to define the research criteria together and to reach consensus on new quantitative biological methodologies and etiology-directed treatments.

© 2018 Elsevier B.V. and ECNP. All rights reserved.

1. Introduction

The neuroscience field is currently advancing insight into the functional processes that underlie central nervous system (CNS) derangement in psychiatric illness. Such progress is the result of the development of more advanced technologies in the field, that include but are not limited to neuroimaging, and various 'omics'-technologies like (epi)genomics, transcriptomics, proteomics and metabolomics. Advances in other medical disciplines, such as clinical genetics and immunology, also contribute to a better understanding of brain disorders. In addition, innovative ways to quantify human and animal behaviour, such as by means of clinical phenotyping, provide new translational research options. By applying sophisticated biological mechanism based methodologies, an increasing number of potential 'druggable' CNS targets have been identified which may potentially benefit both clinical management of psychiatric conditions and psychiatric drug development in the future. However, a major concern is that psychiatry has been unable to effectively exploit the advances that neuroscience has yielded up to now. For many novel neuroscience-based targets, it still remains unclear how they relate to symptoms or to clinical expression of the disorders that make up psychiatric diagnostic entities. Therefore, stakeholders have yet to reach agreement on how to move forward (Hyman, 2016).

The number of US Food and Drug administration (FDA) approved new drugs in the last decades shows that psychiatric drug development is lagging behind compared to other medical disciplines (Bjornsson, 2016). To illustrate, in 2015 the total number of new registered drugs since 1975 was 33 in psychiatry versus 54 in neurology (Bjornsson, 2016). One aspect of the backlog of drug approvals in psychiatry is a limited number of new mechanisms of action. In many areas, such as neurology and oncology, drugs regularly appear on the market that have novel or significantly modified mechanisms of action. In psychiatry, however, only very few mechanisms of action have been introduced since the development of monoamine reuptake inhibitors in the eighties and nineties (Bjornsson, 2016). This can be illustrated by the time course of an 'innovation index', which can be defined as the numbers of mechanism of action divided by the number of registered drugs. Highly innovative disciplines like immunology and oncology have innovation indices of 40%-60%. It is interesting to compare the course of

drug development in psychiatry and neurology, which both deal with the same human organ, the brain. Fifteen years ago, neurology and psychiatry both had innovation indices of about 30%, meaning that in each disciplines three registered drugs shared a single mechanism of action. In neurology, the index has since increased slightly to a stable level of 35%, which reflects developments in multiple sclerosis, epilepsy, Parkinson's disease, stroke and other indications. Psychiatry, however, has seen a steady decline of the index to about 20% (4-5 drugs per mechanism). Psychiatry and cardiology are the only medical fields where the innovation index has decreased since the beginning of this millennium (Bjornsson, 2016). In cardiology, significant advances were made in preventive and innovative surgical and radiological interventions. In psychiatry, however, improvements in cognitive behavioural strategies and changes in the quality of psychiatric care have offered no compensation for the slow development of new psychiatric medications.

The complexity of psychiatric drug development is related to several factors. First, there are pharmacological restrictions due to the inviolability of the human brain. It is difficult to achieve blood-brain barrier (BBB) penetration and to assess target engagement, and complex methods are required to determine this (indirectly, such as in vivo positron emission tomography (PET) imaging, functional CNS tests, post-mortem studies and CSF sampling. Neurology is helped in this respect by its focus on structural abnormalities. Second, there is a disconnection between the definition of the biological processes that underlie animal models and human research, which has limited the identification of cross-species clinically relevant mechanisms. As a consequence, insights from animal studies cannot be translated directly into human drug targets. Innovative disease models in neurology have profited more from scientific advances, particularly in genetics and immunology. Third, there is a clinical heterogeneity in psychiatric disorders since their classification is based on the predominantly phenomenology based Diagnostic and Statistical Manual of Mental Disorders (DSM) and the neurobiological mechanisms for most disruptions of CNS functions (behavioural, emotional, cognitive) have only partly been unraveled.

The treatment of a psychiatric patient may require a multifaceted and interactive approach. This is not an easy situation for drug development, and many large pharmaceutical industries have shied away from this area. Nonetheless, because of the large social, economic, and personal burden of

psychiatric diseases, it remains important to develop innovative therapies, which are only effective for a part of the problem, or for a subgroup of patients, or which merely support other pharmacological or psychosocial interventions. Within this more narrowed scope, new approaches are necessary and possible. Ultimately, this may lead to incremental improvements, which over time may provide more scientific insights and larger clinical benefits. Examples from neurology (stroke, multiple sclerosis, tumors) show that consecutive small developments which in isolation are often highly disputed for their apparent lack of clinical relevance for traditionally defined patients, ultimately provide real improvements for patients with newly defined diagnostic characteristics. This incremental innovation also seems to be related to continuing support for clinical research networks and infrastructure, which rapidly deteriorate if small successes are considered insignificant.

In clinical disciplines with several-fold higher innovation indices than psychiatry (like immunology and oncology), innovation is mainly driven by similar factors as in neurology. Occasionally, the advances are enhanced by a breakthrough that is taken up by several companies (with drugs that are based on the new mechanism or a derived modification). However, most areas are able to sustain a slow but steady supply of alternative or slightly improved medications, on the basis of continuous drug improvements and clinical research with more modest results and expectations.

To stimulate neuroscience-based adaptive approaches to psychiatric drug research and development, the National Institute of Mental Health (NIMH) launched the Research Domain Criteria (RDoC) framework, which also supports new approaches to classification of mental disorders (www.nimh.nih.gov/research-priorities/rdoc/index.shtml) (Insel et al., 2010). The RDoC initiative asks investigators to step back from diagnoses based on heterogeneous clusters of symptoms and, instead, to focus on basic dimensions of functioning across the wellness spectrum that might relate to various aspects of symptoms. 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 behavioural assessments. The RDoC framework can facilitate new approaches for drug development by using the dimensional approach to test new drugs.

The ECNP new frontiers meeting entitled 'New approaches to psychiatric drug development' was held in Nice at 12 and 13 March 2017 and continued its discussions on the 30th ECNP Congress in Paris later that year. The aim of the meetings was to discuss scientific insights, concepts and methodologies in order to improve drug development for psychiatric disorders. Translational gaps between novel targets, CNS functions and clinical phenomena have to be bridged if psychiatry wants to improve the condition of patients with psychiatric disorders by utilizing mechanism-based CNS targets. Hence, it is crucial that neuroscientists, clinicians, industry and regulators understand each other and collaborate. The meeting was dedicated to discuss strategies to address this issue and to promote interactions and discussions between different involved stakeholders from academia, industry, clinicians, methodologists, regula-

tors and patients. During the meeting, different stakeholders from academia, industry and regulatory agencies gave presentations which were followed by plenary discussions. Here, we provide an integrated review of the presentations and discussions of the meeting, which is written from the author's perspectives. This has led to the recommendations for new approaches in psychiatric drug development that are written below.

