Leveraging single-cell ATAC-seq to identify disease-critical fetal and adult brain cell types

Samuel Kim

Alkes Price Group

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Kim et al. bioRxiv 2021

Disclosure Slide

Financial Disclosure for:
Samuel Kim

I have nothing to disclose

Outline

- Motivation
- Methods
- Results: disease-critical cell types using fetal brain data
- Results: disease-critical cell types using adult brain data

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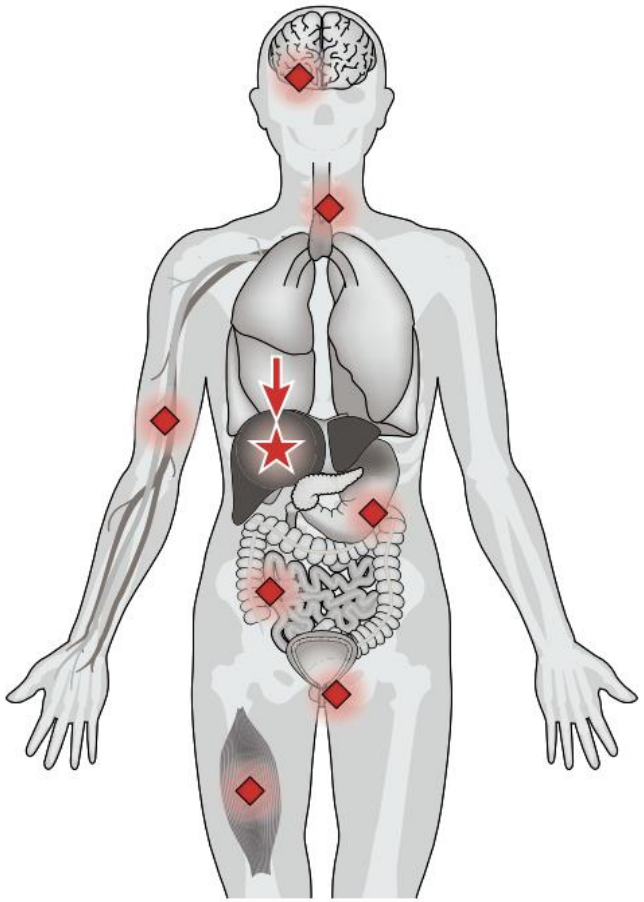
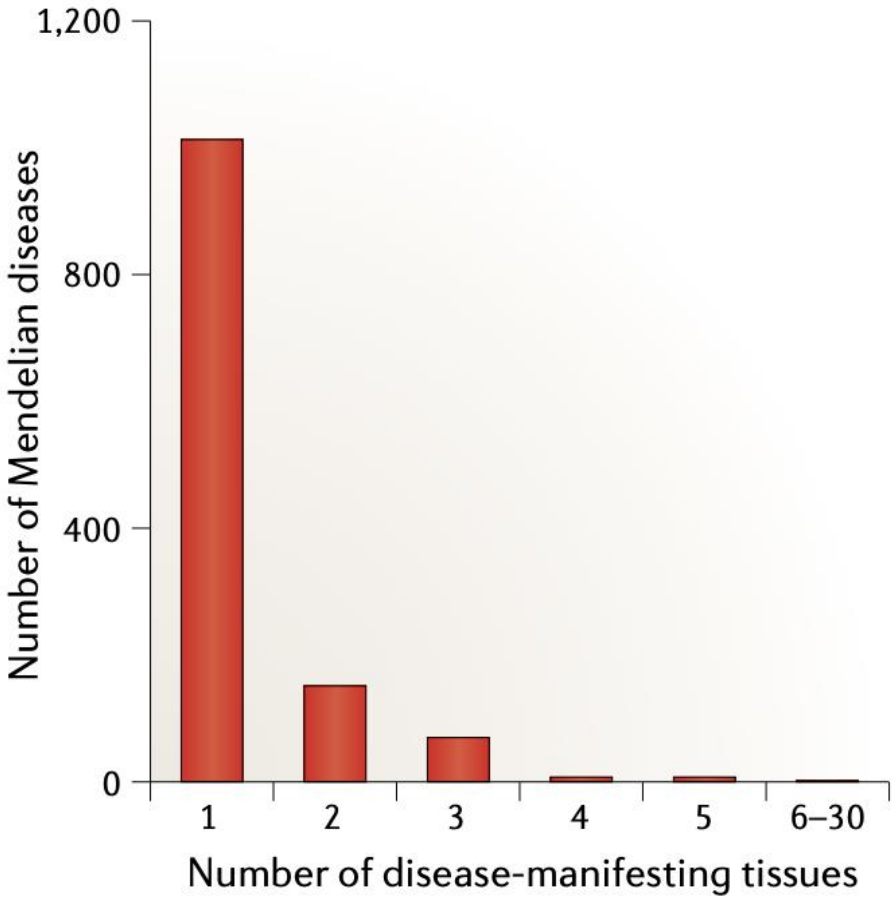
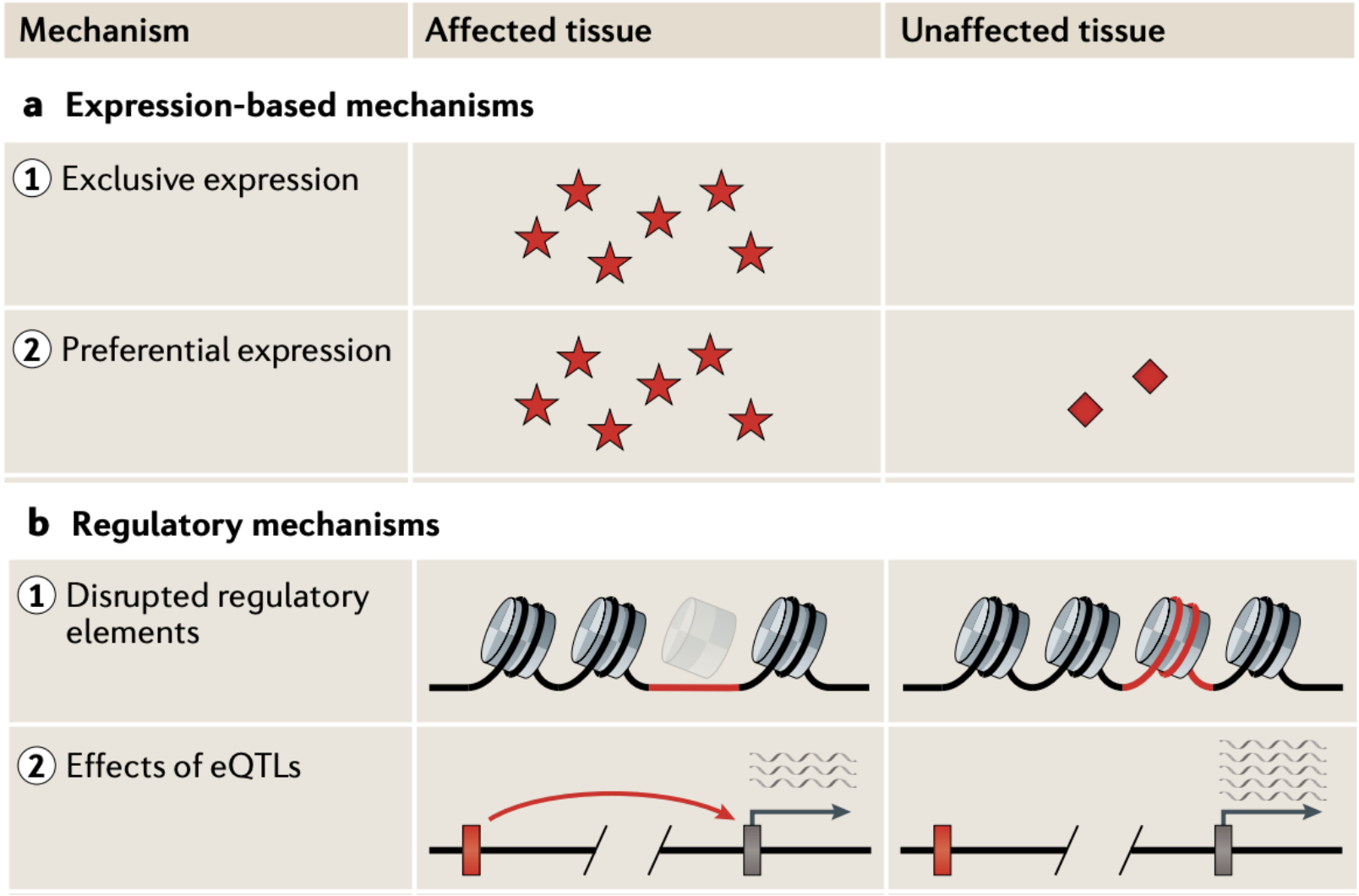
Disease-critical cell types → disease mechanisms





(Figure from Hekselman & Yeger-Lotem. Nat Rev Genet 2020)

Disease-critical cell types → disease mechanisms



(Figure from Hekselman & Yeger-Lotem. Nat Rev Genet 2020, shown in part)

Identifying disease-critical cell types, leveraging the emergence of single-cell profiling of diverse cell types

A human cell atlas of fetal gene expression

Junyue Cao, Diana R. O'Day, Hannah A. Pliner, Paul D. Kingsley, Mei Deng, Riza M. Daza, Michael A. Zager, Kimberly A. Aldinger, Ronnie Blecher-Gonen, Fan Zhang, Malte Spielmann, James Palis, Dan Doherty, Frank J. Steemers, Ian A. Glass, Cole Trapnell*, Jay Shendure*

Scaling single-cell genomics from phenomenology to mechanism

Amos Tanay & Aviv Regev

Leveraging mouse chromatin data for heritability enrichment informs common disease architecture and reveals cortical layer contributions to schizophrenia

Paul W. Hook[1] and Andrew S. McCallion[1,2,3]

