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Review article

A quantitative approach to neuropsychiatry: The why and the how

Martien J. Kas^{a,*}, Brenda Penninx^b, Bernd Sommer^c, Alessandro Serretti^d, Celso Arango^e, Hugh Marston^f

^a University of Groningen, Groningen Institute for Evolutionary Life Sciences, P.O. Box 11103, 9700 CC Groningen, The Netherlands

^b Department of Psychiatry and Amsterdam Neuroscience, VU University Medical Center, Amsterdam, The Netherlands

^c Boehringer Ingelheim Pharma GmbH & Co KG, CNS Diseases Research, Biberach an der Riss, Germany

^d Department of Biomedical and NeuroMotor Sciences, University of Bologna, Italy

^e Hospital General Universitario Gregorio Marañón, CIBERSAM, IiSGM, Universidad Complutense, School of Medicine, Madrid, Spain

^f Translational & Integrative Neuroscience, Eli Lilly and Company, Windlesham, UK



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ABSTRACT

The current nosology of neuropsychiatric disorders allows for a pragmatic approach to treatment choice, regulation and clinical research. However, without a biological rationale for these disorders, drug development has stagnated. The recently EU-funded PRISM project aims to develop a quantitative biological approach to the understanding and classification of neuropsychiatric diseases to accelerate the discovery and development of better treatments. By combining clinical data sets from major worldwide disease cohorts and by applying innovative technologies to deeply phenotype stratified patient groups, we will define a set of quantifiable biological parameters for social withdrawal and cognitive deficits common to Schizophrenia (SZ), Major Depression (MD), and Alzheimer's Disease (AD). These studies aim to provide new classification and assessment tools for social and cognitive performance across neuropsychiatric disorders, clinically relevant substrates for treatment development, and predictive, preclinical animal systems. With patients and regulatory agencies, we seek to provide clear routes for the future translation and regulatory approval for new treatments and provide solutions to the growing public health challenges of psychiatry and neurology.

1. Introduction

1.1. Brief history of drug discovery for neuropsychiatric disorders

Mankind has been using psychoactive substances for millennia both for recreation and to alleviate suffering. Indeed, at least an acknowledgement of abnormal psychiatric behaviour can be definitively traced back at least as far as classical times and pharaonic Egypt. However, attempts to understand these disorders with the aim of effective and systematic treatment really only emerges in the late 1800's; for dementia praecox and depressive states. Effective treatments for the symptoms associated with these disorders did not emerge until after World War II. The first neuroleptic, chlorpromazine, was introduced in 1952 (Rhone Poulenc) shortly followed by the first tricyclic

antidepressant imipramine (Roland Kuhn & Geigy) all from anti-histamine chemistry. In parallel with the newly available pharmaceuticals the nosology of psychiatric disorders took a major step forward in the same decades. In 1949 the International Statistical Classification of Diseases (ICD) included a section on mental disorders for the first time while DSM-1 (Diagnostic and Statistical Manual of Mental Disorders) emerged from efforts by the American Military to accurately classify psychiatric disorders. Current nosography is still largely based on the reliability improvement obtained with DSM-3 (American Psychiatric Association, 1980), which was however based on clinical observation only.

These advances led to huge improvements in society's perception of mental disorders and the ability to effectively treat the symptoms but, neither the classification nor the treatment was based on any

* Corresponding author.

E-mail address: m.j.h.kas@rug.nl (M.J. Kas).

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understanding of biological cause. Indeed, the mechanisms by which the drugs acted was effectively a mystery at this point. The fact that we now have hypotheses relating to the role of dopamine in schizophrenia and serotonin in depression largely results from a careful dissection of the pharmacological mechanisms of molecules of proven clinical benefit based on serendipity rather than either a direct mechanistic study of the human condition or from the consequence of rational drug design. Indeed, it can be argued that we need to wait 30 years from this revolution for the first drugs to be taken to market as a consequence of rational drug discovery (Fluoxetine – marketed by Eli Lilly from 1988). The consequence of this process is that we have become very good at developing “me too” drugs where “psychosis”, for instance, has become a symptomatic surrogate label for a disease process that responds to dopamine antagonism. It is now clear though that the reality of the biology that leads to psychosis is far more complex making the label progressively less useful.

