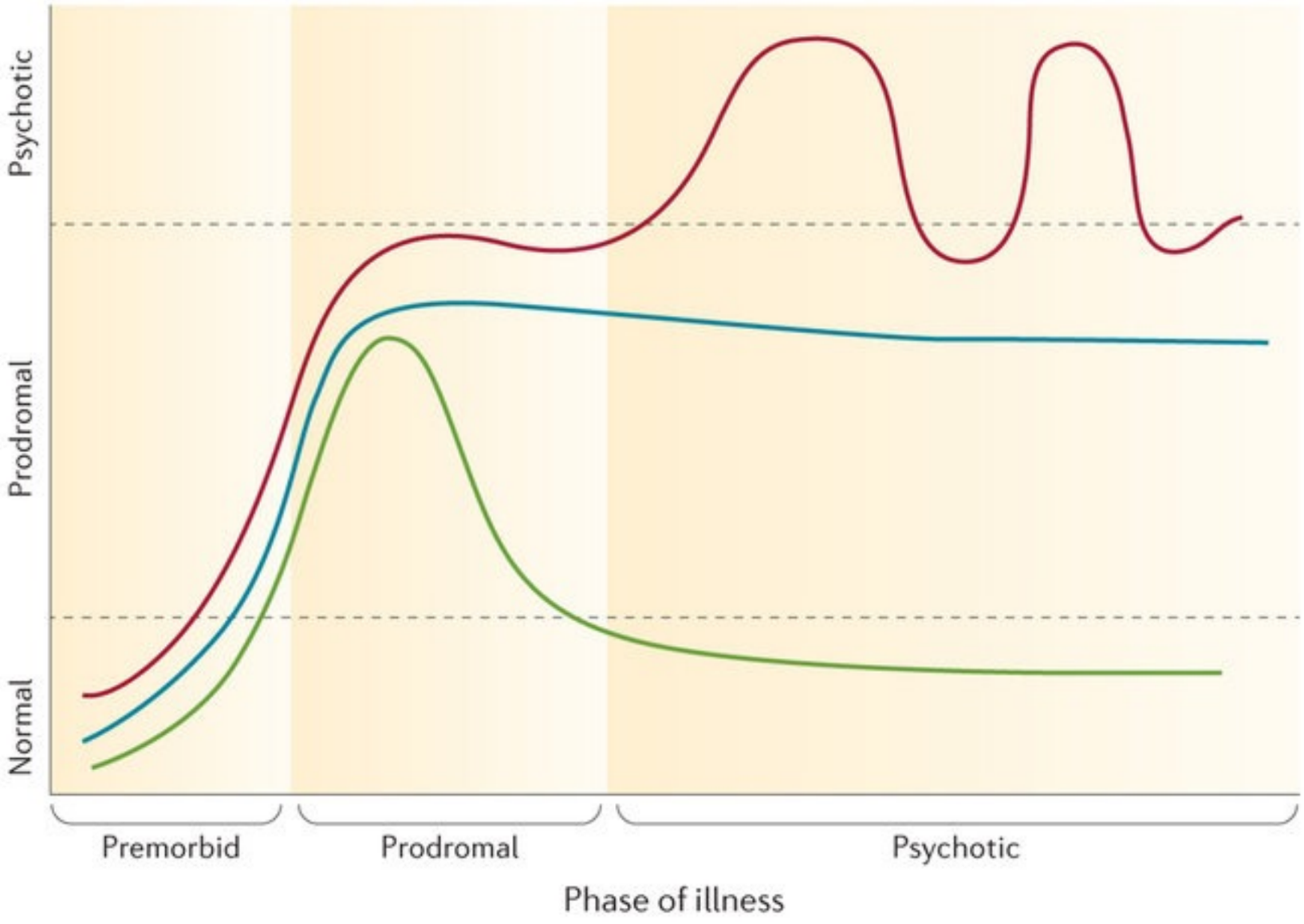
THE ROLE OF MICRO RNA EXPRESSION IN CORTICAL DEVELOPMENT DURING CONVERSION TO PSYCHOSIS

Amanda Zheutlin, Ph.D.
Yale University

DISCLOSURES

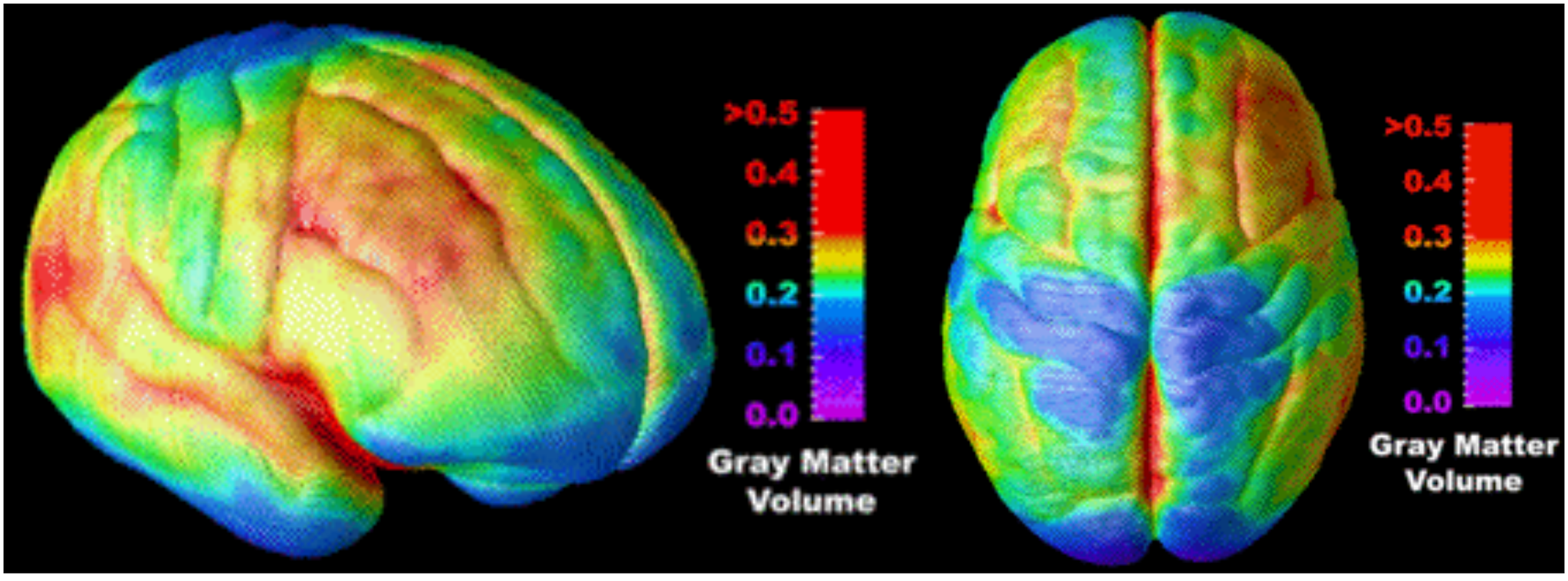
- I have nothing to disclose.

