Sex-specific transcriptional signatures of depression

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Major Depressive Disorder (MDD)

- Chronic, recurrent disease of altered mood regulation

- ~19 million people affected each year in the US (Kessler, 2003)

- ~15% lifetime mortality due to suicide (Mann, 2003)

- Complex disease with many contributing genes that interact with environmental factors

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- Very few new pharmacological approaches in the last 50 years

Sex differences in depression

Differences in Incidence

- Females are 2x as likely to have a single episode, and 4x as likely to have recurrent MDD

Differences in Clinical Phenotypes

- Symptom number, severity, subjective distress: F > M

- Hyperphagia and hypersomnia: F > M

- Comorbid anxiety disorder: F > M

- Comorbid substance abuse: M > F
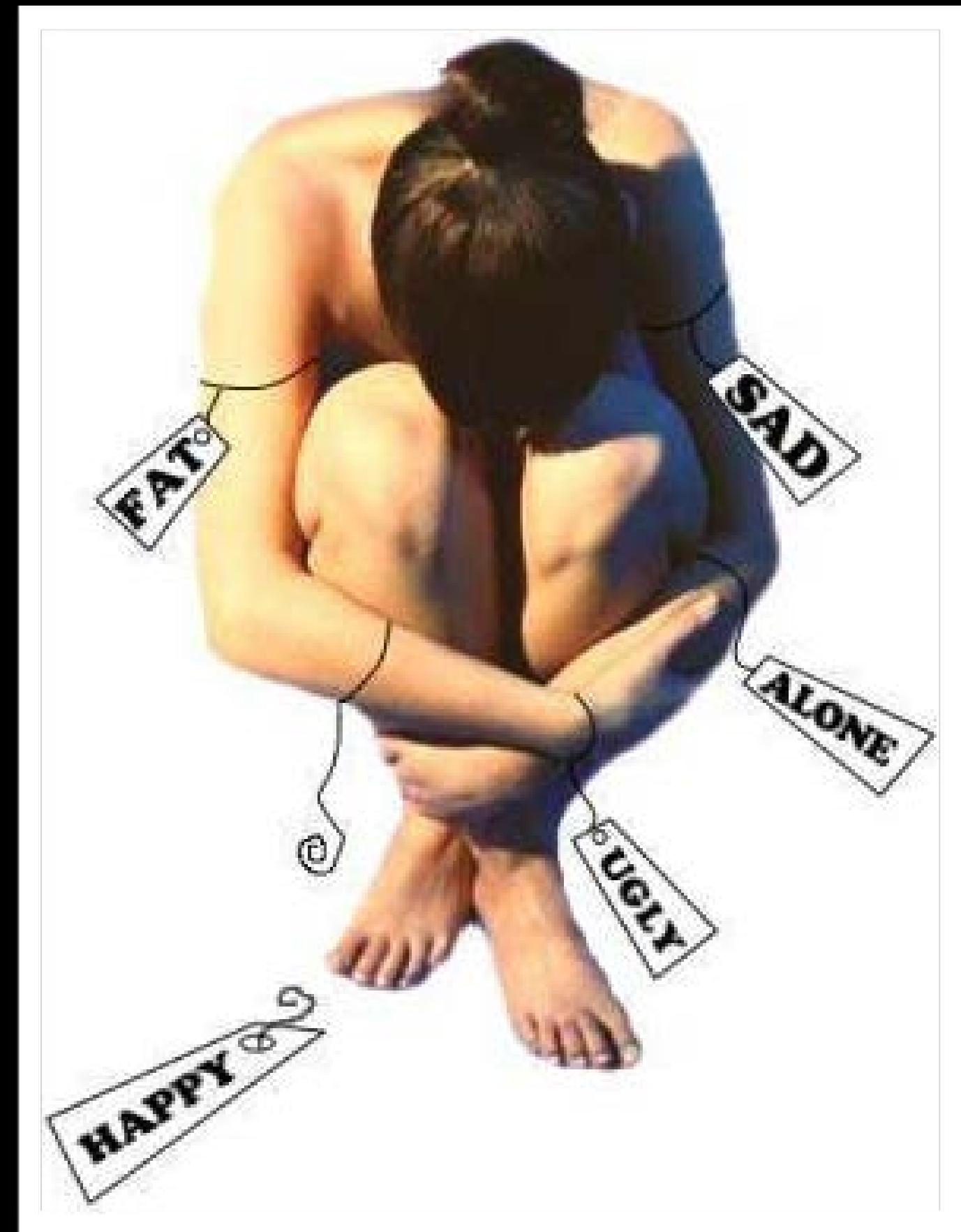
**Do these findings reflect sex differences in the biological pathways to MDD and/or sex-specific brain pathology?**

Could such pathways inform sex-specific treatment development?

Kornstein et al., 2000; Perugi et al., 1990; Angst and Dobler-Mikola, 1984; Frank et al., 1988; Young et al., 1990; Silverstein, 1999, Davis et al., 2005; Najt et al., 2011; Weissman and Klerman, 1977; Kessler et al., 1999; Kornstein et al., 1995; Davidson and Pelton, 1986

Molecular pathology in depression: men vs. women

- Hypothesis 1: Men and women have the same pathology, with potential modulation by sex-related factors.

