NORMENT

Shared Genetic Determinants Between the Brain Functional Connectome and Psychiatric Disorders

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No disclosures to declare

Slide added to comply with ACCME accreditation guidelines

BACKGROUND

Psychiatric conditions are highly polygenic and complex[1]

Psychiatric conditions share symptoms and genetic profiles[2]

MRI studies show that structural and functional changes are widespread across the brain[3]

Investigate distributed nature of genetic effects in the brain and its associations with psychiatric conditions

1. Anttila *et al. Science* (2018), Sullivan & Geschwind *Cell* (2019), Paulus & Thompson *JAMA Psychiatry* (2019)
2. Plana-Ripoll *et al. JAMA Psychiatry* (2019), Bulik-Sullivan *et al. Nature Genetics* (2015)
3. Petterson-Yeo *et al. Neurosci. Biobehav. Rev.* (2011), Arnatkeviciute *et al. NeuroImage* (2021)

DATASET

biobank uk

fMRI

genetics

N=~42k

N=~500k

WHY USE FMRI?

Changes in fMRI features associated with many psychiatric conditions[1]

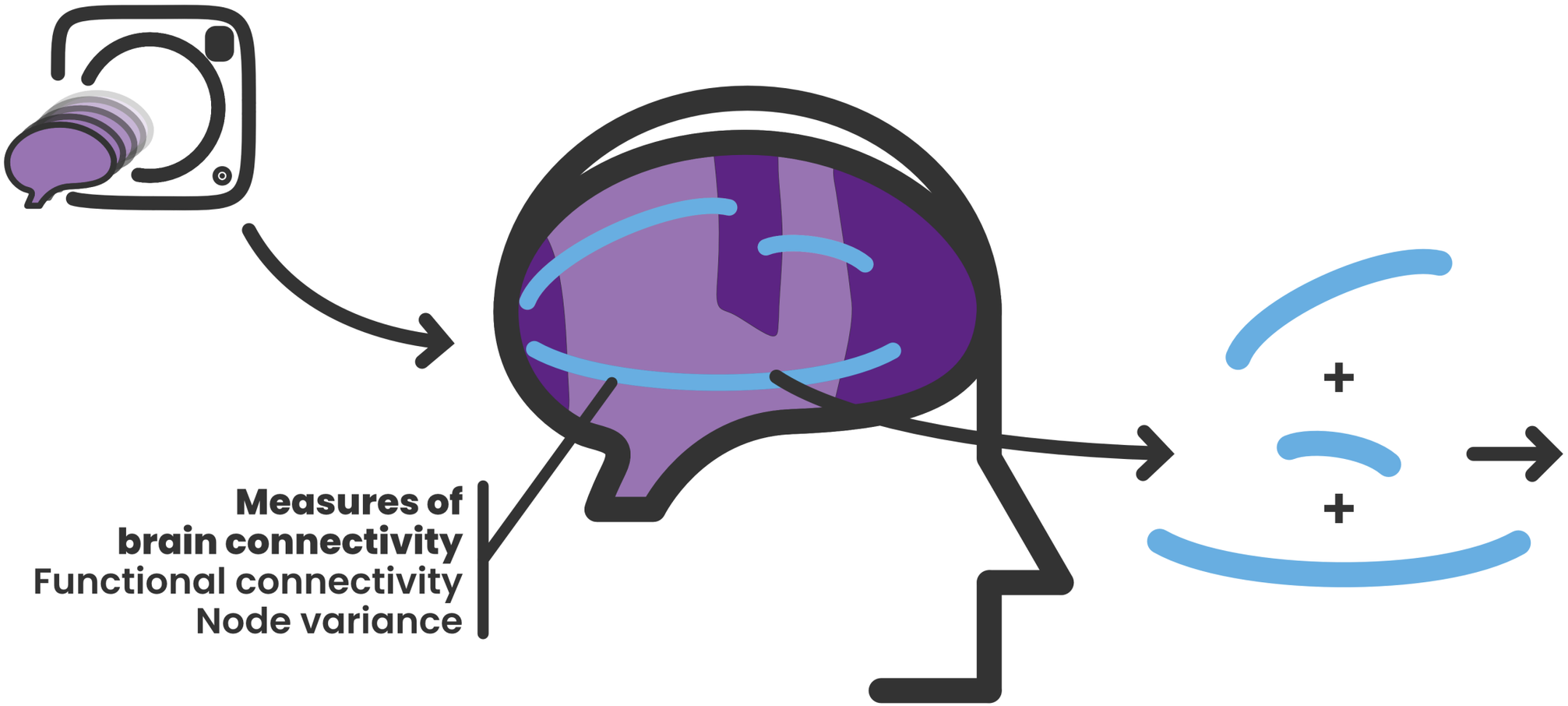
Changes in structural MRI features have been used to study genetic architecture of conditions[2]

fMRI data provides insight into brain function rather than structure

Integrate changes in fMRI features with processes underlying psychiatric conditions