DEVELOPMENT OF PSYCHOSIS



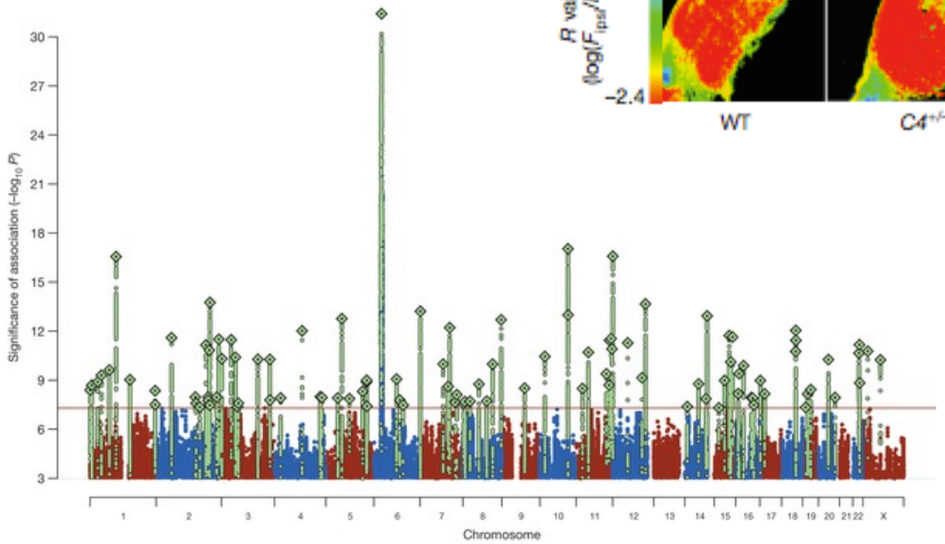
Kahn et al., 2015, *Nature Reviews*

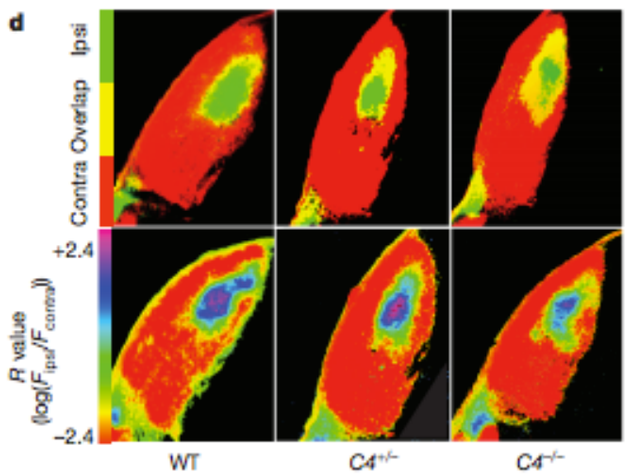
CORTICAL DEVELOPMENT

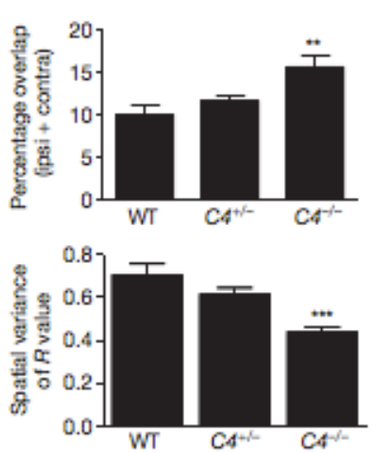


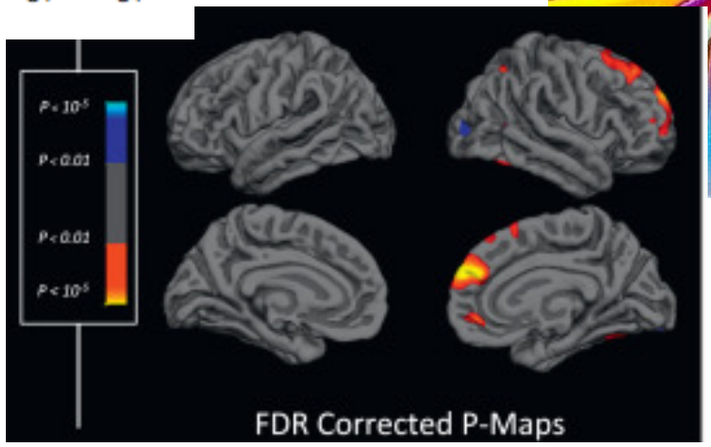
Gogtay et al., 2004, *PNAS*

PLAUSIBLE MECHANISMS





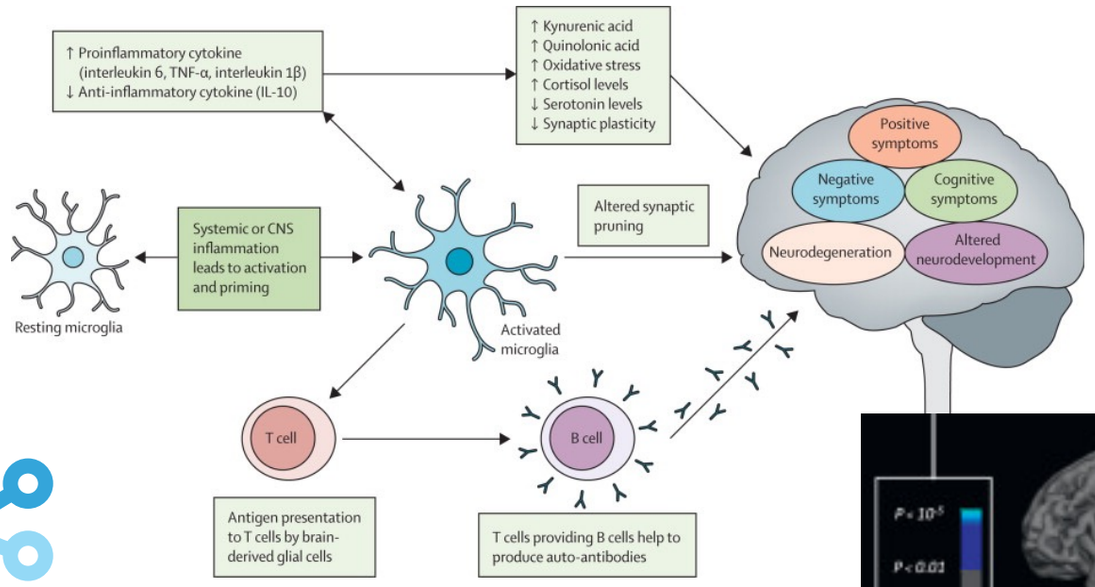


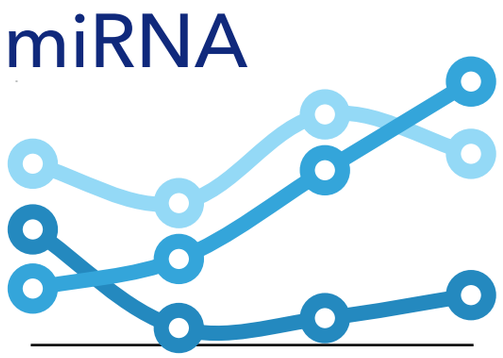


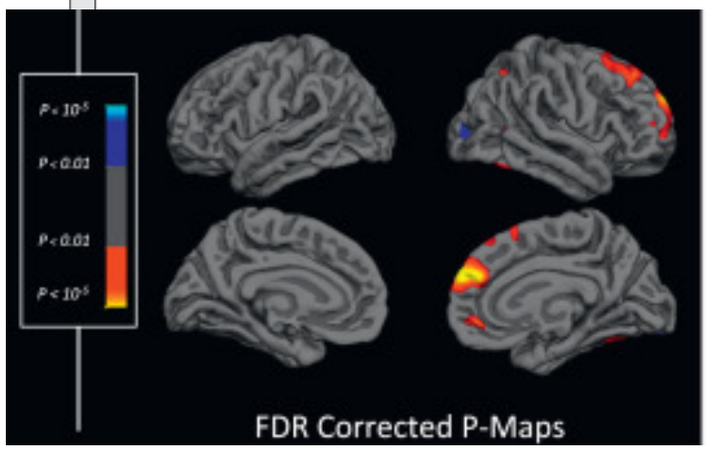
GENES ▸ proteins ▸ cells ▸ circuits ▸ networks ▸ BEHAVIOR

Ripke et al., 2014, *Nature;* Sekar et al., 2016, *Nature;* Cannon, Chung, et al., 2015, *Biol Psych*

CURRENT STUDY







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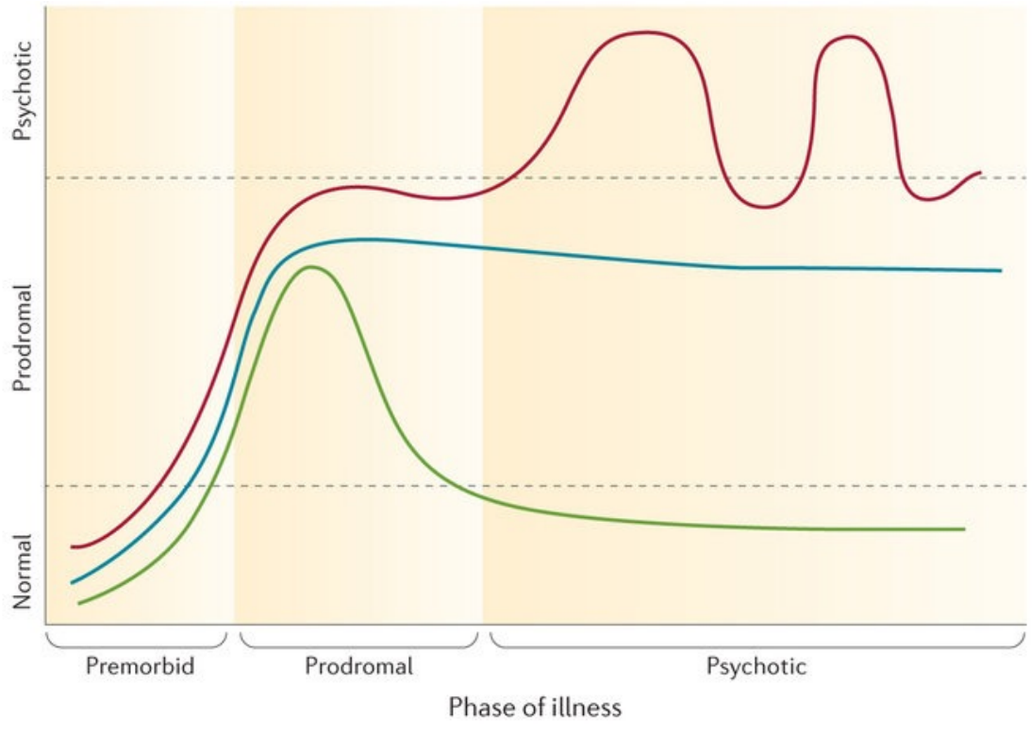
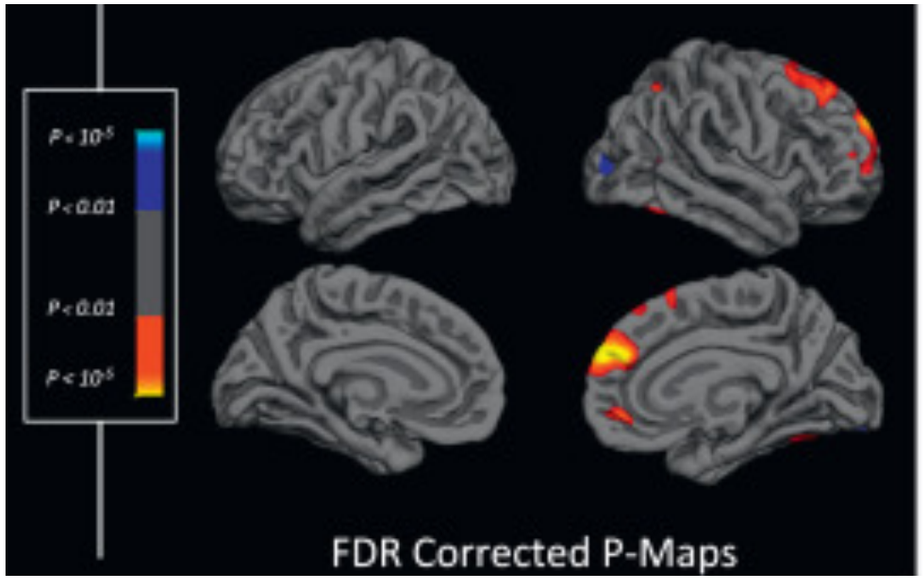
Khandaker, et al., 2015, *Lancet Psych;* Cannon, Chung, et al., 2015, *Biol Psych*