2. From disease category to pharmacology

At the start of the meeting, a conceptual framework of drug discovery in psychiatry was proposed (see Fig. 1). This scheme is based on the notion that the CNS consists of neuronal networks, which use molecular mechanisms to express the brain's various functions. Dysregulations of these functions cause neuropsychiatric symptoms, which form the basis of psychiatric disorders (see top of Fig. 1). Neuropsychiatric drugs act on the molecular level (see bottom of Fig. 1), and thereby induce cascading changes on brain networks that ultimately affect their functionality. The targets of CNS active drugs (neurobiological receptors, enzymes etc.) are only indirectly related to changes of networks and their associated functions. The relationship between CNS functions and DSM-constructs, which are often also remote, further add to the complexity of psychiatric drug development.

Traditional psychiatric drug development is usually aimed at DSM-constructs, and therefore ignores the complex underlying cascade of events. Innovative drug development for psychiatric symptoms will require closer attention to the interactions between drug action and functional disorganization, and to the adaptive nature of brain networks. This may include a reconsideration of psychiatric symptoms or phenotypes, which are modulated by genetics (i.e. genotype), as dysregulations of functional networks. It will also require the development and application of methods, which measure strategic hubs at different levels, i.e. molecular, circuit, functional, of the cascading processes.

Fig. 1 is a schematic illustration which indicates that individual symptoms are more closely related to networks and underlying molecular biology than to multidimensional disease constructs. Psychiatric disorders are currently mainly diagnosed based on qualitative assessment of symptoms, rather than quantitative analysis of aberrant neurobiology. In practice this means that the symptoms are well understood, but the pathophysiology and therapeutic targets still remain unclear. As the patient will adapt to physiological or psychosocial changes and the disease may progress during life, the distance between the underlying pathophysiology and the symptomatology increases. This directly influences drug development, since it is unclear whether the pathophysiology can predict the treatment response. In the future, patients may be selected for different treatment options based on their symptoms and underlying biological profile.

For psychiatry, the most important outputs of brain functioning are behaviour, emotion and cognition. Psychiatric disorders inherently imply a difference between normal (adapted) and abnormal (maladapted). Therefore, as mentioned in the introduction, the diagnostic framework

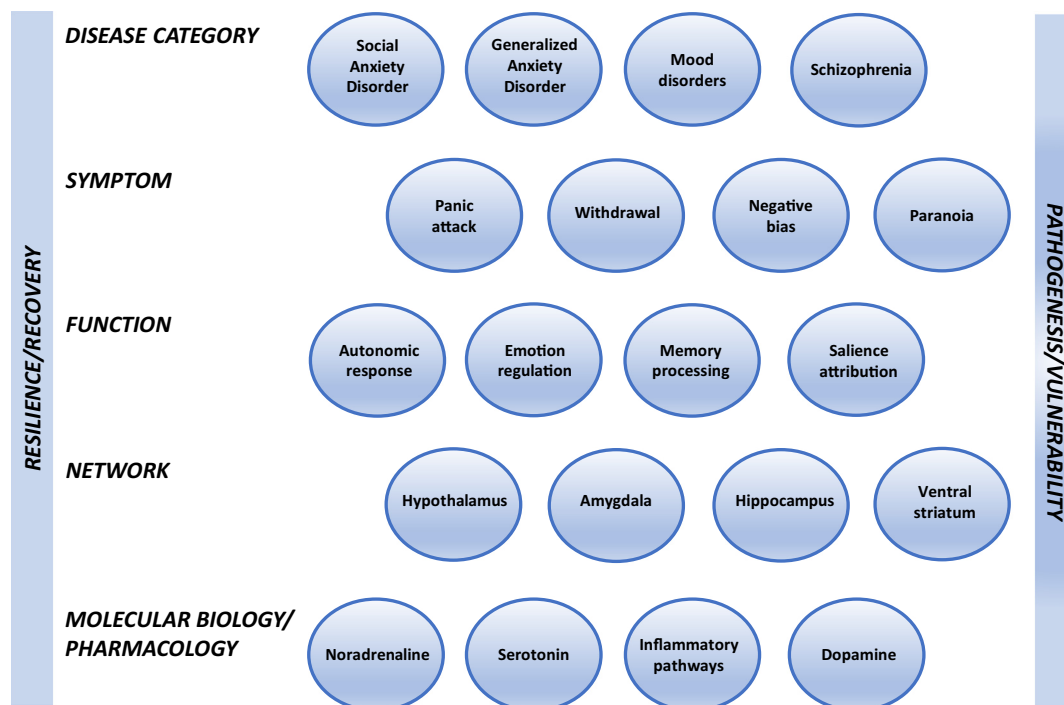


Fig. 1 Multidimensional characteristics of psychiatric disorders.

has been dominated by the DSM and the International Classification of Disorders (ICD), which still play an important role in defining the boundary between well and unwell (Millan et al., 2015). Another criticism has been made that psychiatric disorders form a continuous spectrum with normality, in the way that ‘healthy’ subjects may display transient, mild and isolated symptoms of psychiatric conditions such as anxiety, depressed mood and even psychosis.

Network analysis can be used as a prediction for treatment outcome. Neuroimaging methods, such as pharmacological magnetic resonance imaging (phMRI), electroencephalography (EEG) and PET imaging, can be used as tools for this prediction. The effects of psychopharmacological agents on behavioural domains of large-scale networks can be measured with phMRI, providing information about the pharmacodynamics and underlying neurotransmitter mechanisms (Honey and Bullmore, 2004; Khalili-Mahani et al., 2017). Several factors need to be taken into account with the standardization and refinement of network analysis in order to reduce their susceptibility to possible confounders. The selection of the regions of interest (ROIs), for example, can influence the accuracy of the inferred network organization, since the anatomical separation of the cortex may inaccurately define the functional ROIs resulting in a different definition of the network nodes (Smith et al., 2011). Hierarchy of functional sub-regions based on spatially segregated functional networks can be used for further refinement (connectopic mapping). Recently, Instantaneous Connectivity Parcellation (ICP) has been shown as a specific quantification method to generate (sub)cortical parcellations (top-down functional parcellation) (van Oort et al., 2017). Other refinement methods are found in the implication of multiple imaging techniques together, such as correlation maps that integrate both fMRI and PET data. Studies

of the effects of psychiatric drugs will help to provide more insights into key network phenomena (Khalili-Mahani et al., 2017).

