Immunological Biomarkers for MDD

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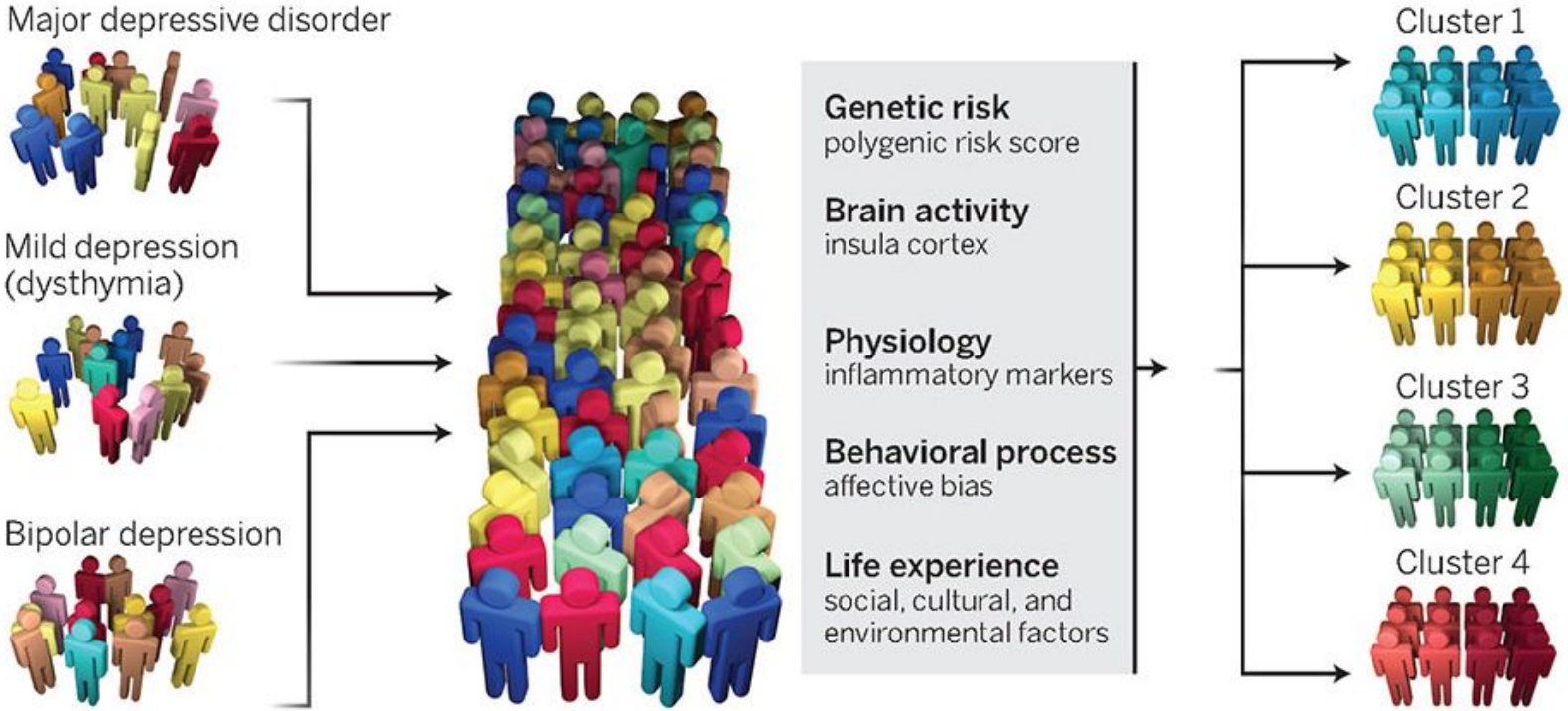
NIMH
National Institute
of Mental Health


RDoC
Research Domain Criteria Initiative

Promise of Precision Psychiatry



Insel, T. R., & Cuthbert, B. N. (2015). Brain disorders? Precisely. Science, 348(6234), 499-500.