SAMPLE

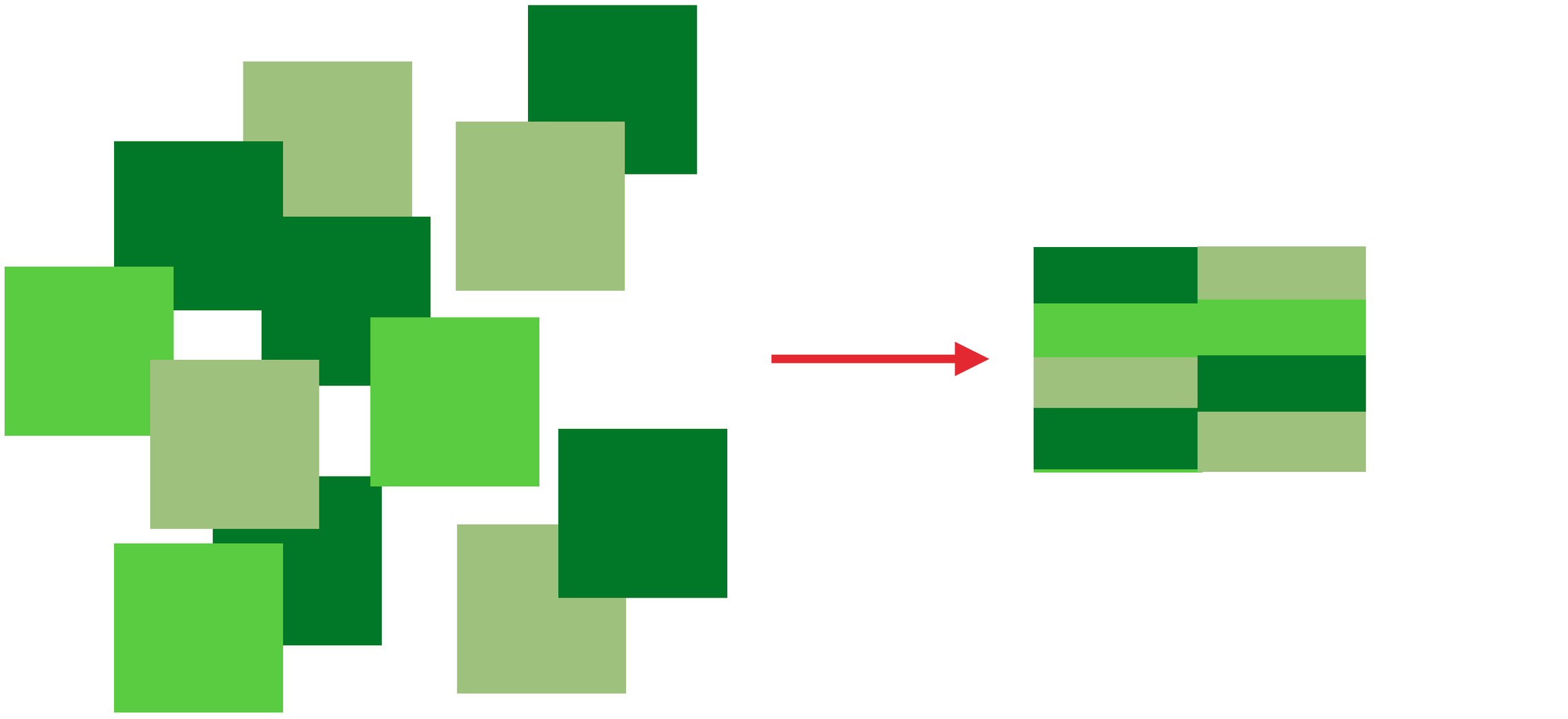
- NAPLS Phase II sub-sample (*N* = 74)
- 47 CHR (13 converters, 34 non-converters); 27 controls
- MRI at baseline and follow-up (12 months or conversion)
- Plasma cytokine levels
- RNA sequencing