A potential helpful concept in dealing with the multi-level complexity during CNS drug development is so-called question-based drug development (Cohen et al., 2015). This basically translates all consecutive steps that connect the drug to its effects (therapeutic or adverse), into questions which need to be addressed during the drug developmental process. Each step constitutes an uncertainty, which can be reduced by appropriate measurements, in a study that employs the proper methodology and design. Table 1 provides an indication of some typical questions for psychiatric drug development, which follows the scheme of Fig. 1, including some suggested methods to (indirectly) address each question.

3. Precision psychiatry

The heterogeneity of psychiatric disorders complicates their definition, which is partly explained by genetic variability. Evidence for different subtypes of psychiatric disorders has been found, which gives an explanation for treatment resistance in several indications, such as depression and schizophrenia.

Precision medicine is based on the clustering of individuals with psychiatric symptoms based on relevant biological phenotypes (biotypes) instead of clinical phenomenological classifications. An example of this approach is provided in Fig. 2 (Clementz et al., 2016). Since the behavioural domains cover the entire neuropsychiatric spectrum, the concept is to stratify patients beforehand on defined subcategories. Combinations (batteries) of clinical measurements

Table 1 Question-based approach to steps that link the pharmacological activity of a central nervous system (CNS)-active drug to functional CNS-effects and related psychiatrically dysregulated functions. Methods are examples of approaches to measure the activity at the relevant step. EEG, electroencephalography; ERP, event-related potential; MRI, magnetic resonance imaging; PET, positron emission tomography.

| | Consecutive step | Question | Method |
|----------------------|---|---|---|
| Target engagement | Target site penetration | Does the drug reach its site of action? | Cerebrospinal fluid concentration, PET imaging |
| | Target binding | Does the drug bind to its molecular target? | PET imaging |
| Cascadic drug action | Pharmacological activity | Does the drug have its intended pharmacological effect? | Neuronal excitability (EEG/ERP, MEG), target substrate, metabolomics |
| | Network activity | How does the pharmacological effect influence a functional neurocircuit? | Resting state functional MRI, EEG network analysis, PET imaging, cognitive and emotional processing tests probing specific circuits |
| | Neurophysiological activity (CNS function) | Which CNS functions are affected by the drug (positively or negatively)? | CNS cognitive or emotional test battery |
| | Symptomatic effect (psychiatric symptomatology) | What are the effects of the drug on the psychiatric dysregulation of the affected CNS function? | Psychiatric core symptom scores/ function tests |
| Therapeutic window | Clinical effect: beneficial | How does the drug affect patients who prominently express the core features of the disease? | Clinical/patient/caregiver rating scales (subgroups) |
| | Clinical effect: adverse | What are the adverse (CNS) effects of the drug (in the vulnerable subpopulation)? | Side effect measurements |

lead to clinical phenotypes, which have been anonymized beforehand. This method not only can distinguish different psychiatric disorders, but is also applicable to differentiate control participants from patients. Here, in Fig. 2, patients with a psychotic disorder underwent a deep phenotyping analysis using cognitive, neuroimaging, oculomotor as well as genetic, clinical and clinical course markers, with multiple markers collected per measurement category. None of these biomarkers feel into any conventional diagnoses with enough power to be diagnostic. So the phenotypic characteristics of the individuals were used independent of the clinical diagnosis to develop biologically based disease clusters. One might assume that ‘psychosis’ is analogous to a diagnosis of ‘congestive heart failure’ and that Biotypes 1, 2, and 3 are analogous to ‘cardiac’ vs ‘renal’ vs ‘pulmonary’ causes of congestive heart failure. This makes it incumbent to identify the distinctive and causal biology of the biotype, providing biological targets.

Thus, precision medicine is a targeted approach to diseases where molecular diagnosis leads to better defined, individualized treatments with improved outcomes (Collins and Varmus, 2015; Insel et al., 2015). Diagnostic tests based on genetics or other molecular mechanisms can be used to better predict patients’ response to targeted therapy (Hamburg and Collins, 2010). However, there are several challenges in genetics or genome-wide association studies (GWAS) studies, such as pleiotropy which results in shared

common genetic bases for different human traits. To overcome this, phenotypes with relatively high genetic correlations can be combined to enhance genomic prediction accuracy in precision medicine (Li et al., 2014; Maier et al., 2018).

The concept of precision medicine has been well defined in other research disciplines, such as oncology and infectious diseases. In these areas, ‘precision therapy’ is conceptually linked to molecular biological properties of the disease (or causative agent) that are relevant for the drug’s mechanism of action. For drug development in precision psychiatry it will also be essential that psychiatric biotypes are based on ‘drugable’ characteristics, and to some extent the patient will have to be matched to the most appropriate drug. So far, however, clustering of psychiatric disorders has not often been based on CNS-functions with close relationships to neuropharmacological processes. At present, clustering is primarily based on neurobehavioural phenotypes that are part of the clinical spectrum of psychiatric disorders. Precision psychiatry is in line with the RDoC framework of the NIMH (Insel et al., 2015).

Several attempts are currently made to deconstruct traditional symptom-based categories. Recently, the Psychiatric Ratings using Intermediate Stratified Markers (PRISM) project received funding through the EU-Innovative Medicine Initiative (IMI) to develop a quantitative biological approach to the understanding and classification of neu-