Neuroimmune Hypothesis

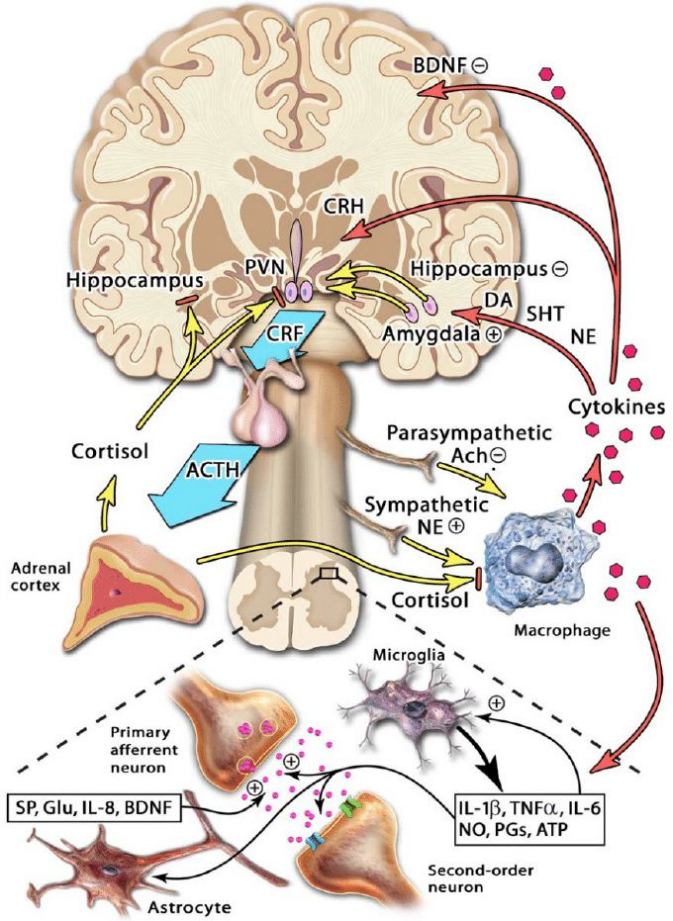
Chronic stress dysregulates

- HPA axis (impaired negative feedback)