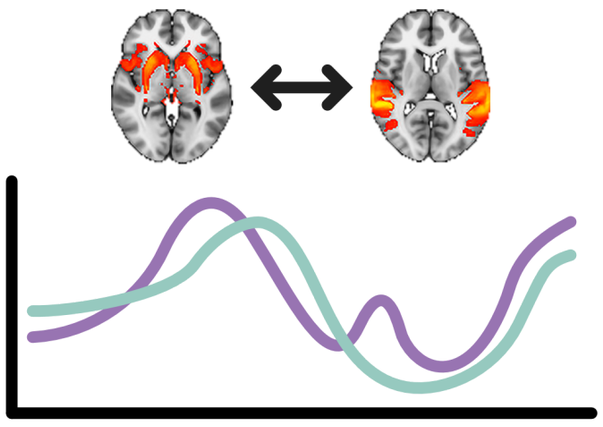
1. e.g. Brakowski *et al. J. Psychiatr. Res.* (2017), Syan *et al. J. Psychiatry. Neurosci.* (2018), etc.
2. Elliott *et al. Nature* (2018), Friston *et al. Schizophr. Res.* (2016)

BRAIN CONNECTIVITY MEASURES

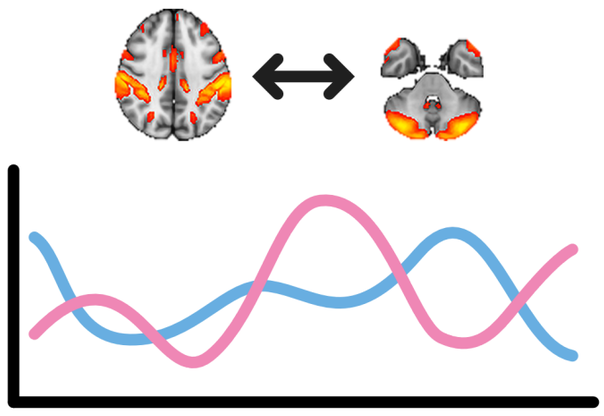


BRAIN CONNECTIVITY MEASURES

Functional Connectivity

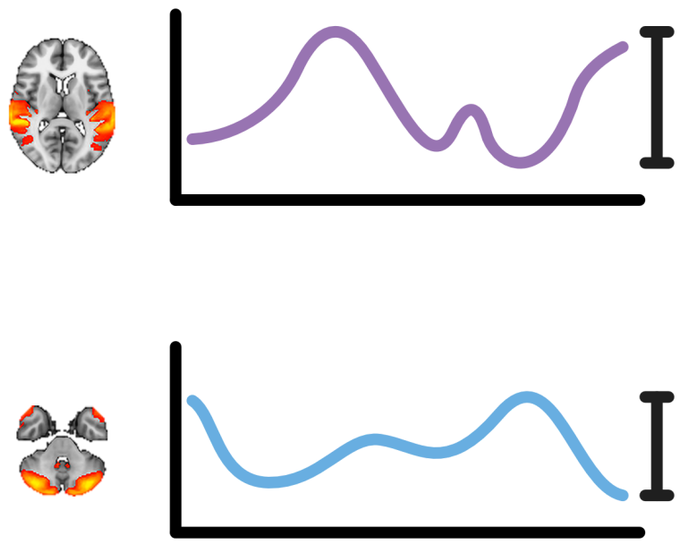


Positive correlation



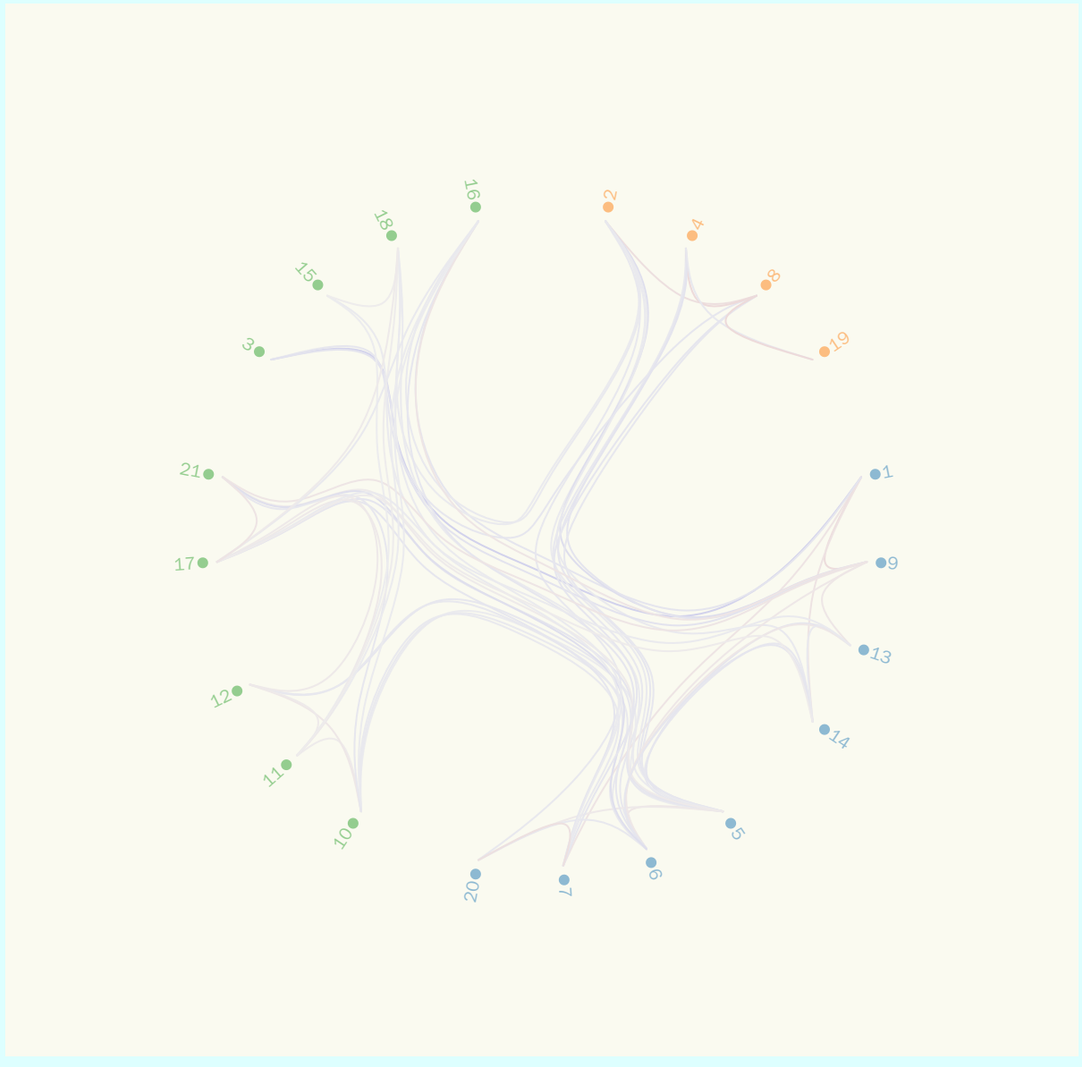