  - Prediction 1: Similar molecular changes in the brains of men and women with MDD.

- Hypothesis 2: The pathology is different in men and women.

  - Prediction 2: Distinct molecular changes in the brains of men and women with MDD.

In either case, knowing the pathology can help us develop novel, possibly sex-specific treatments

Investigate sex differences in gene expression in mood-related brain circuitry

Ladouceur et al., 2015
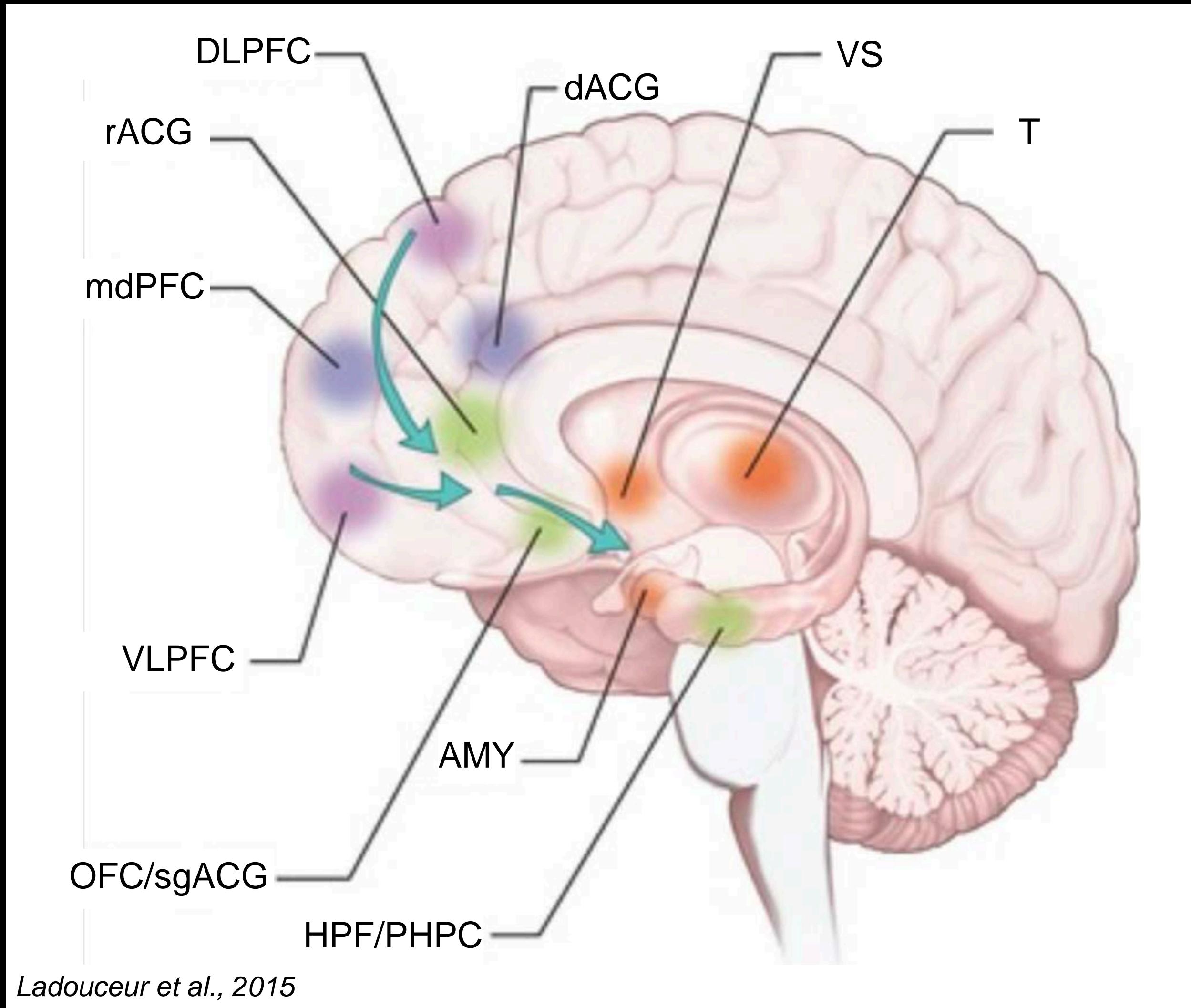
- Human postmortem brain studies: directly examine the diseased organ

Candidate gene vs. large-scale transcriptomics approaches

- **Candidate gene studies:** uncovered potential "hits" for MDD molecular alterations - e.g., GABA-, glutamate-, serotonin-, inflammation-related.

  - Presume that we already know the pathways that should be disrupted in MDD.

- **Unbiased large-scale transcriptomics (microarray, RNA-seq)**: data can be used for network-based approaches to identify key drivers of transcriptional patterns.

- Previous studies included only one sex or were not powered to detect sex differences.

  - Conclusions could: 1) be biased towards male-specific alterations; or 2) only detect alterations consistent between males and females.

