USC Stevens Neuroimaging and Informatics Institute

LONI Laboratory of Neuro Imaging

Understanding the neurobiology of brain development and aging via imaging-omics

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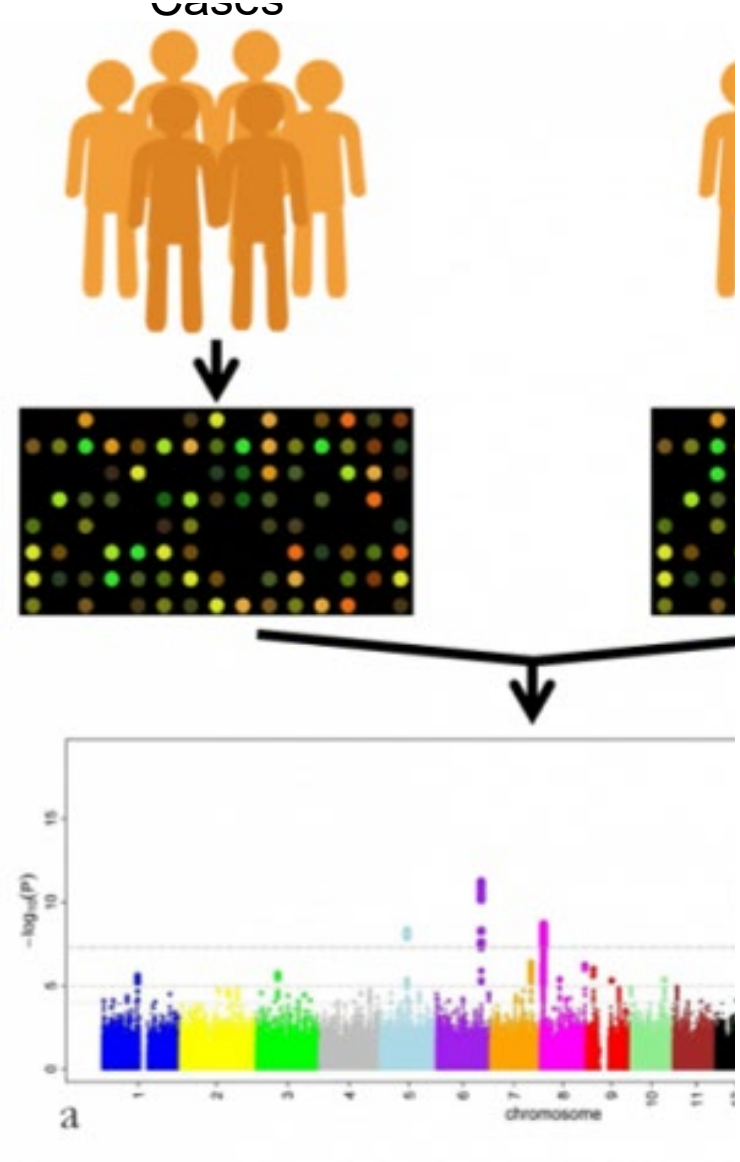
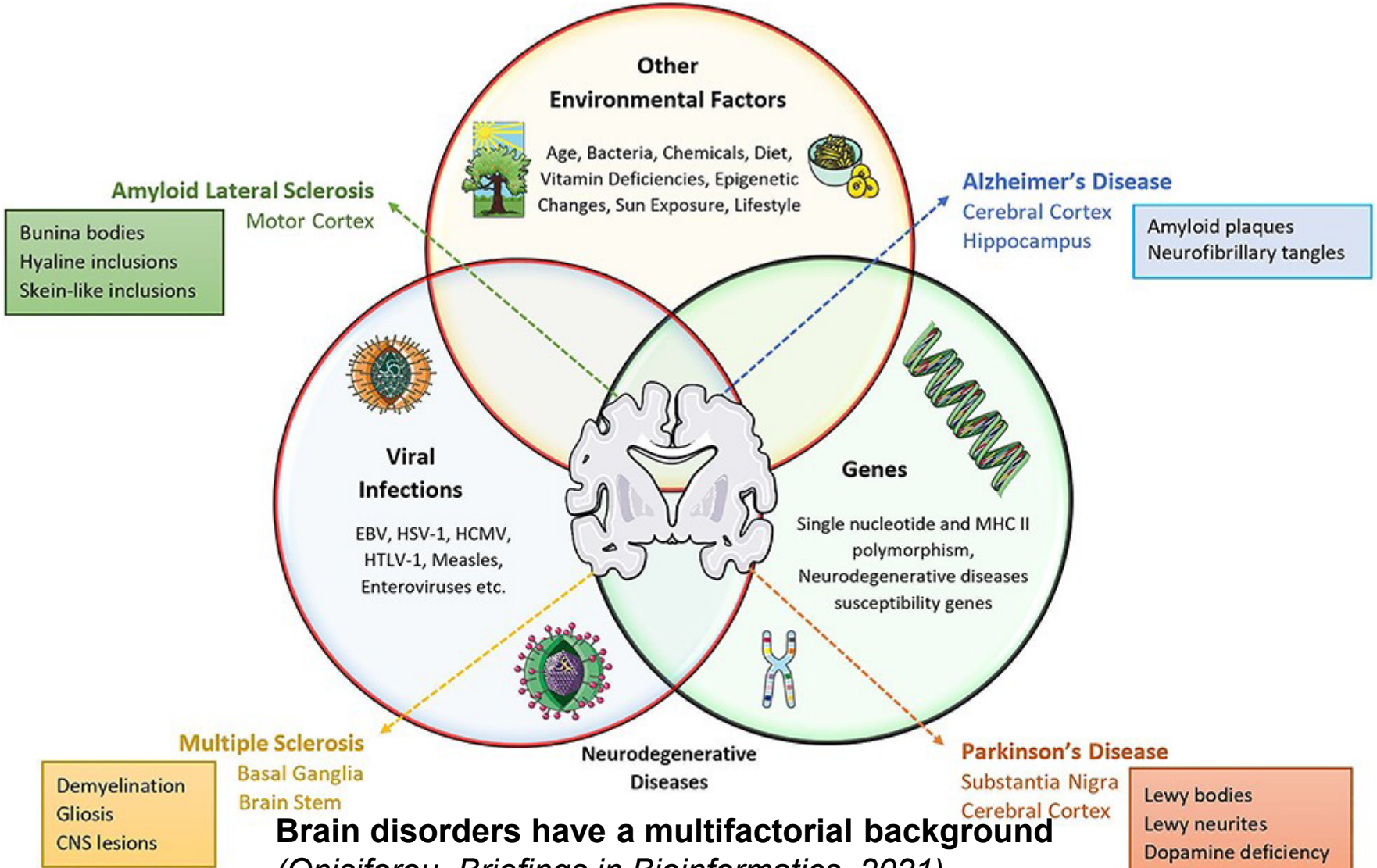
Imaging-omics: joint analysis of neuroimaging, genomics, phenomics and other -omics data for unveiling brain-biological consequences of molecular changes induced by the risk factors for brain disorders.