It is important to remember that most mental health conditions are still classified, diagnosed, and prescribed for solely based on the symptoms observed and that it has not been until very recently that we have had a neuroscience based nomenclature for psychotropic drugs (Caraci et al., 2017; Zohar et al., 2015). This is in contrast to many somatic conditions, such as diabetes, hypertension or cancer. Further we now recognize that many different neuropsychiatric diseases share symptoms, such as cognitive deficits, psychosis, anhedonia, or social withdrawal, which makes it difficult to understand what the underlying pathophysiological mechanisms are. For example, we do not really have an idea how, if at all, the biological cause for social withdrawal in Alzheimer’s disease differs from that in schizophrenia.

This lack of understanding of the root pathophysiological causes of neuropsychiatric disorders is one of the reasons behind the dramatic slowdown in the discovery and development of new drugs to treat these disorders. Modern drug discovery is now very much driven by hypotheses derived from a mechanistic understanding of the disorders for which new therapies are being developed. Without robust hypotheses areas become deprioritized as executing an effective drug discovery programme, as demonstration of mechanistic proof of concept and clinical efficacy proofs difficult. For neuropsychiatric diseases, this approach has been hampered not only by the missing link between diagnostic criteria and underlying pathophysiological causes but also by suitable instruments to assess the brain’s connectivity and circuitry to a sufficient extent. The emergence of new ways of measuring brain activity (e.g. functional Magnetic Resonance Imaging (fMRI) of the brain, which registers blood flow to functioning areas of the brain, or an electroencephalogram (EEG) to assess evoked related potentials of the brain) is opening the door to the development of novel mechanistic hypotheses based on a new understanding of the brain systems and neural circuits perturbed in different mental health conditions. These hypotheses can then form the basis for improved nosology to describe, classify and diagnose disorders, guide prescribing, stimulate novel drug discovery, identify improved regulatory categories and improve the efficiency of clinical trials.

1.2. RDOC’s initiative

In view of the above limitations, in 2009, the National Institute of Mental Health (NIMH) proposed a new research classification system: the Research Domain Criteria (RDoC) (Cuthbert and Insel, 2010). It was clear that despite the best of intentions, DSM-5 has been unable to incorporate neuroscience into its clinical diagnostic criteria, mostly because neuroscience (e.g., genetics, neuroimaging) and behavioural science data map poorly to current symptom-based disorders (Cuthbert and Insel, 2013). With a humble perspective, the RDoC spirit is that we cannot resolve complex problems with simple common solutions, and we need to dissect the different levels of complexity from genes to behaviour, subjective experiences, or even paradigms. This new research classification is based on dimensions of observable behaviour

and neurobiological measures to identify fundamental components that may span multiple disorders. The RDoC framework needs to integrate many different levels of data to develop a research approach in order to classify a mental disorder based on pathophysiology and link it more precisely to interventions for a given individual in a precision medicine paradigm (Insel and Cuthbert, 2015).

It is clear that a number of treatment modalities, including pharmaceutical and psychosocial or behavioural treatments, as well as medical devices, have been shown to be efficacious in a broad range of disorders (e.g., selective serotonin reuptake inhibitors to improve mood in many different categorical disorders or benzodiazepines for anxiety in a variety of DSM or ICD disorders). This would argue in favor of identifying fundamental components that may span multiple disorders (e.g., executive function, affect regulation, social withdrawal) and for the development of reliable and valid measures of those components for use in drug development or clinical trials. The RDoC proposes to focus on a novel mechanism relevant to a clinical problem defined as a domain or construct (e.g., social withdrawal) regardless of DSM/ICD diagnosis and to enroll patients in clinical trials based on deficits in that mechanism and not on DSM/ICD diagnosis. In order to do that, it is important to assess the extent to which the domain has the same or different biological underpinnings across the different categorically defined disorders.