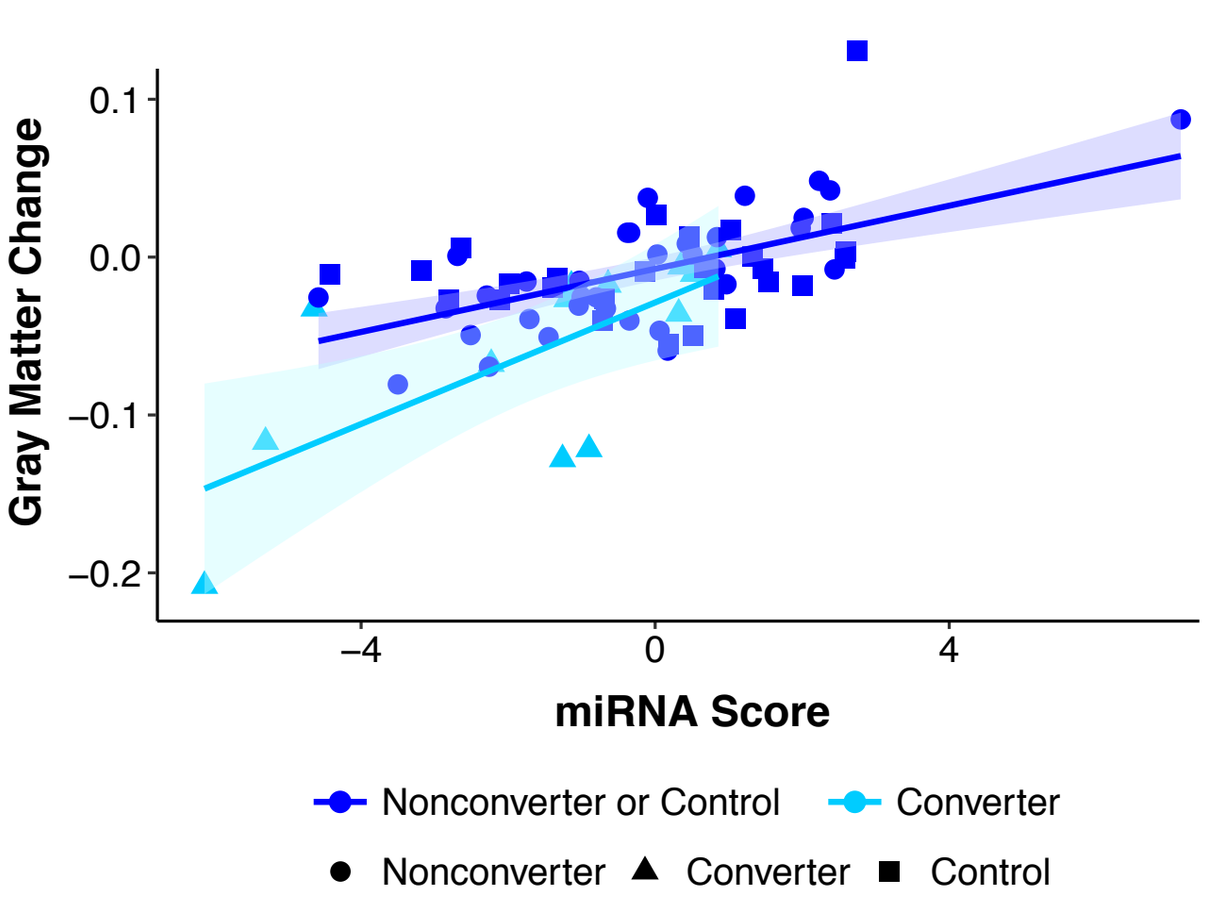


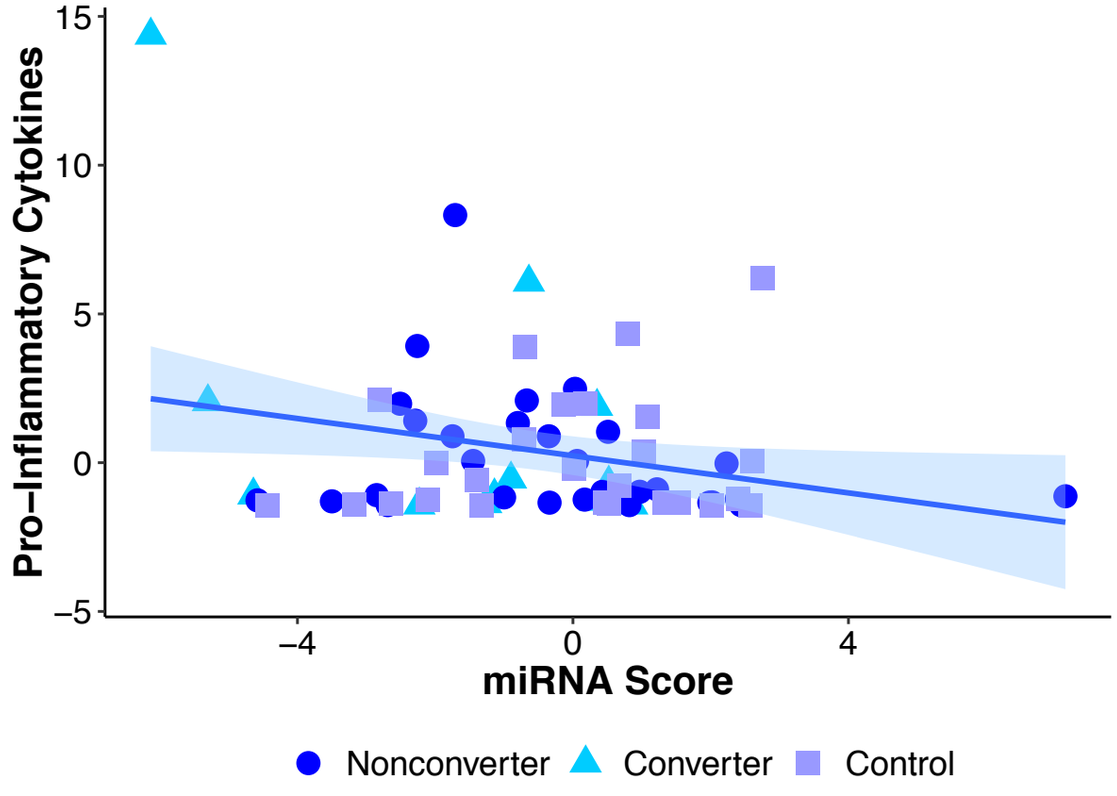
Kahn et al., 2015, *Nature Reviews;* Cannon, Chung, et al., 2015, *Biol Psych*

GENE EXPRESSION CLASSIFIER



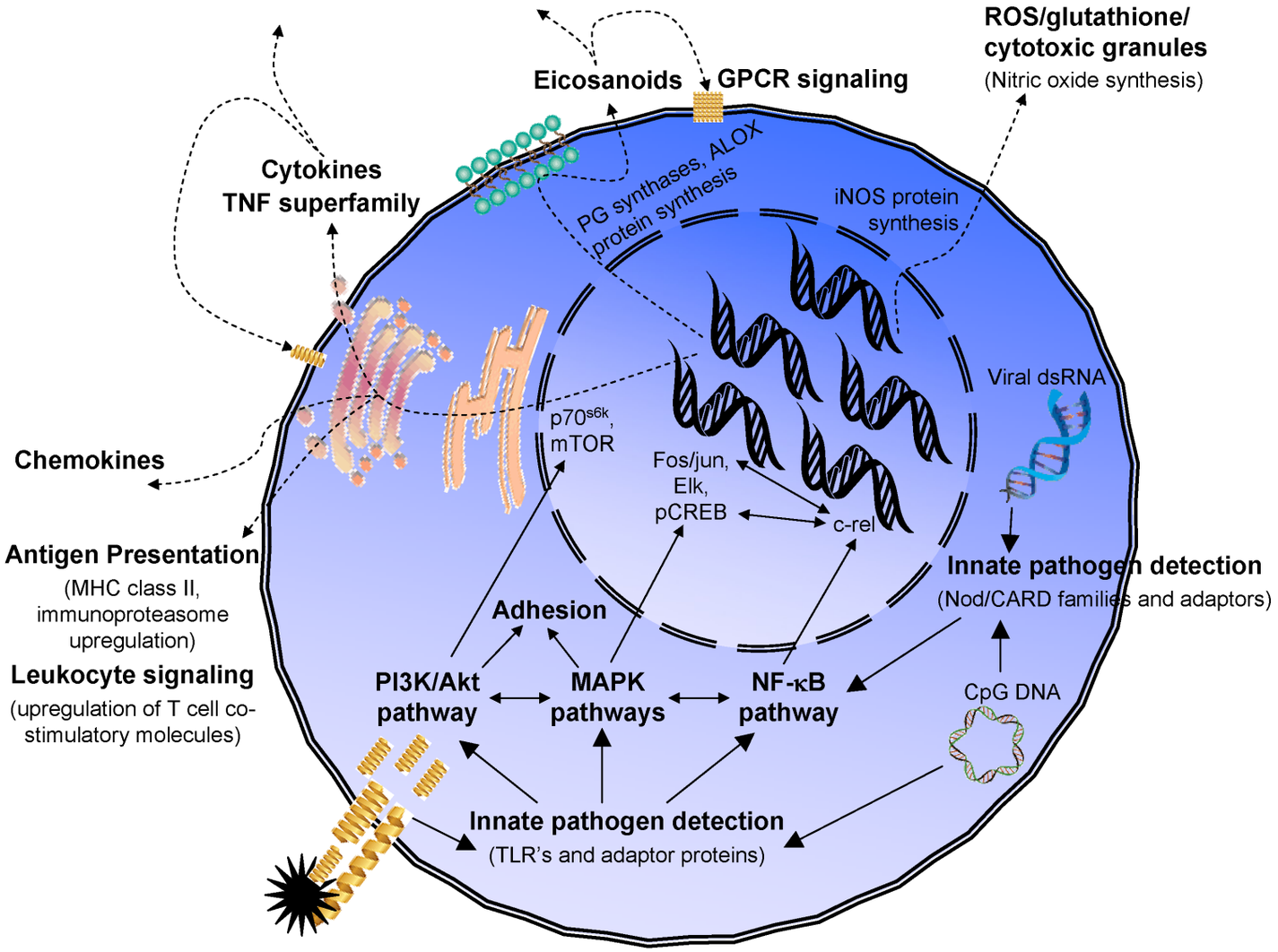
CONVERSION + CYTOKINES





GENE TARGETS

- Significant enrichment for intracellular signaling pathways: PKA signaling, ERK5 signaling, PPARa/ RXRa activation, HGF signaling



Loza et al., 2007, *PLoS One*

CONCLUSIONS

- miRNA regulation of intracellular signaling within immune cells may be abnormal in individuals during conversion to psychosis
- Peripheral immune cell miRNA abnormalities at this critical period may promote microglial activation and impair synaptic pruning via increased pro-inflammatory cytokine signaling and/or systemic inflammation
- Independent replication and experimental validation are both key next steps

ACKNOWLEDGEMENTS

THANK YOU!

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The Role of microRNA Expression in Cortical Development During Conversion to Psychosis

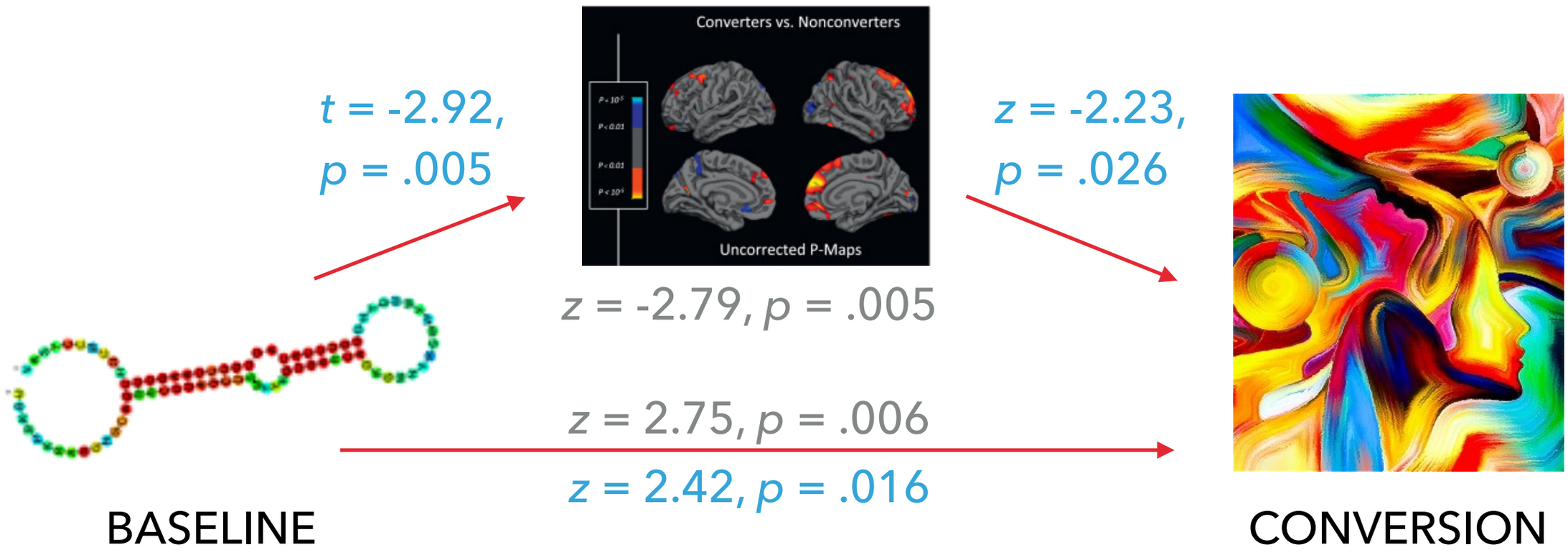
Amanda B Zheutlin, Clark D Jeffries[2], Diana O Perkins[3], Yoonho Chung[1], Adam M Chekroud[1], Jean Addington[4], Carrie E Bearden[5], Kristin S Cadenhead[5], Barbara A Cornblatt[7], Daniel H Mathalon[8], Thomas H McGlashan[9], Larry J Seidman[10], Elaine F Walker[11], Scott W Woods[9], Ming Tsuang[6] and Tyrone D Cannon*[,1,9]