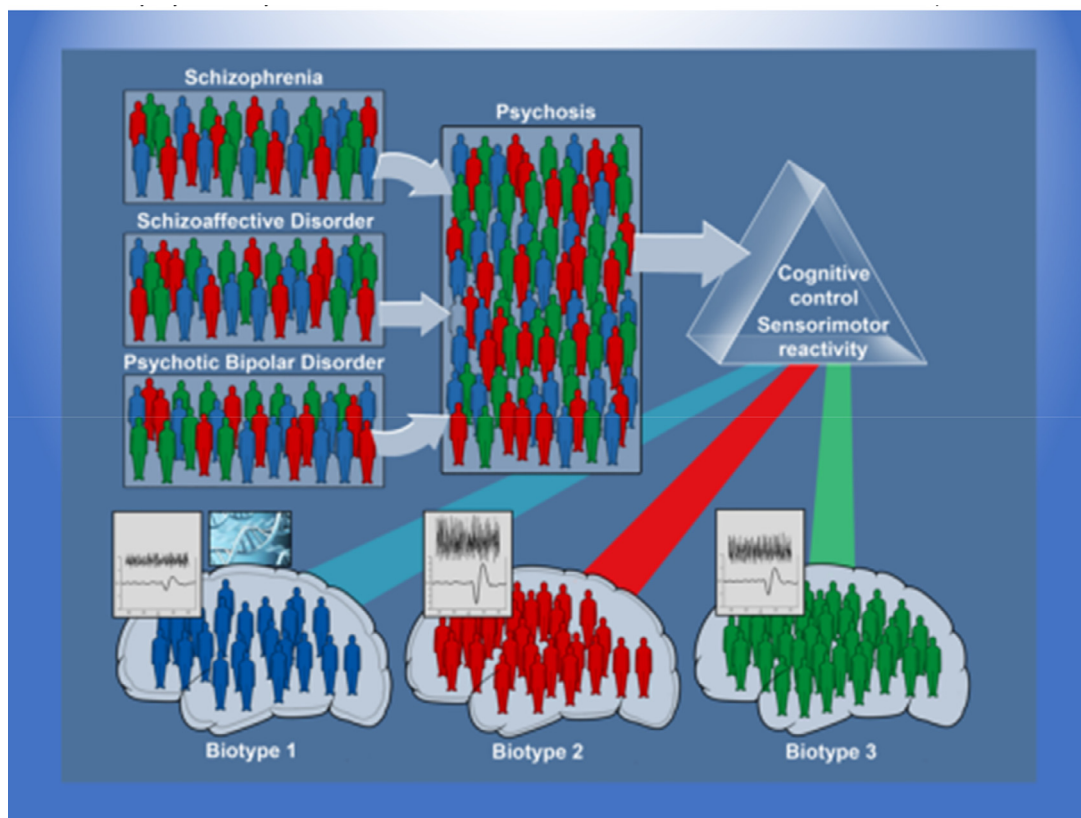


Fig. 2 Clustering patients based on neurobehavioural phenotype instead of diagnostic disorder (Clementz et al., 2016) Reprinted with permission from The American Journal of Psychiatry, (Copyright ©2016). American Psychiatric Association. All Rights Reserved.

ropsychiatric diseases. The idea has been put forward that clustering patients on the basis of the biology rather than their clinical diagnosis will stimulate the discovery and development of better treatments for patients (Kas et al., 2017).

The PRISM project aims to identify and validate clinically relevant biological substrates of neuropsychiatric symptom constellations through the use of quantitative technologies. For that purpose, a clinical deep phenotyping study on common traits, i.e. social withdrawal, sensory processing, attention and working memory, shared between a multifactorial psychiatric disorder (schizophrenia) and a neurodegenerative disorder (Alzheimer's disease, AD) will be performed to cluster patient groups based on quantitative biological parameters, such as EEG and fMRI measures, rather than on conventional diagnosis. Aligned preclinical and clinical research methods will be implemented to provide the best predictive models for future drug discovery studies and for validating human molecular landscaping analyses to develop better understanding of the complex pathophysiological relationships underlying these common traits. It is aimed to provide novel classification and assessment tools for more effective identification of the right patient for a given treatment of a specific symptom constellation that translates into a better function and quality of life (Fig. 3) (Kas et al., 2017). To provide new classification tools for neuropsychiatric disorders based on quantitative biological parameters, schizophrenia and AD patients with

high or low social withdrawal will be selected for a clinical deep phenotyping study at the level of biological substrates (genetic and epigenetics), EEG assessments (e.g., sensory processing), neuroimaging (structural and functional MRI), and behavioural assessments, e.g., smartphone application (app) remote passive behavioural monitoring. A preclinical platform with paradigms homologous to those assessed in patients will be implemented for reverse translation of human findings. Together, these studies will provide new classification, assessment tools and approach strategies for social and cognitive performance across neuropsychiatric disorders, clinically relevant substrates for treatment development, and predictive, preclinical animal systems for subsequent neurobiological and pharmacological testing (Kas et al., 2017).

4. Pathophysiology biomarkers for psychiatric disorders

At present, no diagnostic test or biological battery is available for psychiatric disorders, which are phenomenologically defined. An important goal of phenotyping patients is to develop improved biomarkers. Ideally, biomarkers should be available for multiple mechanisms (1) they can function as predictors of transition to psychiatric disorders in an at-risk population, and (2) they predict and monitor treatment response.