1.3. Technical advances

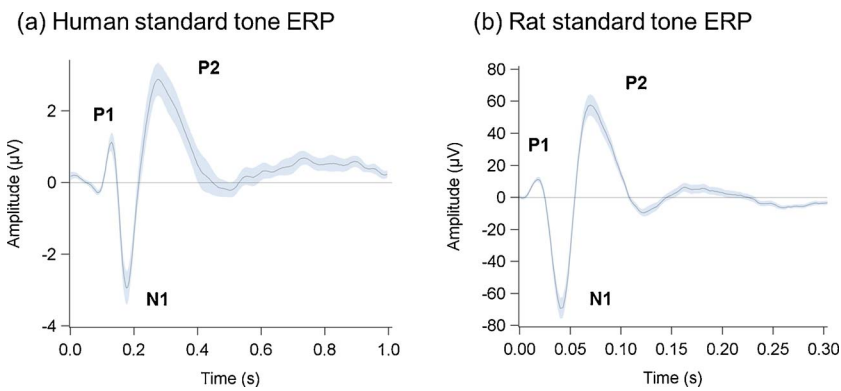
1.3.1. Preclinical research

As there is a growing philosophical concern about trying to “model” complex, possibly species specific, disorders such as schizophrenia and depression the advent of technologies allowing high resolution physiological monitoring offer a potential alternative approach. These approaches include electrophysiology, imaging of structure and function, neurochemistry, which are in many cases now applicable in real world spontaneous or controlled behavioural states. For example, analysis of EEG in a variety of modalities in man is an example of where it is now possible to provide validated pre-clinical homologous techniques. To extend the example an auditory evoked response (AER) can be measured now in both man and freely moving rat or mouse. The relationship between the electrode placements and the underlying neuroanatomical structures is equivalent. The profile of the response is near identical when scaled temporally to compensate for the differences in neuronal path length, and the perturbations induced by drug administration are highly equivalent (Fig. 1). If, therefore, using a pallet of such techniques and parameters a quantitative description of the abnormalities of specific aspects of a particular disorder can be determined we have a real chance of directly back-translating human findings in animals, and to expand our neurobiological knowledge.

These advances have been arrived at through the application of; microelectronics, improved understanding and ability to deploy biosensors, dramatically more powerful data acquisition and analysis software and hardware. Further, approaches are now possible where these technologies can be combined with more traditional behavioural techniques to allow different “states” and “circuits” to be probed in a hypothesis driven manner. In parallel the ability to manipulate the brain in a disease-relevant many is again undergoing a similar revolution. A few examples of these advances include; a better understanding of the application of transgenic technologies, inducing neurodegenerative disease states using clinically identical protein triggers, pharmac- and opto-genetics. Taken together we have a powerful translational toolbox to deploy if we can identify meaningful and discriminating parameters in the clinical setting to back-translate from.

1.3.2. Clinical research

The advances over the last decade in terms of clinical mental health research are numerous. Three potentially ‘game-changing’ innovative techniques will be highlighted. First, brain imaging techniques such as



(often referred to as N100 in humans) and P2—the second positive wave following the stimulus (often referred to as the P200) in humans.

structural or functioning Magnetic Resonance Imaging (sMRI or fMRI) but also electroencephalogram (EEG) have become more widely available and applied in mental health research in the last decade (Milham et al., 2017). This has opened the possibilities to examine structure and activity of the brain, thereby providing opportunities to better understand the role of the brain in mental health conditions and interventions. Second, the system biology approach has become more advanced and applicable to clinical mental health research (Alawieh et al., 2012), which allows for more detailed insights in the pathophysiology of mental health conditions. It is now technically possible and cost-efficient to apply various ‘-omics’ assessments in blood, saliva, brain or other tissue materials. These methods allow a further exploration of gene-expression, epigenetics, metabolomics and proteomics patterns, and their interactions, at a more extensive scale, and relate these to mental health conditions. Third, the application of e-Health and m-Health technology is another technical innovation with a potential big impact on mental health research. This allows us to both passively and actively follow persons over time through ambulatory assessments. Through this technique, innovative assessments of the impact of daily routines and life events become possible, and individual mental health symptom patterns as well as social and physical activity can be tracked over time. Such data allow for more detailed assessments of neuropsychiatric health in a person’s natural environment and therefore for more personalized outcome monitoring and potential intervention strategies (Myin-Germeys et al., 2009).