First large-scale transcriptomics study assessing potential sex-specific MDD pathology

- Labonté et al., *Nature Medicine*, 2017 (Nestler Lab)

Labonté et al., 2017
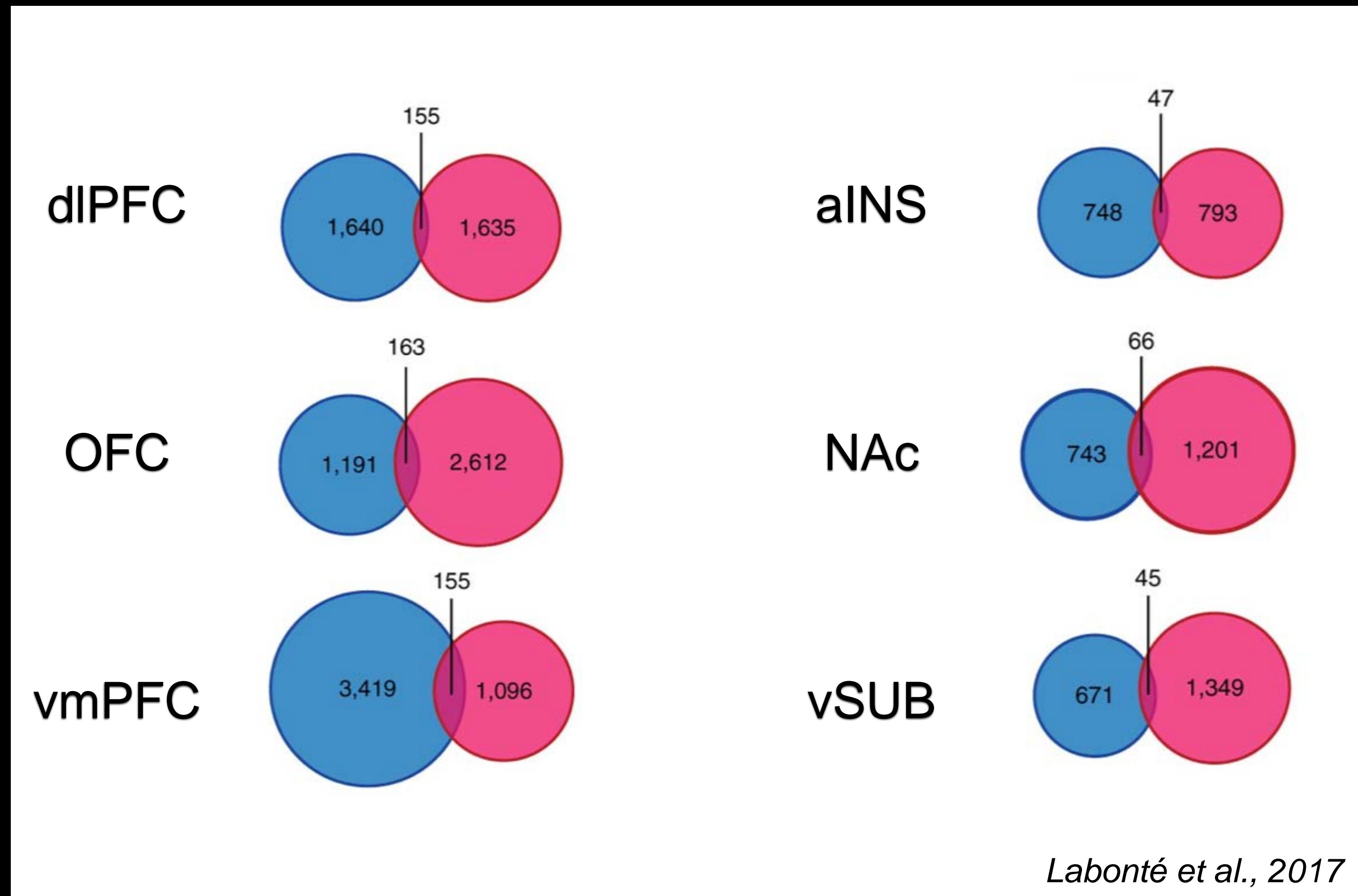
Network-based methods to identify potential upstream drivers of female vulnerability