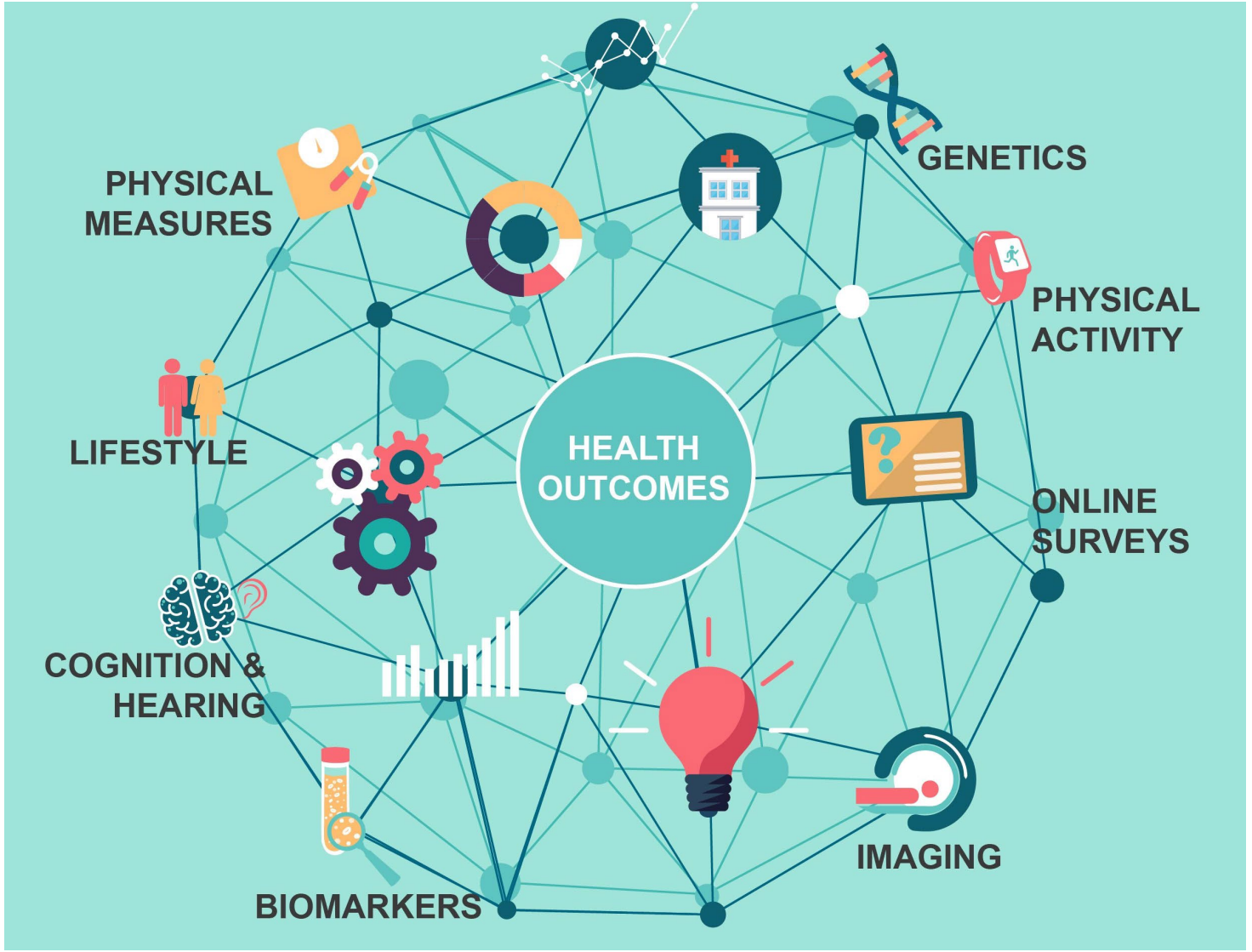




Brain disorders have a multifactorial background
(Onisiforou, Briefings in Bioinformatics, 2021)

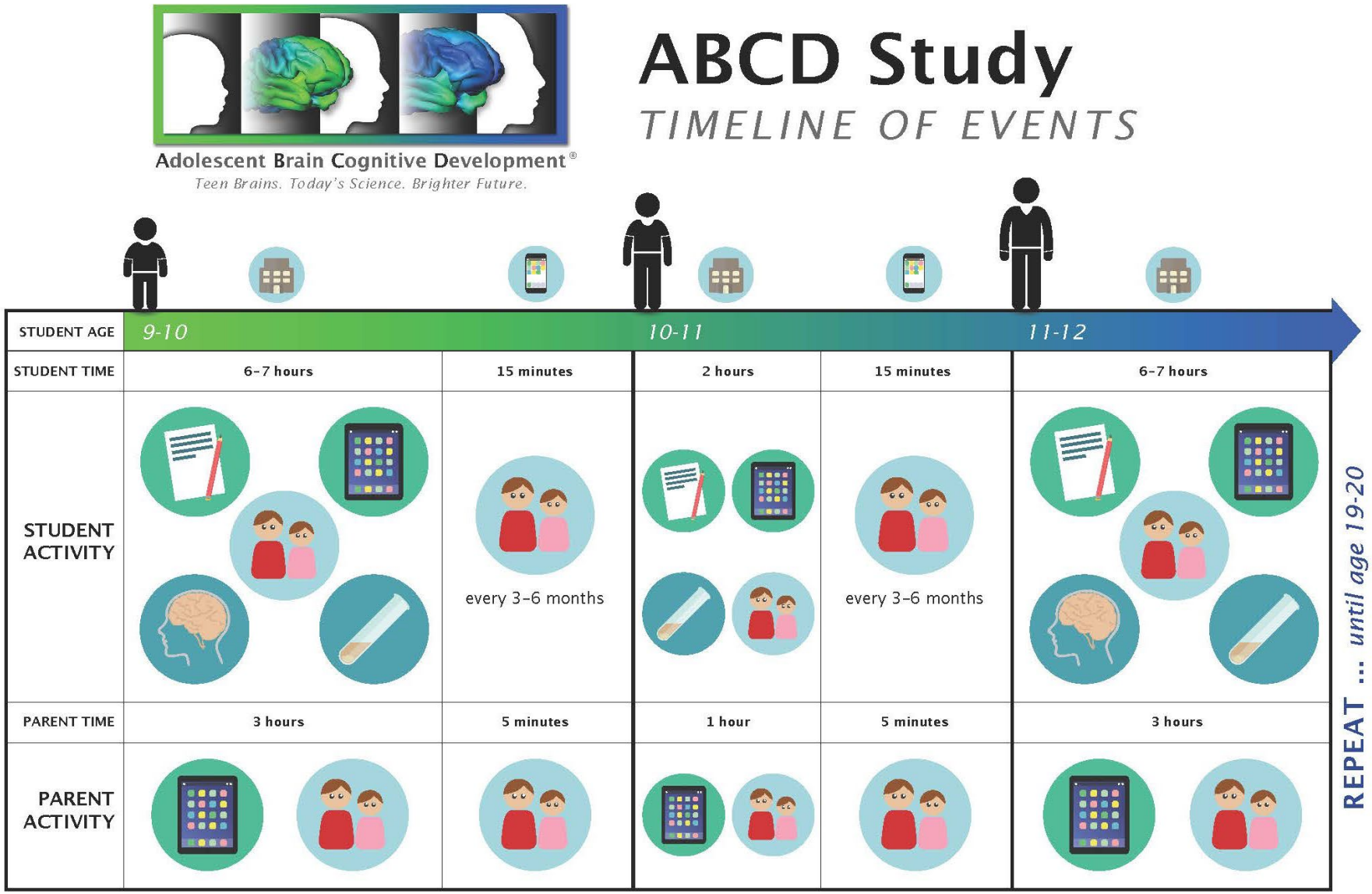
Modern biomedical data collection

- **UK Biobank**: a large-scale biomedical database of in-depth genetic and health information from 500k UK participants (brain imaging for ~50k)



Modern biomedical data collection

- **ABCD**: the largest long-term study of brain development and child heath in the US (N~12,000, baseline age: 9-10)