HUMAN GENOMICS

A human cell atlas of fetal chromatin accessibility

Silvia Domcke*, Andrew J. Hill*, Riza M. Daza*, Junyue Cao, Diana R. O'Day, Hannah A. Pliner, Kimberly A. Aldinger, Dmitry Pokholok, Fan Zhang, Jennifer H. Milbank, Michael A. Zager, Ian A. Glass, Frank J. Steemers, Dan Doherty, Cole Trapnell†, Darren A. Cusanovich†, Jay Shendure†

Single-cell genomics identifies cell type–specific molecular changes in autism

Dmitry Velmeshev[1,2*], Lucas Schirmer[1,3,4], Diane Jung[1,2], Maximilian Haeussler[5], Yonatan Perez[1,2], Simone Mayer[1,2,6], Aparna Bhaduri[1,2], Nitasha Goyal[1,2,7], David H. Rowitch[1,3,8,9], Arnold R. Kriegstein[1,2*]

Single-cell epigenomic analyses implicate candidate causal variants at inherited risk loci for Alzheimer's and Parkinson's diseases

M. Ryan Corces[1,2], Anna Shcherbina[3,4], Soumya Kundu[4,5], Michael J. Gloudemans[1,3], Laure Frésard[1], Jeffrey M. Granja[2,4,6], Bryan H. Louie[1,2], Tiffany Eulalio[1,3], Shadi Shams[2,4], S. Tansu Bagdatli[2,4], Maxwell R. Mumbach[2,4], Boxiang Liu[1,7,8], Kathleen S. Montine[1], William J. Greenleaf[2,4,9,10], Anshul Kundaje[4,5], Stephen B. Montgomery[1,4], Howard Y. Chang[2,4,11,12] ✉ and Thomas J. Montine[1] ✉

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Our goals

1. To identify disease-critical cell types using scATAC-seq data
(and compare with scRNA-seq data)

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1. To identify disease-critical cell types using scATAC-seq data
(and compare with scRNA-seq data)

2. To assess the impact on disease risk of cell types in different developmental stages of the brain
(by comparing fetal vs. adult brain cell-type)

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- Results: disease-critical cell types using fetal brain data
- Results: disease-critical cell types using adult brain data

Analyzed 28 brain-related traits (avg. N = 298K)

28 Brain traits

Major depressive disorder
Ischemic stroke
Anorexia
Alzheimer's disease
Autism spectrum disorder
Schizophrenia
Bipolar disorder
ADHD
Schizophrenia vs. Bipolar

BMI
Years of education
Smoking status
Intelligence
Neuroticism
Morning person
Age at menarche
Worry
Reaction time

Children ever born
Smoking initiation
Sleep duration
General risk tolerance
Insomnia
Drinks per week
Medication use
Cigarettes per day
Smoking cessation
Age of drinking initiation

6 Control traits

Coronary artery disease
Bone mineral density
Rheumatoid arthritis
Type 2 diabetes
Sunburn occasion
Breast cancer

Analyzed 4 single-cell atlases of human brain

Fetal

scRNA

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N (donors) = 28; 2M cells; 34 brain cell types

scATAC

HUMAN GENOMICS

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N = 26; 720k cells; 14 brain cell types

Adult

Single-cell genomics identifies cell type–specific molecular changes in autism

Dmitry Velmeshev[1,2]*, Lucas Schirmer[1,3,4], Diane Jung[1,2], Maximilian Haeussler[5], Yonatan Perez[1,2], Simone Mayer[1,2,6], Aparna Bhaduri[1,2], Nitasha Goyal[1,2,7], David H. Rowitch[1,3,8,9], Arnold R. Kriegstein[1,2]*

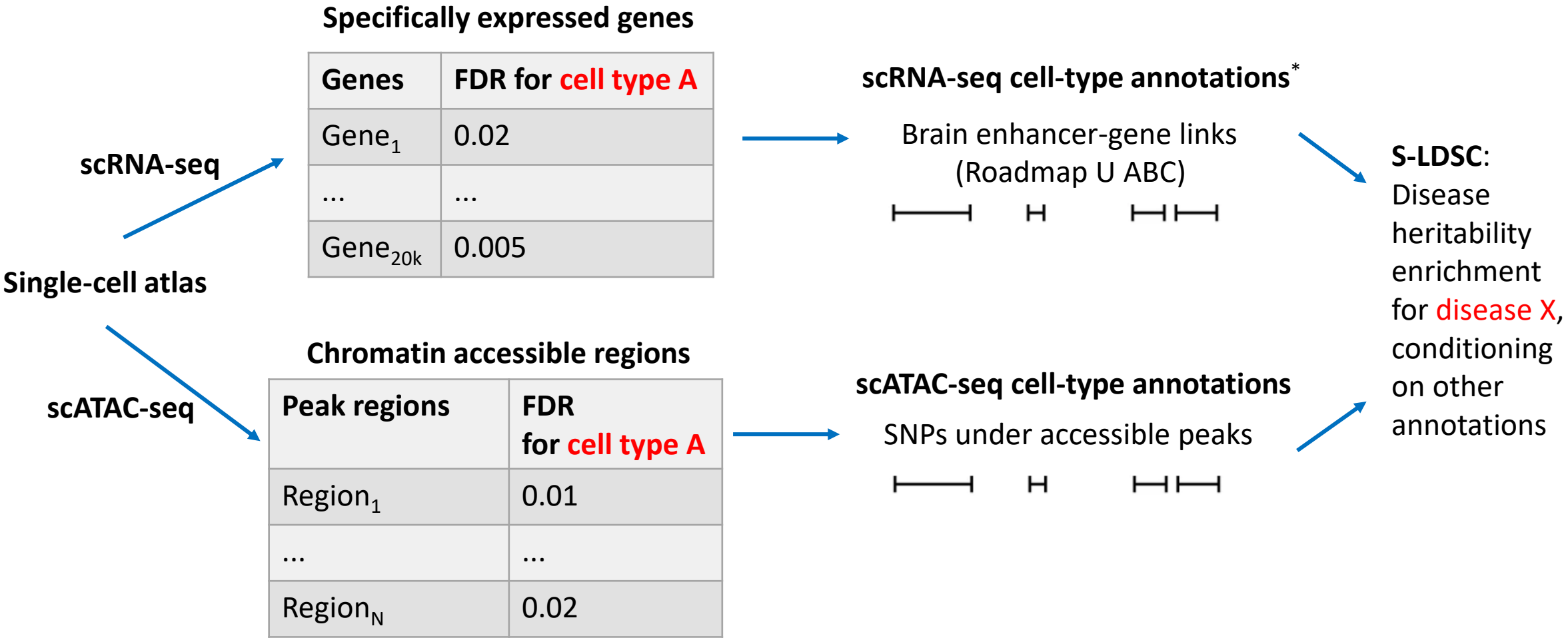
N = 31; 104K cells; 17 brain cell types

Single-cell epigenomic analyses implicate candidate causal variants at inherited risk loci for Alzheimer's and Parkinson's diseases

M. Ryan Corces[1,2], Anna Shcherbina[3,4], Soumya Kundu[4,5], Michael J. Gloudemans[1,3], Laure Frésard[1], Jeffrey M. Granja[2,4,6], Bryan H. Louie[1,2], Tiffany Eulalio[1,3], Shadi Shams[2,4], S. Tansu Bagdatli[2,4], Maxwell R. Mumbach[2,4], Boxiang Liu[1,7,8], Kathleen S. Montine[1], William J. Greenleaf[2,4,9,10], Anshul Kundaje[4,5], Stephen B. Montgomery[1,4], Howard Y. Chang[2,4,11,12] ✉ and Thomas J. Montine[1] ✉

N = 10; 70K cells; 18 brain cell types

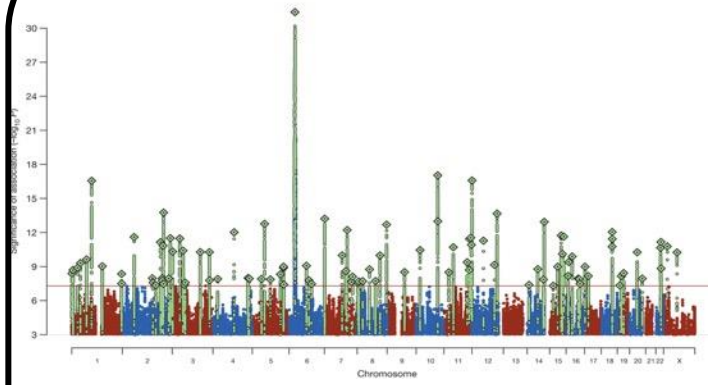
Overview of methods: building and assessing cell-type annotations



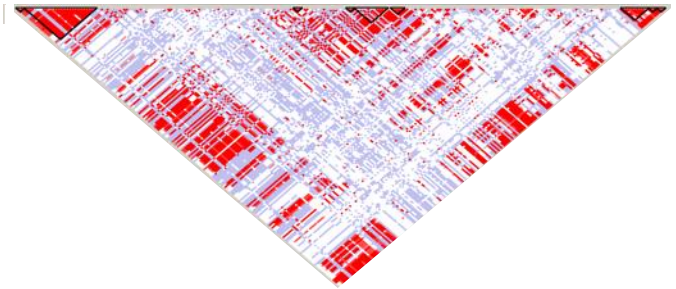
(*: Jagadeesh & Dey et al. biorxiv 2021, Fiucane et al. Nat. Genet. 2018)

To evaluate disease heritability enrichment, applied stratified LD score regression (S-LDSC)