Labonté et al., 2017
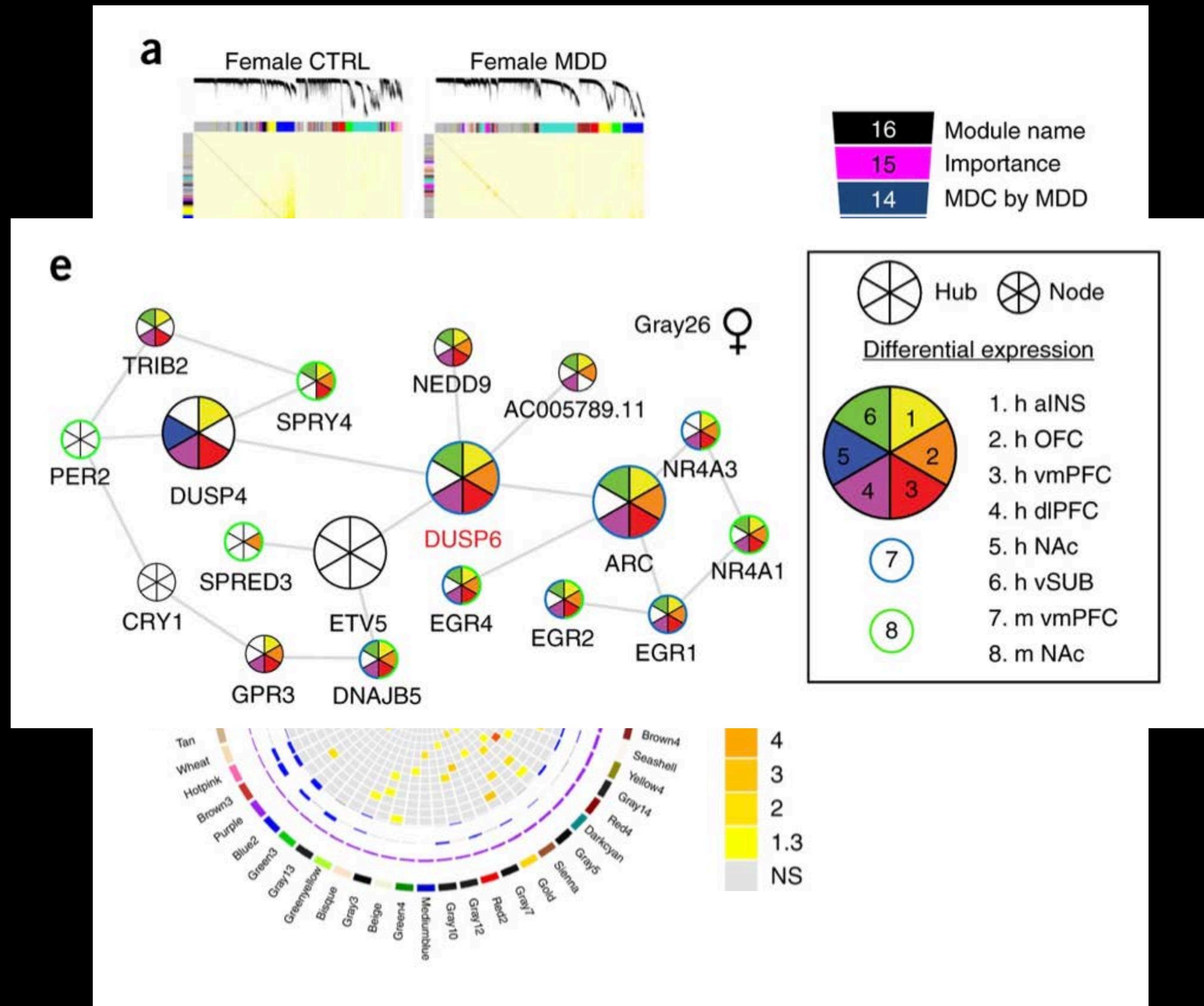
Experimental reduction of *Dusp6* in PFC of mice drives female-specific