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Precision Psychiatry Meets Network Medicine: Network Psychiatry

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Psychiatric medicine is now advancing from solely descriptive disease classification towards a biologically-based taxonomy. This evolution is more protracted than for other branches of medicine, given the complexity of the neural systems that underlie human mental function and the challenge of characterizing psychiatric phenotypes objectively and quantitatively. The ultimate goal of this exercise is to describe the mechanistic and phenotypic variability within and across traditional diagnostic boundaries in a manner that can identify risk and resilience factors, provide early detection, predict clinical outcome, and specify targets for trajectory-altering therapeutics and prevention.

The American Psychiatric Association's DSM classification has been helpful in this regard, standardizing the assessment of symptoms and syndromes in a multi-factorial bio-psycho-social context. In addition, the National Institute of Mental Health's Research Domain Criteria (RDoC) emphasize a move toward the study of intermediate phenotypes (endophenotypes, *vide infra*). While helpful, as implemented in RDoC, the characterization of these endophenotypes may be too limited and less integrative than ideal. The heterogeneity within traditional diagnoses and the co-morbidity among diagnoses requires a more multi-dimensional molecular approach.

Such an approach has been developed in the new field of network medicine (1). Network medicine combines systems biology and network science approaches in the analysis of genomic and pathophenotypic data, moving from correlation to pathway-based causation of disease. Advances in biomedical "omics" and informatics have now permitted a move from traditional organ system-based categorization toward a systems model of the pathobologies of specific diseases. Analyzing these large molecular genomic datasets has begun to transition from seeking simple associations of a molecule or genetic variant with a disease phenotype to creating a complex network of relationships among these molecules based on their physical interactions or mechanistic ties from which much greater insight into causation and consequence can be derived. What emerges is a data-driven molecular interactome that comprises subsets of overlapping biologically and clinically relevant network disease modules, or subnetworks of locally interacting pathways underlying a given disease, as we have recently demonstrated (2). The identification of these modules allows a mapping of underlying mechanistic pathways that drive pathobiology, and may cross conventional disease boundaries (2). It also allows the identification of integrated dynamics

of physiological adaptation (3), environmental effects, and drug effects. Essentially, network medicine represents the next stage of precision medicine, illuminating the true functional interactions among the multifactorial elements of human disease expression and treatment.

The value of this approach has first been demonstrated in internal medicine. For example, common endophenotypes governing all human diseases comprise unique modules within the interactome—the inflammasome, the thrombosome, and the fibrosome—which overlap with each other as a consequence of common pathways and which overlap with the great majority of disease modules, or clusters of interacting molecular mediators of a disease discretely localized within the interactome (4). The exposome (environmental exposures), social determinants of health (5), the microbiome, patient behavior, patient-generated or passive sensor data, and electronic medical record data can also be incorporated for a more complete understanding of disease phenotype, nuanced subtypes of which will be essential for the development of an effective precision medicine platform (6). Disease-disease relationships can be more fully understood and predicted in this context, based upon the degree of genetic or interactome module overlap. Asthma and celiac disease, for instance, overlap in disease space in the immune network for IgA production (2).

In psychiatry, the search for sensitive and specific biomarkers or high-effect genes has been difficult owing to polygenic, epigenetic, and psychobiological complexity. In this case, disease network approaches are better suited to developing “profiles of profiles” or “networks of networks” that may define clinically-relevant distinctions and overlaps. There has been some progress combining a number of measures, such as systems-level functional brain imaging (that identifies circuits and nodes of abnormal activity or connectivity, even in the absence of macroscopic “neurologic” lesions) and endocrinological, neuropsychological, behavioral, symptom-based, and functional genetic variant data. There has also been initial work incorporating metabolomics and lipidomics in these increasingly complex networks. Bringing all of these types and levels of analysis, and more, together into computationally and statistically-intensive, large-scale models is an important next step.

In fact, some preliminary disease network databases and models are currently being developed that point to the potential for this network approach to place psychiatric diseases within broader disease networks. One can imagine an increasingly detailed biological understanding that can recognize certain cases of co-occuring diabetes, depression, and coronary artery disease as a single pathophysiological entity involving inflammation and expressing itself with organ/tissue-specific phenotypic manifestations involving the pancreas, brain, and vasculature (7). Deeper immunogenomics could then bring greater specificity regarding the particular components of the immune system involved in the context of each organ system. This approach moves beyond a traditional understanding of co-morbidity, and may facilitate the identification of novel, parsimonious, mechanism-based treatments, with attention paid to the tissue-specificity of pathophenotypes and its molecular context.

It is worth noting that neurological disorders likely represent a special case in their relationship with psychiatric disorders. In addition to any shared brain pathophysiological processes, one needs to take into account the final common brain pathways that may be

affected and mediate specific functional deficits, excesses, or disruptions in perception, cognition, emotion, and behavior with overlapping phenotypic expression across neurological and psychiatric domains (e.g., psychosis with anterior medial temporal lobe seizures; or anterior medial temporal lobe hyperactivity noted in schizophrenic psychosis).

For the primary psychiatric disorders, there is the prospect of a biologically-based Venn diagram with gradients along a number of clinical dimensions. The construction of this diagram will allow the stratification and sub-typing of clinical conditions, and a greater understanding of permutations of symptoms (that may cross traditional diagnostic borders, such as mood and anxiety) in individual patients. Most importantly, it will provide profiles permitting a mechanism-based understanding and treatment of a single patient's illness, and the factors that affect it. Achieving this goal will take some time given the complexity of objective pathophenotypes underlying psychiatric diseases and their neural network representations. If sufficiently patient and persistent, however, this approach will ultimately lead to the creation of network psychiatry, and engage the clinical and research community's use of it to improve diagnostic and therapeutic outcomes among psychiatric patients. This is a laudable goal that will, if pursued with persistence and commitment, lead to the realization of true precision psychiatry and optimal care for patients.

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