Proteomic associations across neuropsychiatric conditions

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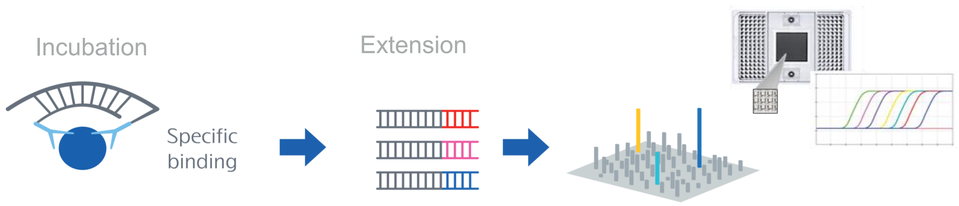
Introduction

The UK Biobank Pharma Proteomics Project provides a large-scale resource for studying links between circulating proteins, genetics, and disease risk. Plasma proteomic data from UK Biobank have previously been used to identify associations with genetic variation and incident disease (1-5). Here, we focus on proteomic associations across selected neuropsychiatric conditions, aiming to identify proteins associated with future disease risk, compare shared and disease-specific patterns, and highlight candidate biomarkers relevant to neurodegeneration, neurological dysfunction, psychiatric disease, and addiction.

Materials and methods

In this data story, we analyzed UK Biobank Olink™ Explore 3072 summary statistics for selected neuropsychiatric conditions, building on the Olink UK Biobank Data Story: Proteomics of Disease Risk, which is available through the open-access, web-based Olink Insight. (6). The analysis demonstrates the value of Olink Explore 3072 data generated using the Proximity Extension Assay (PEA™) within the UK Biobank, which includes longitudinal measurements from more than 50,000 individuals. Protein–disease associations were estimated using Cox proportional hazards models, with time to event defined from baseline sampling to the first recorded diagnosis. Hazard ratios represent the change in disease risk per unit increase in NPX, adjusted for age, sex, BMI, and smoking status. To support biological interpretation, pathway enrichment analysis was performed using pre-ranked GSEA with Reactome gene sets.

Figure 1. Proximity Extension Assay (PEA) principle. Two matched antibodies, each labeled with unique DNA, oligonucleotides bind the target protein. When in proximity, the oligos hybridize and are extended, creating a DNA barcode proportional to protein concentration. After amplification, this signal is quantified via qPCR or next-generation sequencing.



Results

Figure 2. Disease-level overview of significant protein associations across neuropsychiatric conditions. The number of significant protein associations varied markedly across conditions, indicating substantial heterogeneity. Psychiatric and behavioral phenotypes, such as anxiety disorder and tobacco use disorder, showed broad proteomic signatures, whereas neurodegenerative diseases, including Alzheimer's (AD) and Parkinson's disease (PD), were characterized by fewer, more specific associations.