vulnerability to stress

Labonté et al., 2017
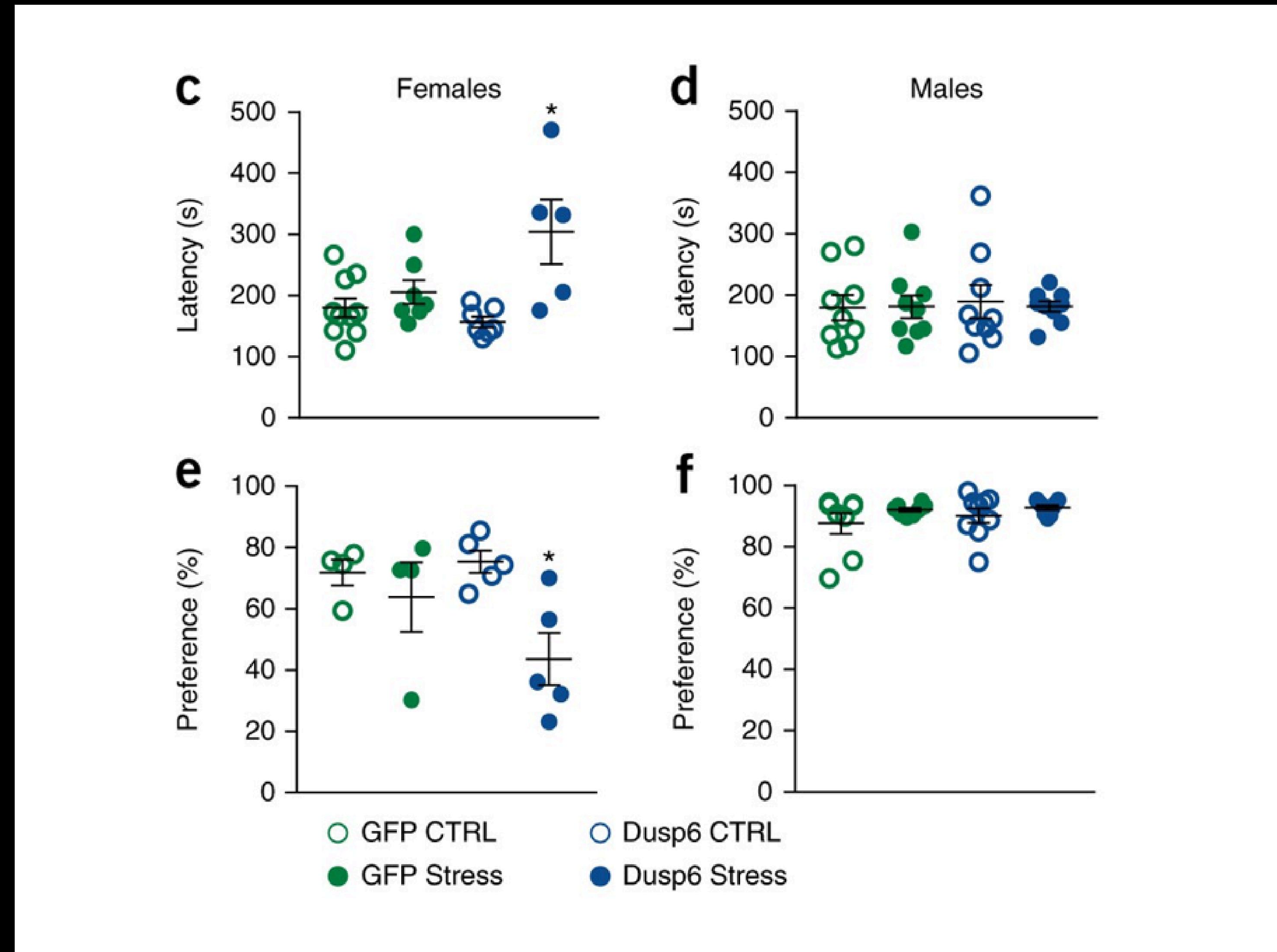
Distinct molecular signatures of MDD in men and women