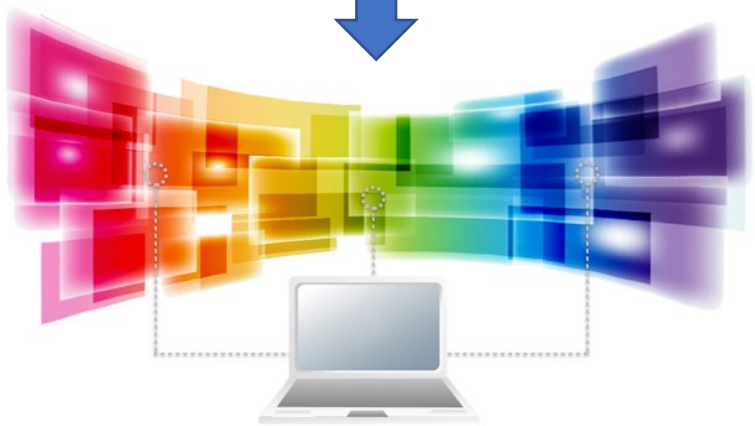
Imaging-omics study using the big biomedical datasets

Big Biomedical Databases

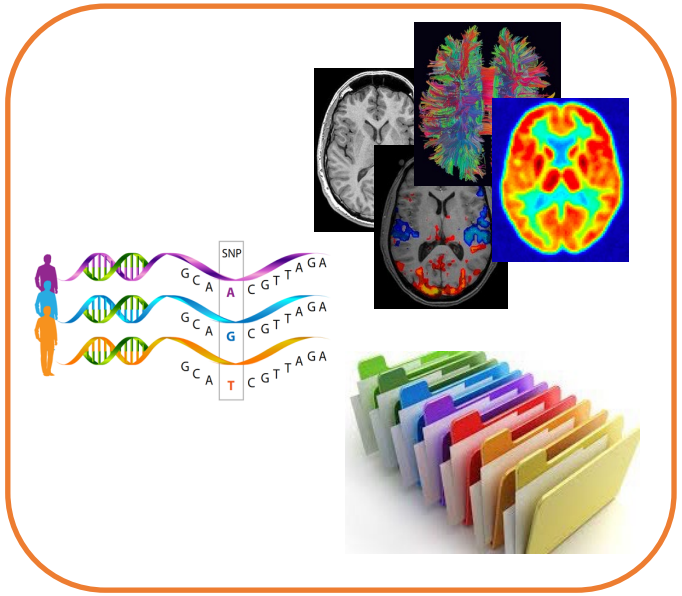
biobank uk

ADNI
Alzheimer's Disease Neuroimaging Initiative

Adolescent Brain Cognitive Development

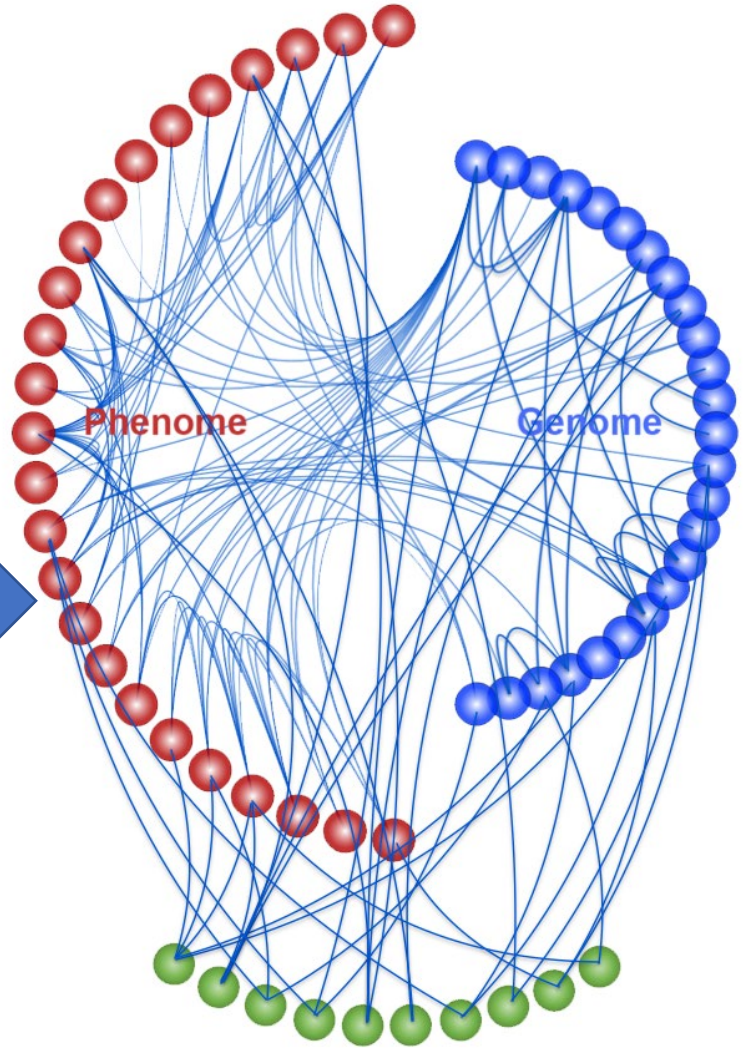


LONI Computational/Storage Infrastructure and Big Data Analytics Tools



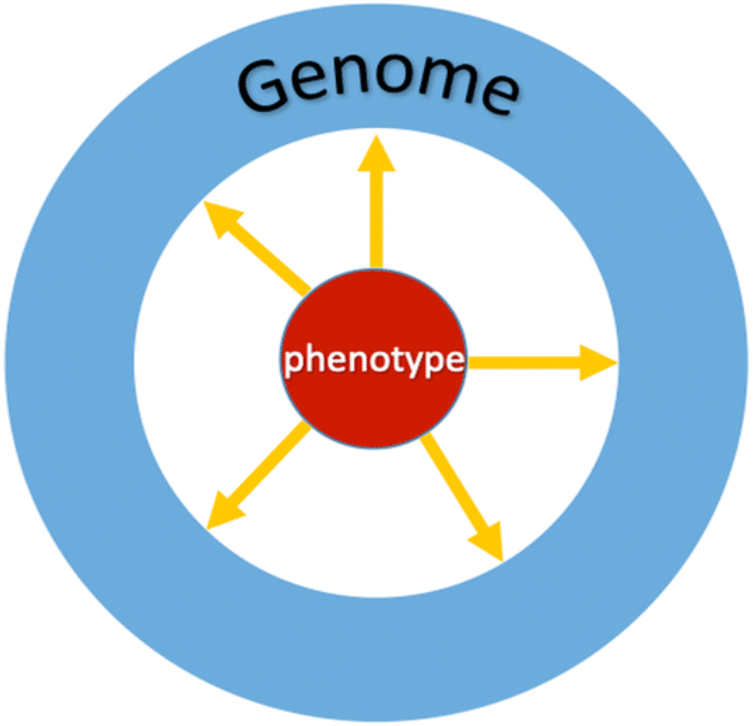
Big Data Management, Aggregation, Processing and Analytics

Brain-Genome-Phenome Interrelations



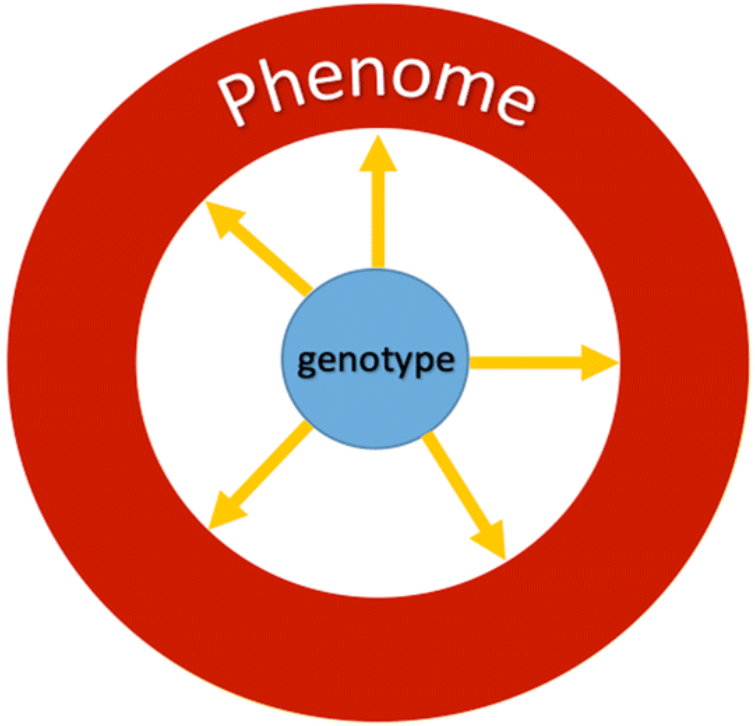
Neuroimaging PheWAS

GWAS: examines associations between specific phenotypes and genetic variants across the genome