1.3.3. Data analyses

Application of new clinical methods, as described above, can generate innovative ‘big data’ in the field of neuropsychiatry. New computational neuroscience is necessary to undertake either theory-driven or data-driven approaches to quantitatively delineate the underlying mechanisms of neuropsychiatric disorders. The data-driven approach is an emerging field in computational neuroscience seeking to identify disorder-specific features among high-dimensional multi-modal big data. Various machine-learning techniques can be applied to e.g. neuroimaging and – omics data and the extracted disorder-specific features can be used for automatic intermediate phenotype status. Emerging techniques – such as those that estimate normative models for mappings between biology and behaviour – can provide new ways to parse the heterogeneity of underlying neuropsychiatric diseases (Marquand et al., 2016). An inherent risk to innovative ‘big data’ analyses is that of producing chance findings when there is no appropriate validation and replication applied. However, when appropriately utilized, these techniques provide promising ways to substantially increase our understanding of the underlying pathophysiology of (clusters or dimensions of) neuropsychiatric disorders. They have great promise in establishing a link between phenomenological and pathophysiological aspects of neuropsychiatric disorders, thereby potentially recasting current nomenclature in more biologically meaningful dimensions.

Fig. 1. The morphological similarities between standard tone responses in humans (a) and rats (b). Rat evoked responses latencies were significantly shorter than their human counterpart, whilst the amplitude of responses were smaller in humans reflecting the use of scalp EEG rather than skull screws in rat. Data are from the placebo arm of analogous human and rat within-subject PK/PD crossover studies (data held on file at Eli Lilly and Co). In both trials, the standard tone presented had a frequency of 1000 Hz, duration of 50 ms with a 5 ms rise/fall time, was 90 dB loud and 90% likely to occur. The human trial occurred over 5.5 min resulting in 300 standard tone stimuli. In the rat trial 1080 stimuli presented were presented over 20 min in order to ensure sufficient time spent in wakefulness during the trial and 300 responses randomly selected when subjects were determined to be awake (via EEG/EMG). Results presented as mean and standard error (Human N = 12, Rat N = 16). P1—the first positive wave following the stimulus (often referred to as P100 in humans), N1—the first negative wave following the stimulus

2. Quantitative biology to neuropsychiatry

2.1. Conceptual outline of the approach

The current classification scheme for the diagnosis of neuropsychiatric disorders separates each disease into non-overlapping diagnostic categories. This separation is not based on their underlying aetiology but on convention based clustering of qualitative symptoms of the disorder. While these diagnostic categories are sufficient to provide the basis for general clinical management, they do not describe the underlying neurobiology that gives rise to individual symptoms. The ability to precisely link these symptoms to underlying neurobiology would not only facilitate the development of better treatments, it would also allow physicians to provide patients with a better understanding of the complexities of their illness facilitating improved management. To realise this ambition, a paradigm shift is needed to raise awareness and to build an understanding of how neuropsychiatric diagnoses can be based on quantitative biological parameters. However, the main difficulty in the construction of biologically valid diagnoses is the lack of objective biomarkers. Moreover, the uncertain relationship between diagnosis and underlying aetiology has created difficulties for aetiological research and made the generation of appropriate disease models and development of targeted treatments very difficult. As aetiological research progresses, there has been a rethinking of these diagnostic boundaries and their usefulness in treatment and classification of neuropsychiatric disorders. This is partly based on the notion that there is more aetiological overlap between psychiatric and neurodegenerative disorders than previously thought, and that they may better be described as domains of cross-disorder-related traits rather than separable categories (Kas et al., 2007; Insel and Cuthbert, 2015).