Genes differentially expressed i ...

Men   Won...

155

1,640   1,635

163

1,191   2,612

155

3,419   1,096

633   73   8...

Consistent results across cohorts
collected from separate brain banks
- suggests "real" phenomenon

Labonté et al., 2017

Seney et al., Biol Psychiatry, 2018

Opposite direction of disease effect in men and women

Genes differentially expressed in MDD
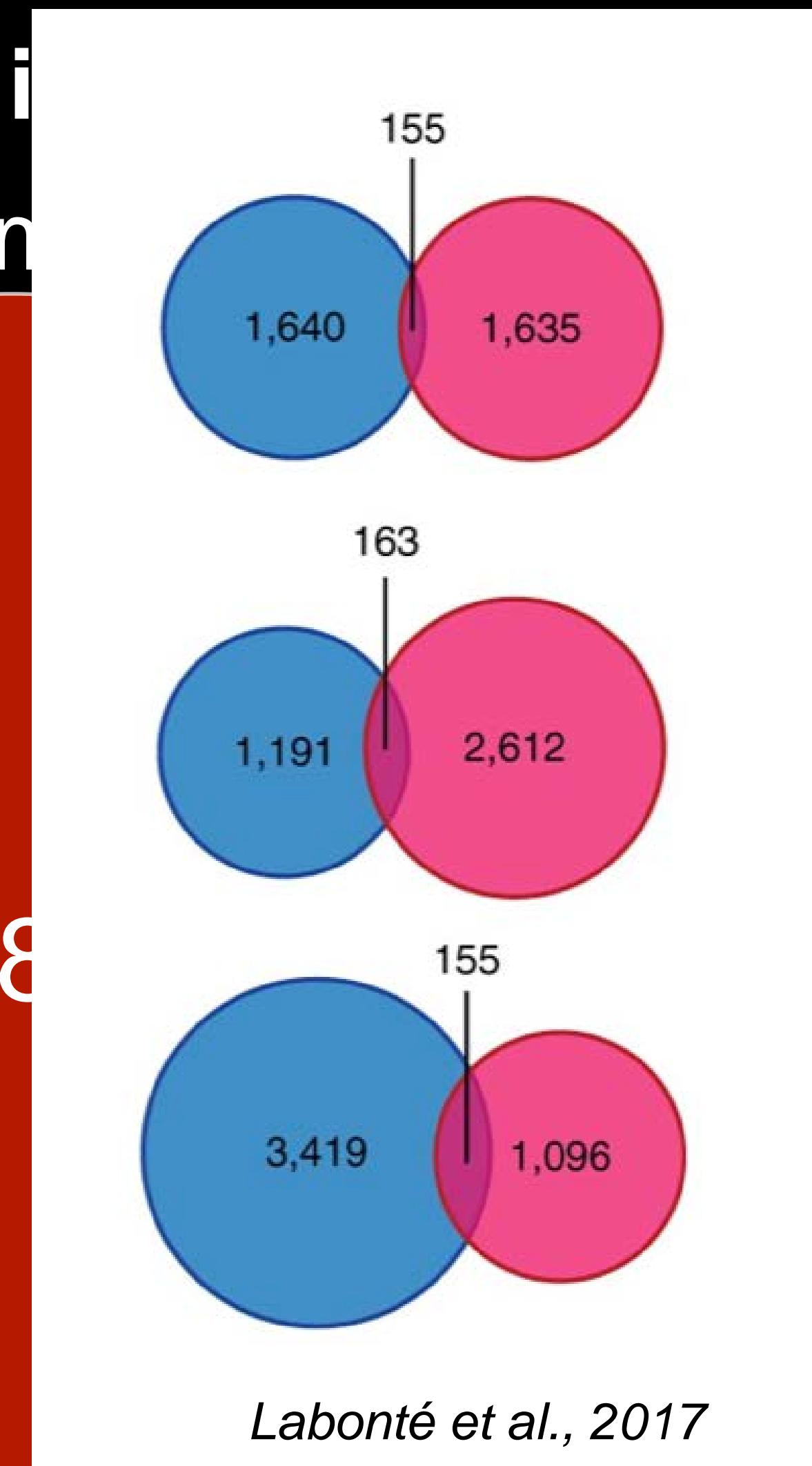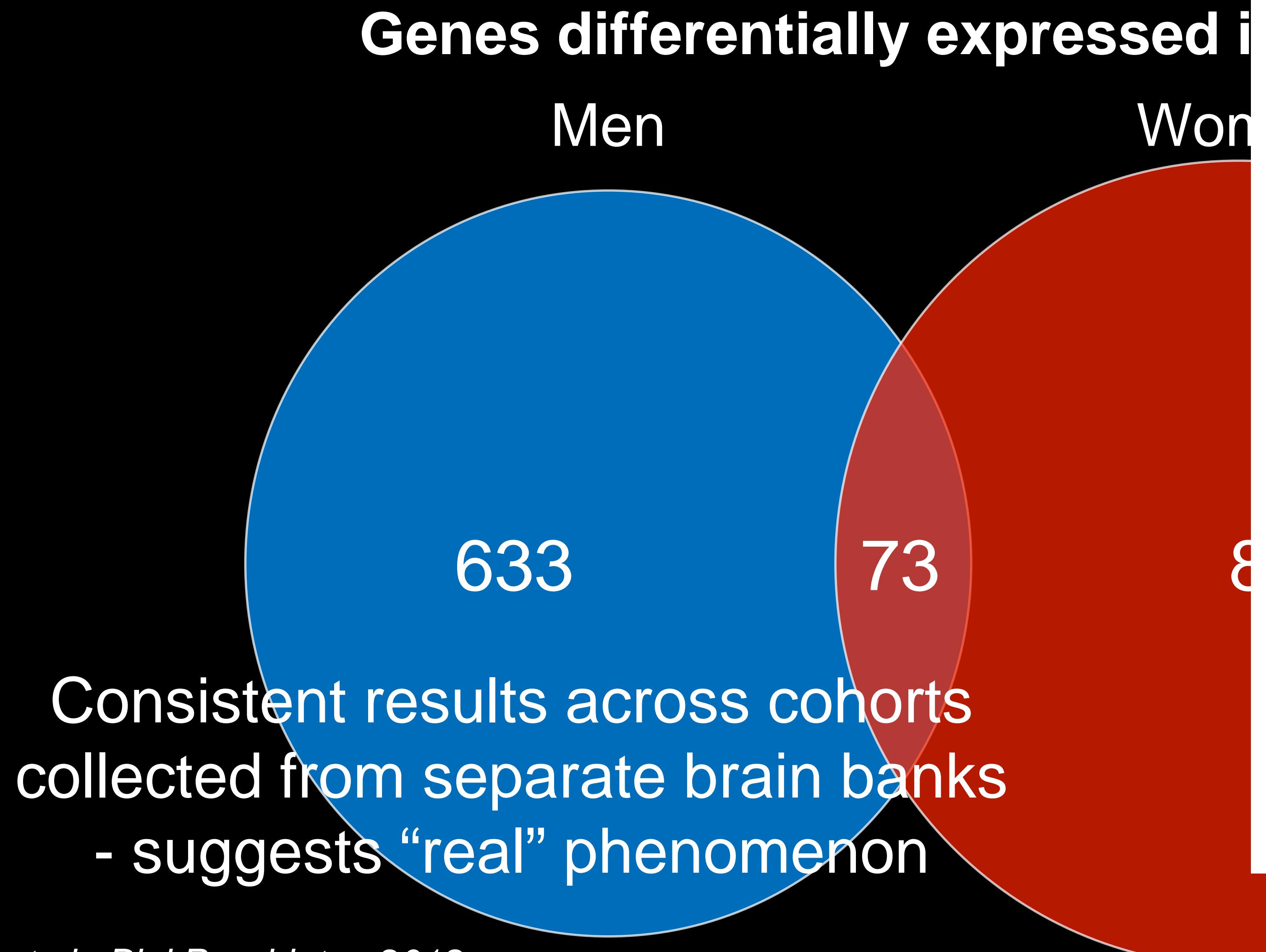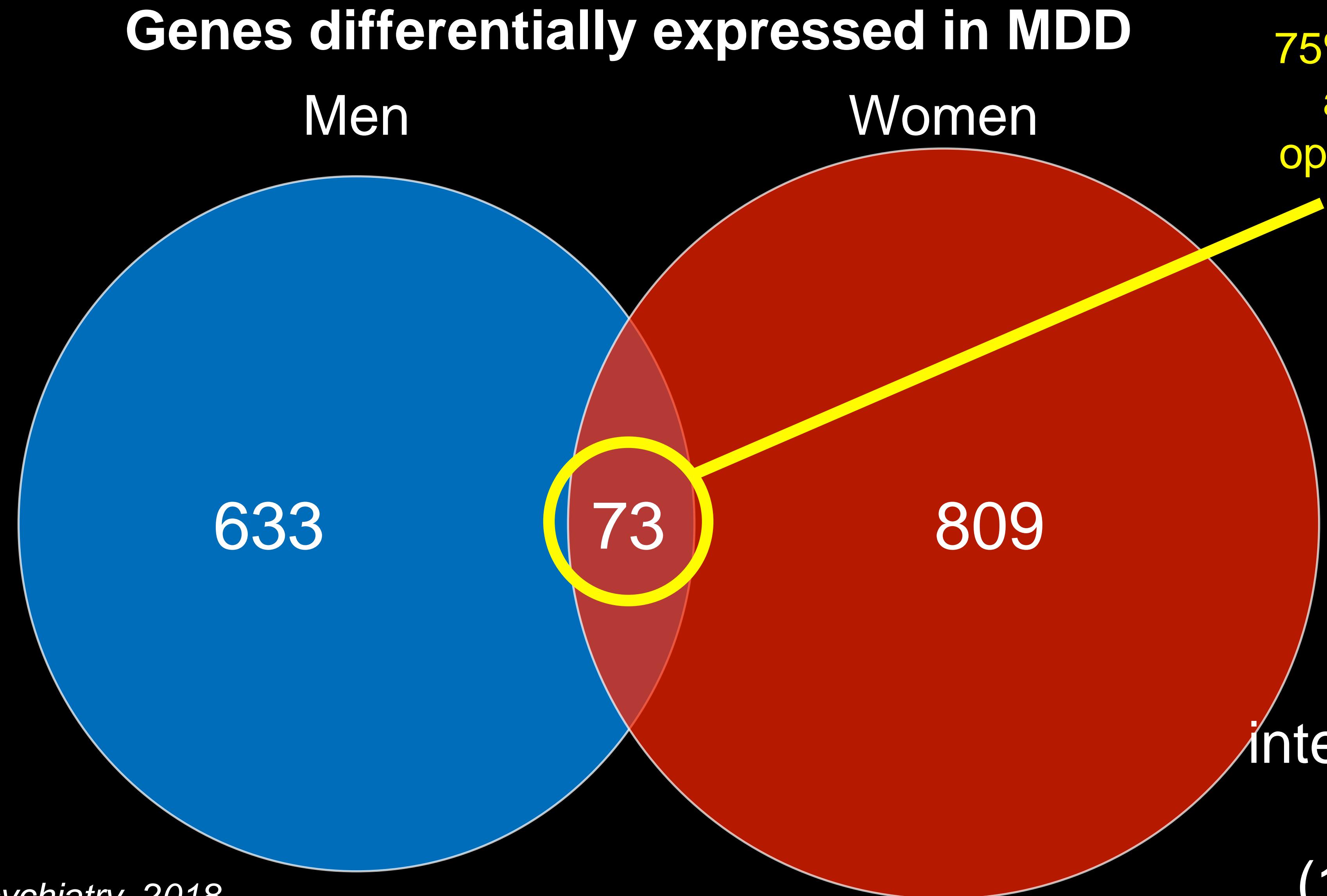
75% of these genes are changed in opposite directions!