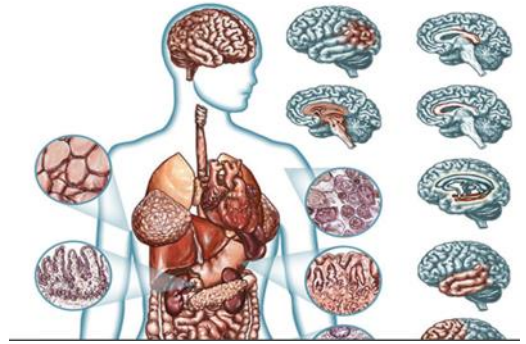
Input



Summary statistics



Reference panel



Cell-type annotations

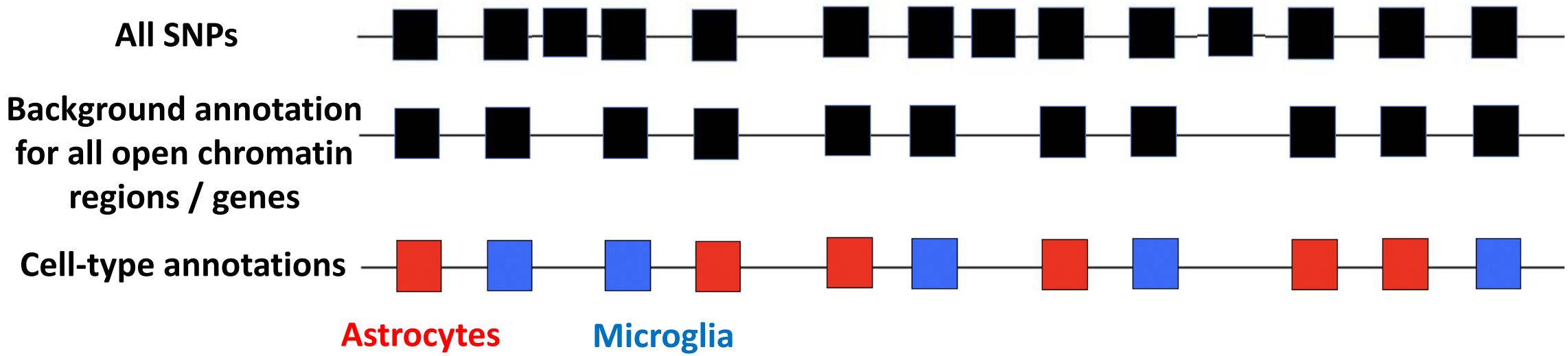
Output

1. Enrichment = Prop. h2g / Prop. SNPs
2. Standardized effect size (τ^*) = $M\tau \cdot csd(c) / h2g$

That is, proportionate change in per-SNP heritability associated to a one sd(annot) increase, conditional on 53 annotations (baseline model) and background annotation.

(Finucane et al. Nat. Genet. 2015)

Assessed τ* after additionally conditioning on background annotation



- Additionally conditioned on the background annotation as a conservative metric to ensure cell-type specificity

- scATAC-seq data: union of per-dataset open chromatin regions
- scRNA-seq data: union of brain enhancer-gene links across all genes analyzed

(Finucane et al. Nat. Genet. 2015)

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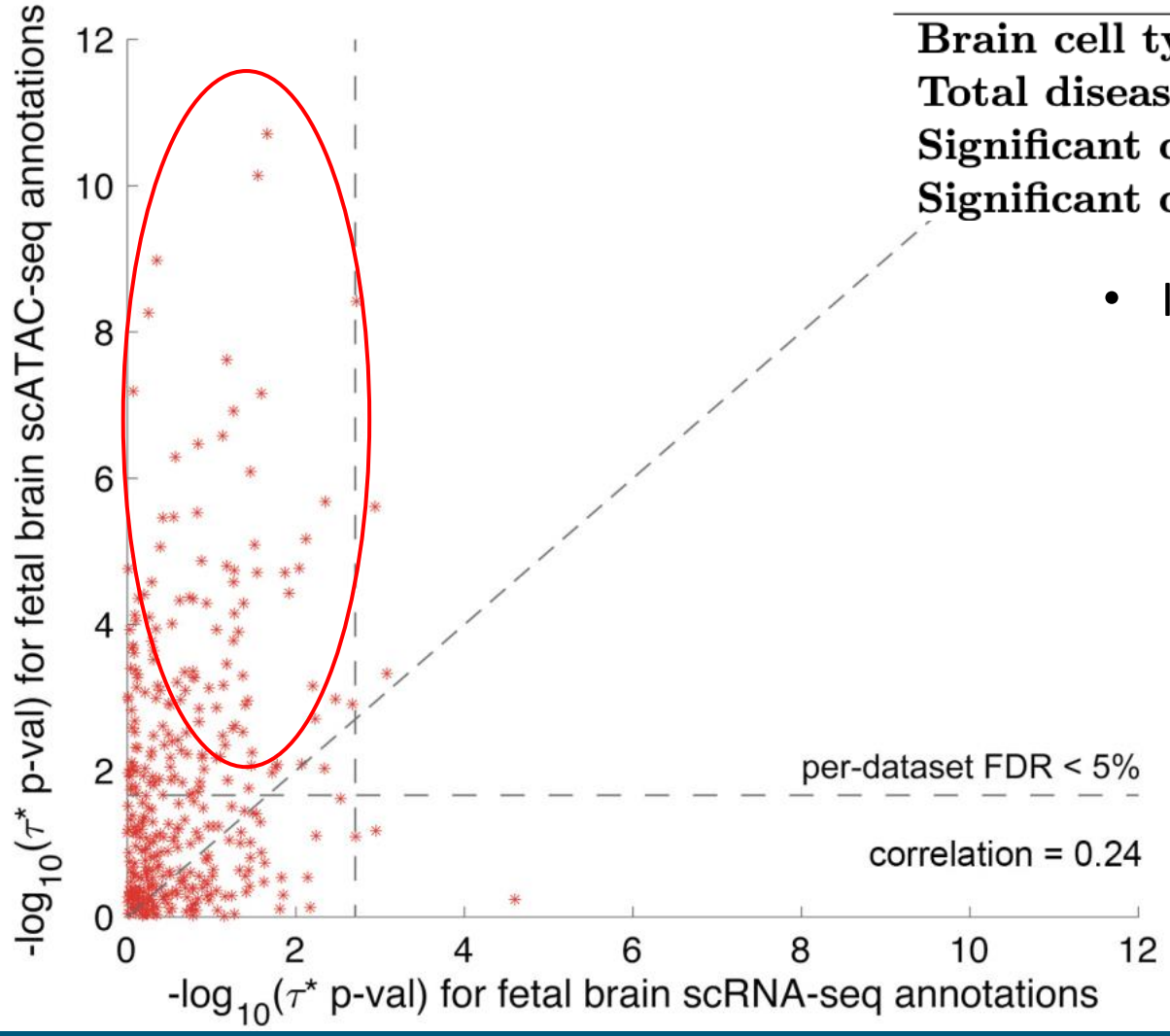
- ✓ Results: disease-critical cell types using fetal brain data
- Results: disease-critical cell types using adult brain data

Identified more significant disease-cell type pairs from scATAC-seq*

For 13 cell types appearing in both data

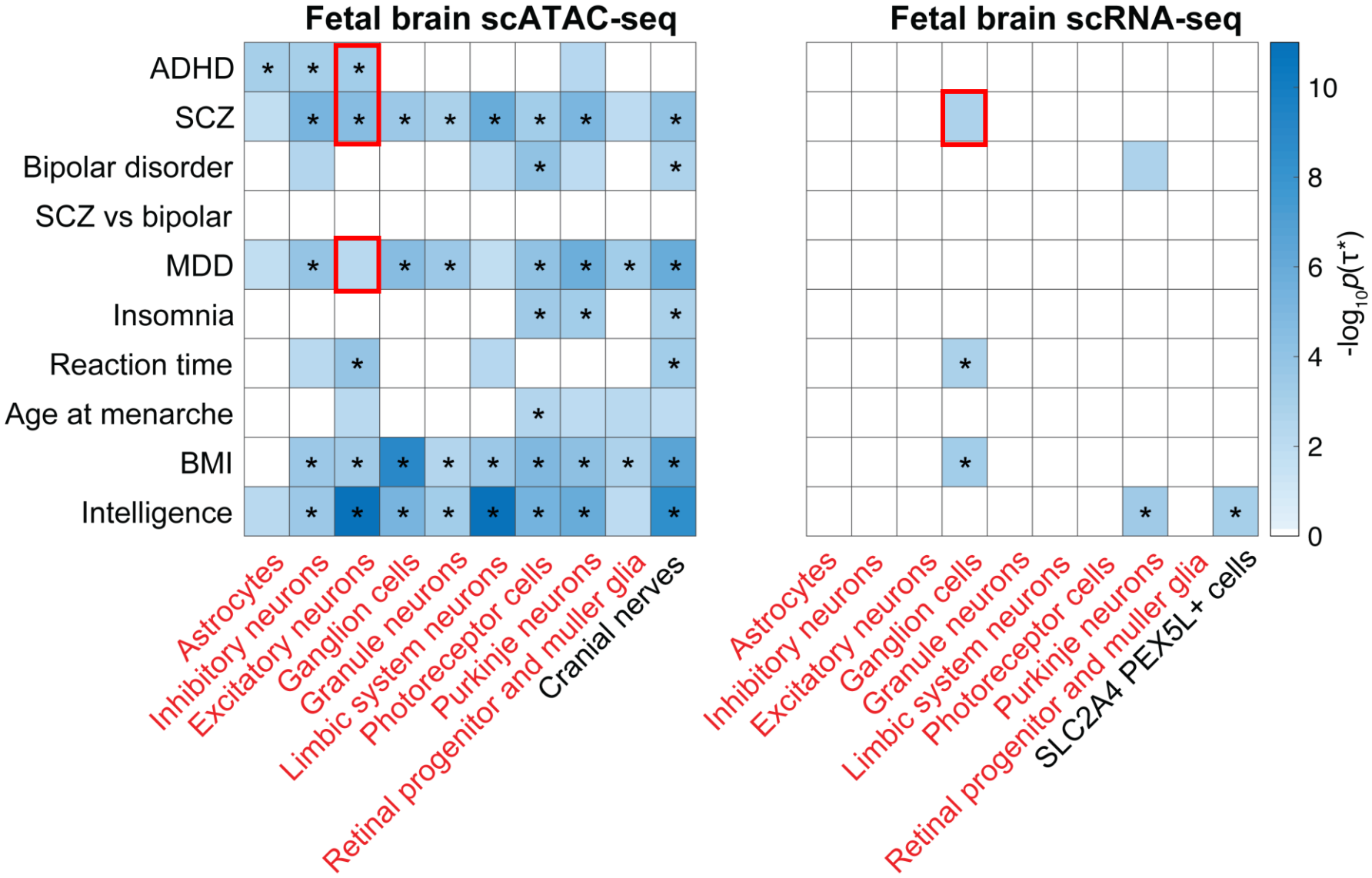


	Fetal scATAC	Fetal scRNA
Brain cell types	14	34
Total disease-cell type pairs	392	952
Significant disease-cell-type pairs	152	9
Significant diseases (out of 28)	22	8