Negative correlation

Temporal node variance

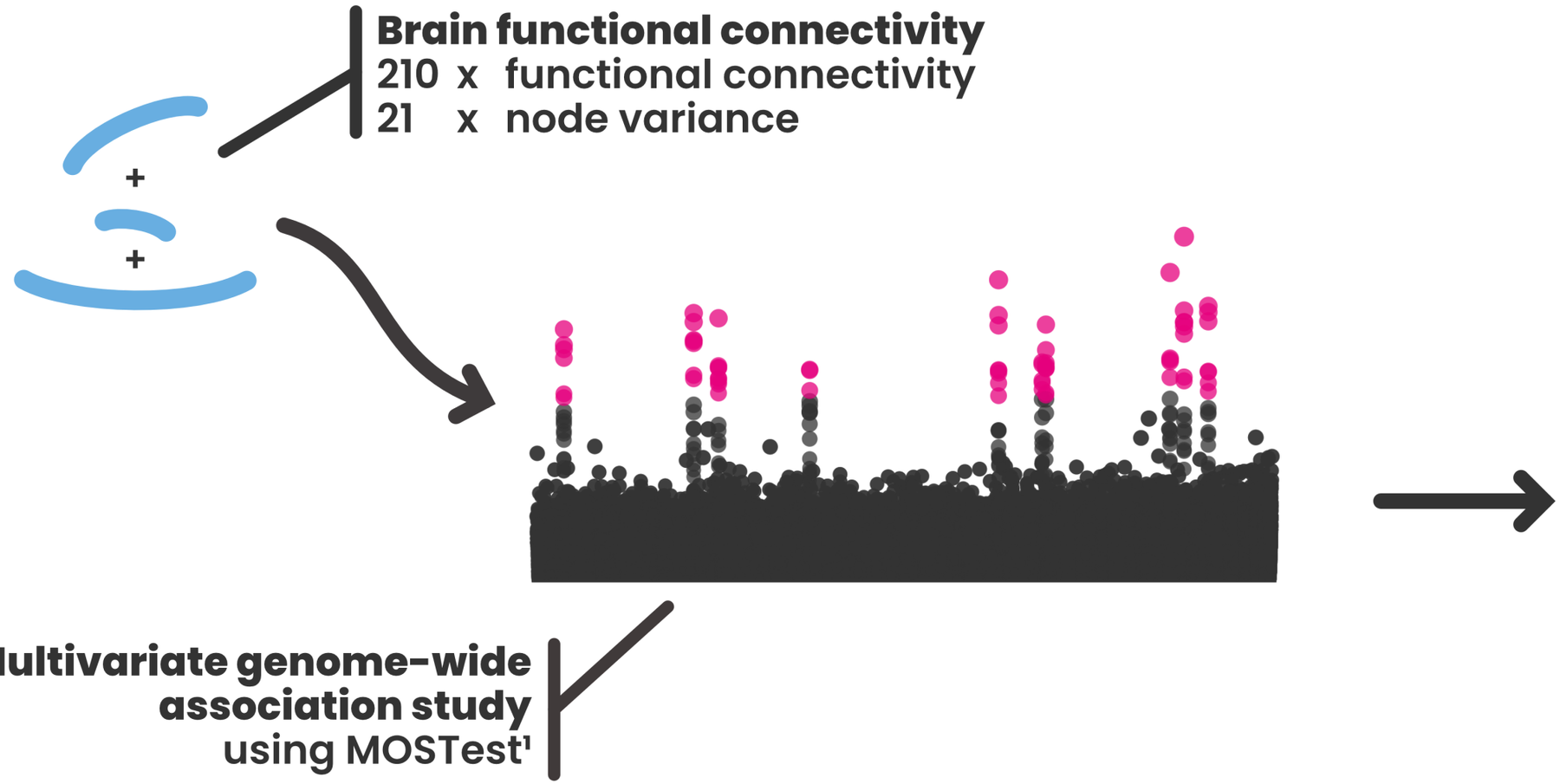


BRAIN FUNCTIONAL CONNECTIVITY

This shows the connections between brain regions (network "nodes"). Click on the Highlight network button to turn on/off viewing of all nodes. When that is turned off, you can click on individual nodes to see their connections. The node numbers here refer to the set of non-artefactual group-ICA components.



MULTIVARIATE GWAS



