Gene expression signatures of fluoxetine response: systematic review and meta-analyses

David G. Cooper, J. Paige Cowden, Parker A. Stanley, Jack T. Karbowski, Victoria S. Gaertig, Caiden J. Lukan, Caleb A. Class

Department of Pharmaceutical Sciences, College of Pharmacy and Health Sciences, Butler University

Some Fish Oil with your Fluoxetine?

Possibly practical results from a big bioinformatics project

Introduction

- Genomics (and other "omics") may help a provider select the best antidepressant for a patient.
- However, individual studies have struggled to identify genetic markers of response.

Generated with Leonardo.AI. Prompt: "An abstract visualization of the complex genetic and transcriptomic signatures associated with major depressive disorder"
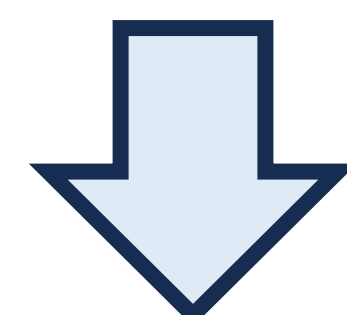
Objective: Synthesize gene expression studies to identify biological pathways distinguishing response to fluoxetine.
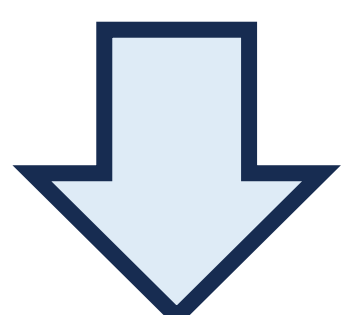
Systematic Review

Gene Expression Omnibus Database (>200,000 Datasets)
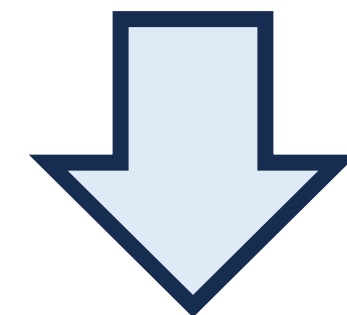
Keyword Search:
"fluoxetine" OR "SSRI" OR "selective serotonin reuptake inhibitor"

Filters:
Study Type = RNA-Seq or Microarray
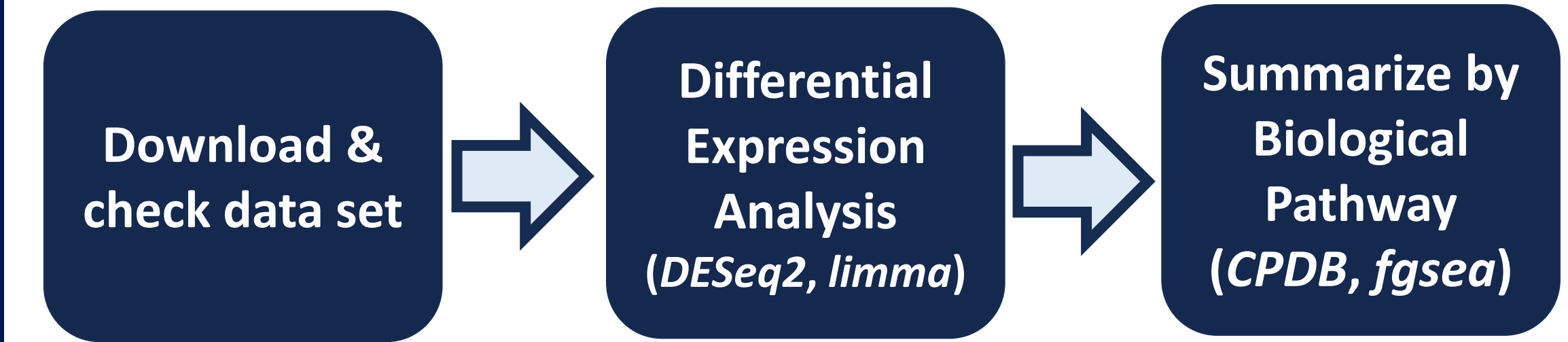Entry Type = Series (full dataset)
Organism = Human, Rat, or Mouse