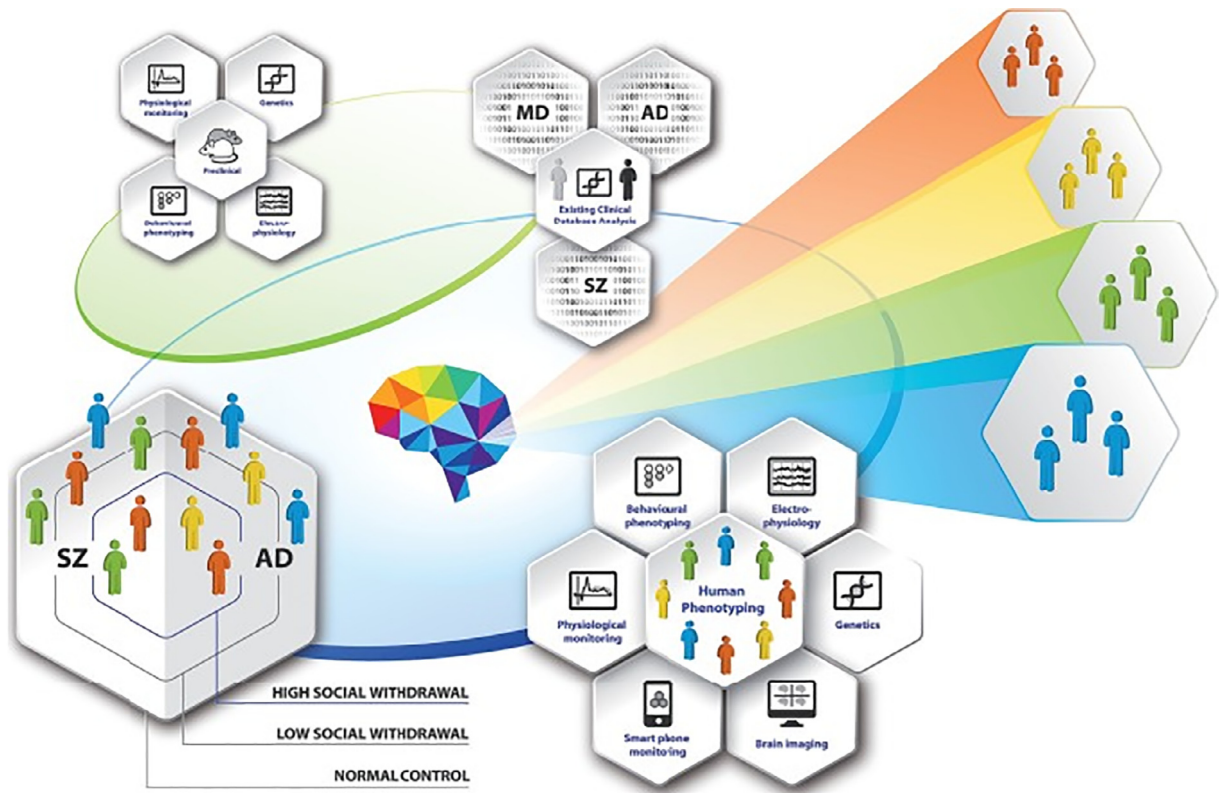


Fig. 3 Schematic representation of the research elements addressed within the PRISM project (Kas et al., 2017).

The term ‘biomarker’ has been widely used and can apply to a wide range of measurements including markers in biological material, e.g. serum, plasma, cerebrospinal fluid, DNA, and mRNA, neuroimaging measurements including (ph/f)MRI and PET, cognitive test-batteries, and physiological measurements, such as heart rate, saccadic eye movements and many more. Since one measurement has insufficient predictive value, combined methods are examined to enhance the validity. For example, the results of markers in serum can be combined together with neuroimaging and physiological measurements.

Thus, there are many potential biomarkers, and even more possible associations with disease or patient characteristics. From a drug developmental perspective, biomarkers are most informative if they represent well-defined steps along the pathophysiology cascade (Danhof et al., 2005).

Driven by the boost of immunological research in many areas of medicine, there is growing interest in biomarkers of the immune system in several psychiatric disorders. Clearly, this will have an effect on the design of clinical trials, in which patients can be stratified on immunological parameters. During the meeting, it was discussed that major depressive disorder is associated with an increase in peripheral markers like interleukin-6 (IL-6) and C-reactive protein (CRP) (Khandaker et al., 2017). Given that these immune markers are also increased in treatment resistant depression suggests that patients may be stratified based on their serum profile. A niche for new interventions for psychiatric disorders could be monoclonal antibodies (mAbs) that are prescribed for other immune disorders. For ex-

ample, IL-6 antibodies like siltuximab, which is prescribed for rheumatoid arthritis (RA), and IL-12/23 antibodies like ustekinumab, which is used for psoriasis, may have antidepressant effect. Targeting the immune system may provide a promising second line option for treatment of resistant patients.

Most of the biomarkers that are currently investigated in psychiatry, focus on neurophysiological and neurobehavioral characteristics of DSM-based disease concepts. Clustering based on truly ‘deep’ psychopathological phenotyping will also require measurements of the biomarker course and neuropharmacological processes that underlie derangements of behavioural, emotional, and cognitive functions. Other factors that have been studied are predictors of antidepressant treatment response like negative emotional bias in depression. Negative emotional bias has been associated with depression and changes in emotional bias can predict later clinical changes in symptoms. Recent studies suggests that antidepressant drug administration modulates emotional processing in depressed patients very early in treatment (Harmer et al., 2017, 2009).

5. Translational medicine approaches

Preclinical and clinical research should complement each other. Preclinical research provides insight about potential mechanisms underlying neuronal dysfunction and clinical research provides human relevance. To move the field of psychiatry forward, an integrated experimental medicine approach is needed which integrates both preclinical and

clinical data. The lack of distinct endophenotypes of psychiatric disorders has complicated the development of specific animal models. The question is how to develop cross-species, clinically relevant quantitative phenotypes? During the meeting, it was recommended to use reverse translation from clinical to preclinical research. The concept of the reverse translational approach is that homologous human and animal endpoints, which are highly quantitative and neutrally based, are being defined to facilitate the translation from humans to mice and vice versa. The question remains how to address this homology? For example, Perry and colleagues explored 'open field' studies in rodents and human patients at the level of face validity (Perry et al., 2009). In this study, exploratory behaviour of patients with bipolar disorder and schizophrenia was quantified using a human open field paradigm. Exploratory behaviour has been well defined in animal studies, but has been less studied in patients with psychiatric disorders. In the study of Perry et al. (2009), a difference was found in exploratory behaviour between healthy controls and bipolar patients, although this was not demonstrated in schizophrenia. A similar phenotype as that of the bipolar group was shown in a mouse model with a genetic or pharmacological inhibition of the dopamine transporter compared to controls. According to these results the current amphetamine model of mania, which is considered the standard model, may be refined. In addition, physiological measurements could be considered, such as event-related potentials (ERPs), that can be assessed both in rodent species and human, and may be more closely related to pathophysiology of the disorders at the level of neurocircuitry (Kas et al., 2017). For drug studies, reverse translational endpoints can be selected, which characterize relevant aspects of psychiatric disorders and are drug sensitive in animal models. In general, translational endpoints will be measures of distinct functions and behaviours, rather than of disease constructs. Further research is needed to identify homologous phenotypes in human and animals. Ideally, these homologous phenotypes should become quantitatively assessed and are associated with processes underlying disease origin.

6. Digital technology

As mentioned previously, the multidimensional definition of psychiatric disorders constitutes a problem for development of psychiatric medications. On the one hand, this is related to the heterogeneity of phenomenology-based, psychiatric diagnostic categories and their poorly understood pathophysiology, which is probably just as heterogeneous. On the other hand, drugs act at targets that interfere with specific CNS functions, which in most psychiatric conditions only play a partial or modulatory role. Precision psychiatry could facilitate the switch from a symptom-based diagnosis to a biological-based diagnosis, as has been suggested with the RDoC dimensions (Insel et al., 2010). To identify subgroups that have biological validity novel technology is required. The question remains how digital technology may help the field forward. A current issue is the definition of the read outs of the clinical research studies. It is questioned whether these are robust and clinically relevant and whether the methods actually measure what is needed.