1. van der Meer *et al. Nature Communications* (2020), github.com/precimed/mostest

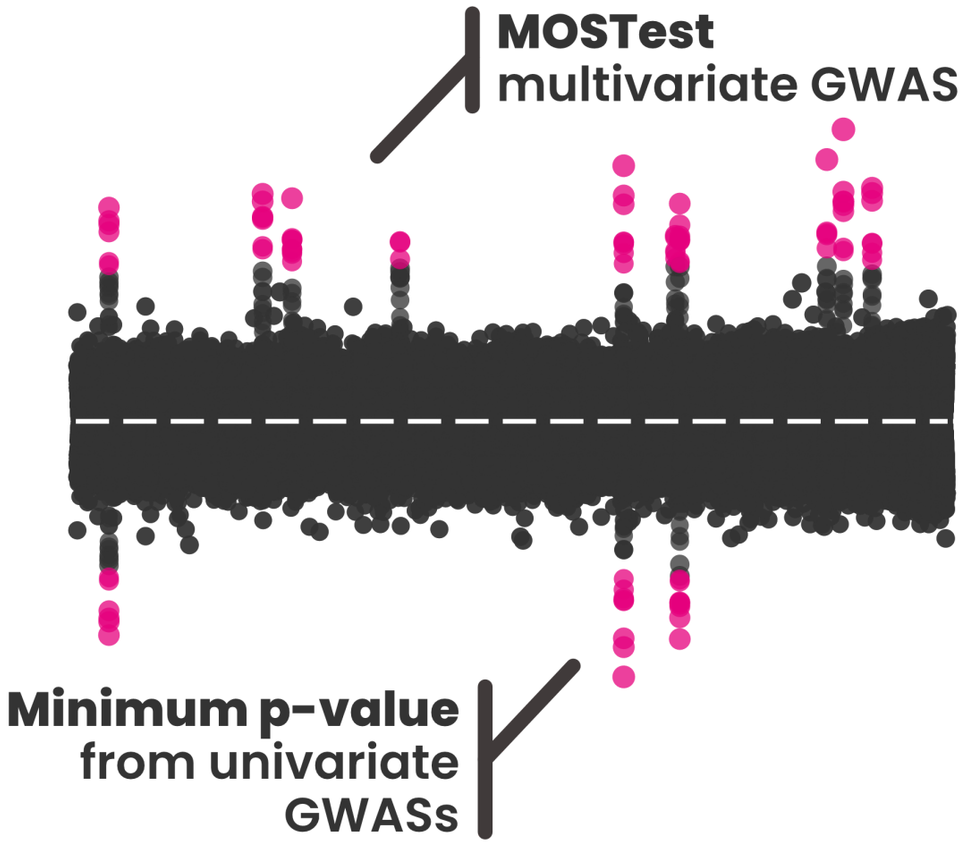
WHAT IS MOSTEST?

Identifies small and distributed effects not detectable in univariate GWAS

Takes univariate *z*-scores for each SNP across all phenotypes

↓

Integrates into multivariate test statistic through Mahalanobis distance



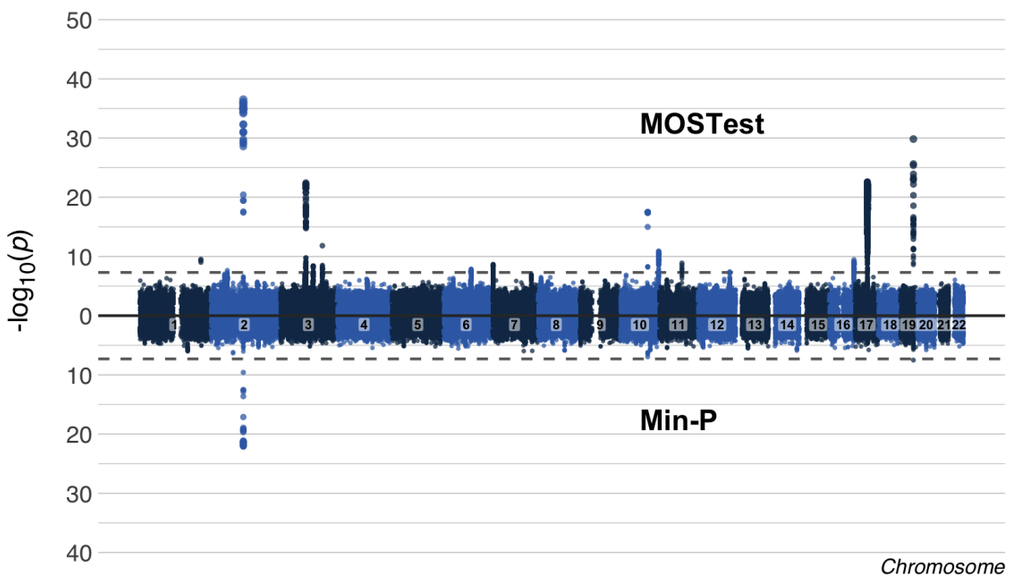
Details in van der Meer *et al. Nature Communications* (2020), github.com/precimed/mostest