- Identified no significant enrichments for control traits

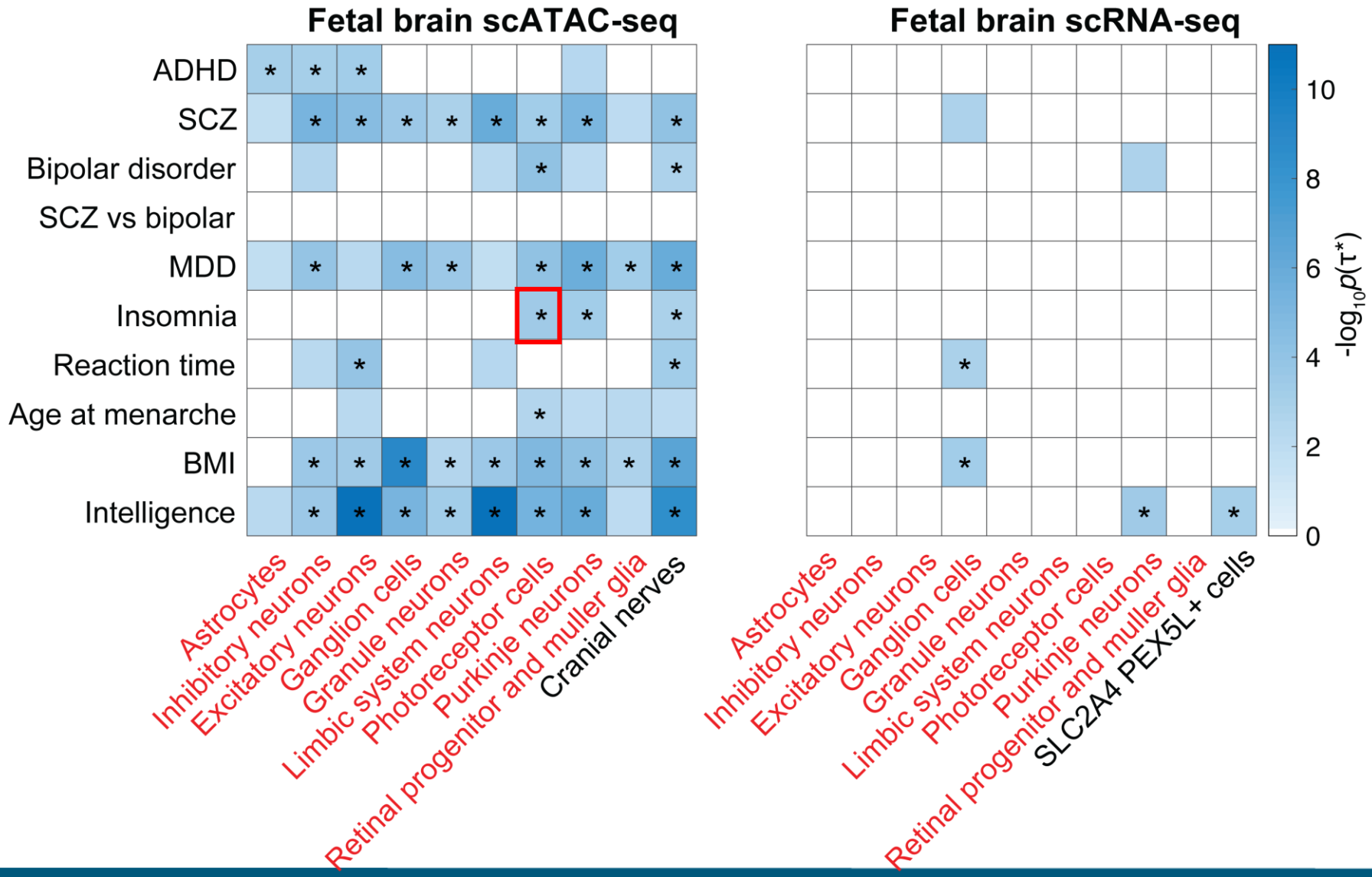
*for the datasets we have analyzed

Confirming associations: SCZ/MDD/ADHD – excitatory neurons



(Finucane et al. NG 2018, Bryois et al. NG 2020, Corces et al. NG 2020; Moriguchi et al. Mol. Psychiatry 2019)

Interesting associations: insomnia - photoreceptor cells



(Freedman et al. *Science* 1999, Paul et al. *Rev Endocr Metab Discord*. 2010)

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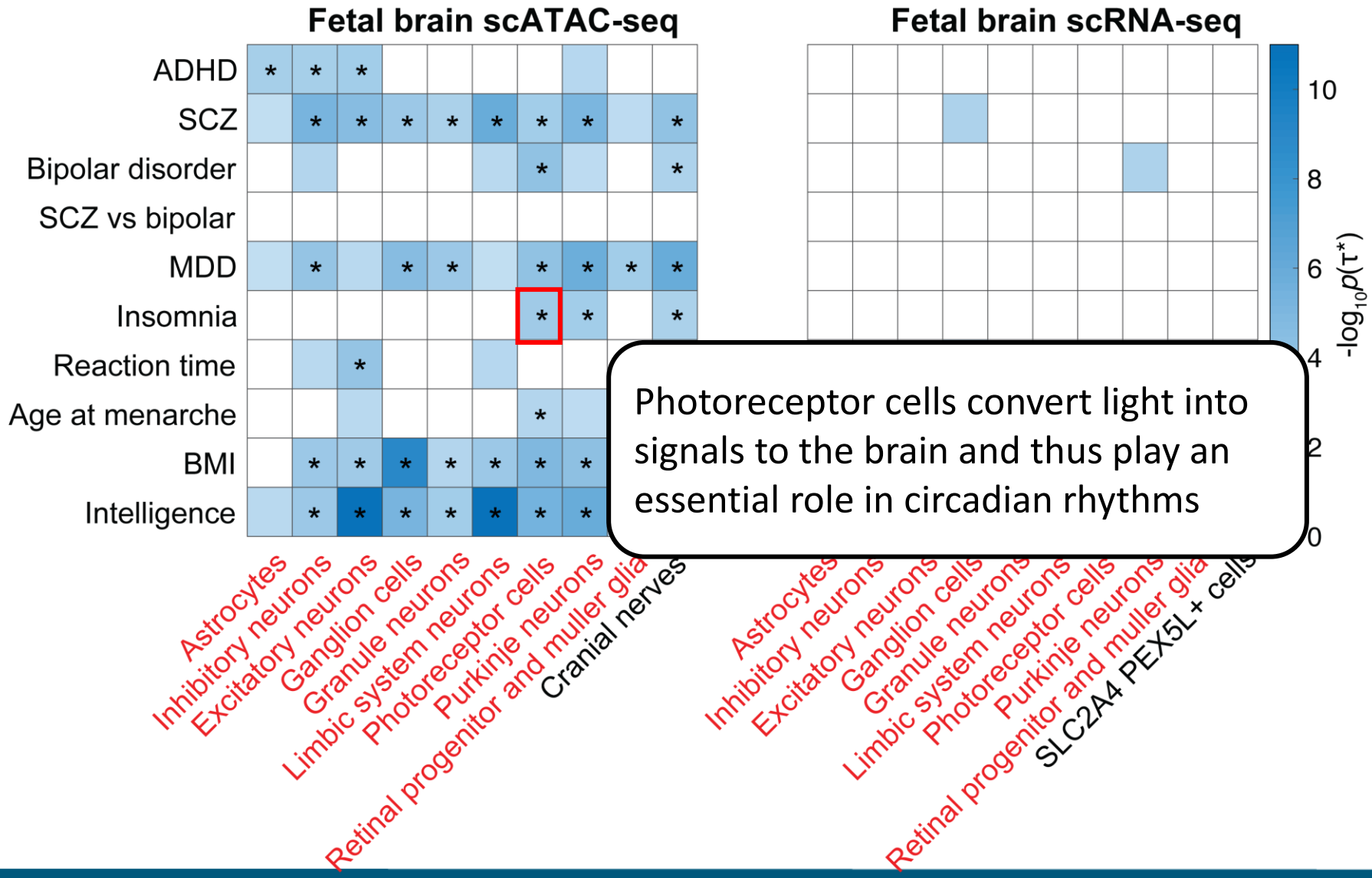
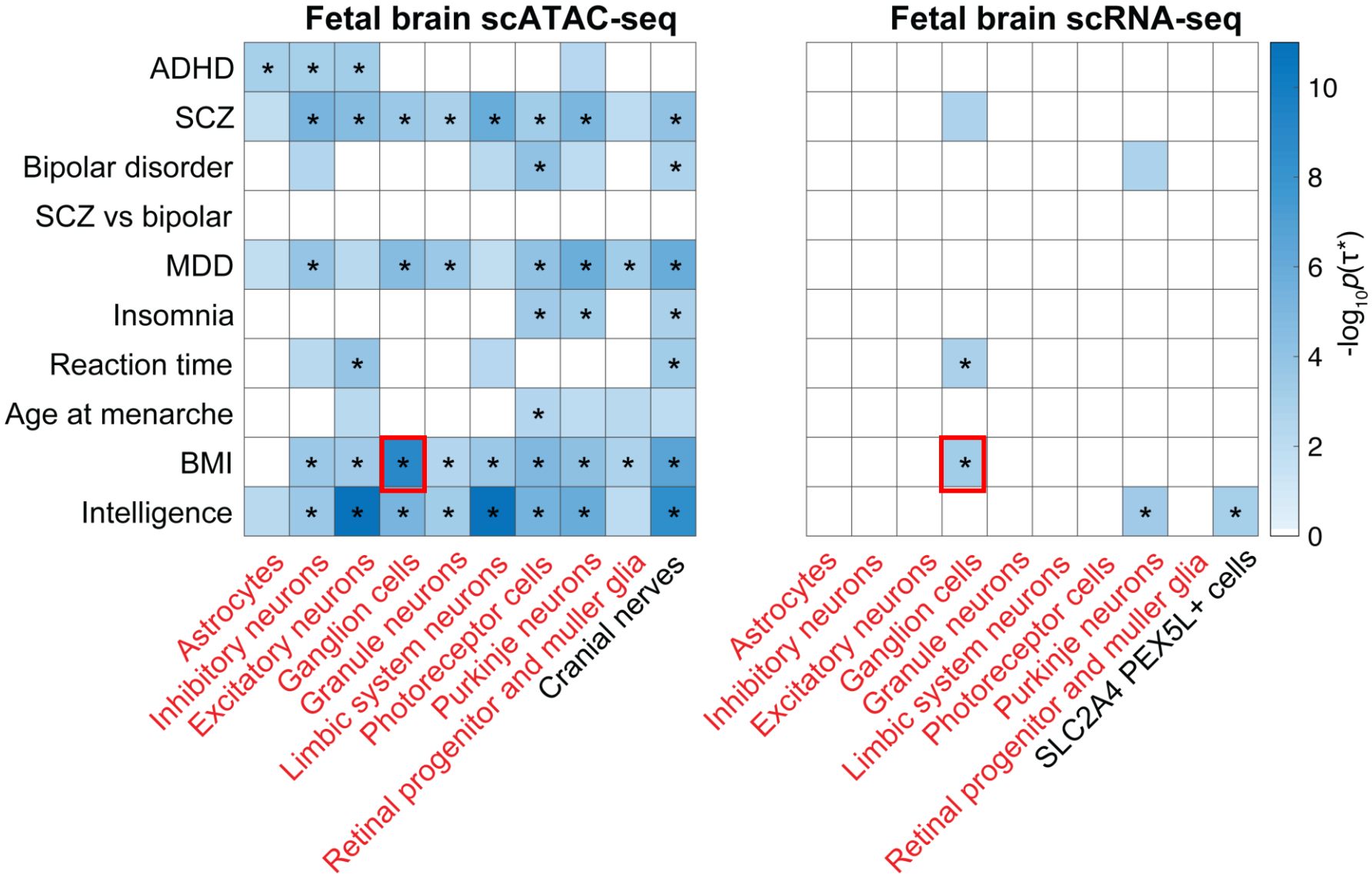