[1]Department of Psychology, Yale University, New Haven, CT, USA; [2]Renaissance Computing Institute, University of North Carolina, Chapel Hill, NC, USA; [3]Department of Psychiatry, University of North Carolina, Chapel Hill, NC, USA; [4]Department of Psychiatry, University of Calgary, Alberta, Canada; [5]Department of Psychiatry & Biobehavioral Sciences, University of California—Los Angeles, Los Angeles, CA, USA; [6]Department of Psychiatry, University of California—San Diego, San Diego, CA, USA; [7]Department of Psychiatry, Zucker Hillside Hospital, Long Island, NY, USA; [8]Department of Psychiatry, University of California—San Francisco, San Francisco, CA, USA; [9]Department of Psychiatry, Yale University, New Haven, CT, USA; [10]Department of Psychiatry, Beth Israel Deaconess Medical Center and Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [11]Department of Psychology, Emory University, Atlanta, GA, USA

- NIMH for funding NAPLS2

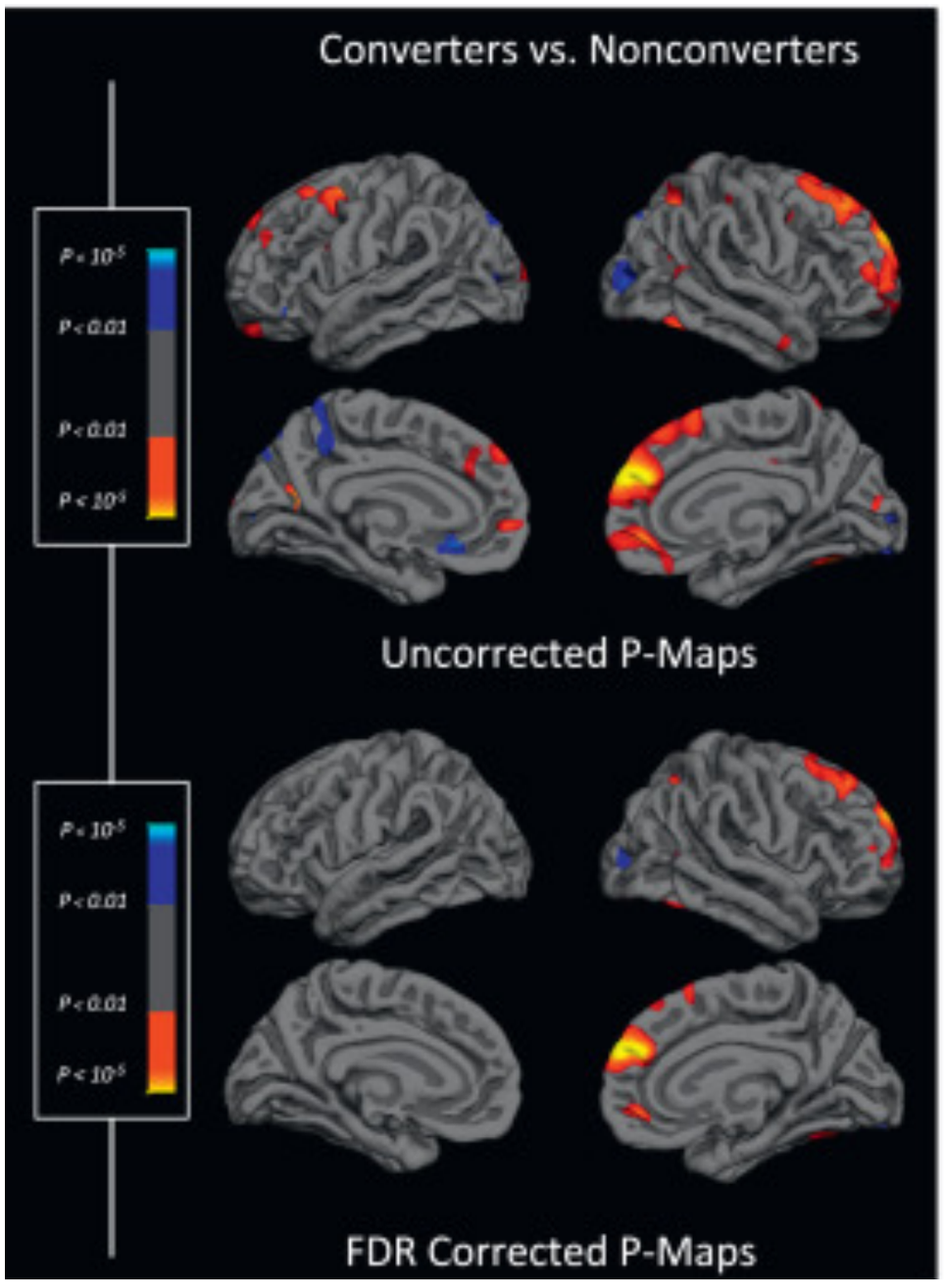
MICRO RNA EXPRESSION

- Gray matter reduction partially mediated effect of miRNA score on conversion (~18% of direct effect accounted for by mediator)



CORTICAL THICKNESS

- Rate of reduction in prefrontal thickness across time
  - Baseline + follow-up (12mo or conversion)
  - Converters show **greater annualized rates of change** (faster reduction) than non-converters
- Scans, QC, analysis
  - 8 sites, ADNI protocol
  - FreeSurfer
  - FDR-corrected comparisons in annualized rates of change by group