2.2. Implementation in the PRISM project

Recently, the PRISM (Psychiatric Ratings using Intermediate Stratified Markers) project was funded through the EU-Innovative Medicine Initiative (IMI) to develop a quantitative biological approach to the understanding and classification of neuropsychiatric diseases to accelerate the discovery and development of better treatments for patients. In PRISM, patients with a range of neuropsychiatric symptoms will be assessed using several analytical platforms to parse current heterogeneous syndromes into homogeneous clusters. Furthermore, the project will develop deeper understanding of the quantitative biology of social withdrawal using clinical data from Schizophrenia (SZ), Major Depression (MD) and Alzheimer’s Disease (AD) patients and by establishing a network of pre-clinical research sites able to perform high quality back-translation studies. This way, PRISM implements an important call for integration of research across traditionally defined psychiatric and neurological disorders. Finally, first steps will be undertaken to develop the regulatory path for social withdrawal across

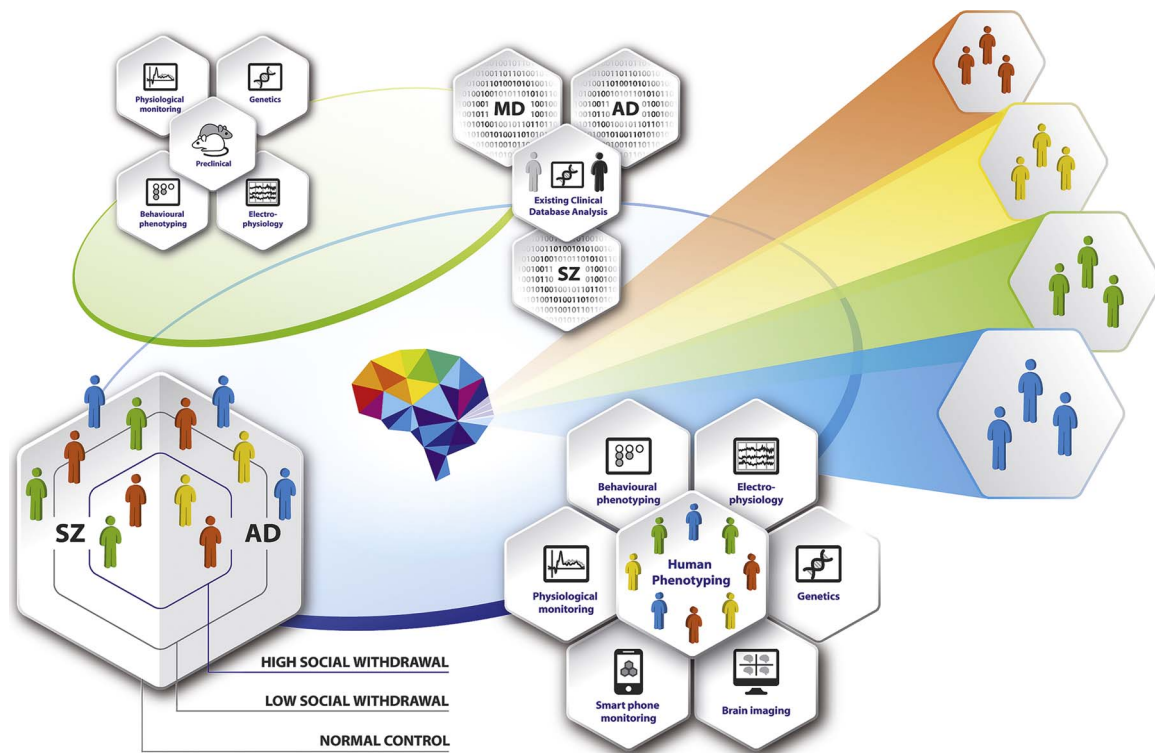


Fig. 2. In order to provide new classification tools for neuropsychiatric disorders based on quantitative biological parameters, schizophrenia (SZ) and Alzheimer's disease (AD) patients with high or low social withdrawal will be selected for a deep phenotyping study. This study will focus on assessing social withdrawal, attention, sensory processing, working memory and epigenetic biomarkers. In addition, a cross-disorder genome-wide genetic analysis will be performed in the largest world-wide available samples of SZ, AD, and major depression (MD) patients to identify shared genetic factors potentially related to the common social withdrawal symptom observed in these disorders. Data integration of genetic and epigenetic studies through a molecular landscape building approach will lead to new biological substrates and candidate genes for construct validation studies in genetic rodent models. Molecular landscaping is an unbiased systems biomedicine approach and offers a new platform for data integration. Given that complex traits are modulated by a large number of genetic factors (Boyle et al., 2017), molecular landscaping provides an effective way to integrate big genetic and other genome-wide data for any complex disease into a model. It involves the application of gene enrichment, protein–protein interaction, and bioinformatics-based tools. In addition, it is complemented by manual curation and iterative integration of findings from extensive, thorough and systematic literature evaluations of the top-ranked genes. For more description and examples, see (Poelmans et al., 2011, 2013). Together, these studies will provide new classification and assessment tools 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.

disorders (Fig. 2).