Photoreceptor cells convert light into signals to the brain and thus play an essential role in circadian rhythms

(Freedman et al. *Science* 1999, Paul et al. *Rev Endocr Metab Discord*. 2010)

Interesting associations: BMI - ganglion cells



(Dogan et al. *Eur Rev Med Pharmacol Sci.* 2016; other sets of interesting associations: Kim et al. biorxiv 2021)

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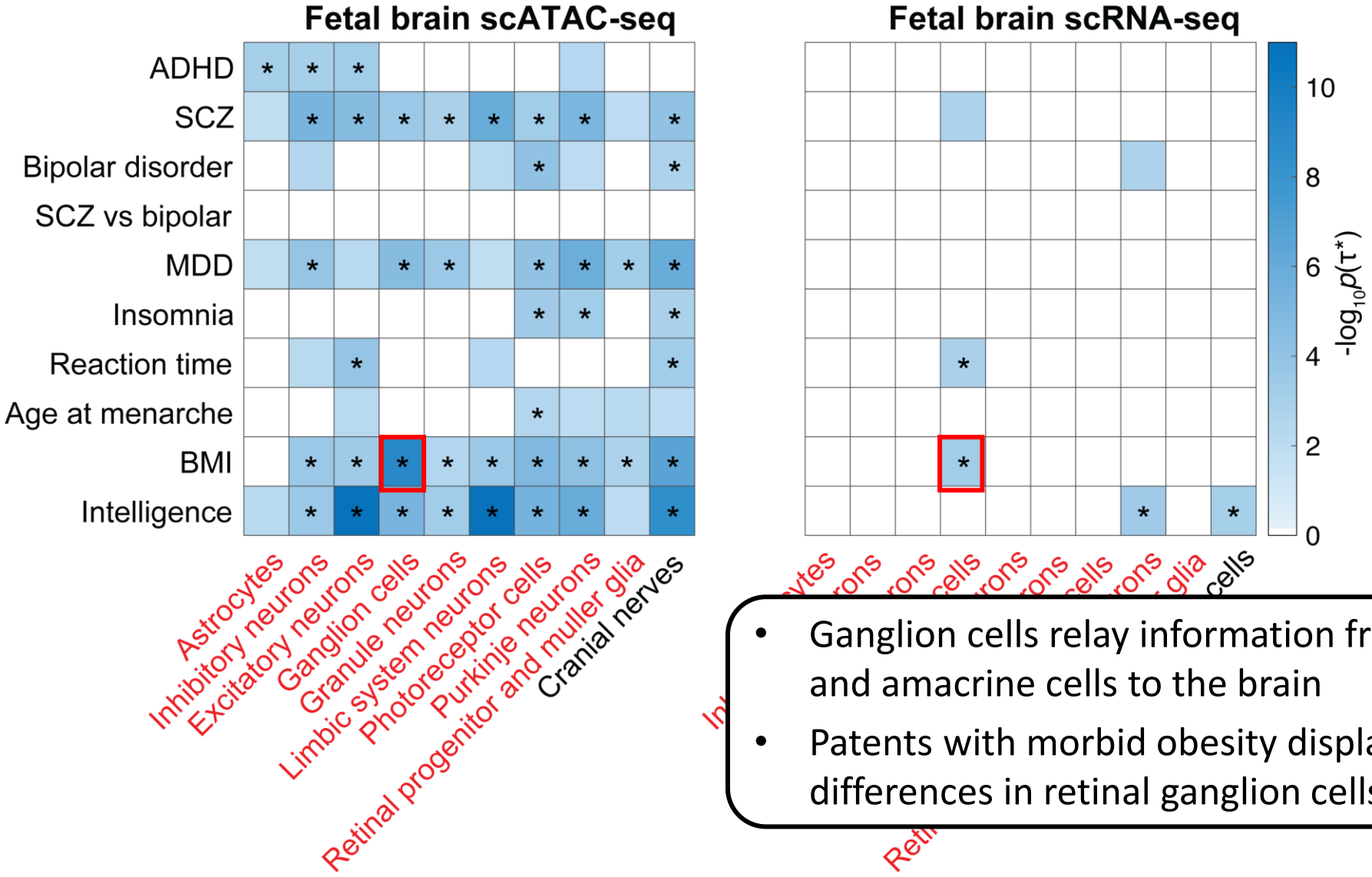

- Ganglion cells relay information from bipolar and amacrine cells to the brain
- Patents with morbid obesity display significant differences in retinal ganglion cells

(Dogan et al. *Eur Rev Med Pharmacol Sci.* 2016; other sets of interesting associations: Kim et al. biorxiv 2021)

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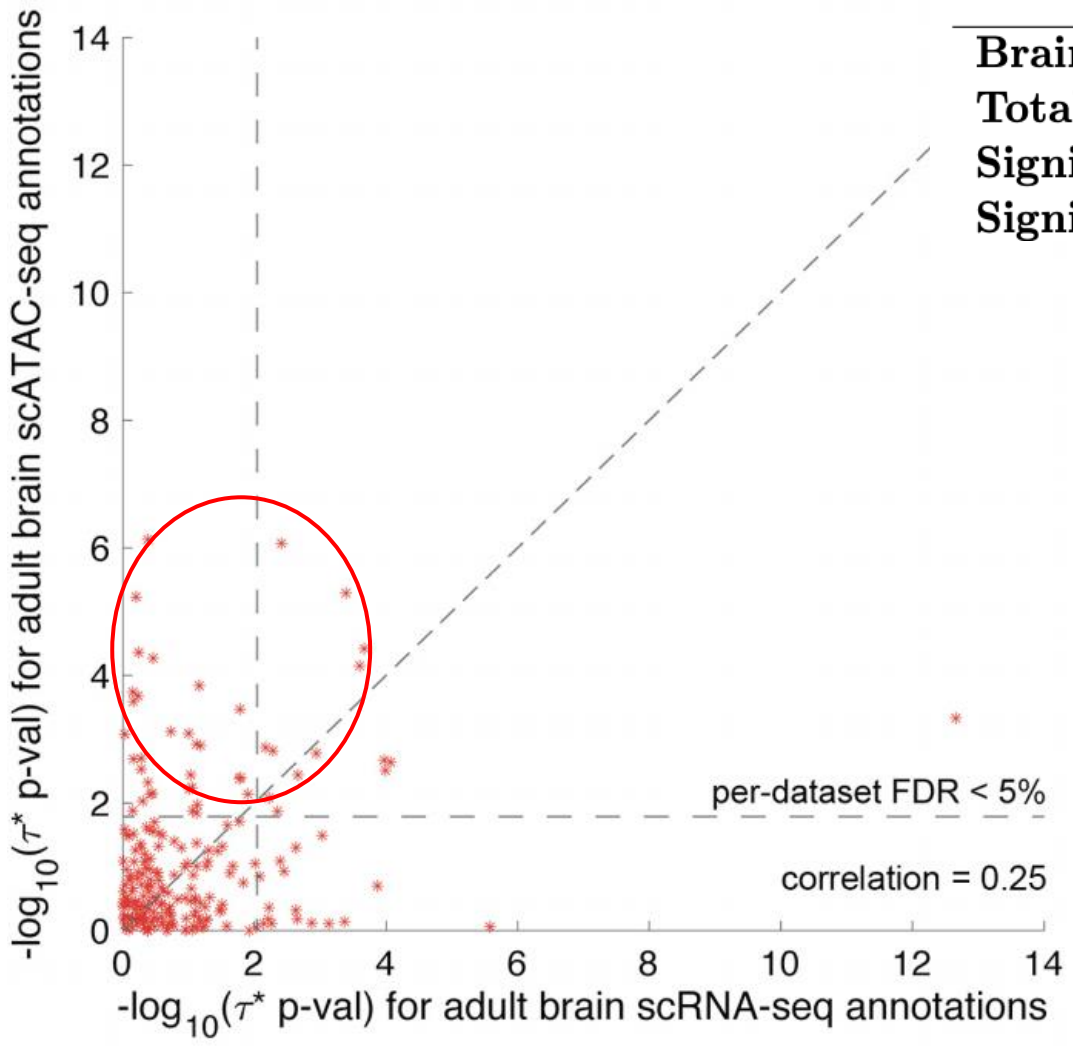
Identified more significant disease-cell type pairs from scATAC-seq*