Genome-Wide Association Study (GWAS)

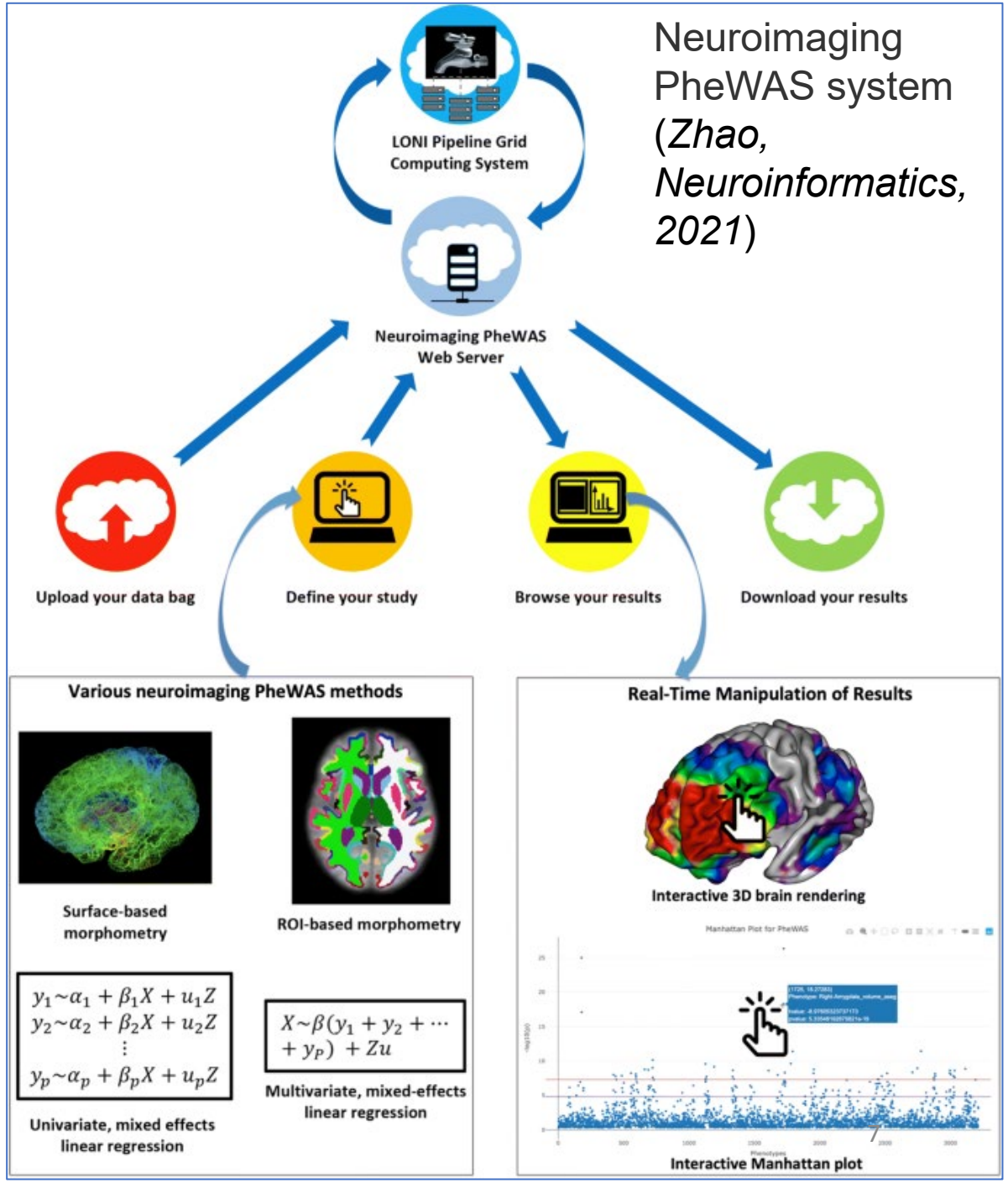
PheWAS: examines associations between specific genetic variants and a large number of different phenotypes (phenome)



Phenome-Wide Association Study (PheWAS)

Neuroimaging PheWAS: a cloud-computing platform for big-data, brain-wide imaging association studies

- User-friendly GUI for data uploading, study definition and management
- Cloud-based computational infrastructure
- State-of-art methods for statistical association analysis
- Interactive result visualizations
- Applicable to generic association analysis



Neuroimaging PheWAS system (*Zhao, Neuroinformatics, 2021*)

SHMOOSE mtSNP-omics associations

- SHMOOSE: a novel mitochondrial microprotein related to AD

Integrative Mitochondrial Omics

Mitochondrial sORF candidate identified through a series of integrative omics techniques: (1) MiWAS, (2) SNP-DeSEQ, (3) PheWAS, and (4) Proteomics

MiWAS

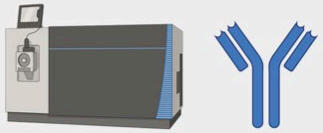
Identify a mitochondrial sORF variant that associates with AD