Cannon, Chung, et al., 2015, *Biol Psych*

MIRNA

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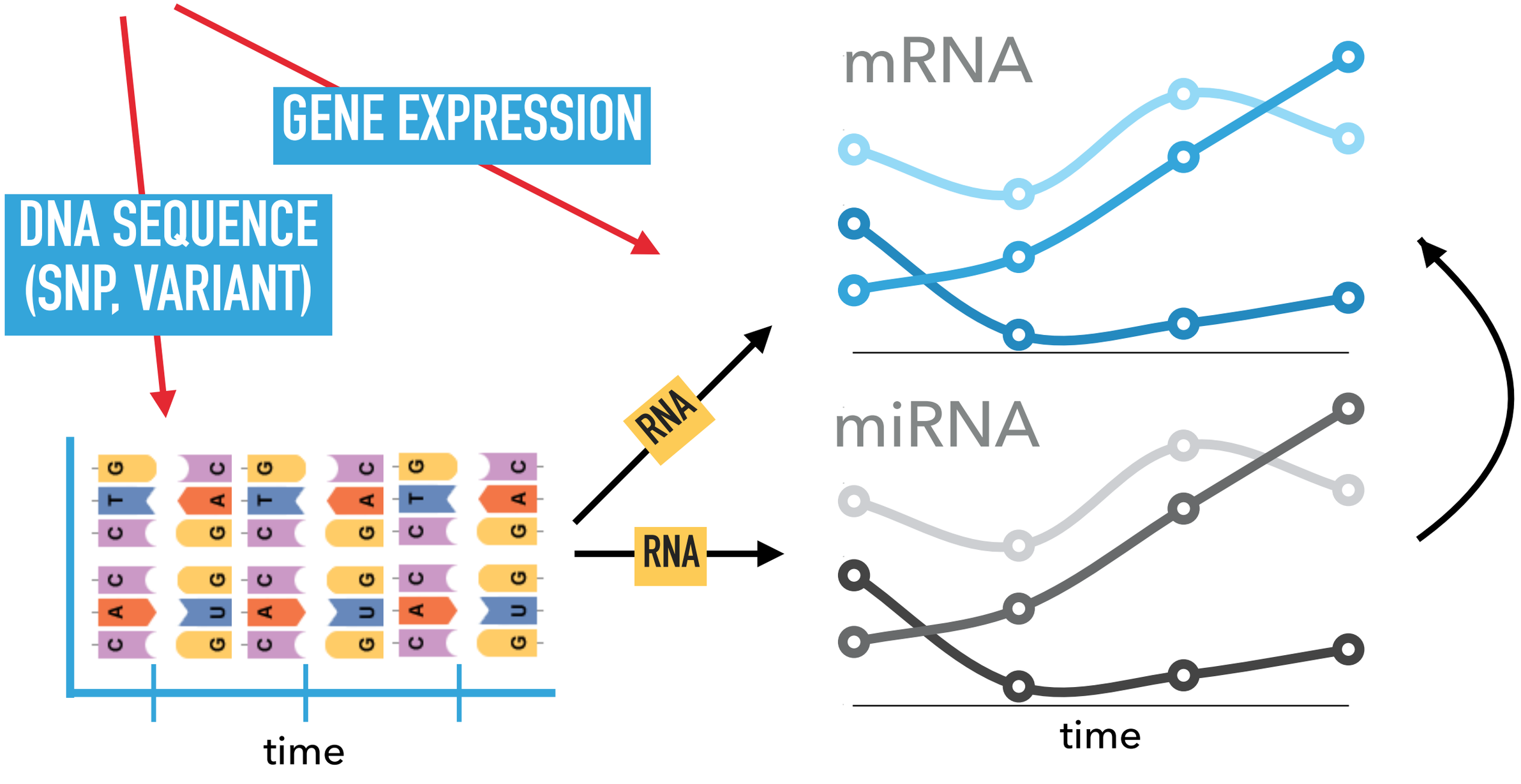
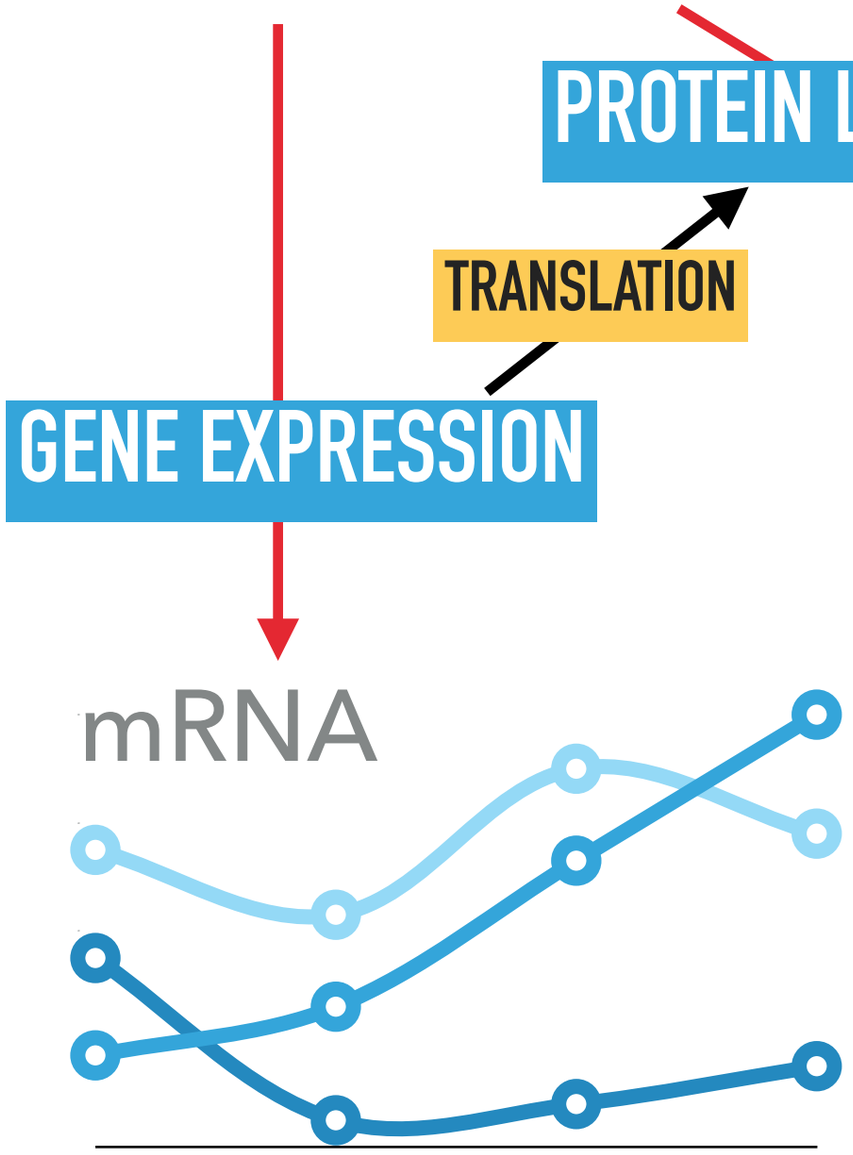
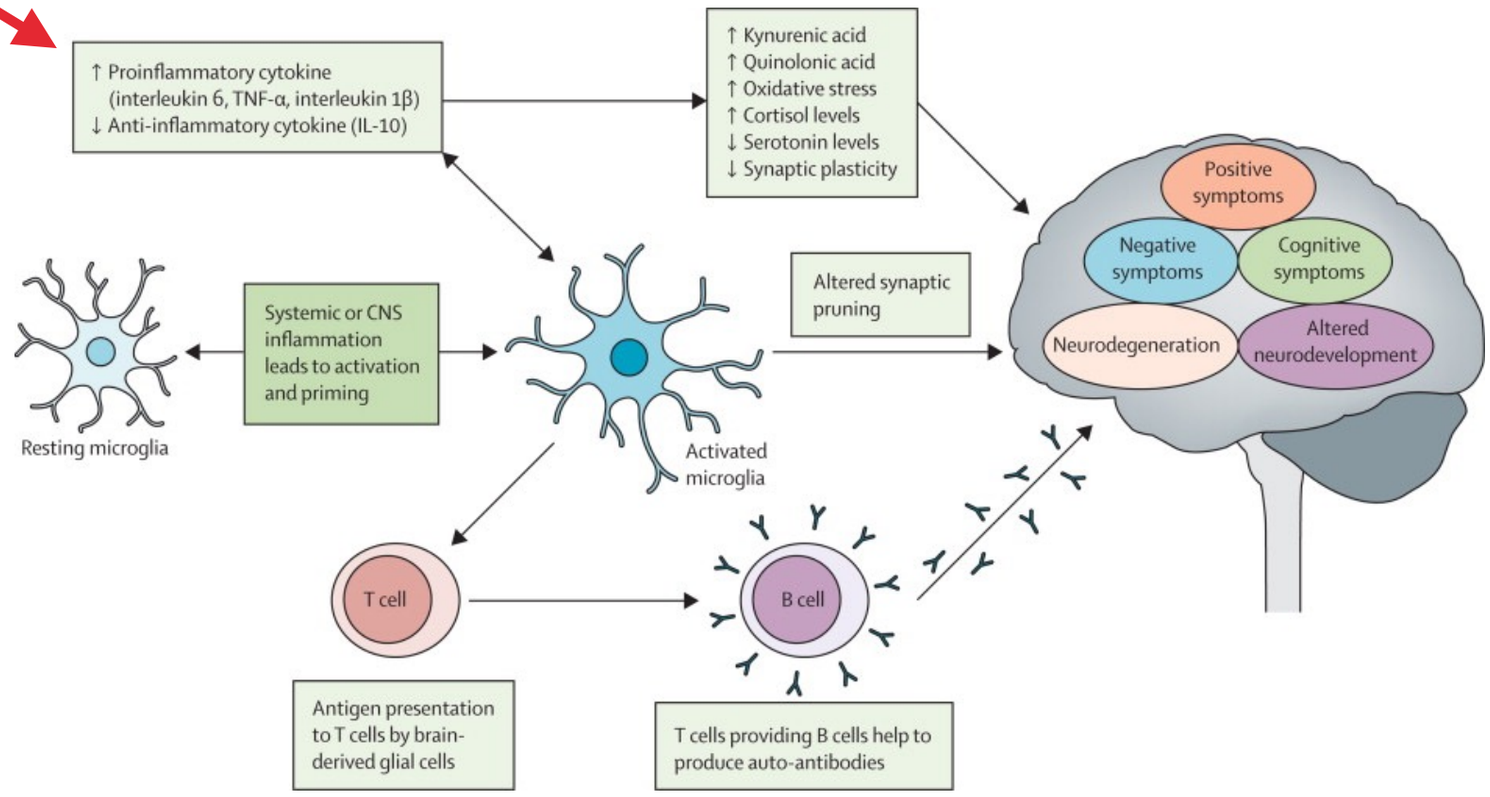