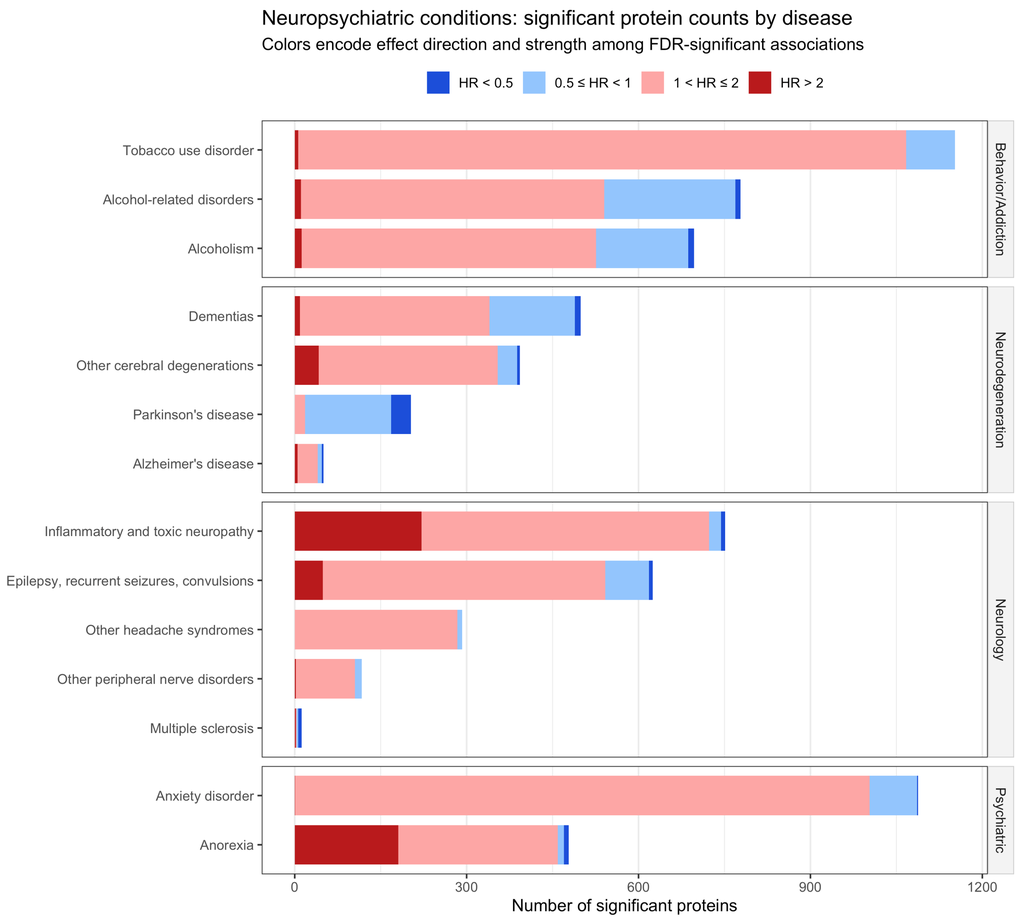
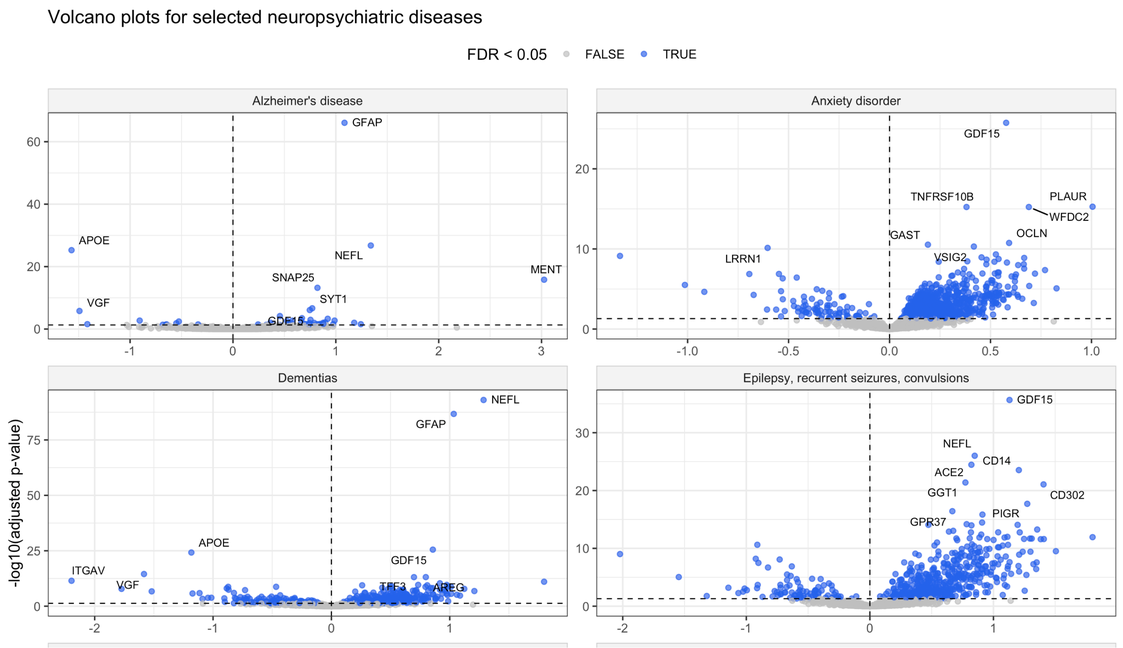


Figure 3. Volcano plots for selected neuropsychiatric diseases, revealing distinct patterns across diseases. Alzheimer's disease and related dementias showed concentrated signals driven by a limited set of highly significant proteins. Anxiety disorder also showed a wide proteomic profile, potentially reflecting systemic processes such as stress or inflammation.