SNP-DeSEQ

Brain transcriptome differences by mitochondrial sORF gene variant

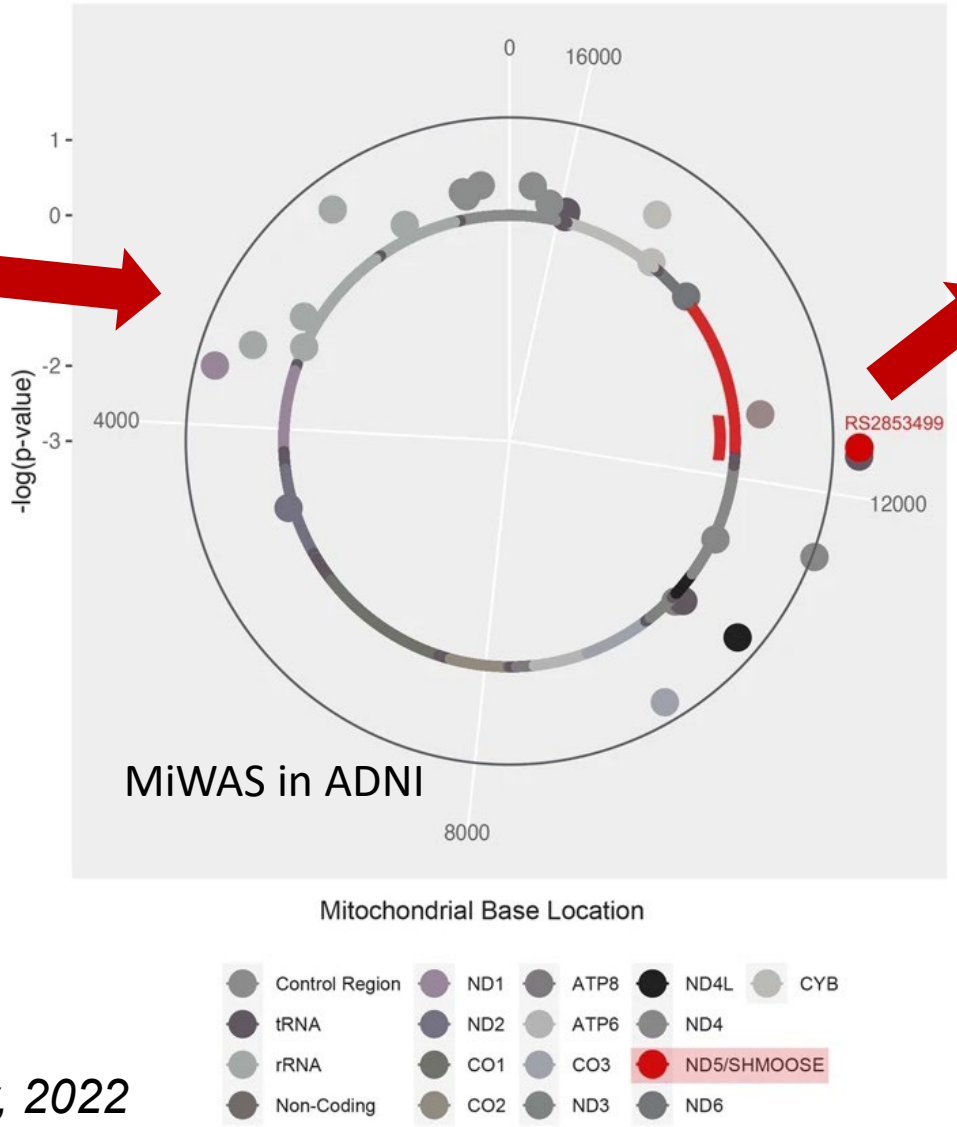
PheWAS

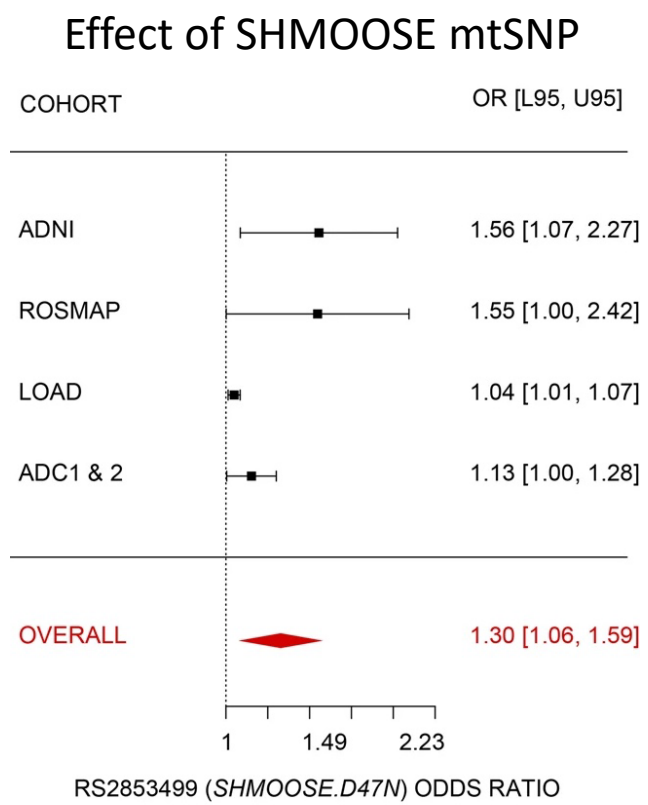
Human brain structural differences by mitochondrial sORF gene variant



Proteomics

Detect bonafide mitochondrial sORF-encoded microprotein





Miller, Nature Molecular Psychiatry, 2022

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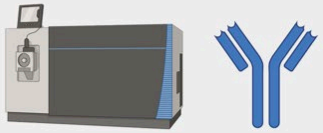
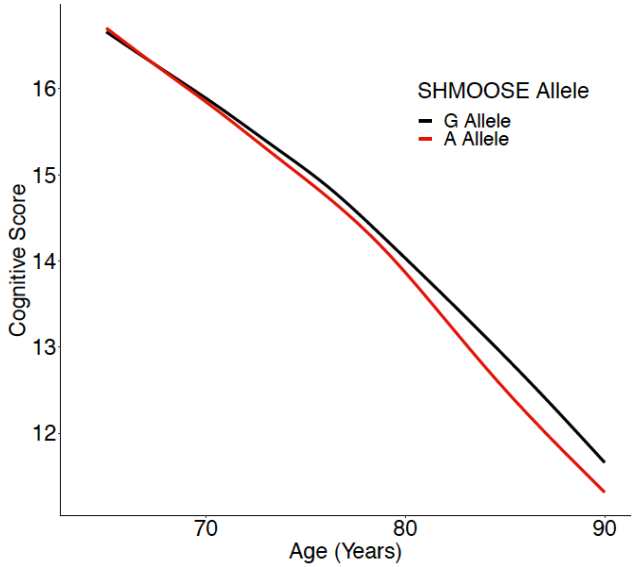
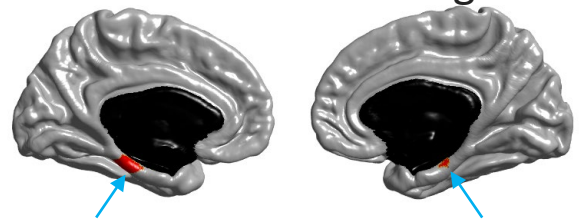


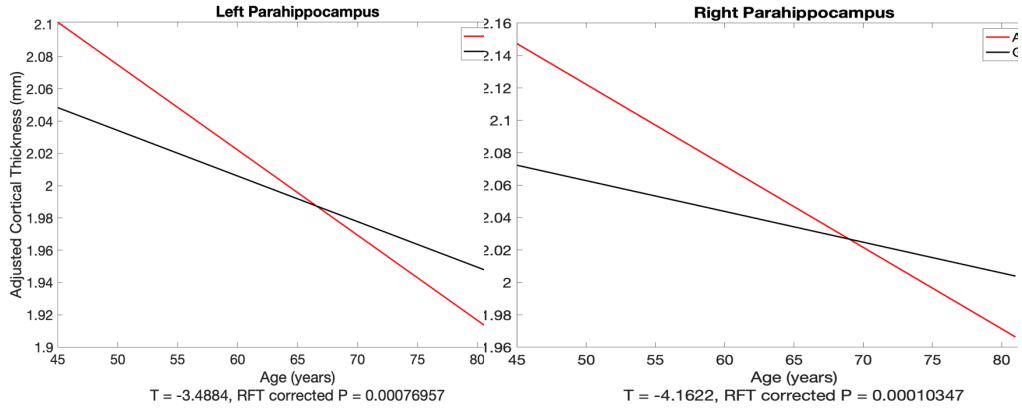
Proteomics

Detect bonafide mitochondrial sORF-encoded microprotein

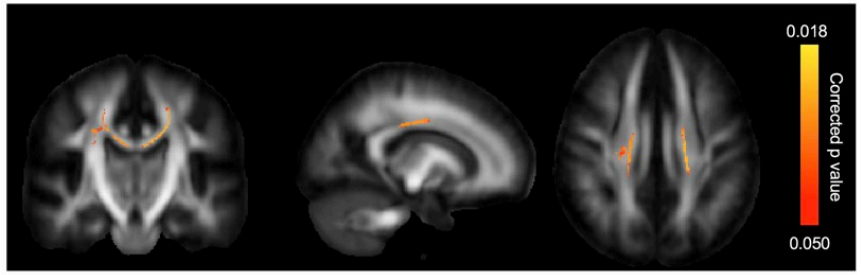
SHMOOSE effects on cognitive and brain structural changes