- Immune function

Inflammation: Peripheral → Central

Dysregulated Reward & Threat Circuitry



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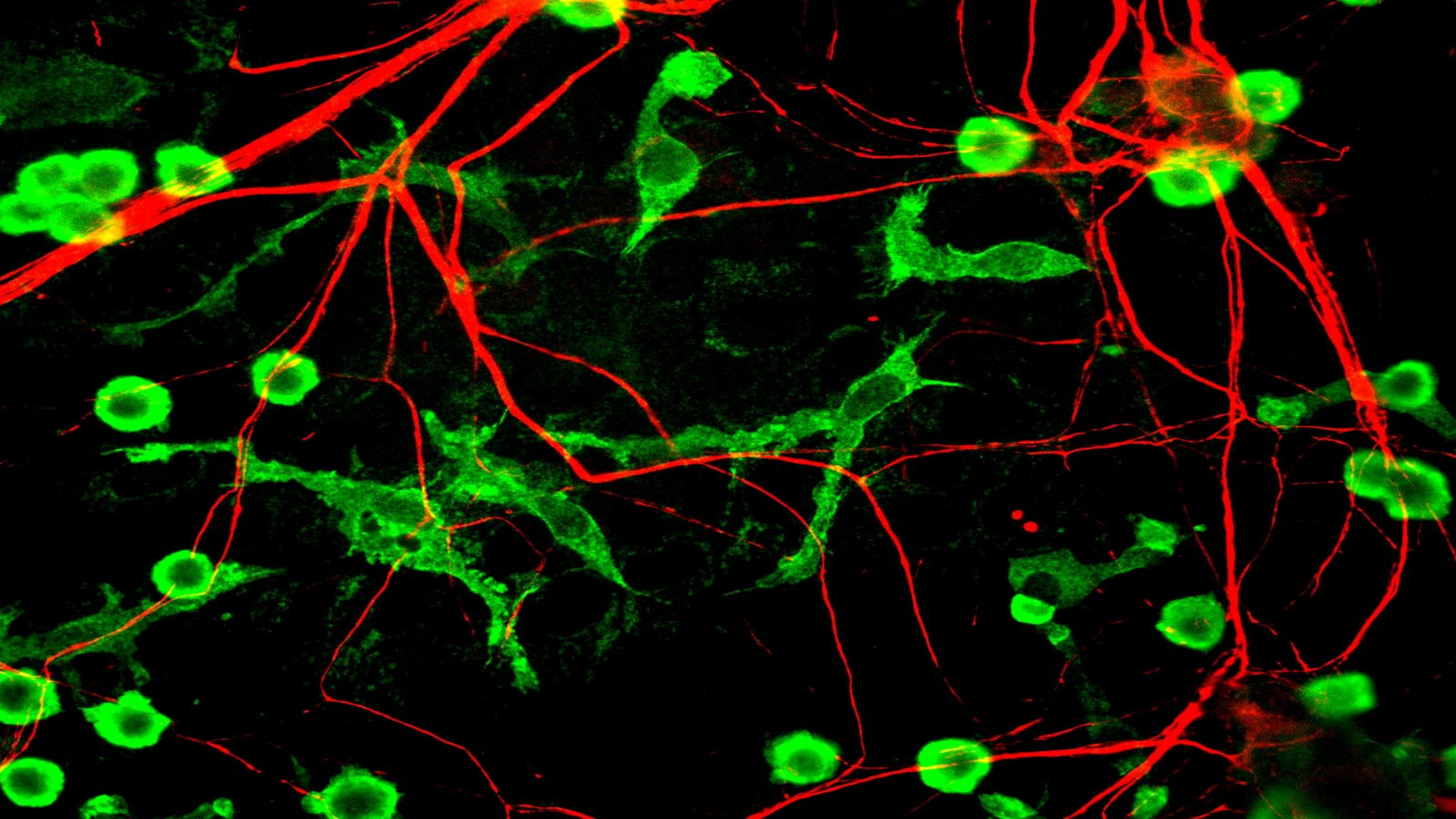

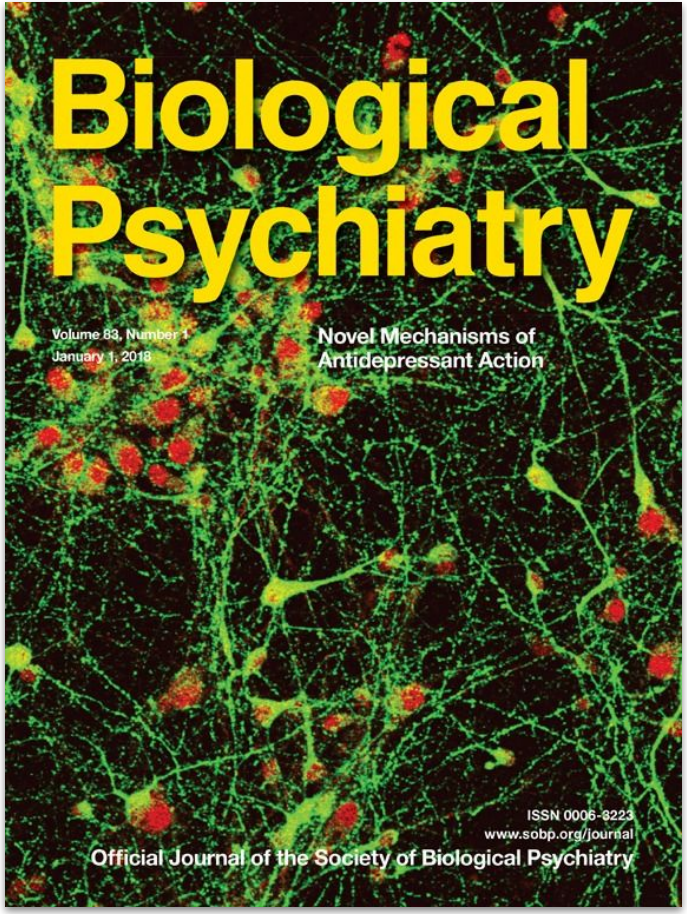

Replicable and Coupled Changes in Innate and Adaptive Immune Gene Expression in Two Case-Control Studies of Blood Microarrays in Major Depressive Disorder

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ABSTRACT

BACKGROUND: Peripheral inflammation is often associated with major depressive disorder (MDD), and immunological biomarkers of depression remain a focus of investigation.

