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- Alzheimer's disease (AD) represents an urgent and growing public health crisis, with over 6 million Americans currently affected.
- **Sex is a major determinant of AD** risk and resilience, influencing disease onset, severity, and responsiveness to pharmacological and non-pharmacological interventions
- To address these critical gaps, we leveraged single-nucleus RNA sequencing (snRNA-seq) data from **1,494 postmortem brain samples** collected by the PsychAD Consortium, encompassing donors with neurodegenerative and neuropsychiatric disorders as well as neurotypical controls.
- In this study, we systematically characterized **sex-specific cellular composition and gene expression** in AD, identifying widespread cell-type-specific differences in transcriptional programs between males and females.

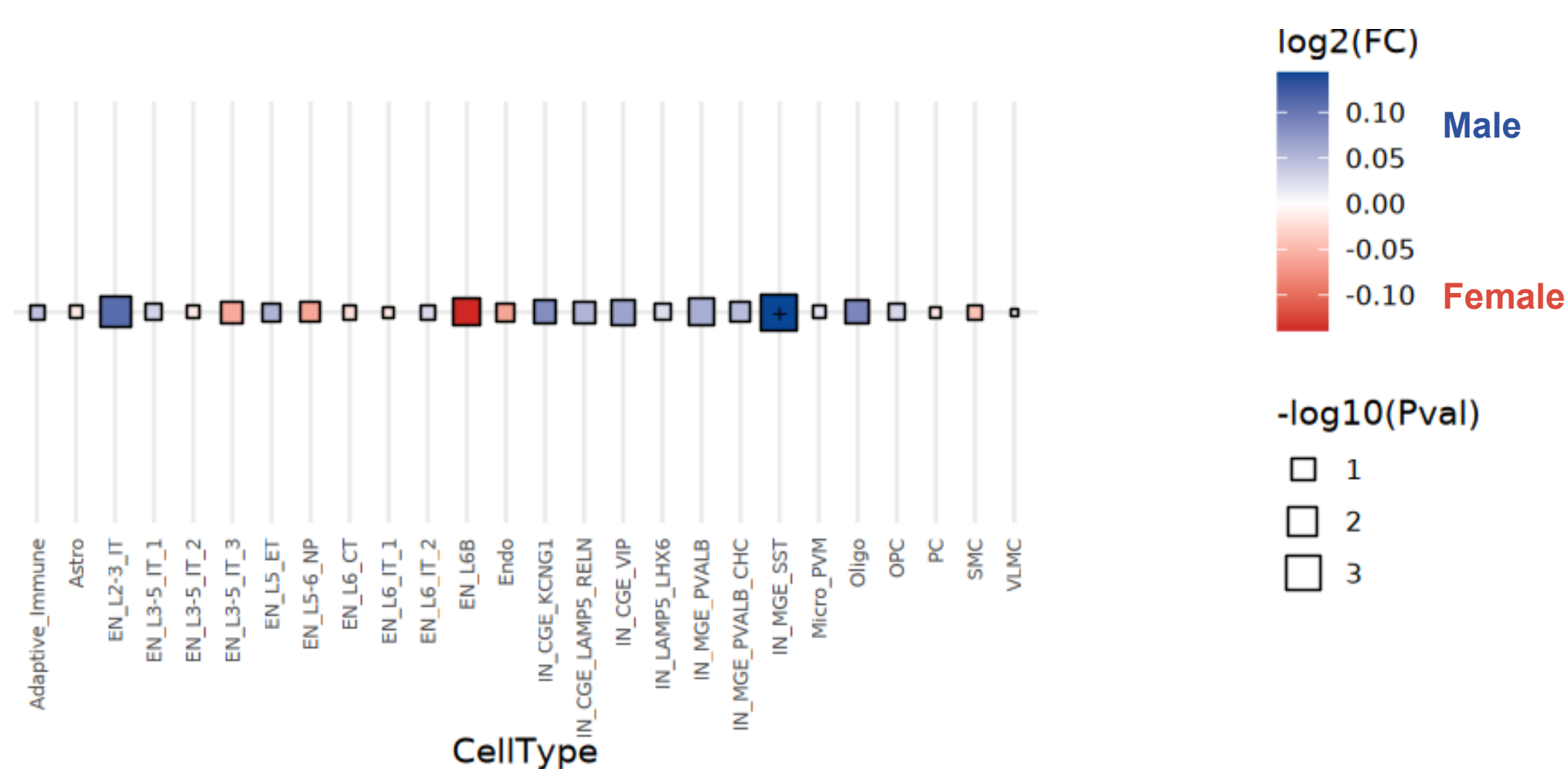
PsychAD

Sex	Dx	n
Female	AD	326
Female	Control	164
Male	AD	193
Male	Control	119

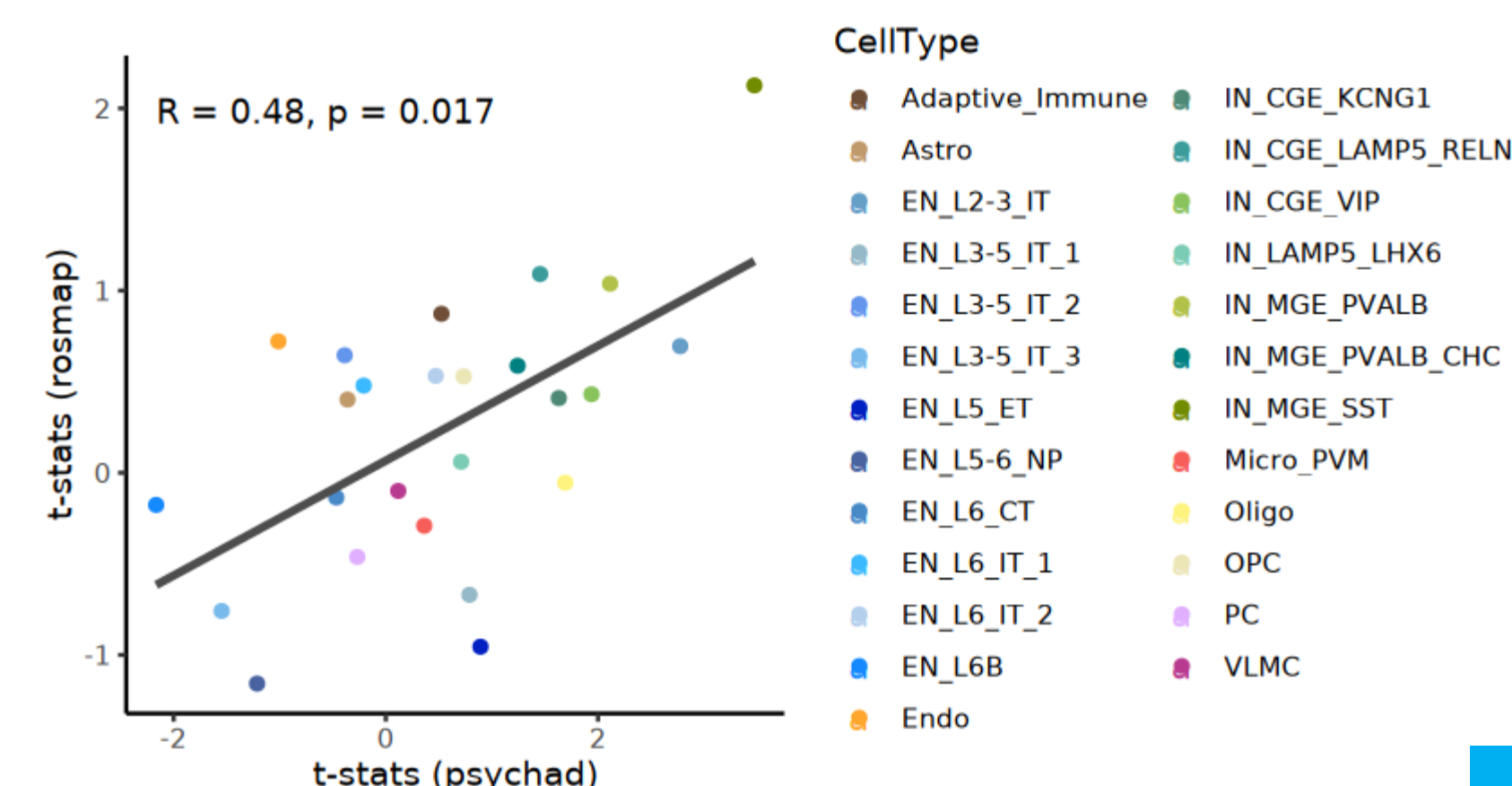
ROSMAP

Sex	Dx	n
Female	AD	186
Female	Control	96
Male	AD	73
Male	Control	57

Sex differences in cellular composition in the PsychAD



CellType	Number of Genes (approx.)
Adaptive_Immune	180
Astro	120
EN_L2-3_IT	100
EN_L3-5_IT_1	80
EN_L3-5_IT_2	80
EN_L3-5_IT_3	80
EN_L5_ET	80
EN_L5-6_NP	80
EN_L6_CT	80
EN_L6_IT_1	80
EN_L6_IT_2	80
EN_L6B	80
Endo	80
IN_CGE_KONG1	80
IN_CGE_LAMPS_RELN	80
IN_CGE_NIP	80
IN_LAMPS_THX6	80
IN_MGE_PVALB	80
IN_MGE_PVALB_CHC	80
IN_MGE_SST	80
Micro_PVM	80
Oligo	80
OPC	80
PC	80
Vt_MC	80