MOSTEST MANHATTAN PLOTS

Functional connectivity

MOSTest 15 loci

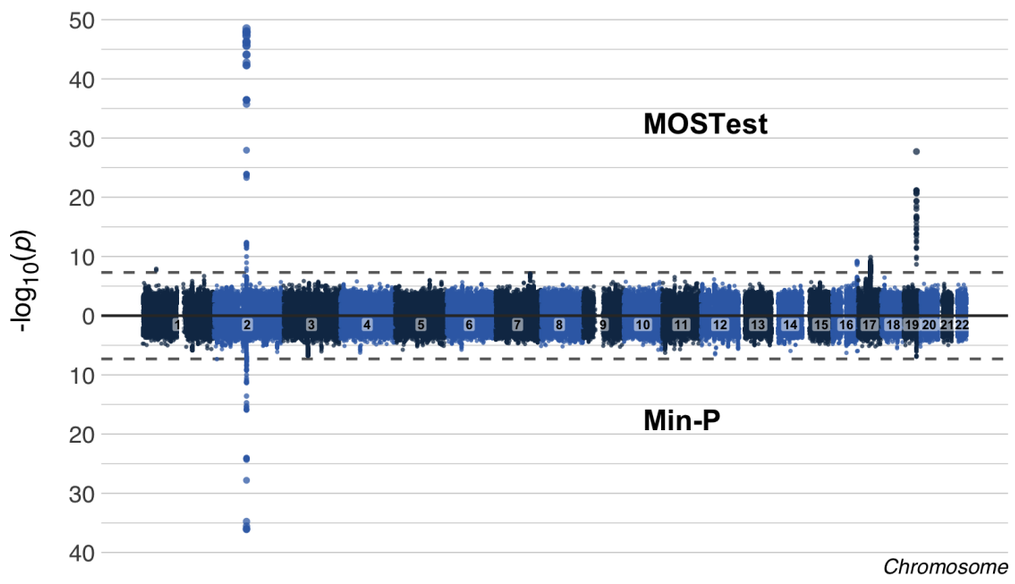
Min-P 2 loci



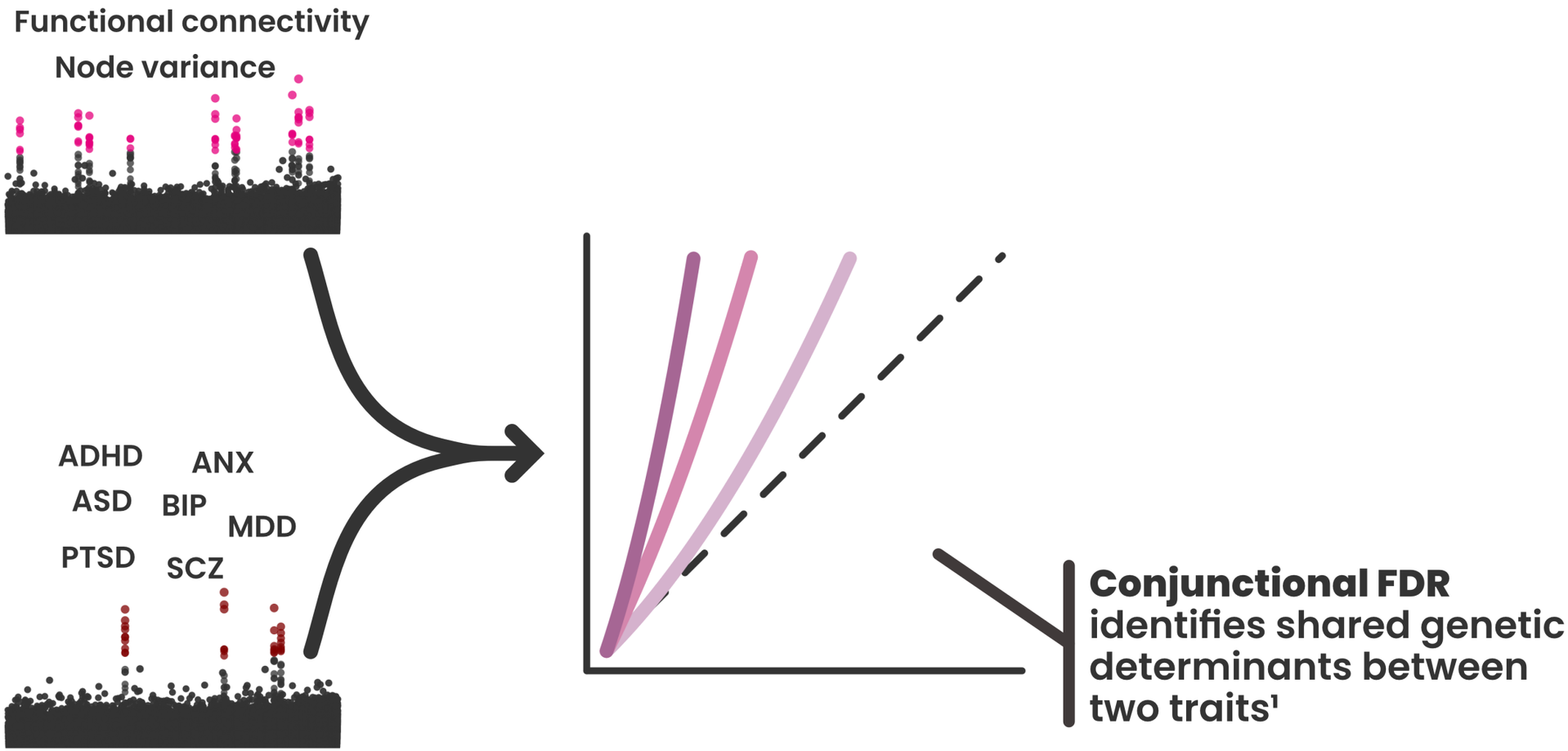
Node variance

MOSTest 5 loci

Min-P 3 loci

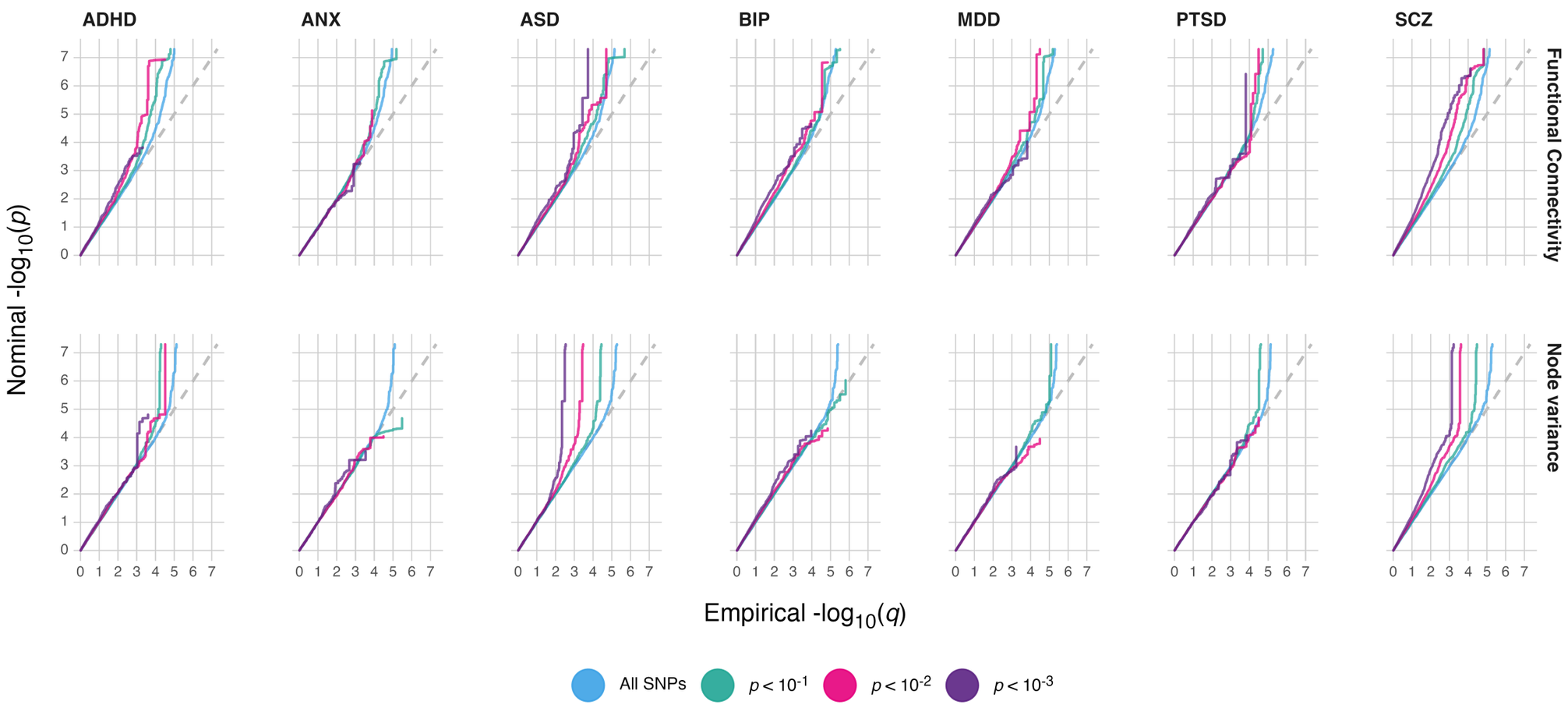


GENETIC OVERLAP