For example, several clinical outcome assessment (COA) tools like questionnaires are available to set a diagnosis for psychiatric disorders and to evaluate symptom severity. However, most questionnaires are subjective and/or do not provide quantitative outcomes. Second, since psychiatric disorders are complex brain disorders it is difficult to grasp these brain deficits in the existing COAs like questionnaires. As such, the questionnaires may not cover the whole spectrum of cognitive, behavioural or emotional functions as this is far too complex for a questionnaire. This may be the niche for novel technology.

New technologies are required to provide quantitative biological parameters to define patient subgroups. Advanced techniques in the field, such as neuroimaging, and the omics technologies may provide suitable measures of relevant biological processes. Digital technologies and innovative methods can also be used to measure functionally and clinically relevant parameters in patients' daily lives. This could include medical devices, more sophisticated computerized batteries of neurocognitive tests, and mobile health applications (apps). There is growing interest for research using smartphone data or mobile health apps. This leads to all kind of new possibilities, from actively asking patients how they feel at different time points a day, which is called ecological momentary assessment (Shiffman et al., 2008), to monitoring a subject's spontaneous behaviour. Passive monitoring can result in collecting multiple data including location using GPS signaling, time, social behaviour measured by telephone calls and duration, and use and content of text-messenger applications and social media platforms (Marzano et al., 2015; van Os et al., 2017). When these data sources are combined, a social rhythm of a subject can be identified. If anomalies in these rhythms occur, this gives relevant information which may help to predict or identify functional deficits like social withdrawal. This could help predict psychiatric illness exacerbation, or the responsiveness to drugs that are targeted at functional derangements rather than nosological entities.

At present, real-life ('smartphone') research in psychiatry is still in its infancy, and for most psychiatrically relevant behaviours, emotions and functions, validated ambulatory measurements are still unavailable. There are many technical and methodological as well as ethical issues. As such, it is recommended to have validation studies in the upcoming years to gain experience with the procurement and analysis of these big data sets. At present, there are already several successful examples like the development of devices to monitor treatment compliance, and devices to measure Patient Reported Outcomes (PROs), which is highly encouraged by regulatory agencies. For example, Wacean, an online platform created by the Dravet Syndrome Foundation, is a patient-driven tool for data capture of PRO assessment.

In order to succeed, the novel technology including apps measuring behaviour should be pre-validated by regulatory bodies before they can be accepted as endpoint in clinical trials. The European Medicines Agency (EMA) has an expedite drug development program to facilitate this request and is used to accelerate the process for initiatives at this level. It is getting ever easier to build smartphone applications and web-based tools for psychiatry or drug development. This is already leading to an abundance of methods, most of which are unvalidated and incomparable to other

similar tools. There is an increasing need for more structured approaches. A centralized European network would be helpful to resolve questions by offering communication between groups with past experiences. There is also a need for harmonization and development of standards, comparable to ICH-GCP.

7. Regulatory and advisory agencies

At the ECNP meeting, academia, industry and regulatory agencies were brought together during focused discussions. There was agreement that collaboration of academia and industry with regulatory and advisory agencies together could be strengthened. In general, academia, biotech and pharmaceutical industries are the drivers of innovation on clinical endpoints and have a close collaboration in which they can easily connect and discuss these outcome measurements. Moreover, these groups are the source of the large groups of volunteers needed to advance the field, but this will require common projects and collaborations. Regulatory and advisory agencies (RAs) advise on clinical endpoints to include in study protocols and provide approval for specific clinical endpoint measurements. They are the main drivers for the final COA and COA instrument selection. In principle, regulatory agencies are open to suggestions from academia and industry, but the outcome of the study needs to be predefined. Problems occur when innovative outcome measurements are developed by academia and industry without timely communication with the regulatory agencies. Without appropriate validation and prior agreement, it may be difficult to achieve regulatory acceptance of such novel methodologies in drug development. It might be worthwhile to perform validation studies examining COAs that can be used in further development plans. As such, pre-competitive strategies can be advised to different pharmaceutical companies with the aim to develop applicable instruments for specific indications (IMI funded projects).

Another issue is that the definition of innovative endpoints in relation to diagnostic or therapeutic objectives, which is provided to RAs, is often not specific enough. Therefore, the disease-specific guidance issued by RAs are open to discussion, and consequently COA instrument selection requires a more interdisciplinary approach. There is a tendency to replicate previous study designs for new drugs, which leads to repetition of the same problems that occurred in the past and refutes innovation. The use of scales which in themselves are well accomplished, may be unacceptable for RAs if they are used for other indications for which they were not validated. For example, batteries in dementia clinical trials like the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog) (Rosen et al., 1984) has been designed to measure cognitive outcome in AD, but its sensitivity varies with disease severity with poor sensitivity in early AD (i.e. large ceiling effects on most items of the scale in patients with Mini-Mental State Examination (MMSE)'s above 20 (Karin et al., 2014). Despite this knowledge, clinical trials continue to use this measure in all stages of the illness limiting the ability to detect a true drug effect (Frölich et al., 2011; Gold et al., 2010).

Learnings from success and failure in innovative drug development in neurosciences, shows that more emphasis should be placed on development of more sensitive end-point/outcome measures and validation of these outcome measures in experimental medicine studies ahead of phase 2 and 3 studies with drug candidates, aiming for markers and outcome measures that are sensitive (i.e. disease and pharmacological activity) and able to capture pathophysiologically relevant phenotypes. In an early stage of drug development, the development of new tests and outcome measures and validation of these measures needs to be performed in cooperation with regulatory agencies. This is particularly relevant for new methods that will be used not only for internal decision making, but also for registration or marketing. Regular communications with the FDA and the EMA, and collaborations or pre-competitive initiatives between academic, industry and funding bodies, are also important to exchange views and share expertise.

Thus, collaboration between academy and industry with regulatory agencies in an early stage is warranted to define the research criteria together for clinical endpoints. This is essential if the new drugs require gradual adaptations of study designs and methodologies, and of clinical indications and effects. Such fundamental developments may also have important consequences for patients and clinicians, and sometimes even for the health care system and society. Similar changes also occurred when currently available psychiatric medications became widely used. Therefore, these important stakeholders should also be involved in designing studies, selective methods and redefining relevant outcomes.

8. Patient participation

Drugs are intended to treat individuals who seek help, and their needs are the central drivers of drug development. This must be realized if new approaches are adopted to select drug targets, design diagnostic tools and redefine disease entities. New diagnostic or therapeutic approaches may affect many aspects of patients' lives. At the most basic level, this will influence their trust in the treatment and influences drug compliance. Psychiatric disorders are often chronic after a first episode and present sometimes for a lifetime, which means that a long-term maintenance pharmacological treatment may be required. In order to fulfill the drug compliance, the pharmacological treatment should be attractive and easy to administer. However, the smell, taste, or effect of the drug should be not too tempting to prevent substance misuse or addiction. New tools to monitor aspects of behaviour also pose new ethical and societal questions. Diagnostic classifications have a major impact on the position of patients in society, and new ways to define 'disease' will also turn new people into 'patients'.

