Post-mortem molecular profiling of three psychiatric disorders reveals widespread dysregulation of cell-type associated transcripts and refined disease-related transcription changes

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Introduction

- Schizophrenia (SZ), bipolar disorder (BPD), and major depression disorder (MDD) are multisystemic disorders with complex etiology and are large sources of morbidity and mortality in the population. While clinically distinct, these disorders share many symptoms, suggesting potential common genetic etiology. While this is supported by recent large-scale genome-wide association studies, this overlap has not been fully characterized with functional genomic approaches.

- To assess gene expression changes associated with psychiatric disease, we (Pritzker Neuropsychiatric Disorders Research Consortium) performed RNA-seq on macrodissected postmortem tissues in four well-characterized cohorts of 24 patients each with SZ, BPD, MDD and controls (CTL). (9) We explored whether these samples could be reliably assigned to any putative subgroups. 

- Additionally, we conducted metabolic profiling in AnCg tissue from the same samples.

- RNA-seq results were validated in an independent cohort of 35 cases each of SZ, BPD, MDD and CTL. 

- We then performed consensus clustering on cingulate cortex samples from the Stanley Neuropsychology Consortium Integrative Database (SNCID) to fully characterize with functional genomic approaches.

- Metabolomic profiling in AnCg tissue from the same individuals total) across the anterior cingulate cortex (AnCg), dorsolateral prefrontal cortex (DLPFC), and nucleus accumbens (NAcc) regions. 

- By recent large-scale genome-wide association studies, this overlap has not been fully characterized with functional genomic approaches.

- We explored cell-type differences as driving a behavioral phenotype by assigning a panel of scalp-capsule dermal cells into the major neural, glial, and vascular cell-types in the brain (Danemars et al., PMAS 2015) and generating cell-type indices using the median normalized counts for each cell-type specific transcript set.

- Examining AnCg cell-type composition in the context of the patient clustering patterns, we found that the subset of SZ and BPD patients that cluster separately from CTLs is enriched for a subset of SZ and BPD patients.

- To explore further this relationship and bin samples in an unbiased manner, we performed consensus clustering on cingulate cortex samples.

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- Examining these clusters' cell-type composition in the context of the patient clustering patterns, we identified a subset of SZ and BPD patients that cluster separately from CTLs.

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