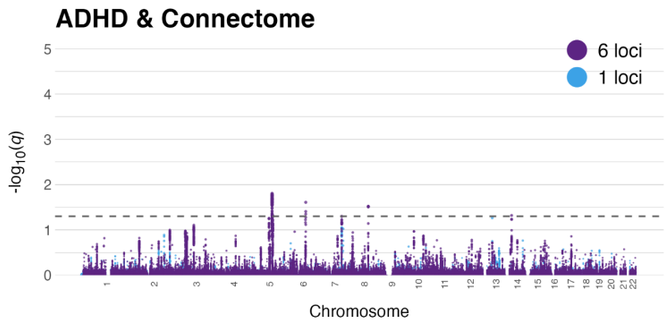


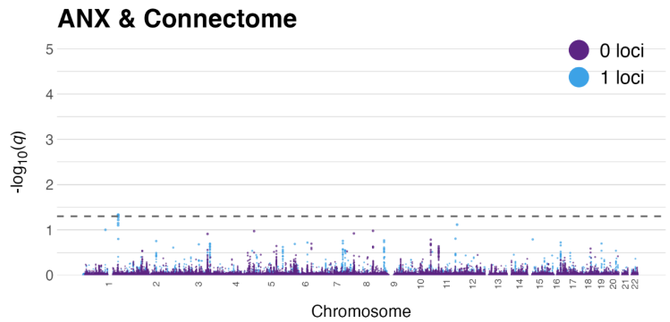
1. *PleioFDR*, Andreassen *et al. PLoS Genetics* (2019), github.com/precimed/pleiofdr

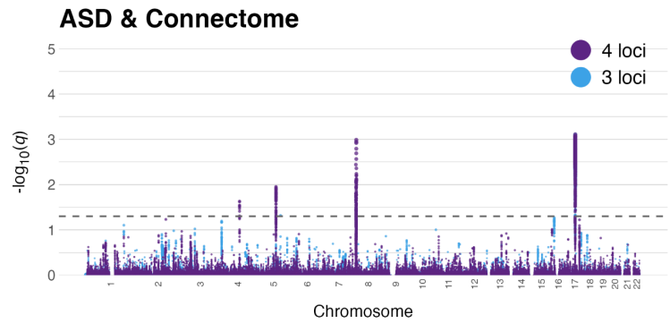
CONJUNCTIONAL FDR

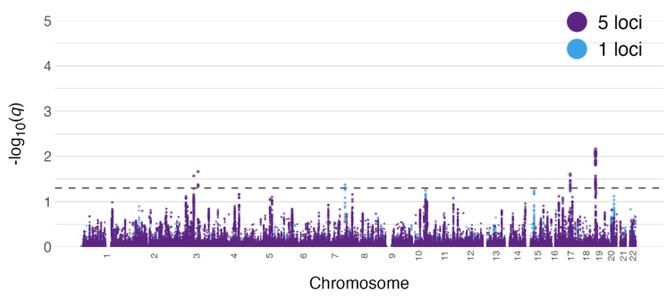