In all areas of medicine the principles of Early Detection and Early Treatment are a given. Now that evidence is emerging that Early Treatment will result in better overall recovery from a mental illness, psychiatry will have to respond with an emphasis on both early detection and early treatment along with a full range of treatments which include cognitive, psychological and neurostimulation as well as pharmacological forms, for help-seekers.

Table 2 Research ideas for new approaches in psychiatric drug development.

| | |
|---|--|
| 1 | Deconstruct the multidimensional characteristics of psychiatric disorders into distinct neurobiological functional abnormalities. |
| 2 | Cluster patients primarily on biological phenotypes that represent pathophysiologically relevant and 'drugable' processes. |
| 3 | Develop and validate biomarkers that underlie the pathophysiology of psychiatric disorders and/or which represent pharmacological processes. |
| 4 | Base experimental approaches in humans on reverse translation from clinical to preclinical research, focusing on evolutionarily preserved neurobiological and neuropharmacological systems. |
| 5 | Digital technologies can be useful to quantify pathophysiologically relevant biological parameters, which can provide mechanism-based characterizations of patient subgroups and clinical effects. |
| 6 | Collaboration between academy and industry with regulatory agencies in an early stage is recommended to define the research criteria together for clinical outcome endpoints. |
| 7 | Involve patients in the design of new diagnostic tools and therapeutic approaches, clinical trials and definition of clinical outcome measurements. |

It is recommended therefore that patients and patient societies are closely involved in the design of clinical trials and definition of clinical outcome measurements, preferably in an early stage. Although much has been changed in consideration of the patients' perspectives during the last decades, it is not the current standard in each clinical trial to include patients and patient societies. In some European research institutes the involvement of patients has been standard practice already. For example, the National Institute for Health Research (NIHR) Maudsley Biomedical Research Centre (BRC) has a Service User Advisory Group which consists of people with experience of mental illness and an interest in mental health research. Researchers from the NIHR Maudsley BRC discuss their study design with this advisory committee to receive feedback in an early stage (before finalization of the protocol).

Individuals with a disorder, caregivers, and health professionals do not always have the same views on the impact of the disease symptoms or adverse drug effects. The appreciation of drug-induced sedation for instance can differ considerably between patient, caregiver, employer and physician. New diagnostic or therapeutic approaches may have complex unexpected consequences for the patient and his or her social environment. This largely unexplored territory may be particularly suitable for new digital technologies, which can only be designed in close interaction with the patients and their social structures.

9. Discussion

Based on the presentations and discussions in the meeting, several suggestions for new approaches to drug development in psychiatry are summarized in [Table 2](#).

How can we put these new approaches into practice? When psychiatric disorders are classified according to the principle of precision psychiatry, patients can be clustered on mechanistic biological phenotypes. Measures of pharmacological responsiveness could strengthen the links with 'drugable' targets. The knowledge about the biological phenotypes is largely driven by the availability of appropriate methods, which are continuously renewed by technological innovations. The outcome measurements of available techniques, such as neuroimaging, 'omics' and 'smartphone'

applications, may be integrated in order to assess the biological phenotypes and to provide simple, and accurate biomarkers. In addition, reverse translation from clinical to preclinical research may help to unravel the biological background of important aspects of psychiatric disorders. When models that can translate between preclinical and clinical results are also drug sensitive, the effects of pharmaceuticals of different species can be more easily translated as well.

If drug development will follow this pattern, patients may be stratified for different treatment options based on their symptoms and underlying biological (drug-sensitive) profiles. A new approach to drug development may require closer attention to the interactions between drug action and functional disorganization. This may include a reconsideration of psychiatric symptoms as dysregulations of functional networks.

Novel approaches to psychiatric drug development affect many aspects of psychiatry. This can only be accomplished if all stakeholders collaborate at early stages of drug development, when new methodological approaches often still largely need to be validated. Not only academia and industry should work closely together with regulatory and advisory agencies, but societies of patients and representatives should also be involved. In order to achieve these ambitious goals, communication between the stakeholders is key. This can be accomplished by regular meetings like the ECNP meetings and conferences. Furthermore, communication can be strengthened via technology platforms with the aim to share expertise. As an example, the Innovative Medicines Initiative (IMI) provides a pre-competitive platform to initiate such collaborations.

Acknowledgements

The authors would like to acknowledge the presenters and participants of the New Frontiers Meeting 2017.

Conflict of interest

The views expressed in this publication are the personal views of the authors and may not be understood nor quoted

as being made on behalf of or reflecting the position of EMA or one of its committees or working parties or any of the national agencies.

Contributors

Participants of the New Frontiers Meeting 2017. Chairs: Martien Kas and Joop van Gerven. Co-chairs: Thalia van der Doef and Gabriel Jacobs. Presenters: Christian F. Beckmann, Edward T. Bullmore, Wayne C. Drevets, Catherine J. Harmer, Hugh Marston, Pradeep J. Nathan, Carol A. Tamminga, Maria B. Tome

Role of the funding source

The New Frontiers Meeting was financially supported by the ECNP that had no influence on the content of this manuscript.