CYTOKINES

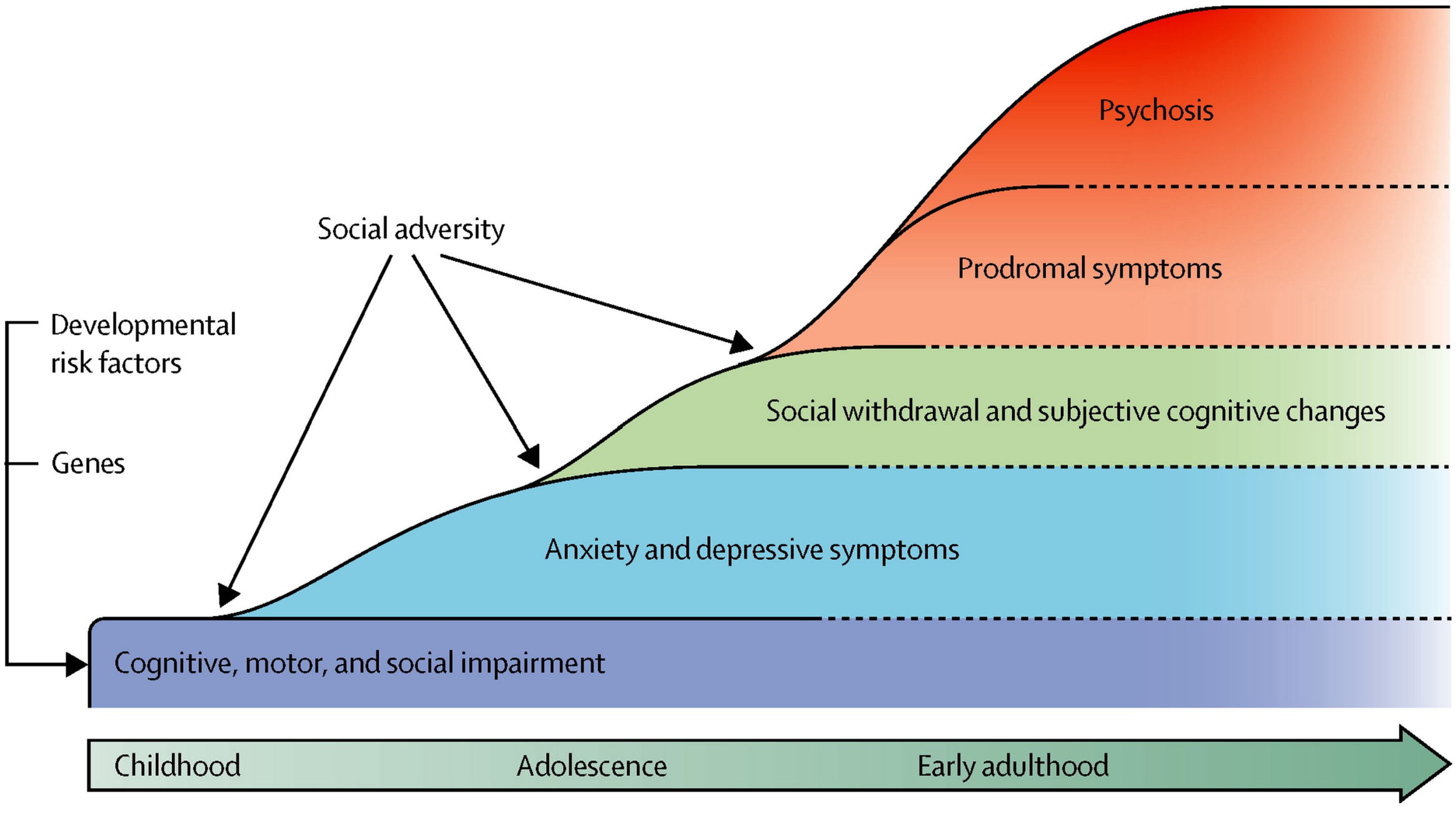
GENES proteins cells circuits networks BEHAVIOR





Khandaker, et al., 2015, *Lancet Psych*

DEVELOPMENT OF SCHIZOPHRENIA

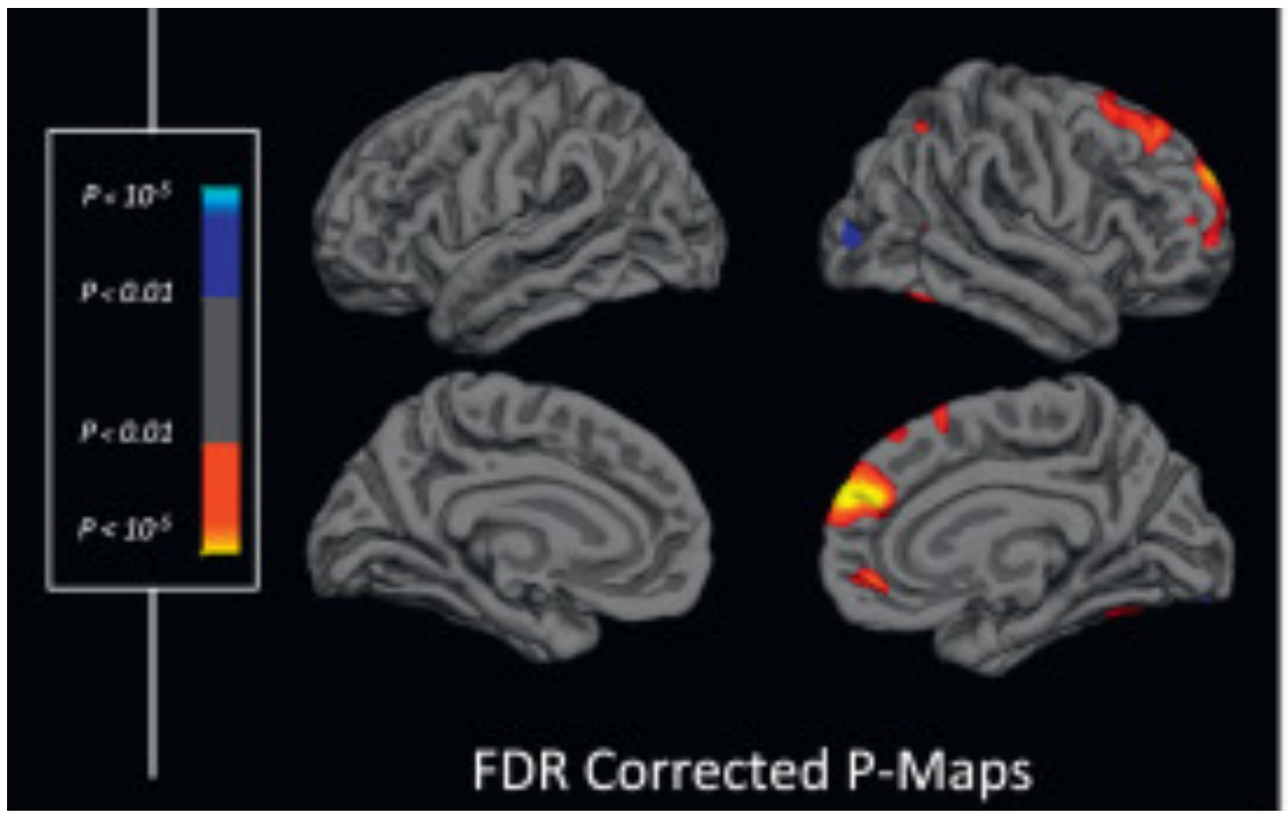


Howes & Murray, 2014, *Lancet*

STUDY 3

CORTICAL THINNING

- Rate of reduction in prefrontal thickness across time
- Baseline + follow-up (12mo or conversion)
- Converters show **greater annualized rates of change** (faster reduction) than non-converters