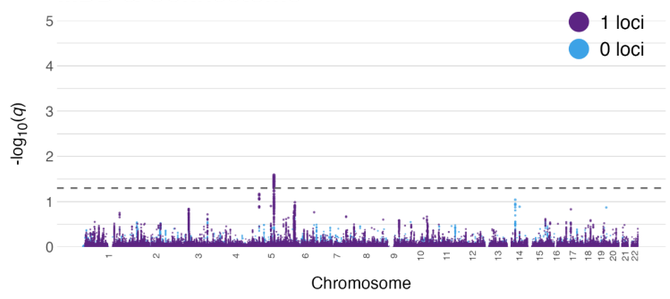
CONJUNCTIONAL FDR

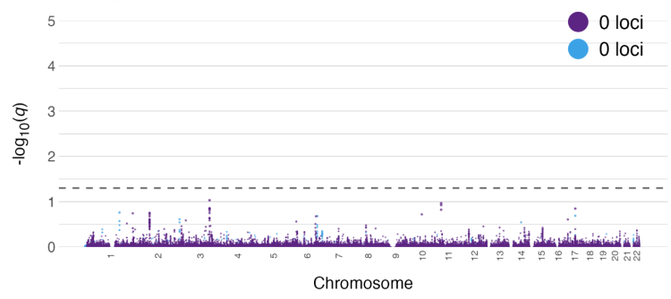


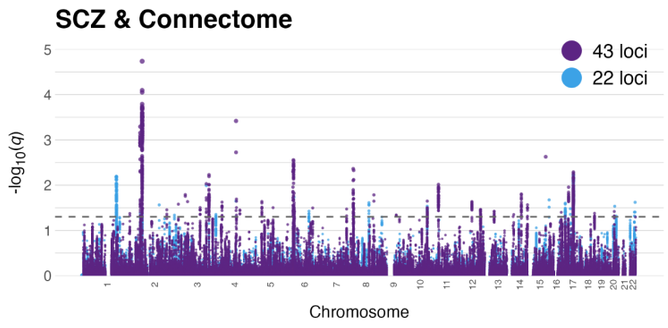












Functional connectivity (FC)
Node variance

MAPPED GENES

Functional annotation and mapping of genome-wide assocation studies (FUMA[1])