74 Datasets Screened

Exclusion Criteria:
- Not Depression/Anxiety
- Not relevant tissue
- No fluoxetine treatment
- < 3 samples per group

20 Datasets Included

Subset of data providing clinical (human) or behavioral (mouse) **response determination**

Six datasets included in synthesis for fluoxetine response

| GEO Series ID	Platform	Organism	Tissue(s)	Stress Method / Diagnosis	Fluoxetine Treatment	Drug Response Determination
GSE83386	Microarray	Human	Lymphoblastoid cell lines	Major Depressive Disorder	3-weeks 0.5 µg/mL	Hamilton Depression Rating Scale
GSE28644	Microarray	Mouse	Cortex	N/A	3-weeks 18 mg/kg/day	Open-field test
GSE43261	Microarray	Mouse	Dorsal dentate gyrus, Ventral dentate gyrus	Corticosterone	>1-week 160 mg/L in drinking water	Novelty suppressed feeding, Forced swim test
GSE84183	Microarray	Mouse	Anterior cingulate cortex, Dentate gyrus	7-weeks unpredictable chronic mild stress	5-weeks 120 mg/L in drinking water	Coat state measurement
GSE84184	Microarray	Mouse	Whole blood	7-weeks unpredictable chronic mild stress	5-weeks 120 mg/L in drinking water	Coat state measurement
GSE202172	RNA-Seq	Mouse	S100a10 cortical cells	7-weeks single-housing	3-weeks 167 mg/L in drinking water	Homecage time spent in shelter zone

Systematic Re-Analysis

Download & check data set → **Differential Expression Analysis (_DESeq2, limma_)** → **Summarize by Biological Pathway (_CPDB, fgsea_)**

Meta-Analysis

We used three meta-analysis techniques to identify pathways with differential expression between responders and non-responders: in *any* study (Fisher), in *all* studies (Max-P), and in *half* of studies (Freq50).
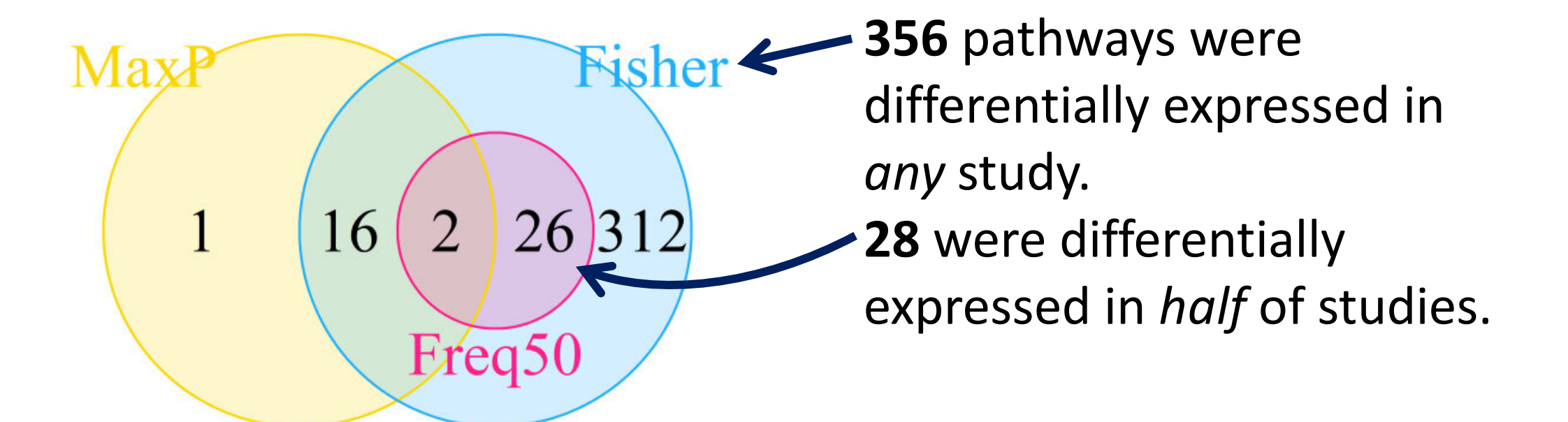
356 pathways were differentially expressed in *any* study.

28 were differentially expressed in *half* of studies.