2.3. Key areas for PRISM implementation

The challenge of the PRISM project was to identify a target dimension which satisfies a set of eligibility criteria, i.e. a target that is independent from clinical psychiatric and neurological diagnoses, has a large epidemiological impact, has at least some known biological determinants, for which an advance of knowledge of the biologic determinants is realistic and that could be the target of possible specific innovative treatments. In the PRISM project, social withdrawal (Porcelli, in this issue) was identified as an innovative investigational domain that matches the proposed criteria.

While the spectrum of neuropsychiatric disorders is heterogeneous, they largely share the expression of negative symptoms, in particular social withdrawal (Peralta et al., 1992; Reichman and Negron, 2001; Winograd-Gurvich et al., 2006). Indeed, social withdrawal is one of the first indicators of emerging psychiatric disorders such as SZ and MD and neurological disorders such as AD. It is characterized by the withdrawal of the individual from their social networks established in work places and friendship circles. Although social withdrawal is a multi-determined complex behaviour, which can be modulated by several factors – such as personality traits, disability status, aging process, social environment, socio-economic status, among others – a growing body of evidence suggests that it could be also, at least in part, an independent behavioural trait with a specific biological substrate at its basis. Moreover, studies on AD patients have reported that negative

symptoms, social withdrawal included, cannot be solely accounted for by depression, co-morbid medical illness, medication exposure, or positive symptoms (Reichman and Negron, 2001). Studies on SZ patients have also consistently shown that impairment in social functioning is largely independent from psychotic symptoms and medications (Heinssen et al., 2000; Bellack et al., 2004; Arango et al., 2004), although a weak association with positive symptoms has been reported (Cella et al., 2014). Furthermore, impairment in social functioning is largely impacted in MD, which is only partly by MD severity (Kitamura and Suga, n.d.; Galynker et al., 2000). Finally, a psychiatric syndrome mainly characterized by pure social withdrawal has been recently described (i.e. Youth social withdrawal behaviour or “Hikikomori”) and it is receiving growing attention because it seems to be more common than previously thought and it does not appear to be limited to specific cultures (Li and Wong, 2015).

Social withdrawal is a complex behaviour which is the final outcome of a large series of processes and which is sensitive to more basic domain deficits. As an example, a focused deficit in attention may largely impair social withdrawal independent from motivational drives. Therefore, after a careful analysis of current evidence (Porcelli, in this issue), we identified attention (Serretti, in this issue), working memory (Gilmour, in this issue) and sensory processing (Danjou, in this issue) as possible confounders of social withdrawal variability and decided to control for their possible deficits in order to reduce background noise. Interestingly, these are also shared cognitive deficits in SZ, AD and MD patients (Weintraub et al., 2012; Cohen et al., 2007; Martinez-Aran and Vieta, 2015; Millan et al., 2012; McIntyre et al., 2013; Lepage et al.,

2014), and are known to contribute to interpersonal behaviour (Bowie et al., 2008).