↓

Gene set mapped from the significant loci in the GWAS

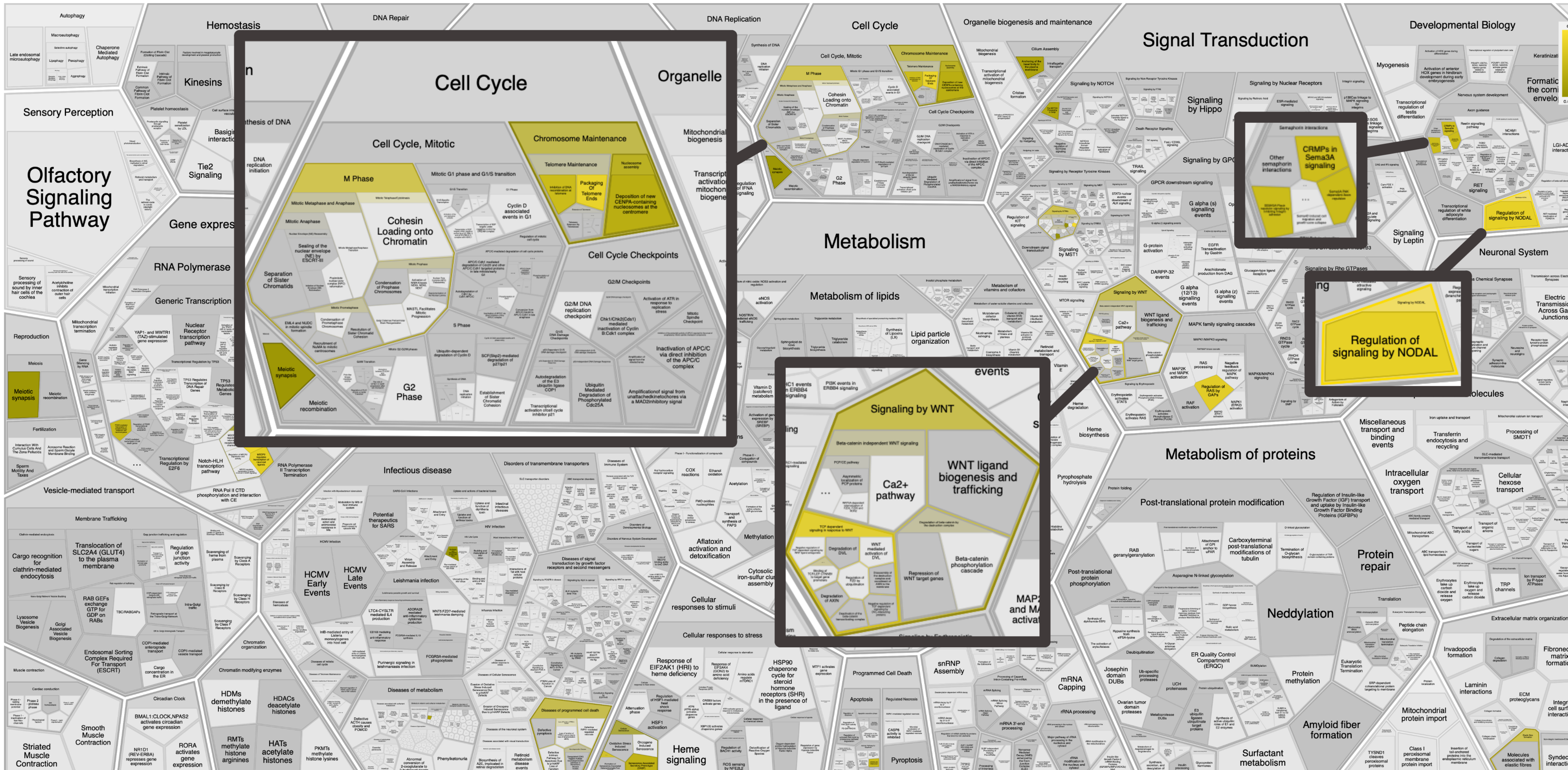
↓

Compare identified genes to genes involved in synapses (e.g. BDNF, NRXN1 etc.)[2]

↓

1. Watanabe *et al. Nature Communications* (2017)
2. *SynGO*, Koopmans *et al. Neuron* (2019)

MAPPED BIOLOGICAL PROCESSES



Reactome Pathway Database, Jassal *et al. Nucleic Acids Res.* (2020)

CONCLUSION

Genetic overlap between the brain functional connectome and psychiatric conditions

Link shared genetic loci back to biological processes implicated in psychiatric conditions

Identified a number of synaptic processes associated with shared loci

Genetic overlap between multivariate measures of human functional brain connectivity and psychiatric disorders

Daniel Roelfs, Dennis van der Meer, Dag Alnæs, Oleksandr Frei, Robert Loughnan, Chun Chieh Fan, Anders M. Dale, Ole A. Andreassen, Lars T. Westlye, Tobias Kaufmann

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bit.ly/network_genetics_pre

NORMENT

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Neuron

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SYNSCHIZ

Linking synaptic dysfunction to disease mechanisms in schizophrenia

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