19 pathways were *consistently* differentially expressed, including 10 immune pathways.

q-value: p-value adjusted for false discovery
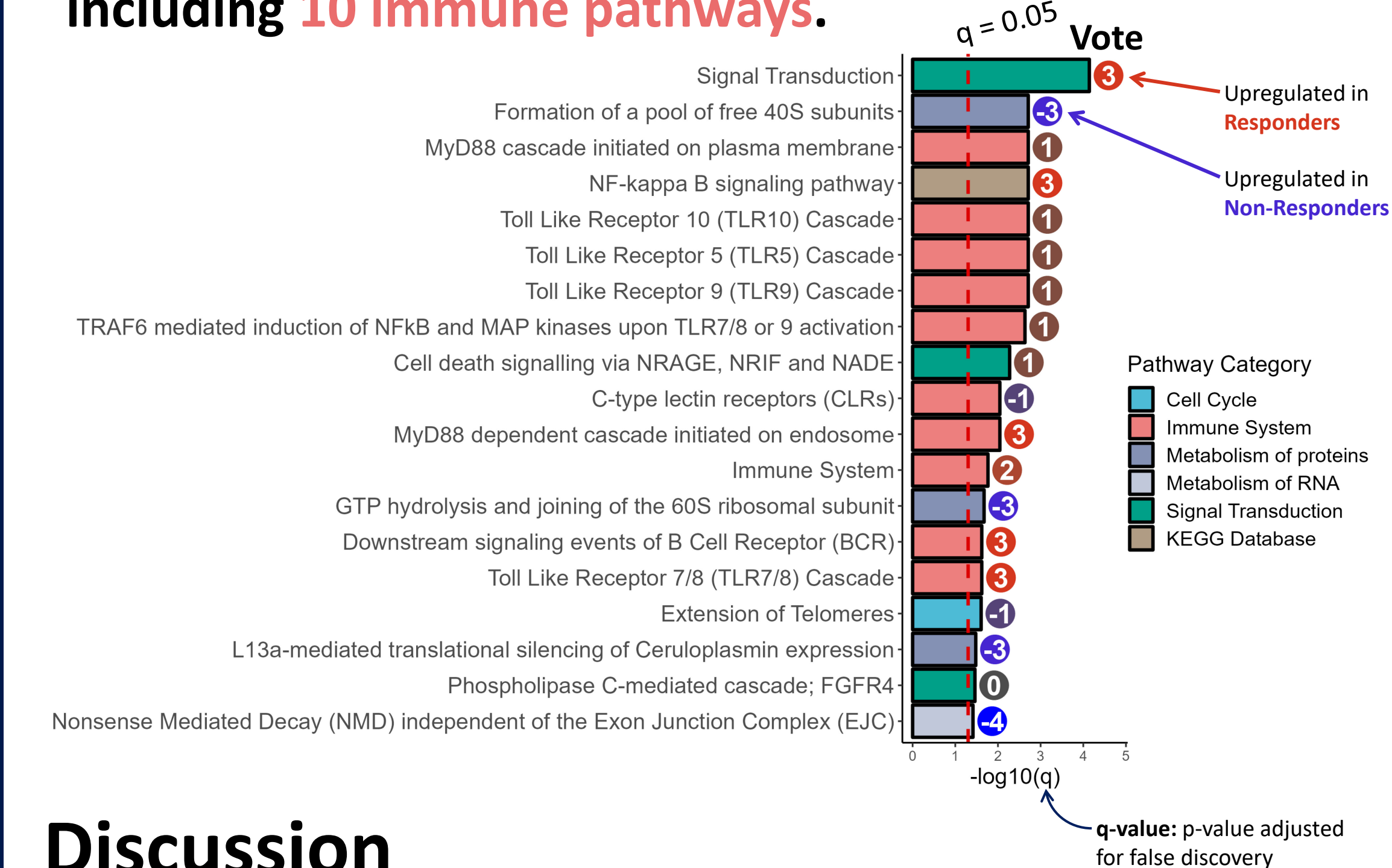
Discussion

- Multiple studies have implicated the immune system and inflammation in depression and antidepressant response.
- Integrating data from other 'omics levels and environmental factors will help us understand more about this heterogeneous disorder.

Funding