For 9 cell types appearing in both data

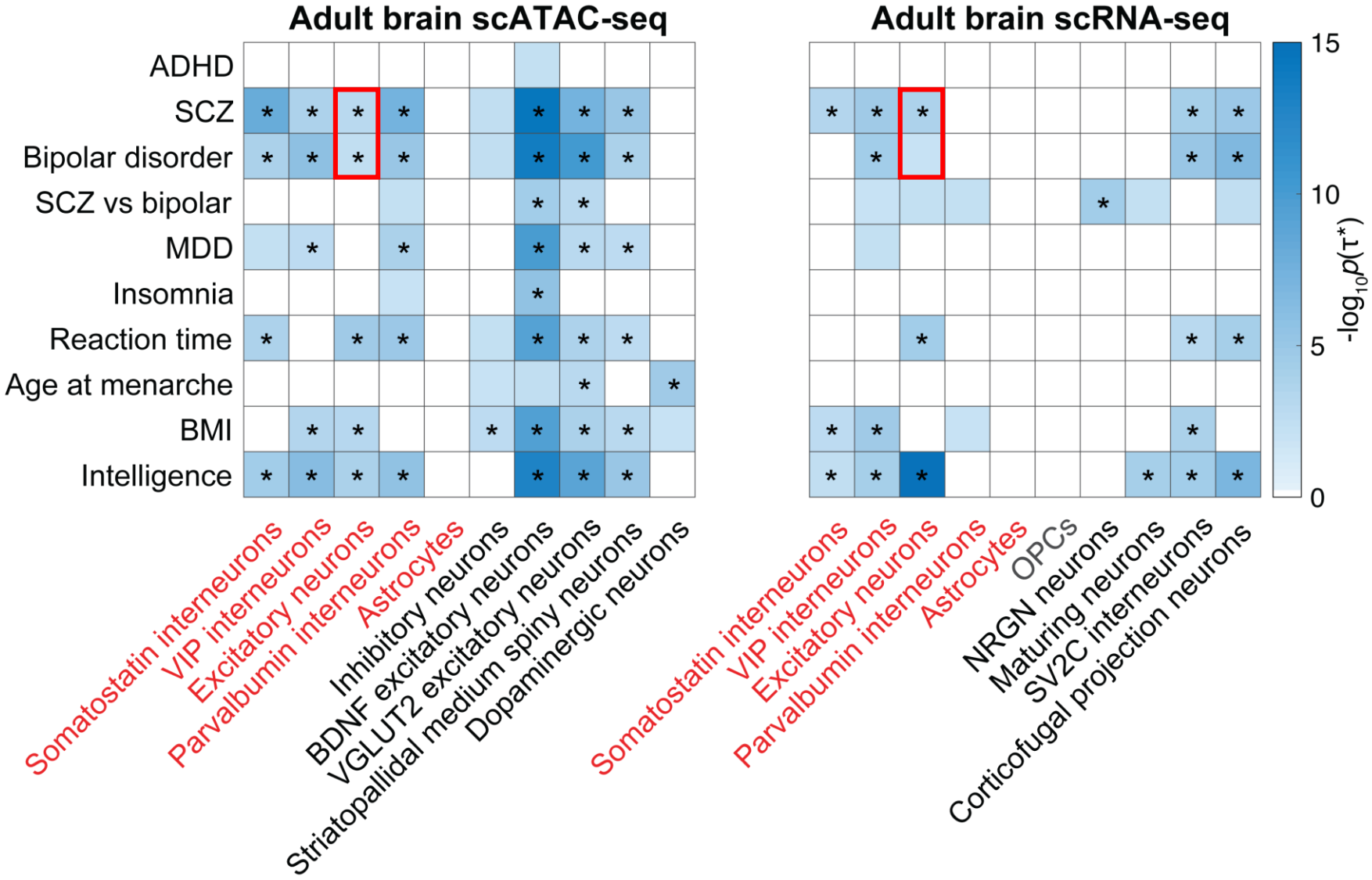


	Adult scATAC	Adult scRNA
Brain cell types	18	17
Total disease-cell type pairs	504	476
Significant disease-cell-type pairs	168	64
Significant diseases (out of 28)	23	17