METHODS: We used microarray data on whole blood from two independent case-control studies of MDD: the GlaxoSmithKline–High-Throughput Disease-specific target Identification Program [GSK-HiTDiP] study (113 patients and 57 healthy control subjects) and the Janssen–Brain Resource Company study (94 patients and 100 control subjects). Genome-wide differential gene expression analysis (18,863 probes) resulted in a p value for each gene in each study. A Bayesian method identified the largest p-value threshold (q = .025) associated with twice the number of genes differentially expressed in both studies compared with the number of coincidental case-control differences expected by chance.

RESULTS: A total of 165 genes were differentially expressed in both studies with concordant direction of fold change. The 90 genes overexpressed (or UP genes) in MDD were significantly enriched for immune response to infection, were concentrated in a module of the gene coexpression network associated with innate immunity, and included clusters of genes with correlated expression in monocytes, monocyte-derived dendritic cells, and neutrophils. In contrast, the 75 genes underexpressed (or DOWN genes) in MDD were associated with the adaptive immune response and included clusters of genes with correlated expression in T cells, natural killer cells, and erythroblasts. Consistently, the MDD patients with overexpression of UP genes also had underexpression of DOWN genes (correlation $>$ .70 in both studies).

CONCLUSIONS: MDD was replicably associated with proinflammatory activation of the peripheral innate immune system, coupled with relative inactivation of the adaptive immune system, indicating the potential of transcriptional biomarkers for immunological stratification of patients with depression.

Keywords: Affymetrix, Bayesian, Biomarker, Inflammation, Systems, Transcriptome

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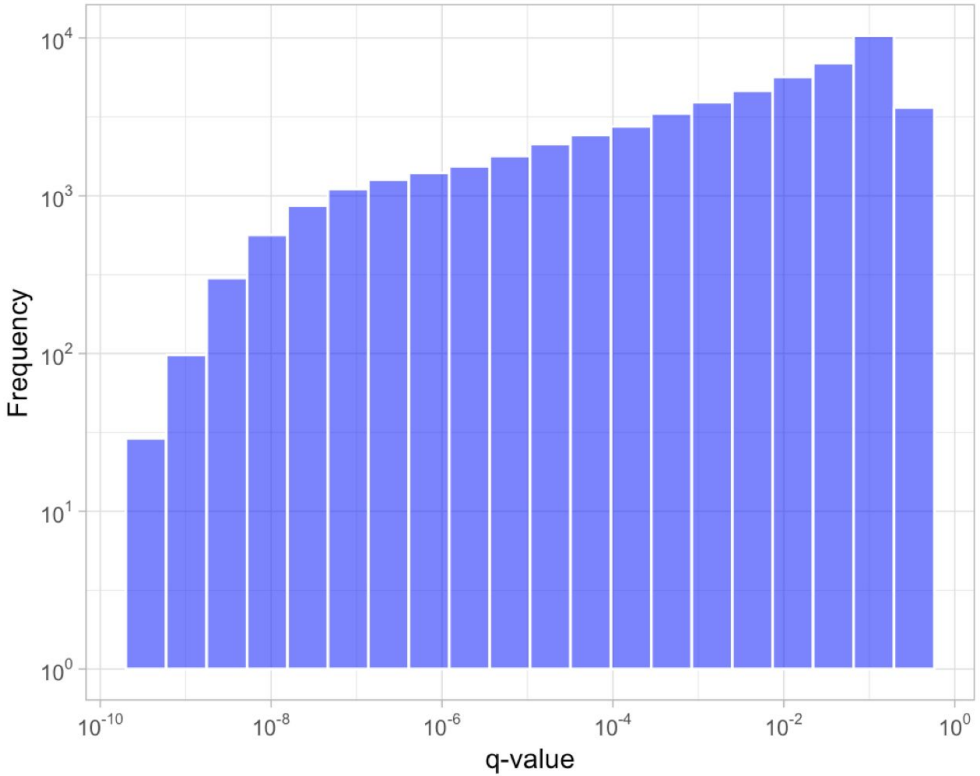
Differential Expression Analysis

