Charting the Proteome Landscape in Major Psychiatric Disorders: From Biomarkers to Biological Pathways to Precise Drug Development

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SUBMISSION DETAILS

What is the Methodological Question Being Addressed? Which biological pathways are shared or unique in major psychiatric disorders? Can biological pathways inform precision drug development and pathway-guided clinical trials?

Introduction Precision Psychiatry is a recognized priority. Schizophrenia (SZ), Bipolar Disorder (BD), and Major Depressive Disorder (MDD) share many of their underlying biologies and there is a lack of biological validity in their diagnosis, which is a hindrance to developing diagnostic tests and discovering and developing new drugs that would be a perfect molecular fit to a given person. Proteomic studies have evolved the field by identifying several proteins that could be biomarkers in those disorders, however, their results have varied widely, and individual biomarkers have failed to advance diagnostics and therapeutics. Our goal is to leverage the broad variability among different studies and strengthen the knowledge provided by individual proteins by systematically interrogating the literature to uncover biological pathways with stronger biological meaning.

Methods This study is a systematic review of all proteomics studies in BD, MDD, and SZ compared to controls in serum or plasma. We extracted all differentially expressed proteins in BD, MDD, or SZ. Protein identification was made according to the UniProt Database. We mapped each protein to its corresponding gene. We then conducted over-representative analysis (ORA) and gene set enrichment analysis (GSEA) in WebGestalt to unveil which biological pathways were shared or unique to each disorder. Analyses were adjusted for multiple testing corrections.

Results We included 51 studies with 9,423 participants. 486 proteins were found altered in cases compared to controls (192 in SZ; 190 in BD; and 365 in MDD). The majority of the enriched pathways were shared among SZ, BD, and MDD. The top pathways in all three disorders were associated with the immune system and complement cascade. Other pathways shared among SZ, BD, and MDD were interleukin-12 signaling, MAPK1/MAPK3 signaling, PI3K-Akt Signaling, Toll-like Receptor Signaling, Activation of Matrix Metalloproteinases, Class A/1 (Rhodopsin-like receptors), GPCR downstream signaling, Advanced glycosylation end-product receptor signaling, JAK-STAT signaling, and Regulation of Insulin-like Growth Factor (IGF) transport. Pathways shared between SZ and BD were integrin cell-surface interactions and syndecan interactions. Shared between BD and MDD were the NRF2 pathway, signaling by EGFR, and the Ras signaling pathway. Unique to SZ were interleukin receptor SHC signaling and TFAP2 (AP-2) family regulation of growth factors; unique to MDD were oncostatin M signaling, ECM-receptor interaction, plasminogen activating cascade, and PPAR signaling pathway.

Conclusion We curated an ensemble knowledge of 486 altered serum proteins in BD, MDD, and SZ and uncovered their biological pathways. Alterations in pathways related to immune-inflammation

were pervasive and transdiagnostic. The immunoinflammatory response, as assessed in peripheral blood, is a shared mechanism across SZ, BD, and MDD, which might imply that the periphery is an unspecific representation of a mechanism placed in the brain and probably a secondary phenomenon to a primarily central origin; it also implies that the biological boundaries among SZ, BD, and MDD mostly do not resemble current nosological categories and need to be completely redefined by the identification of new sub-types. Future drug development for SZ, BD, and MDD could target those identified pathways and be tested in transdiagnostic clinical trials guided by the specific biological pathways altered in a particular person.

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