More precisely, the deficits in working memory and attention found in drug-naïve and first episode patients with SZ (Mesholam-Gately et al., 2009; Fatouros-Bergman et al., 2014) are also found in the very early stages of AD (including in patients with Mild Cognitive Impairment (Weintraub et al., 2012). Interestingly these deficits are also among the most recognized cognitive impairments seen in patients with MD (McIntyre et al., 2013). Further, sensory processing – a term that refers to the way the nervous system receives messages from the senses and turns them into appropriate motor and behavioural responses (Hornix, in this issue) is found to be impaired in all three disorders at the earliest stage of disease (Mesholam-Gately et al., 2009; Weintraub et al., 2012; McIntyre et al., 2013). Hypofunction of the prefrontal cortex and over-activity of the anterior cingulate cortex are hypothesized to be correlated with these deficits, reflecting a functional disconnection between cortical and subcortical structures (MacQueen et al., 2003; Waltz et al., 2004; Malykhin et al., 2010; Howes et al., 2012) and likely involves the catecholamine system (Stahl, 2003; Howes et al., 2012). Consistent with these overlapping biological putative factors, cognitive impairments have also been partially associated with negative symptoms (Cohen et al., 2007; Strauss et al., 2015; Kahn and Sommer, 2015).

Working memory, attention and sensory processing abnormalities are thus similar across diagnostic groups and are an ideal complement to determining a causal model of social withdrawal. In fact, recent data suggest that interpersonal behaviour could be predicted by processing speed, attention and working memory, together with executive functions and depressive and negative symptoms (Bowie et al., 2008). Interestingly, the effects of attention, working memory and processing speed seem to be mediated by their effects on social competence. Therefore, it can be hypothesized that these cognitive deficits induce impairments in the patient's social competence which eventually results in high social withdrawal, a hypothesis that receives support from studies with subjects at high-risk of SZ (Jahshan et al., 2012). In turn, social withdrawal, and the resulting social isolation, may cause a worsening of these cognitive deficits (Cacioppo and Hawkey, 2009), resulting in a vicious circle of progressive worsening of the general functioning and the patient's quality of life. Therefore, a deep and combined investigation of these domains may lead to significant advances in the understanding of the biological underpinning of these impairments, paving the way for the development of novel treatments targeted at both social withdrawal and cognitive deficits in SZ, AD, and MD patients. The similarity of these symptoms suggests that they may have a common neurobiological basis, but further investigations are needed to confirm these relationships. If we can design and develop biomarkers based on quantitative phenotypes that share a common neurobiological basis, the development of better pre-clinical assays and treatments will follow (Hengerer, in this issue).

3. Future outlook

3.1. Clinical practice

We have seen that current nosology is mainly based on the historical effort performed during the seventies mainly aimed to ensure reliability of psychiatric diagnoses (Spitzer et al., 1975). After many decades it is still based on reported subjective experiences and patterns of behaviour of the subject and, though it received some degree of validation from family and prospective studies, it is still largely unsatisfying (Jablensky, 2016). Prognostic, biologic and treatment validity are in fact moderate to poor depending of the specific diagnosis. They do not constitute separate entities such as in other medical fields. This impairs the research of biological determinants as well as the individualization of treatments and this has prompted the development of the RDoC initiative as mentioned above. Indeed, as an example, bipolar disorder

and schizophrenia have been considered for over a century different disorders because of their different symptomatology, course, outcome, partially different treatment response and because to a certain degree they cluster in families, suggesting a separate biologic background. However, from a clinical perspective they share many features (such as psychotic symptoms) and also from a biologic perspective it has been recently reported that there is a considerable overlap in genetic risk factors (Cross-Disorder Group of the Psychiatric Genomics Consortium et al., 2013). This perspective boosted interest in the recent years with the aim of identifying cross diagnostic biological and clinical constructs (Kendler, 2013). This is why the focus on the transdiagnostic domain of social withdrawal feature in the present project is an unprecedented effort which follows the line of current research with the aim of identifying a potential independent entity in terms of biologic roots, classification advances and new targeted treatments.

Current treatments are in fact already becoming cross-diagnostic. The classical Anatomical Therapeutic Chemical indication based classification of psychotropic drugs in antidepressants, antipsychotics, anxiolytics, hypnotics and mood stabilizers is no more adequate to current treatments. Quetiapine exemplifies this limitation. It is a hypnotic at low doses (< 100 mg), an antidepressant at intermediate doses (150–300 mg), a mood stabilizer at 300–600 mg and an antipsychotic at higher doses. This is possible because of its pharmacodynamic profile which targets different systems at different doses. Similarly, different indications based on dosages apply to sulpiride and pregabalin. The newly spreading Neuroscience-based Nomenclature (Zohar et al., 2015), follows this line by defining compounds by their mechanism of action and their approved efficacy profile across all diagnoses or conditions.