- Identified no significant enrichments for control traits

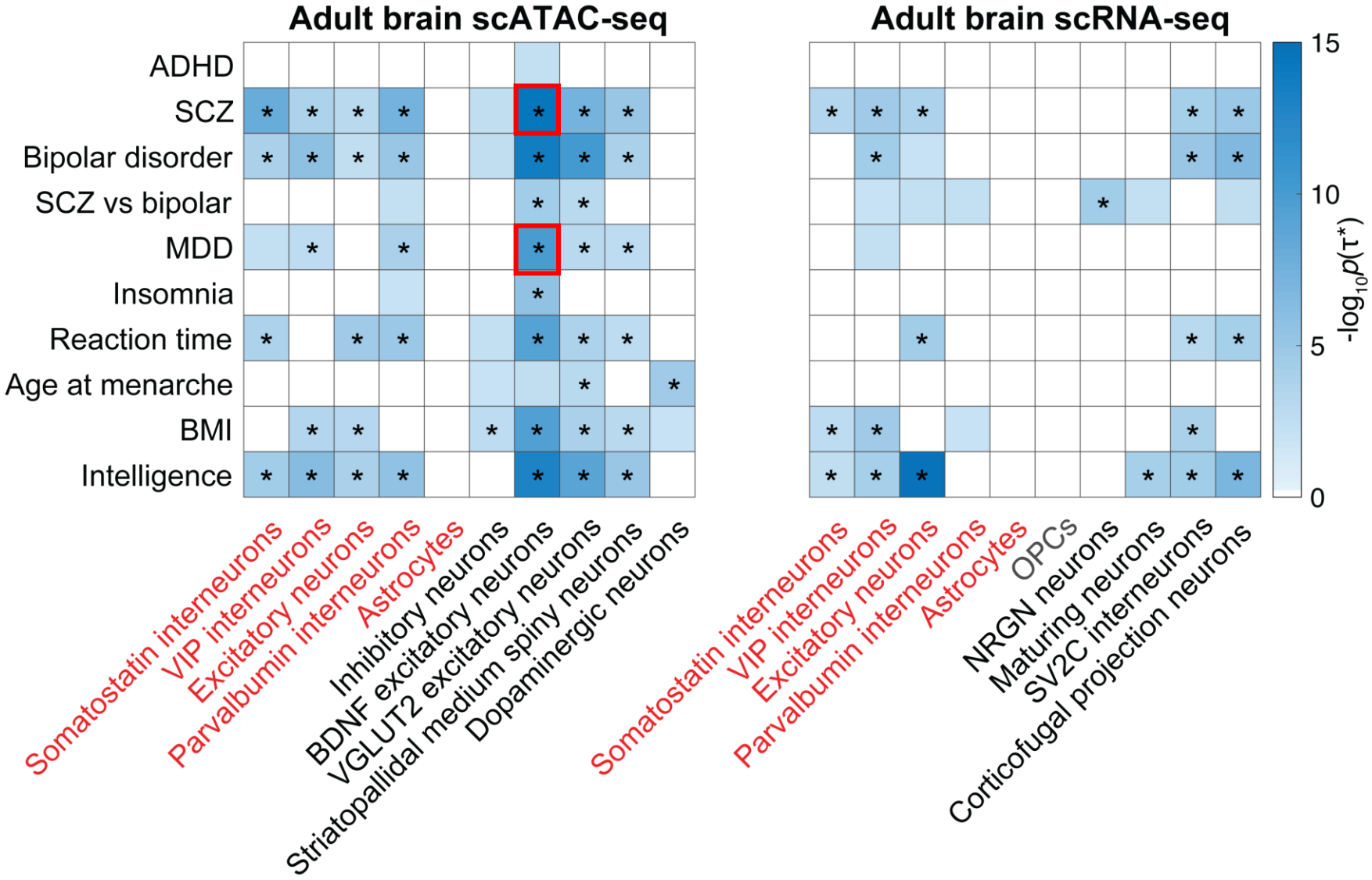
*for the datasets we have analyzed

Confirming associations: SCZ/BP – excitatory neurons



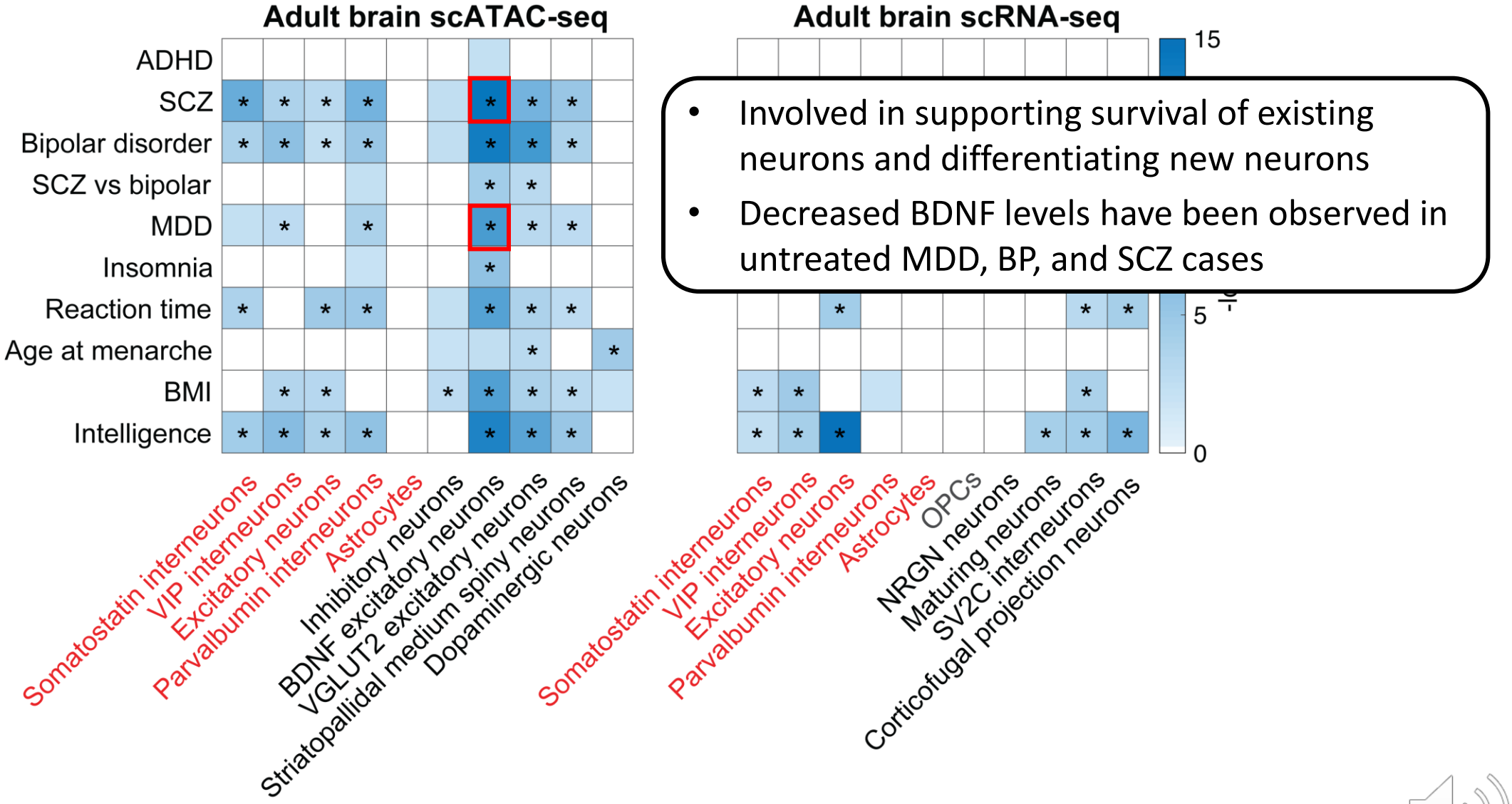
(Finucane et al. NG 2018, Hook et al. GR 2020, Corces et al. NG 2020, Ziffra et al. biorxiv 2020)

Interesting associations: SCZ/MDD - BDNF excitatory neurons



(Favalli et al. *J Psychiatr Res*. 2012, Tsai et al. *Neuropsychobiology.* 2014, Liu et al. *Mol Neurobiol.* 2015)

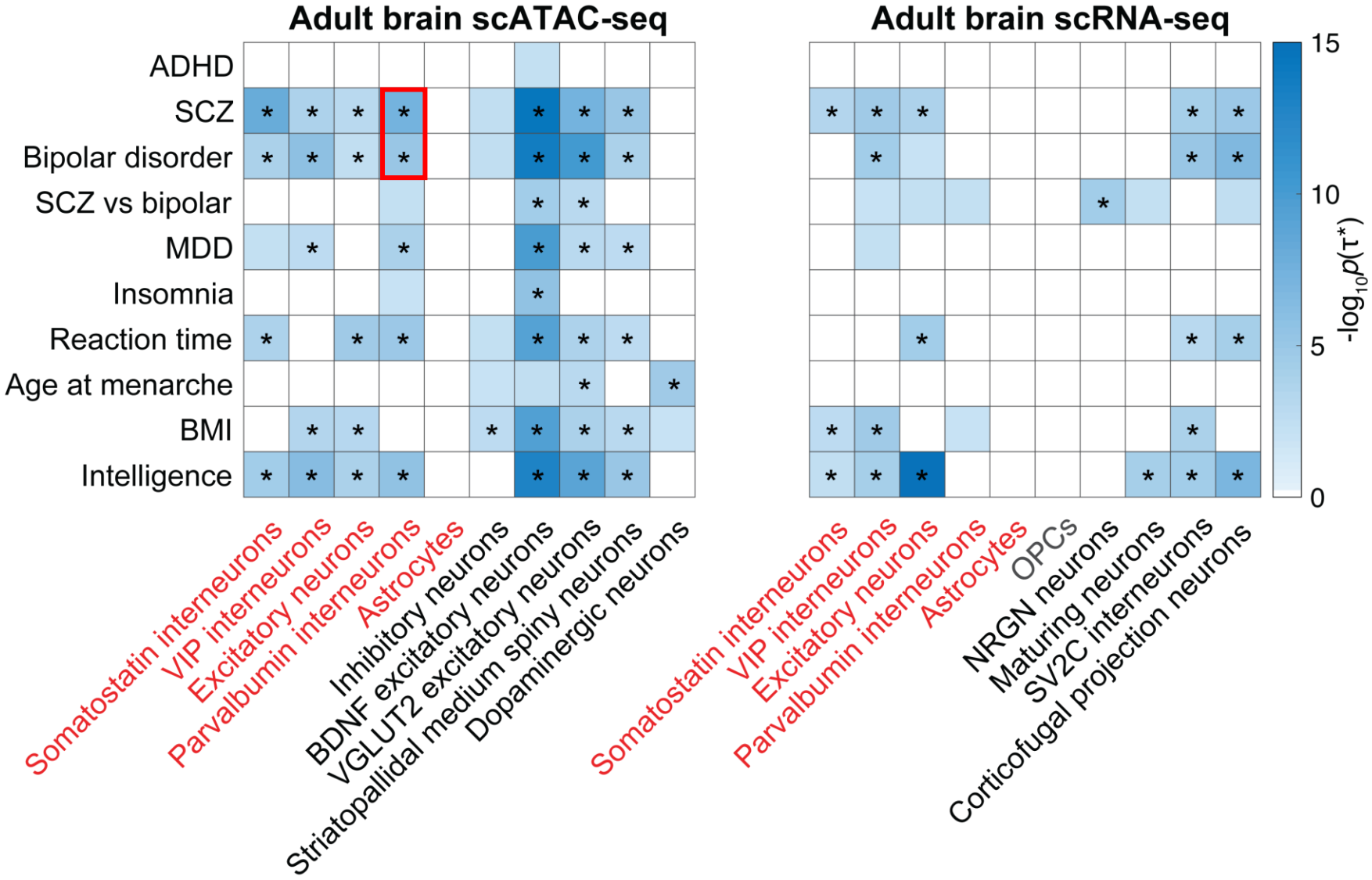
Interesting associations: SCZ/MDD - BDNF excitatory neurons



- Involved in supporting survival of existing neurons and differentiating new neurons
- Decreased BDNF levels have been observed in untreated MDD, BP, and SCZ cases

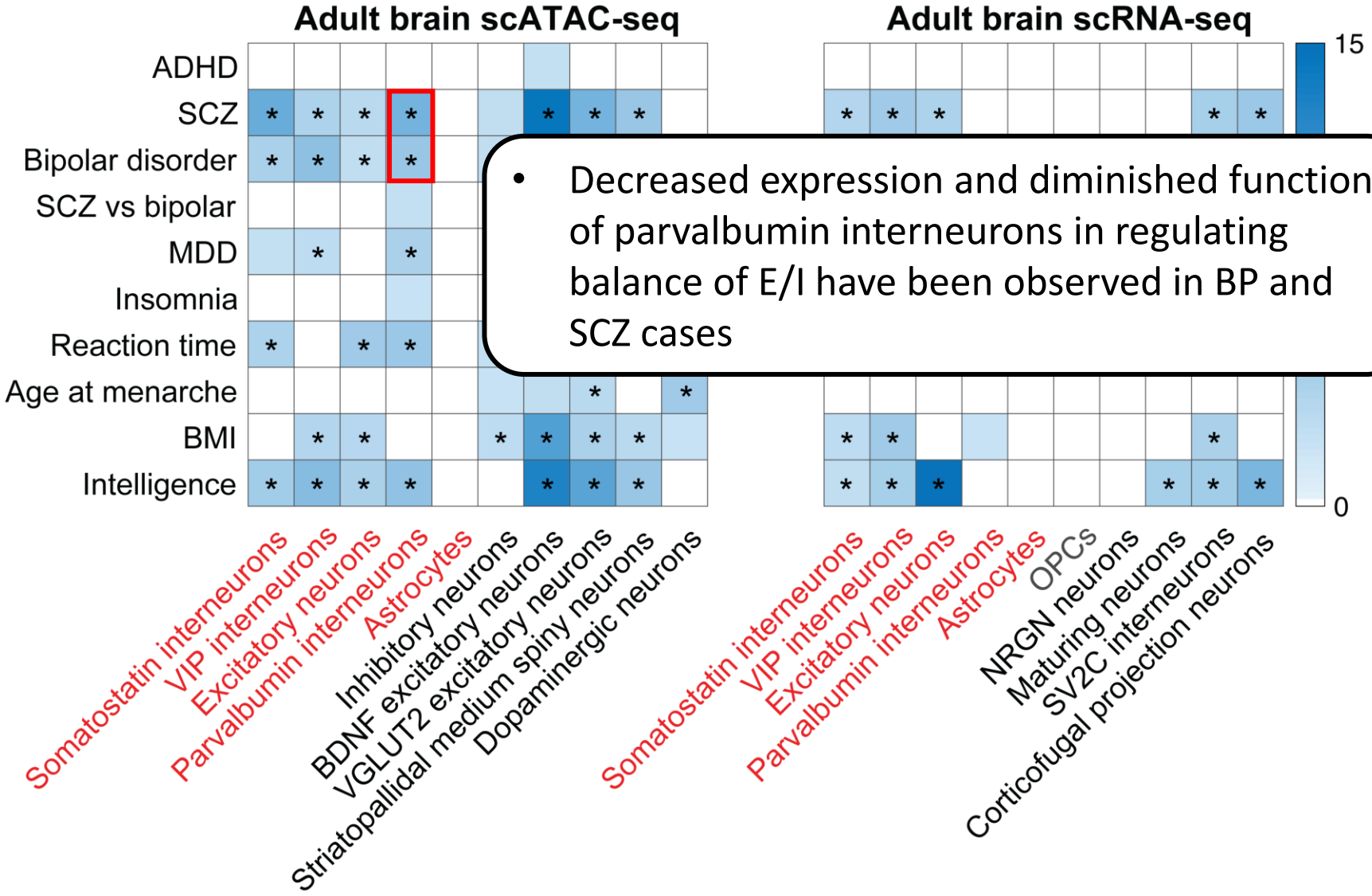
(Favalli et al. *J Psychiatr Res*. 2012, Tsai et al. *Neuropsychobiology.* 2014, Liu et al. *Mol Neurobiol.* 2015)