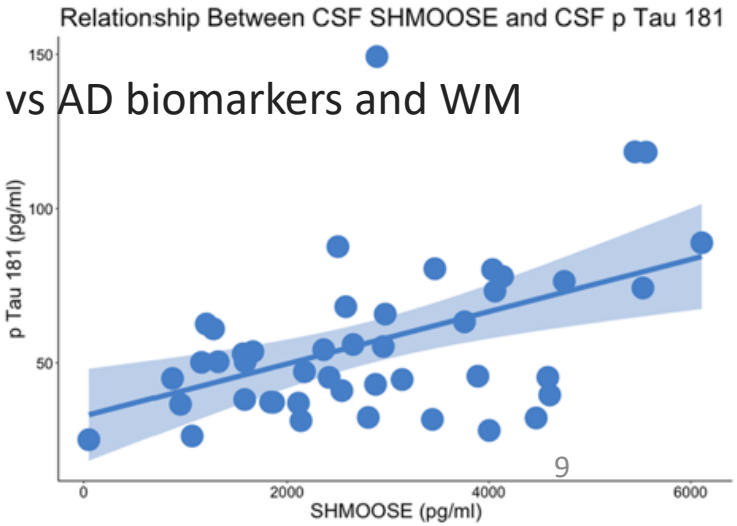






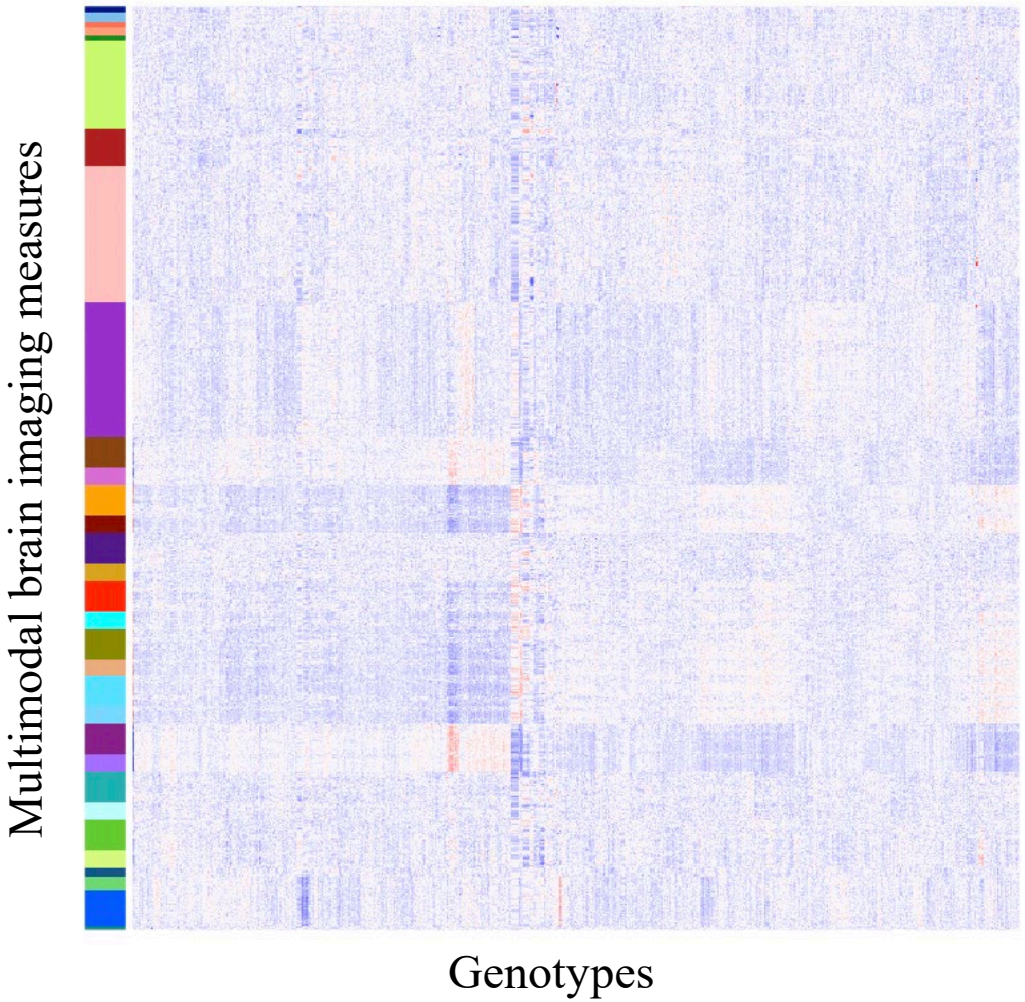
SHMOOSE level vs AD biomarkers and WM



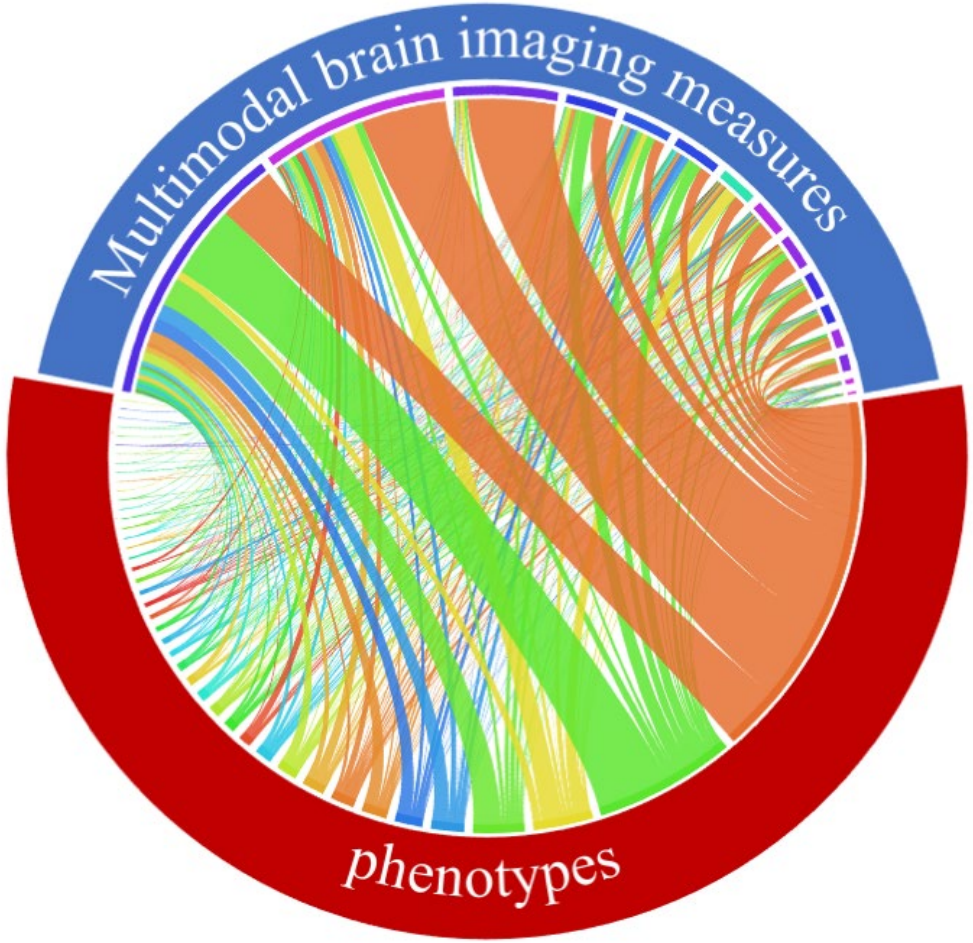


Miller, Nature Molecular Psychiatry, 2022

Multi-trait omics association studies

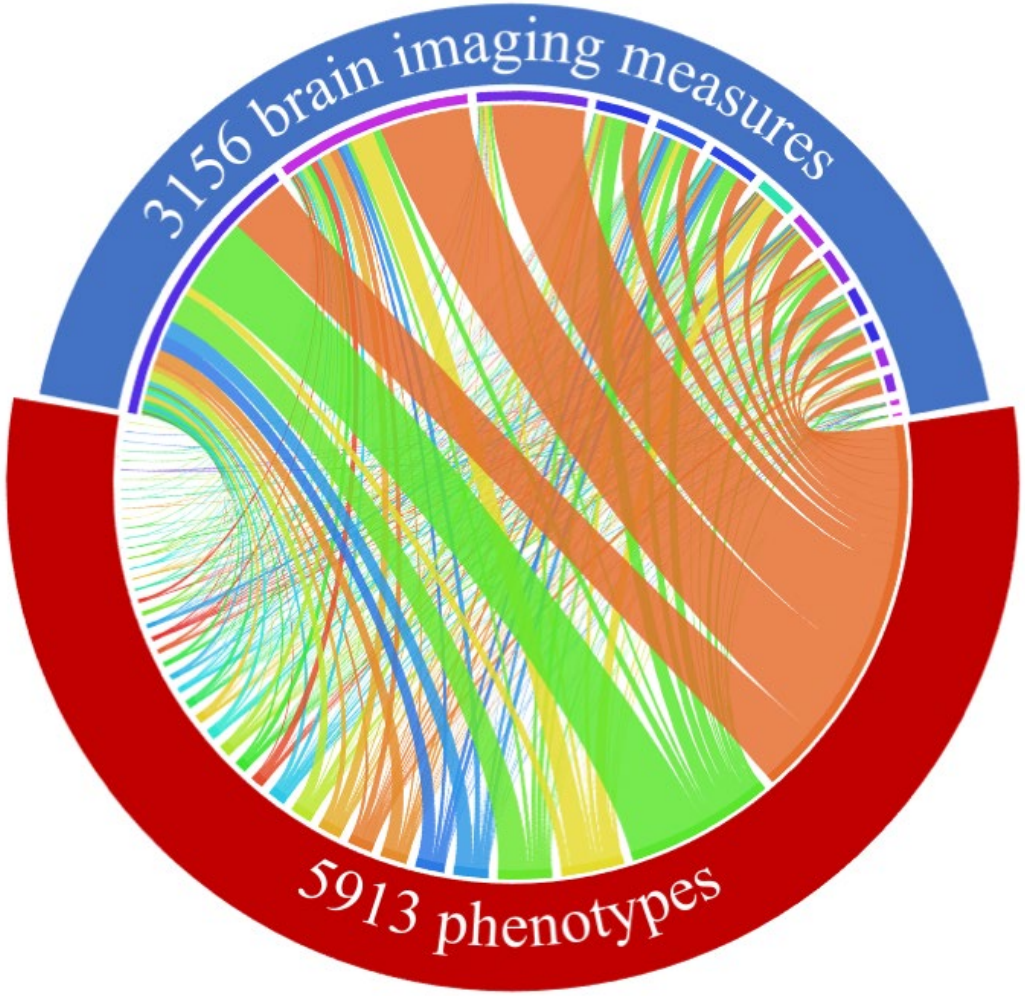


GWAS of all brain imaging measures in UK Biobank
(*Elliot, Nature, 2018; Smith, Nat Neuroscience, 2021*)



PheWAS of all brain imaging measures in UK Biobank
(*Miller, Nat Neurosci, 2016; Zhao, in preparation, 2022*)

PheWAS of all brain imaging measures in UK Biobank



- ~40,000 subjects (2/3 for discovery, 1/3 for replication)
- 3156 brain imaging measures (T1, T2, DWI, tfMRI, QC, rfMRI connectivity)
- 5913 UKB phenotypes
- Univariate associations
  - Discovery: 70,997 associations ($p < 0.05/5913/3156$) out of19 millions
  - Replication: 27,818 associations replicated at $p < 0.05/5913$

(*Zhao, in preparation, 2022*)

PheWAS of all brain imaging measures in UK Biobank

- Multivariate associations (CCA+ICA)
  - Canonical correlation analysis (CCA): combine IDPs and non-IDPs to identify modes of population covariation linking hem
  - Independent component analysis (ICA): decompose mixture in canonical variants into independent components
- 17 modes were identified (permutation corrected p < 0.05)

(*Zhao, in preparation, 2022*)

Mode A: Blood pressure and dMRI

ICA	Variance (%)	Variable
-8.28	15.45	End systolic pressure during PWA
-8.23	18.152	Central systolic blood pressure during PWA
-8.17	17.452	Mean arterial pressure during PWA
-7.86	17.946	Systolic brachial blood pressure during PWA
-7.74	17.528	Systolic brachial blood pressure
-6.82	24.422	IDP_dMRI_TBSS_L3_External_capsule_L
-6.82	25.857	IDP_dMRI_TBSS_MD_External_capsule_L
-6.61	24.522	IDP_dMRI_TBSS_L3_External_capsule_R
-6.6	26.814	IDP_dMRI_ProbtrackX_L3_atr_l
-6.59	27.008	IDP_dMRI_ProbtrackX_L3_atr_r
-6.55	22.272	IDP_dMRI_TBSS_L3_Superior_longitudinal_f
-6.51	25.823	IDP_dMRI_TBSS_MD_External_capsule_R