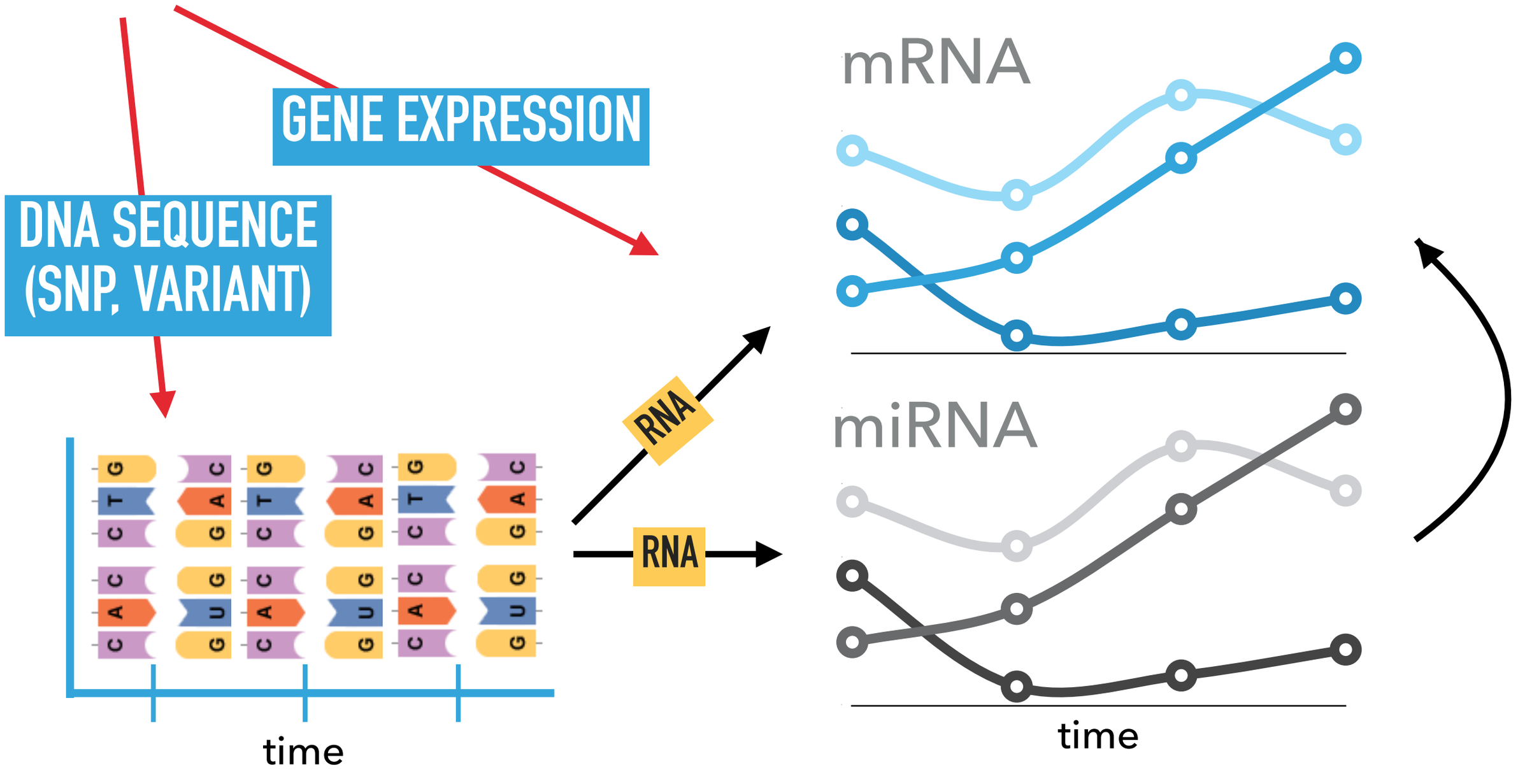


Cannon, Chung, et al., 2015, *Biol Psych*

STUDY 2

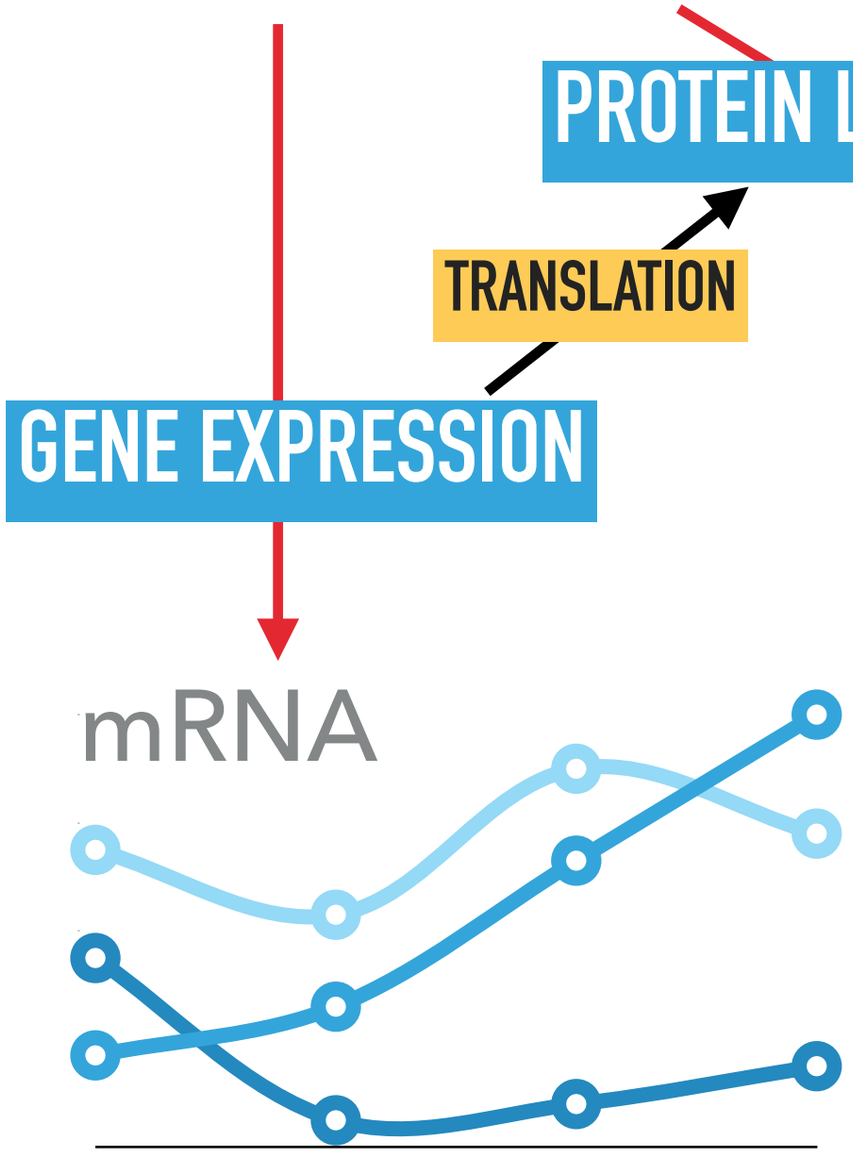
GENETICS

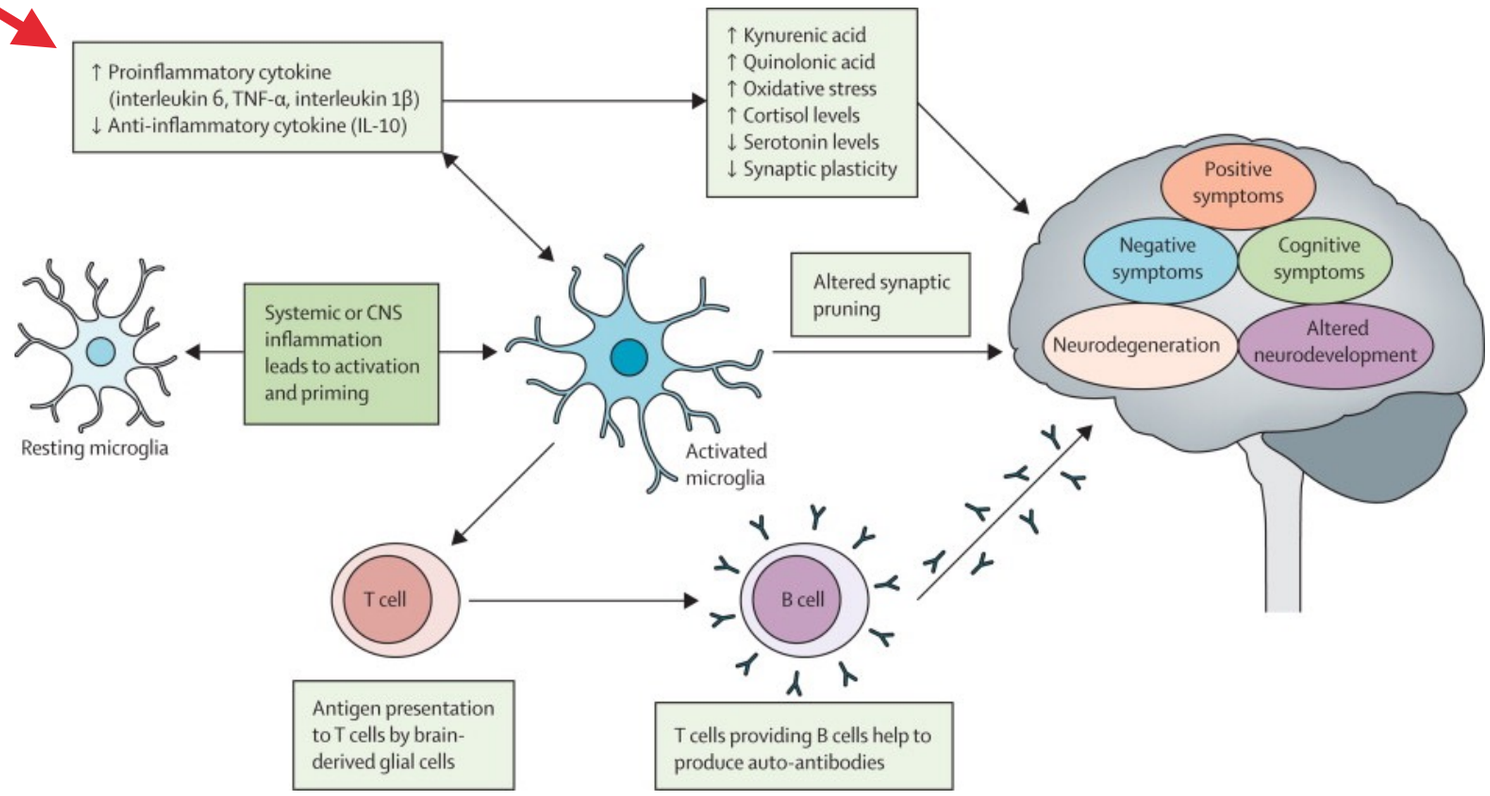
GENES ▸ proteins ▸ cells ▸ circuits ▸ networks ▸ BEHAVIOR



CYTOKINES

GENES proteins cells circuits networks BEHAVIOR





Khandaker, et al., 2015, *Lancet Psych*