Results

Figure 4. Cross-disease heatmap of signed proteomic association scores across selected neuropsychiatric conditions. The heatmap highlights both shared proteomic signals across multiple neuropsychiatric conditions and disease-group-specific patterns, with prominent positive signals observed for NEFL, CHI3L1, and GDF15 in several neurodegenerative, neurological, and addition-related phenotypes. Importantly, the heatmap also demonstrated that the same protein could show different effect directions across diseases, underlining the value of a signed score that captures both statistical strength and HR direction.

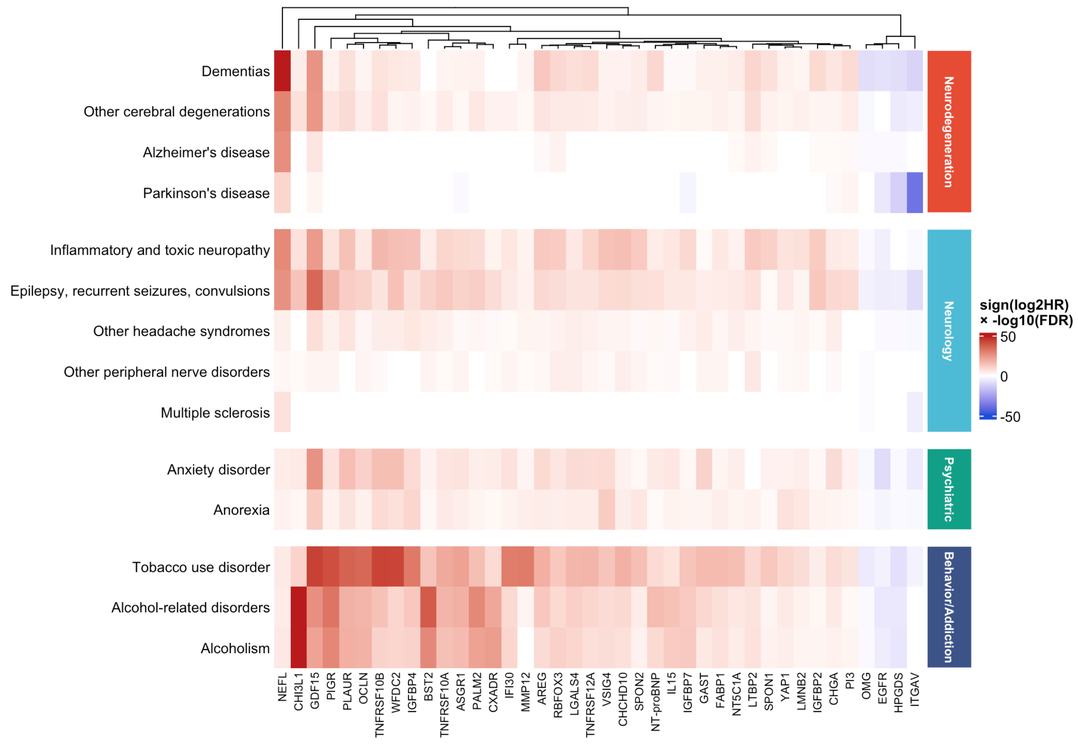
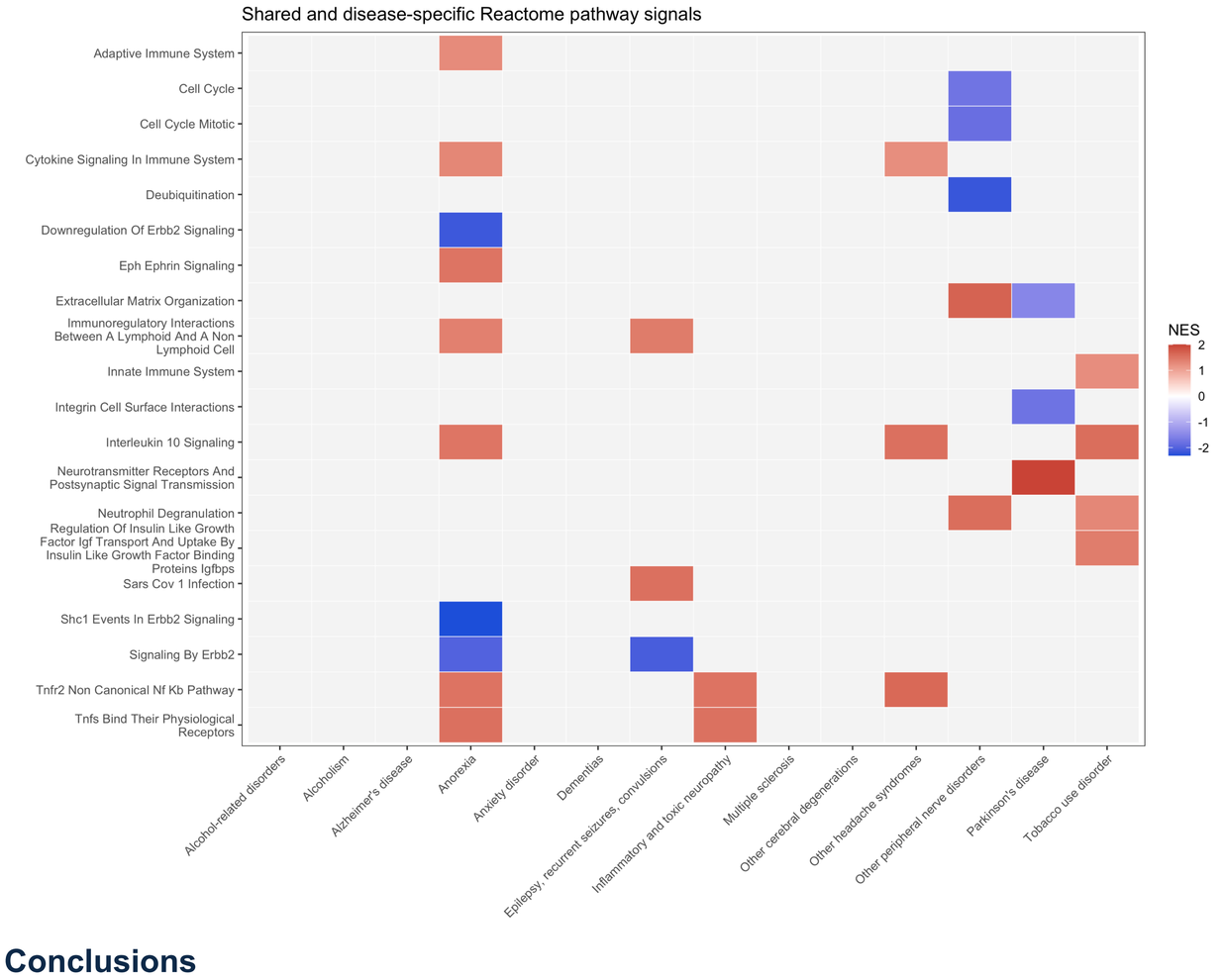


Figure 5. Pathway-level overview of Reactome enrichment across neuropsychiatric conditions. GSEA provided complementary biological interpretation. Reactome pathways captured signals into specific mechanisms, including immune signaling, vesicle transport, extracellular matrix organization, and neuronal processes.



Conclusions

Proteomic association patterns vary substantially across neuropsychiatric conditions but also reveal meaningful overlap. Shared protein signals suggest common biological mechanisms, while disease-specific profiles highlight distinct pathophysiology. Reactome analyses adds a valuable pathway-level perspective, linking broad biological programs to more precise mechanistic pathways. Together, these findings provide a framework for prioritizing candidate biomarkers and guiding downstream validation in neuropsychiatric research.

References

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6. Olink UK Biobank Data Story: Proteomics of disease risk (https://insight.olink.com/olink-data/ukb-diseases)

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