-6.49	21.665	IDP_dMRI_ProbtrackX_L3_slf_l
-6.47	21.324	IDP_dMRI_ProbtrackX_L3_slf_r
6.43	19.154	IDP_dMRI_ProbtrackX_FA_atr_l
-6.42	21.679	IDP_dMRI_TBSS_L3_Superior_longitudinal_f
-6.39	26.591	IDP_dMRI_ProbtrackX_L2_atr_r
6.36	18.406	IDP_dMRI_ProbtrackX_FA_atr_r
-6.34	8.629	Diastolic brachial blood pressure during PWA
-6.29	22.148	IDP_dMRI_TBSS_MD_Superior_longitudinal_
-6.28	24.504	IDP_dMRI_TBSS_L2_External_capsule_L
-6.27	22.746	IDP_dMRI_ProbtrackX_MD_slf_l
-6.27	8.506	Diastolic brachial blood pressure
-6.26	25.813	IDP_dMRI_TBSS_L3_Anterior_corona_radiat
-6.24	21.744	IDP_dMRI_TBSS_MD_Superior_longitudinal_
-6.23	25.2	IDP_dMRI_TBSS_L3_Anterior_corona_radiat
-6.22	25.587	IDP_dMRI_ProbtrackX_L2_atr_l

B: Cardiovascular, alcohol and dMRI

ICA	Variance (%)	Variable
8.707	13.181	Ever had cataract surgery
-7.592	6.434	Age diabetes diagnosed
-7.074	0.178	Mean arterial pressure during PWA
6.741	2.351	Alcohol intake frequency.
-6.693	2.553	Frequency of drinking alcohol
-6.558	0.26	End systolic pressure during PWA
-6.524	5.126	Cholesterol
6.277	7.248	Diabetes diagnosed by doctor
-6.143	0.089	Central systolic blood pressure during PW
6.112	6.519	Why reduced smoking: Illness or ill heal
6.036	10.028	IDP_dMRI_TBSS_L2_Superior_cerebella
-6.029	0.245	Diastolic brachial blood pressure during
6.008	9.778	IDP_dMRI_TBSS_L2_Superior_cerebella
-5.937	0.224	Diastolic brachial blood pressure
-5.924	9.98	IDP_dMRI_TBSS_FA_Superior_cerebella
5.911	9.192	IDP_dMRI_TBSS_L3_Superior_cerebella
-5.856	9.89	IDP_dMRI_TBSS_FA_Superior_cerebella
5.817	9.202	IDP_dMRI_TBSS_L3_Superior_cerebella
-5.717	2.401	HDL cholesterol
-5.643	4.478	LDL direct
5.623	5.387	Operative procedures - OPCS4: C75.1 Ins
5.612	5.362	Operative procedures - OPCS4: C71.2 Ph
5.601	5.325	Operative procedures - secondary OPCS
-5.565	4.735	Forced expiratory volume in 1-second (FE
5.552	5.19	Operative procedures - main OPCS4: C7
5.528	4.117	Forced expiratory volume in 1-second (F
-5.469	0.297	Diastolic blood pressure
5.373	7.902	Medication for cholesterol