3.2. Drug discovery

The unmet medical need in psychiatry and AD remains to be high. It is estimated that in any one year 27% of the adult (18–65 years of age) EU population, approximately 83 million subjects, suffer from at least one mental disorder. Incidence data also suggest that almost every second person in the EU is, or has been, affected by mental disorders at some point in his/her lifetime (Wittchen et al., 2011) much of which is inadequately treated with the consequence that neuropsychiatric disorders are among the 3 highest causes for disabilities worldwide imposing a huge economic burden on societies. Consequently, significant resources are being devoted to find a disease-modifying treatment for neuropsychiatric disorders. However, a successful treatment would ideally prevent rather than reverse the effects of the disease and if so, at least one if not two generations of neuropsychiatric patients will continue to require treatments for relief of symptoms such as social withdrawal.

However, despite the recognized unmet medical need drug discovery efforts for the treatment of neuropsychiatric disorders have been rather unsuccessful over the past decades. For example, at this stage, no new treatment for social withdrawal has been registered since the 1990s. As elaborated on above, there is a wide consensus in the field that this is mainly accounted for by the evident disconnect between disease classification and diagnosis and an understanding of the underlying pathophysiological causes for diagnosed symptoms. Implications of this disconnect in the drug discovery process are manifold. For example, preclinical models and tests unrelated to clinical endpoints and in combination with the lack of biomarkers preclude a systematic, iterative clinical trial design. Trial populations heterogeneous with respect to disease cause and etiologies dilute efficacy signals and disguise positive outcome. In consequence all contribute to limited predictability and increased attrition.

PRISM's new approach is in line with IMI2's Strategic Research Agenda, which calls for a 'reclassification of diseases based on their root cause', rather than symptoms, and with the recent NIH/NIMH RDoC initiative. It will help to address 'unmet therapeutic needs' which is a

key objective of this project. One of the expected outcomes of the PRISM project is that it will identify the neurobiological underpinnings of symptoms shared across different diseases. Specifically, it will take the first steps in achieving this objective by determining the neurobiological basis of social withdrawal and cognitive deficits providing a plausible cause and effects analysis of their relationship in AD and schizophrenia. Thus it will eventually provide relevant targets for novel treatments that cut across existing disease boundaries in both psychiatry and neurology. In addition, it will provide biomarkers capable of bridging the fatal gap between preclinical read-outs and clinical endpoints, therefore facilitate translation of preclinical findings into clinical testing as well as refinement of preclinical models and tests by systematic back-translation from patients. Furthermore, these biomarkers may enable patient stratification along quantifiable biological criteria, hence create more homogeneous trial populations. IMI2 also underlines the need for new biomarkers and methods to support the stratification of patients to rationalise the way in which clinical trials are conducted and in particular to predict which patient will respond to which treatment. PRISM will address these goals by combining new smartphone technology with the latest imaging techniques to deliver links between real world data, symptoms and neurobiology. All together this will lead to the design of more efficient and effective seamless clinical trials with iterative decision points, which may ultimately yield more rapid and cost-effective drug development and higher success rates. Finally, PRISM will provide a European-wide multi-centered clinical trials network based in university centres of excellence to support drug development in all clinical phases with reliable and reproducible data from clinical trials (Bilderbeck, in this issue).

In summary, the project introduces an unprecedented systematic approach to link relevant symptoms going across neurodegenerative and psychiatric conditions with quantifiable biological dimensions. In this sense it is truly integrative as it embraces all phases of the medicines development cycle reaching from early drug discovery to registration and market access, i.e. regulatory acceptance of newly identified biomarkers or indications for drugs improving clinical conditions across different brain disorders. Thereby the project paves the way into a paradigm shift for drug discovery and development in neuropsychiatry and has the potential to serve as a role model for RDoC guided approaches, including their rapid take-up and acceptance by the scientific community.

Conflict of interest

The authors declare no conflict of interest. B.S is fully employed by Boehringer Ingelheim. H.M is fully employed by Eli Lilly and Company.

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