American College of Neuropsychopharmacology

HOT TOPICS

Brain-based graph-theoretical predictive modeling: a novel approach to prospectively map psychiatric symptoms

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Predicting the trajectory of symptoms in individuals is one of the main goals of psychiatric research and can aid in treatment selection and prognosis. Predictive modeling, i.e., data-driven machine-learning models, is emerging as a promising approach for mapping clinical symptoms from functional MRI data at the individual level. There are several possible ways to define predictors from brain measurements. Recently, there has been growing interest in utilizing the brain's functional connectome, i.e., the structure and organization of the brain's functional network, for prediction. One well-established method is the connectome-based predictive modeling (CPM) [1], which uses a summary score of functional connections to predict a given phenotype and has been increasingly used to model clinical conditions, including substance use disorders [2].

A key challenge in predictive modeling of clinical symptoms is the limited sample sizes of brain imaging datasets, typically less than a few hundred individuals. To overcome this limitation, an innovative meta-matching approach has been recently proposed [3]. Meta-matching exploits the correlations between related behavioral/clinical phenotypes to translate predictive models from large-scale to small-scale studies, thus improving prediction accuracy and reproducibility.

To date, however, most predictive models, including the above, rely on functional connections, i.e., the level of synchronization between pairs of brain regions. As a complex system, the brain is highly integrative, comprising dynamic, multiscale, and efficient communication pathways between its elements. This structure leads to emergent properties, i.e., novel features that can only be observed at the network level when multiple elements interact [4]. Elements of a complex network function differently as part of the network than they would on their own. Some known examples include the "v" shape of bird flocks and the complex functioning of ant colonies. Accordingly, methods focused on pairwise relationships (e.g., functional connections) cannot truly capture the brain's network organization and its collective behavior. Embracing the

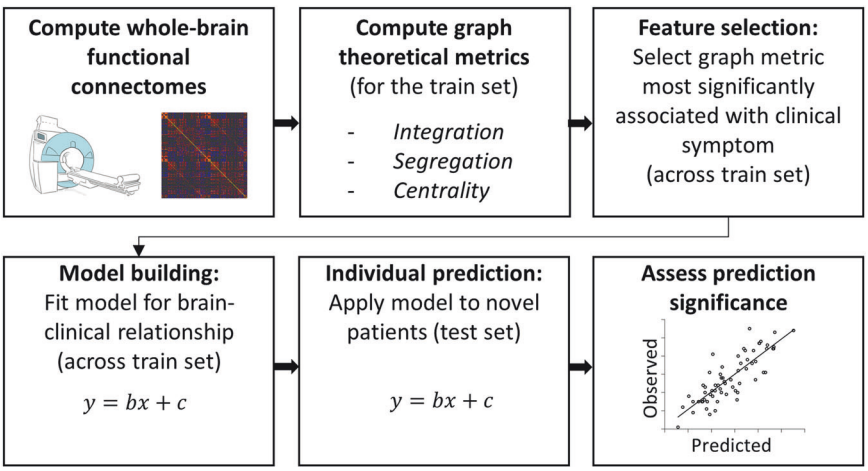

Fig. 1 The brain-based graph-theoretical predictive modeling (GPM) for symptom prediction. The GPM includes the following steps within a cross-validation framework: (i) computing functional connectomes; (ii) calculating graph-theoretical metrics; (iii) selecting the graph metric most strongly associated with the clinical symptom; (iv) model building: mapping between the graph metric and clinical symptom; (v) prediction for unseen data. Steps i-iv are done on the train set and step v is done on the test set (adapted from [6] with permission from the publisher).

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brain's network-level complexity through appropriate mathematical tools can greatly benefit our understanding of mental processes and, importantly, dysfunctions in clinical disorders. Indeed, there have been increasingly growing calls to integrate network science into neuroscience [5].

Following this rationale, we recently developed an innovative modeling framework, the brain-based graph-theoretical predictive modeling (GPM) [6] (Fig. 1). After computing a functional connectome, the GPM employs graph theory to define brain predictors. Graph theory is a branch of network science that describes the organization principles of a network. It allows to quantify processes of integration, segregation, and centrality, across the entire brain and for a given region/network [5]. The GPM leverages these network properties to predict clinical symptoms. We applied the GPM to map transdiagnostic symptoms prospectively in individuals with mood disorders. We found that efficiency and centrality of the reward circuit predicted symptoms of anhedonia, impulsivity, and (hypo)mania, cross-sectionally and at 6-month follow-up, and demonstrated generalization to an external validation sample.

Collectively, these studies highlight current advances and challenges in predictive modeling in psychiatry. Future work leveraging individual-level approaches to characterize brain function and organization more accurately, together with careful evaluations of model generalizability, may ultimately inform clinical decision-making.

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AUTHOR CONTRIBUTIONS

RD and DAP wrote the manuscript.

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COMPETING INTERESTS

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ADDITIONAL INFORMATION

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