Interesting associations: Bipolar/SCZ – parvalbumin interneurons



(Toker et al. Biol Psychiatry 2018, Fergusen et al. Front Neural Circuits 2018)

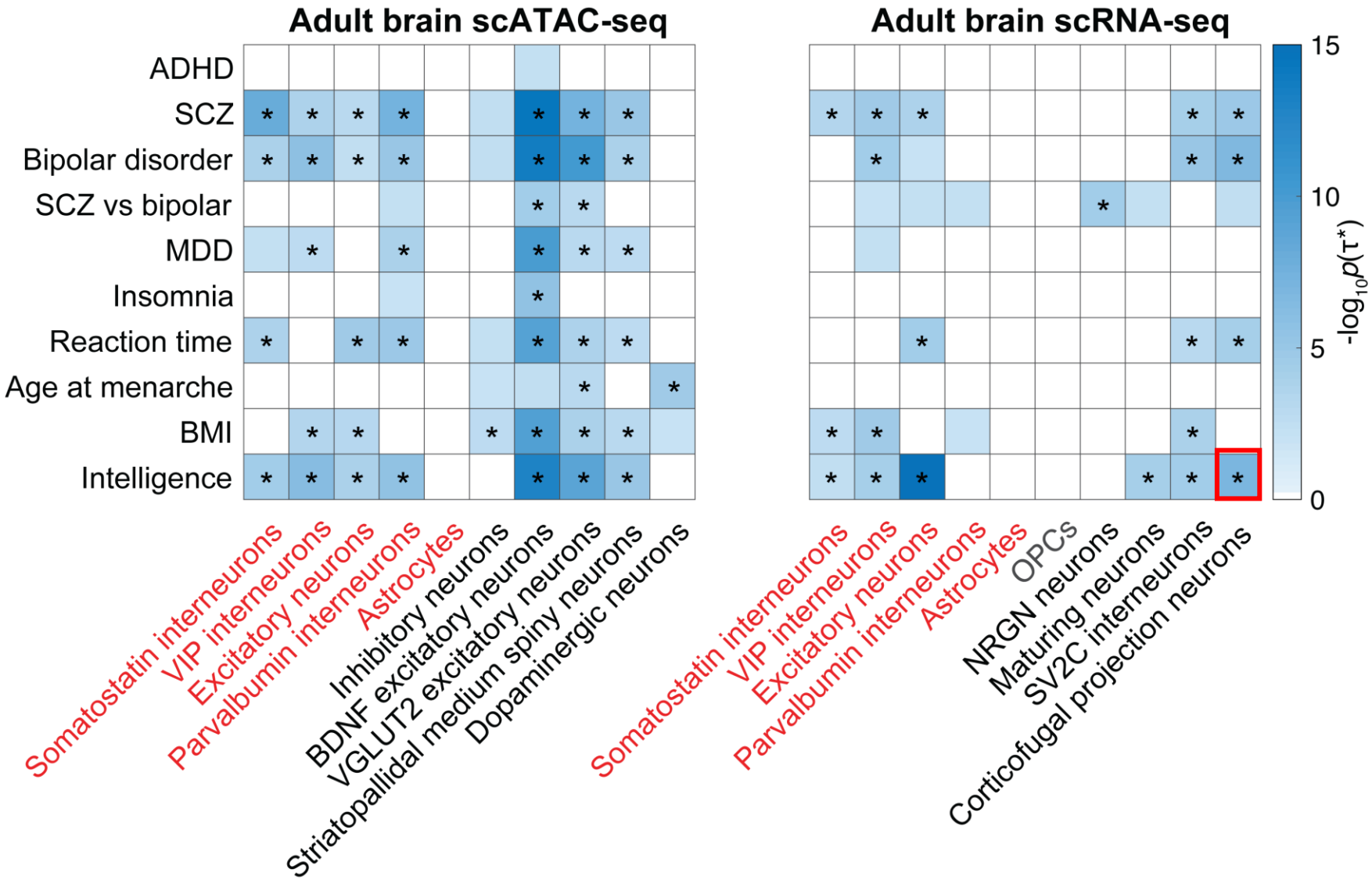
Interesting associations: Bipolar/SCZ – parvalbumin interneurons



- Decreased expression and diminished function of parvalbumin interneurons in regulating balance of E/I have been observed in BP and SCZ cases

(Toker et al. Biol Psychiatry 2018, Fergusen et al. Front Neural Circuits 2018)

Interesting associations: intelligence – corticofugal projection neuron



(Fernandez et al. *Trends Neurosci* 2007, Runge et al. biorxiv 2020)

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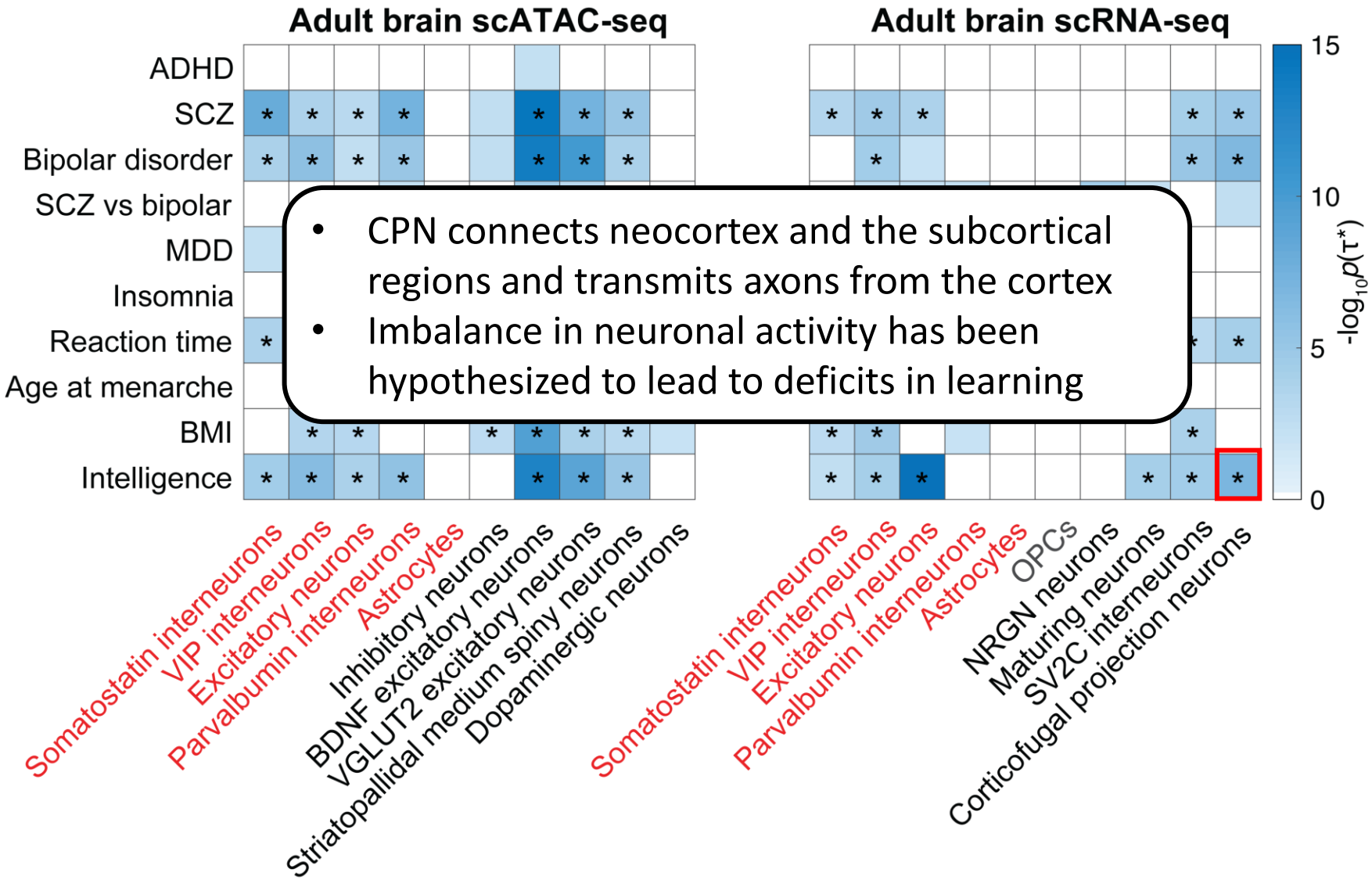

- CPN connects neocortex and the subcortical regions and transmits axons from the cortex
- Imbalance in neuronal activity has been hypothesized to lead to deficits in learning

(Fernandez et al. *Trends Neurosci* 2007, Runge et al. biorxiv 2020)

Conclusions

- Identified significant trait-cell type pairs that can confirm previously associated critical cell types for disease and suggest distinct associations
- Determined that cell-type annotations derived from scATAC-seq were particularly powerful in the data that we analyzed
- Highlight the benefits of analyzing data from different sequencing platforms and different developmental stages to identify disease-critical cell types

ASHG VIRTUAL MEETING 2021 OCTOBER 18-22

Thank you!

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“Leveraging single-cell ATAC-seq to identify disease-critical fetal and adult brain cell types.”
bioRxiv 2021.

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