Quantitative neurosymptomatics

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Editorial

Quantitative neurosymptomatics: Linking quantitative biology to neuropsychiatry

The treatment of neuropsychiatric disorders currently involves the use of over 100 compounds. Clinical benefit is still far from being optimal, issues of tolerability and poor efficacy still remain major challenges in disorders, such as Schizophrenia and Alzheimer Disease. Even after 50 years of drug discovery following the identification of first antidepressant and antipsychotic drugs we are still dependent on the modulation of dopaminergic and serotonergic systems for the treatment of psychiatric disorders. Similarly, in the area of neurodegeneration, modulation of acetylcholine remains our principle tool for treating the symptoms of dementia. The benefits of these classes of compounds should not be underestimated but neither should their shortcomings. Few new mechanisms of action have been identified in the last decades. *Paralleling, this innovative deceleration in the identification of novel therapeutic approaches our diagnostic framework has also only gone through a limited evolution over this same time-period. Despite many significant advances, in quantitative neuroscience, clinical practice is still based principally on a qualitative assessment of perceived symptoms.* It is clear therefore that we need a paradigm shift to rekindle the drug discovery process and facilitate better matching of patient to therapeutic. A number of projects have been recently proposed in order to innovate the field (see for example NEWMEDS (Artigas et al., 2017)), but converging evidence, summarized in the first paper (Kas et al in this issue (Kas et al., 2017)) suggests the need for a more radical change of this perspective. The core of this thesis is that the direction for innovation should focus on the biological systems that can be quantitatively demonstrated as being altered in disease. From this understanding new transdiagnostic hypotheses explaining the clinical deficits, independent from traditional categorical designations (O'Donnell and Ehlers, 2015), should be encouraged to emerge.

Having relied entirely on a clustered symptomatic classification of neuropsychiatric illness there is much discussion currently, such as the RDoC (Cuthbert, 2018 in this issue) and ROAMER initiative (Haro et al., 2014), as to whether a more pragmatic quantitative biology approach may now be achievable. Converging evidence in fact suggests that we are close to the point of achieving this goal. As a consequence the transdiagnostic approach is gaining adherents in many areas, including neuropsychiatry (Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2018; Kas et al., 2007). Amongst these an industry consortium came together in 2014 and working *through* the Innovative Medicine Initiative (IMI) to develop a call based on the emergence of the improved ability to integrate imaging, electrophysiological, cognitive, genetic and real world parameters. This advent being viewed as an opportunity to bring a quantitative biological approach to the classification and understanding of this complex area. In particular, the call looked to determine whether similar symptomatologies, that are assumed to result from different pathological processes, could be dissociated using quantitative parameters. The identification of homogeneous subgroups of subjects sharing similar pathophysiological mechanisms would then facilitate the rejuvenation of discovery of innovative treatments. Further, it would also offer improved stratification of patients, providing improved alignment of the right drug to the right patient, as well as offering more rational clinical trial designs. Finally, this would in turn influence regulatory processes (Tome and Isaac, 2018 in this issue). From an academic perspective a biologically based clinical understanding also offers dramatic improvements in our ability to effectively reverse translate into the preclinical milieu.

The PRISM project (Psychiatric Ratings using Intermediate Stratified Markers), which developed from this call, has taken the theme of Social Withdrawal as the symptomatic dimension. While schizophrenia and Alzheimer's dementia provide the two differing pathologies which share this transdiagnostic symptomatology (https://prism-project.eu). In view of this symptomatic dimension, William Carpenter has provided a commentary manuscript for this special issue focusing on clinical concepts and the relevance of social engagement in psychopathology (Carpenter, 2017 in this issue).

The PRISM project aims to provide new classification tools, based primarily on quantitative biological parameters, focusing on this psychiatric domain common to these two disorders. This classification will be based on a deep phenotyping assessment of newly recruited subjects covering social withdrawal, attention, sensory processing, and working memory utilising digital, brain imaging, EEG and epigenetic biomarkers. In addition, a cross-disorder genome-wide genetic analysis will be performed in the largest worldwide available cohorts of patients. The aim being to identify shared genetic factors related to the common social withdrawal symptoms in these disorders. Furthermore, a preclinical platform will be implemented *to allow back translation* from human findings into rodents. This will facilitate studies designed to deepen our understanding of the neurobiology of these disorders. For example, as was addressed by Hornix et al. in this issue, studies on the combined analyses of neural circuit development and functioning will become necessary to expand our understanding of sensory processing and behavioural deficits that are relevant across the neuropsychiatric spectrum (Hornix et al., 2018 in this issue).

The manuscripts presented in this special issue review the pertinent literature and detail the PRISM concept from a variety of perspectives. The first paper (Kas et al in this issue (Kas et al., 2017)) addresses the background to the arguments in favour of a quantitative as opposed to a purely symptomatic approach in this area, the potential benefits if successful, and a broad brush outline as to how it is planned to achieve this goal. Specifically, this involved identifying, what turned out to be, four key areas for analysis. Porcelli and colleagues (Porcelli et al., 2018 in this issue) then lay out a comprehensive account of the current understanding of the neurobiology of social withdrawal that provides the

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foundation for the rest of the project. The innovative nature of this review is to combine existing evidence about neurobiology of social withdrawal in a way that makes clear how its determinants are, at least in part, independent from the clinical diagnosis of the subject. Moreover, determinants have been studied in previous human and animal studies but never combined in a unitary interrelated mechanism of action, which is presented in the paper. This model will constitute the working hypothesis to be tested within the project. From these starting points the structure of the clinical recruitment work was devised based upon an assessment of four key areas of research within the clinical study protocol (Bilderbeck in this issue (Bilderbeck et al., 2018)). These four areas are: social withdrawal itself (Van der Wee, et al in this issue (van der Wee et al., 2018)), sensory processing (Danjou, et al in this issue (Danjou et al., 2018)), as well as attention and working memory (Gilmour et al. in this issue). Furthermore, the potential for back translation of human findings using homologous paradigms in rodents is then reviewed in detail (Peleh et al. in this issue). These areas also share the key attribute that we believe they are robust and deliverable within the practical constraints of the resources available to the project. There are though other areas that have transdiagnostic relevance. A good example of this is sleep disturbance. Winsky-Sommerer et al., aware of the PRISM initiative, have taken the transdiagnostic perspective to review whether sleep; its quality, timing and structure, could be another rich vein to explore if certain technical challenges can be addressed (Winsky-Sommerer et al., 2018 in this issue).

The material included in this issue, it is hoped, will therefore inform the reader about the background and evidence of a potentially fruitful improvement in the understanding of neuropsychiatric disorders based on quantitative biological parameters. The ultimate goal being more effective clinical and pre-clinical research and drug discovery. Further, should the project prove fruitful our need to challenge the literature across traditional classifications will become vital. These reviews will therefore provide a template for this novel perspective while also retaining a pragmatic realism derived from the technical challenges of such transdiagnostic approaches.

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