References

- Bjornsson, T.D., 2016. Progression of Modern Therapeutics (2015 Report).
- Clementz, B.A., Sweeney, J.A., Hamm, J.P., Ivleva, E.I., Ethridge, L.E., Pearlson, G.D., Keshavan, M.S., Tamminga, C.A., 2016. Identification of distinct psychosis biotypes using brain-based biomarkers. *Am. J. Psychiatry* 173, 373-384.
- Cohen, A.F., Burggraaf, J., Van Gerven, J.M.A., Moerland, M., Groeneveld, G.J., 2015. The use of biomarkers in human pharmacology (Phase I) studies. *Annu. Rev. Pharmacol. Toxicol* 55, 55-74.
- Collins, F.S., Varmus, H., 2015. A new initiative on precision medicine. *N. Engl. J. Med* 372, 793-795.
- Danhof, M., Alvan, G., Dahl, S.G., Kuhlmann, J., Paintaud, G., 2005. Mechanism-based pharmacokinetic-pharmacodynamic modeling—a new classification of biomarkers. *Pharm. Res.* 22, 1432-1437.
- Frölich, L., Ashwood, T., Nilsson, J., Eckerwall, G., 2011. Effects of AZD3480 on cognition in patients with mild-to-moderate Alzheimer's disease: a phase IIb dose-finding study. *J. Alzheimer Dis.* 24, 363-374.
- Gold, M., Alderton, C., Zvartau-Hind, M., Egginton, S., Saunders, A.M., Irizarry, M., Craft, S., Landreth, G., Linnamagi, U., Sawchak, S., 2010. Rosiglitazone monotherapy in mild-to-moderate Alzheimer's disease: results from a randomized, double-blind, placebo-controlled phase III study. *Dement Geriatr Cogn Disord* 30, 131-146.
- Hamburg, M.A., Collins, F.S., 2010. The path to personalized medicine - perspective. *N. Engl. J. Med.* 363 (11), 1092.
- Harmer, C.J., Duman, R.S., Cowen, P.J., 2017. How do antidepressants work? New perspectives for refining future treatment approaches. *Lancet Psychiatry* 27 (2), 141-142.
- Harmer, C.J., Goodwin, G.M., Cowen, P.J., 2009. Why do antidepressants take so long to work? A cognitive neuropsychological model of antidepressant drug action. *Br. J. Psychiatry* 195 (2), 102-108.
- Honey, G., Bullmore, E., 2004. Human pharmacological MRI. *Trends Pharmacol. Sci* 25 (7), 366-374.
- Hyman, S.E., 2016. Back to basics: luring industry back into neuroscience. *Nat. Neurosci* 19 (11), 1383-1384.
- Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D.S., Quinn, K., Sanislow, C., Wang, P., 2010. Research Domain Criteria (RDoC): toward a new classification framework for research on mental disorders. *Am. J. Psychiatry* 167 (7), 748-751.
- Insel, T.R., Cuthbert, B.N., Whiteford, H.A., Collins, F.S., Varmus, H., Insel, T., Lee, S.H., Goodkind, M., Dichter, G.S., Cole, M.W., Karalunas, S.L., Tamminga, C.A., Hall, B.S., McCoy, T.H., Schumann, G., Rosa, M.A., Lisanby, S.H., Crocker, L.D., 2015. Medicine. Brain disorders? Precisely. *Sci.* 348, 499-500.
- Karin, A., Hannesdóttir, K., Jaeger, J., Annas, P., Segerdahl, M., Karlsson, P., Sjögren, N., von Rosen, T., Miller, F., 2014. Psychometric evaluation of ADAS-Cog and NTB for measuring drug response. *Acta Neurol. Scand.* 129, 114-122.
- Kas, M.J., Penninx, B., Sommer, B., Serretti, A., Arango, C., Marston, H., 2017. A quantitative approach to neuropsychiatry: The why and the how. *Neurosci. Biobehav. Rev* doi:10.1016/j.neubiorev.2017.12.008, in press.
- Khalili-Mahani, N., Rombouts, S.A.R.B., van Osch, M.J.P., Duff, E.P., Carbonell, F., Nickerson, L.D., Becerra, L., Dahan, A., Evans, A.C., Soucy, J.P., Wise, R., Zijdenbos, A.P., van Gerven, J.M., 2017. Biomarkers, designs, and interpretations of resting-state fMRI in translational pharmacological research: A review of state-of-the-art, challenges, and opportunities for studying brain chemistry. *Hum. Brain Mapp.* 38, 2276-2325.
- Khandaker, G.M., Zammit, S., Burgess, S., Lewis, G., Jones, P.B., 2017. Association between a functional interleukin 6 receptor genetic variant and risk of depression and psychosis in a population-based birth cohort. *Brain. Behav. Immun* 69, 264-272.
- Li, C., Yang, C., Gelernter, J., Zhao, H., 2014. Improving genetic risk prediction by leveraging pleiotropy. *Hum. Genet* 133 (5), 639-650.
- Maier, R.M., Zhu, Z., Lee, S.H., Trzaskowski, M., Ruderfer, D.M., Stahl, E.A., Ripke, S., Wray, N.R., Yang, J., Visscher, P.M., Robinson, M.R., 2018. Improving genetic prediction by leveraging genetic correlations among human diseases and traits. *Nat. Commun* 9 (1), 989.
- Marzano, L., Bardill, A., Fields, B., Herd, K., Veale, D., Grey, N., Moran, P., 2015. The application of mHealth to mental health: opportunities and challenges. *Lancet Psychiatry* 2 (10), 942-948.
- Millan, M.J., Goodwin, G.M., Meyer-Lindenberg, A., Ove Ogren, S., 2015. Learning from the past and looking to the future: Emerging perspectives for improving the treatment of psychiatric disorders. *Eur. Neuropsychopharmacol* 25 (5), 599-656.
- Perry, W., Minassian, A., Paulus, M.P., Young, J.W., Kincaid, M.J., Ferguson, E.J., Henry, B.L., Zhuang, X., Masten, V.L., Sharp, R.F., Geyer, M.A., 2009. A reverse-translational study of dysfunctional exploration in psychiatric disorders: from mice to men. *Arch. Gen. Psychiatry* 66, 1072-1080.
- Rosen, W.G., Mohs, R.C., Davis, K.L., 1984. A new rating scale for Alzheimer's disease. *Am. J. Psychiatry* 141 (11), 1356-1364.
- Shiffman, S., Stone, A.A., Hufford, M.R., 2008. Ecological momentary assessment. *Annu. Rev. Clin. Psychol* 4, 1-32.
- Smith, S.M., Miller, K.L., Salimi-Khorshidi, G., Webster, M., Beckmann, C.F., Nichols, T.E., Ramsey, J.D., Woolrich, M.W., 2011. Network modelling methods for FMRI. *Neuroimage* 54, 875-891.
- van Oort, E.S.B., Mennes, M., Navarro Schröder, T., Kumar, V.J., Zaragoza Jimenez, N.I., Grodd, W., Doeller, C.F., Beckmann, C.F., 2017. Functional parcellation using time courses of instantaneous connectivity. *Neuroimage* 170, 31-40.
- van Os, J., Verhagen, S., Marsman, A., Peeters, F., Bak, M., Marcelis, M., Drukker, M., Reininghaus, U., Jacobs, N., Lataster, T., Simons, C., Lousberg, R., Gülöksüz, S., Leue, C., Groot, P.C., Viechtbauer, W., Delespaul, P., 2017. The experience sampling method as an mHealth tool to support self-monitoring, self-insight, and personalized health care in clinical practice. *Depress. Anxiety* 34, 481-493.