Men

Women

633

73

809

Significant interaction of sex and MDD (1027 genes)

Seney et al., Biol Psychiatry, 2018

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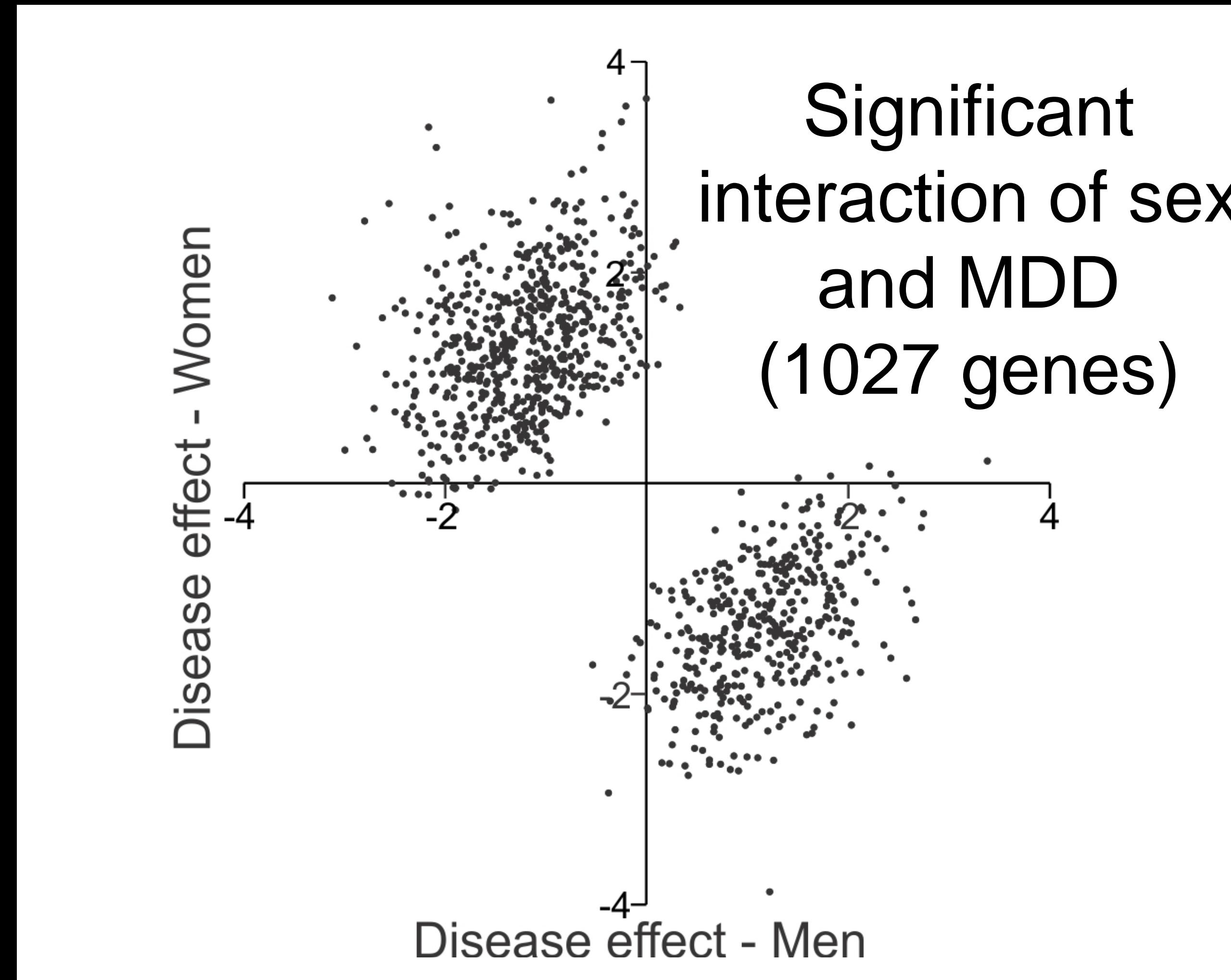
What pathways and cell types are represented by genes with significant interactions of sex and MDD?

	p-value	Men Direction	Women Direction
Regulation of synapse structure or activity	$< 10^{-8}$	↓	↑
Regulation of synapse organization	$< 10^{-7}$	↓	↑
Neurons	< 0.12	↔	↑
MHC protein complex	$< 10^{-7}$	↑	↓
Antigen processing and presentation	$< 10^{-7}$	↔	↓
Microglia	$< 10^{-7}$	↑	↓

Sex differences in synapse- and immune-related changes in MDD

Seney et al., 2018

Take-home messages

- Well-powered, large-scale transcriptional studies have uncovered novel insights into sex-specificity of brain pathological changes in MDD.

- Very little overlap in consistent molecular alterations in depressed men and women.

- Together, these studies have uncovered novel targets for future treatment development - sex specific MDD treatment

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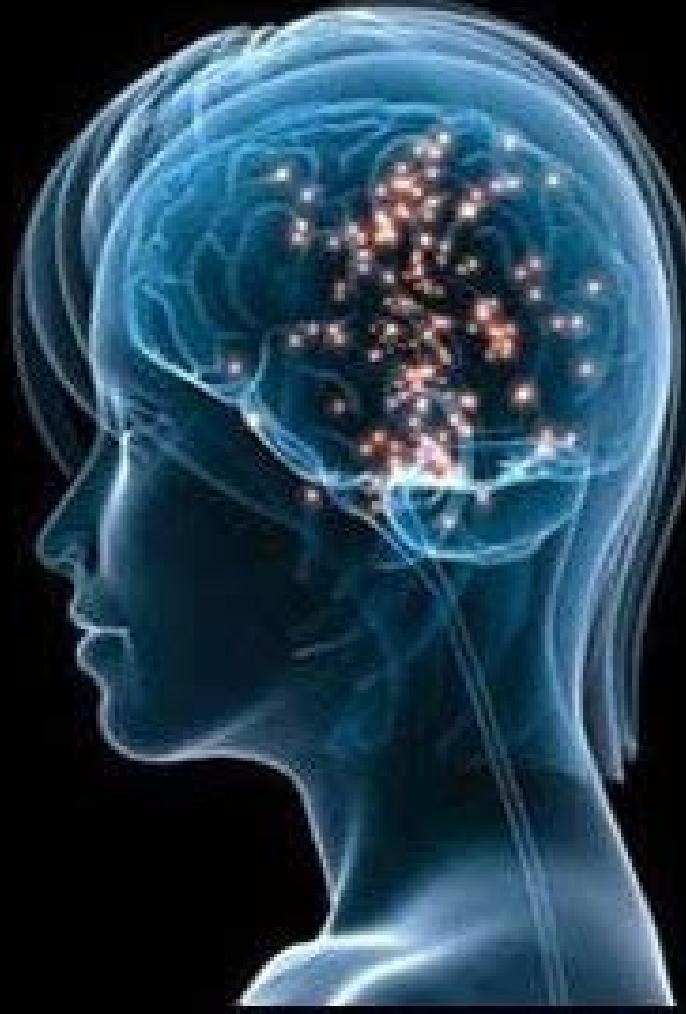
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