Category	Number of significant genes (adj.P.Val < 0.05)
VLMC	40
SMC	12
PC	57
OPC	274
Oligo	938
Micro_PVM	135
IN_MGE_SST	257
IN_MGE_PVALB_CHC	69
IN_MGE_PVALB	135
IN_LAMP5_LHX6	63
IN_CGE_VIP	213
IN_CGE_LAMP5_RELN	104
IN_CGE_KCNG1	67
Endo	43
EN_L6B	149
EN_L6_IT_2	63
EN_L6_IT_1	113
EN_L6_CT	81
EN_L5-6_NP	77
EN_L5_ET	126
EN_L3-5_IT_3	270
EN_L3-5_IT_2	234
EN_L3-5_IT_1	318
EN_L2-3_IT	291
Astro	583
Adaptive_Immune	31

Legend:

- Adaptive_Immune
- Astro
- EN_L2-3_IT
- EN_L3-5_IT_1
- EN_L3-5_IT_2
- EN_L3-5_IT_3
- EN_L5_ET
- EN_L5-6_NP
- EN_L6_CT
- EN_L6_IT_1
- EN_L6_IT_2
- EN_L6B
- Endo
- IN_CGE_KCNG1
- IN_CGE_LAMP5_RELN
- IN_CGE_VIP
- IN_LAMP5_LHX6
- IN_MGE_PVALB
- IN_MGE_PVALB_CHC
- IN_MGE_SST
- Micro_PVM
- Oligo
- OPC
- PC
- SMC
- VLNC

[illegible]

Heatmap showing t-statistic values for various biological processes across different gene sets. The y-axis lists gene sets, and the x-axis lists biological processes. A color scale on the right indicates t-statistic values from -10 (blue) to 10 (red), with 0 being white. Asterisks (*) indicate significant differences.

Gene sets (Y-axis):

- G00099054: presynapse assembly
- G00001941: postsynaptic membrane organization
- G00035176: social behavior
- G00030521: androgen receptor signaling pathway
- G00071773: cellular response to BMP stimulus
- G00030509: BMP signaling pathway
- G00070646: protein modification by small protein removal
- G00016579: protein deubiquitination
- G00007156: homophilic cell adhesion via plasma membrane adhesion molecules
- G00002456: T cell mediated immunity
- G00006414: translational elongation
- G00002181: cytoplasmic translation
- G00099550: trans-synaptic signaling, modulating synaptic transmission
- G00001516: prostaglandin biosynthetic process
- G00019228: neuronal action potential
- G00071625: vocalization behavior
- G00007158: neuron cell-cell adhesion
- G00006765: regulation of androgen receptor signaling pathway
- G00097105: presynaptic membrane assembly
- G00097104: postsynaptic membrane assembly
- G00007090: presynaptic membrane organization
- G00060816: random inactivation of X chromosome
- G00010587: miRNA catabolic process
- G00031048: regulatory ncRNA-mediated heterochromatin formation
- G00009048: dosage compensation by inactivation of X chromosome
- G00007549: sex-chromosome dosage compensation
- G02000630: positive regulation of miRNA metabolic process
- G00140719: constitutive heterochromatin formation
- G02000628: regulation of miRNA metabolic process
- G00035194: regulatory ncRNA-mediated post-transcriptional gene silencing

Biological Processes (X-axis):

- Adaptive Immune
- EN_L3-3-T1
- EN_L3-3-T2
- EN_L3-3-T3
- EN_L3-3-T4
- EN_L3-3-T5
- EN_L3-3-T6
- EN_L3-3-T7
- EN_L3-3-T8
- EN_L3-3-T9
- EN_L3-3-T10
- EN_L3-3-T11
- EN_L3-3-T12
- EN_L3-3-T13
- EN_L3-3-T14
- EN_L3-3-T15
- EN_L3-3-T16
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- EN_L3-3-T20
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- EN_L3-3-T225

- At the level of cellular composition, sex differences are generally modest. With one notable exception, **IN_MGE_SST interneurons** show a significant difference.
- Sex has a widespread effect on gene expression. Gene expression responses are partly shared across subclasses but also show clear cell-type specificity. Autosomal genes highlight this specificity, while sex chromosome genes show more global, shared effects.
- Male-enriched pathways are largely related to **synaptic function** and **neuronal signaling**, whereas female-enriched pathways are more related to **X chromosome inactivation**, RNA processing and regulatory mechanisms.