Discover a panel of genes that significantly distinguish clinically depressed patients from healthy controls

q - value Distribution



54,676 gene probes

X

192 Participants (160 MDD, 30 Control)

p-value = P(observed data | true null)

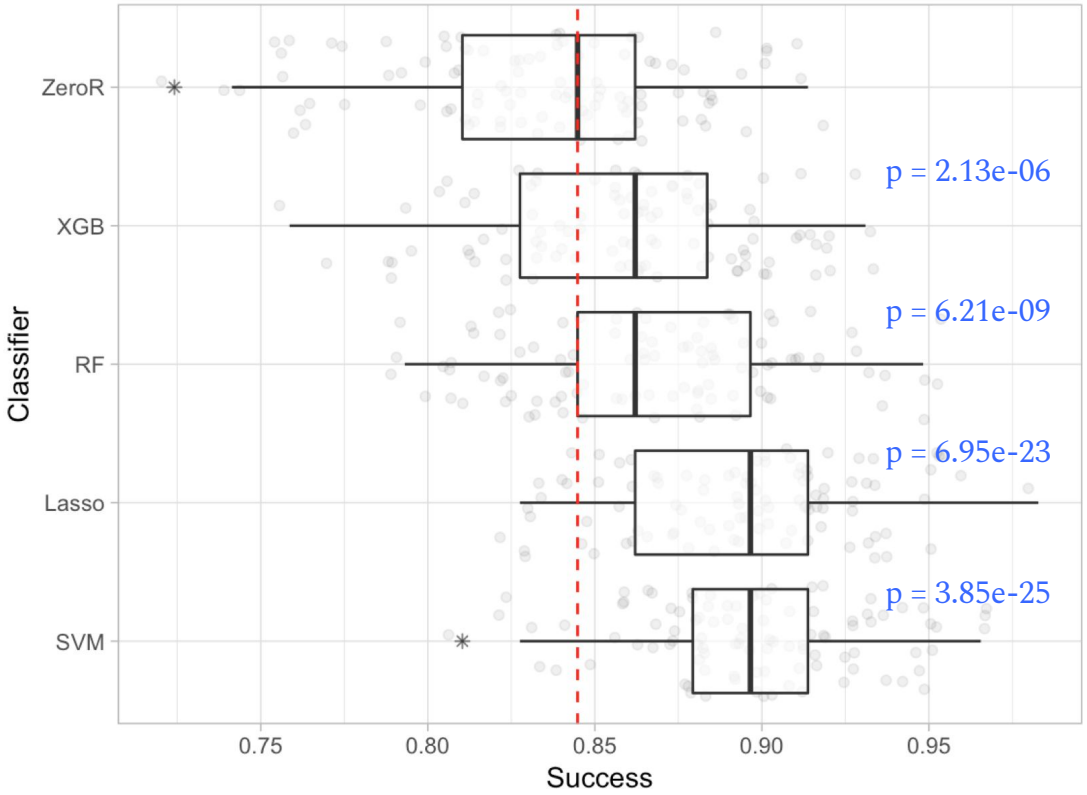
q-value = P(true null | observed data)

$$= \frac{\#\ false\ significant\ discoveries}{\#\ significant\ discoveries}$$

Patient Classification

Train predictive models to distinguish clinically depressed patients from healthy controls.

Binary Classifier Performance



Validation set approach: 70/30 split

Predictors: Top 133 probes by q-value

192 participants (160 MDD, 32 Control)

Models fit & tested 100 times each

two-sample t-test (unequal variance)

Next Steps

Patient Stratification

Dimension Reduction (PCA)

Immune Probe Characterization