C: Cognitive and tfMRI

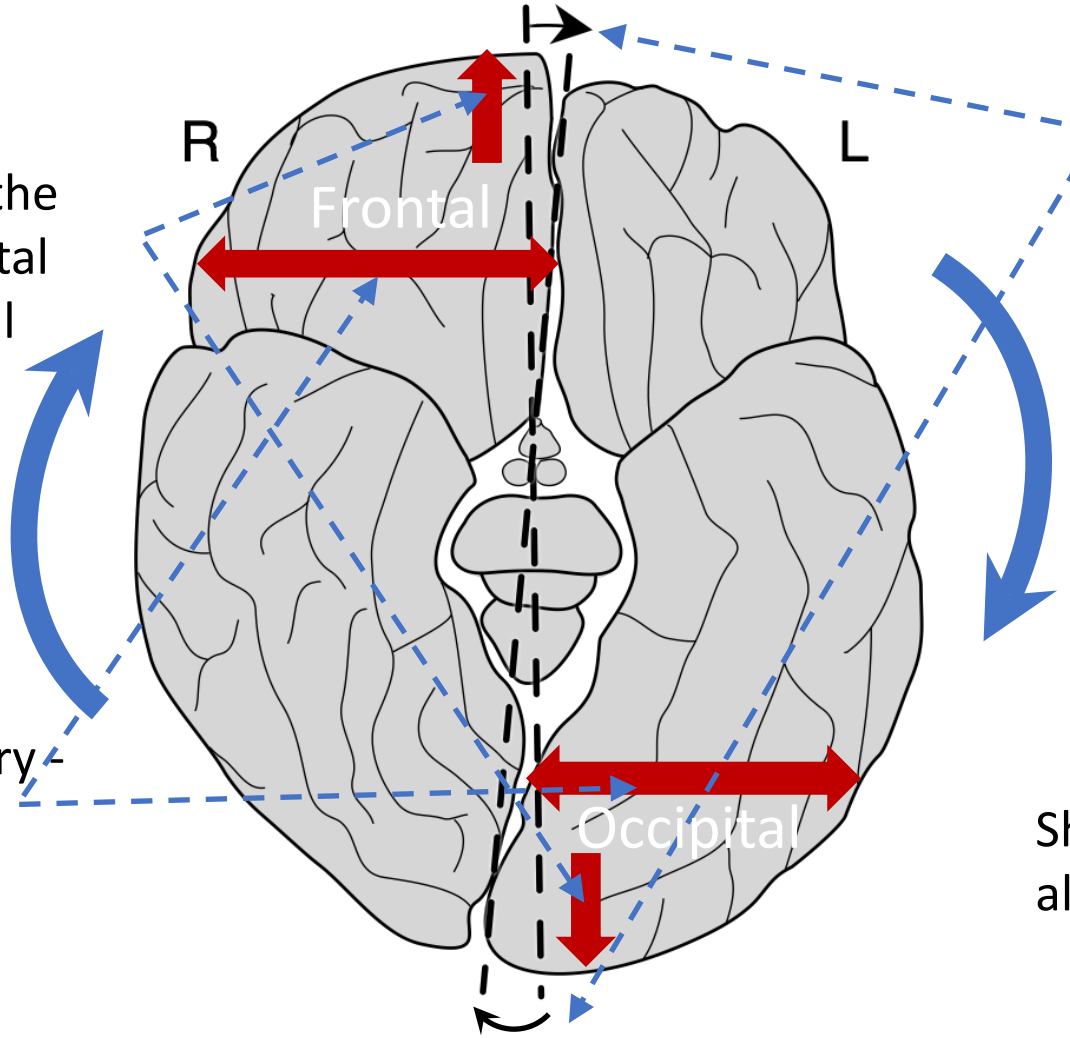
ICA	Variance (%)	Variable
-11.91	24.657	Duration to complete alphanumeric path (t
-11.89	24.517	Interval between previous point and current
-11.41	23.096	Duration to complete alphanumeric path (t
-11.37	22.761	Interval between previous point and current
-11.28	22.697	Duration to entering value
10.817	21.205	Number of symbol digit matches attempte
10.45	19.947	Number of symbol digit matches made cor
-9.768	16.844	Interval between previous point and current
-9.727	16.695	Duration to complete numeric path (trail #1
9.694	16.028	Fluid intelligence score
9.638	17.354	Number of symbol digit matches attempte
9.305	15.165	Number of puzzles correctly solved
9.262	16.156	Number of symbol digit matches made cor
9.193	14.571	Fluid intelligence score
8.997	13.267	Number of puzzles correct
-8.761	13.528	Duration to complete numeric path (trail #1
-8.44	12.698	Interval between previous point and current
-8.172	6.768	IDP_tfMRI_90th-percentile_BOLD_shapes
-8.018	10.685	Time to complete round
-8.002	10.619	Duration screen displayed
7.764	10.391	Number of word pairs correctly associated
-7.48	5.398	IDP_tfMRI_median_BOLD_shapes
7.366	8.881	Number of fluid intelligence questions atte
7.21	8.394	IDP_tfMRI_median_zstat_faces-shapes
-7.031	8.302	Time to complete round
6.832	6.608	IDP_tfMRI_median_zstat_faces-shapes_ar
6.693	6.346	IDP_tfMRI_90th-percentile_zstat_faces-sha
-6.336	6.359	Time first key touched
6.211	5.578	IDP_tfMRI_median_BOLD_faces-shapes_ar
6.173	6.555	IDP_tfMRI_median_BOLD_faces-shapes

D: Mental health and sMRI

ICA	Variance (%)	Variable
8.147	11.246	Neuroticism score
5.949	6.388	Mood swings
5.902	6.04	Frequency of tenseness / restlessness i
5.878	6.21	Miserableness
5.863	6.057	Ever worried more than most people w
5.846	6.234	Frequency of depressed mood in last 2
5.686	7.512	Degree bothered by feeling tired all the
5.607	6.13	Fed-up feelings
5.539	3.46	IDP_T1_FAST_ROIs_L_ventral_striatum
5.507	5.234	Ever sought or received professional he
5.492	5.022	Activities undertaken to treat depressior
5.444	6.776	Recent feelings of tiredness or low ene
5.44	5.83	Ever been offered/sought treatment fo
5.438	6.77	Frequency of tiredness / lethargy in last
5.373	5.747	Substances taken for depression: Medic
5.371	5.141	Ever thought that life not worth living
5.356	5.607	Mental health problems ever diagnosed
5.34	5.117	Recent worrying too much about differe
5.3	5.228	Ever suffered mental distress preventin
5.297	5.043	Recent trouble relaxing
5.285	4.957	Recent feelings of inadequacy
5.212	4.792	General happiness
5.177	3.638	IDP_T1_FIRST_left_caudate_volume
5.156	2.856	IDP_T1_FAST_ROIs_R_ventral_striatum
5.131	4.996	Recent feelings of depression
5.127	5.218	Recent trouble concentrating on things
5.12	7.677	General happiness with own health

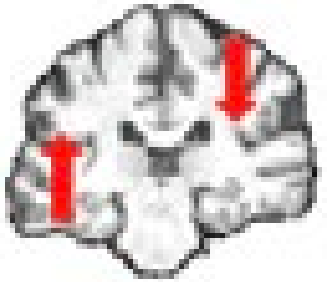
Mapping genetic architecture and phenomic associations of the human brain torque in 24,112 Individuals (UKB, ABCD, HCP, PING, PNC, ICBM cohorts)

Petalia - the protrusion of the right frontal and left occipital poles over the contralateral extremities



Bending - the right frontal lobe and the left occipital lobe is bended across the midline

Tissue Distribution Asymmetry - wider/larger right frontal lobe and left occipital lobe



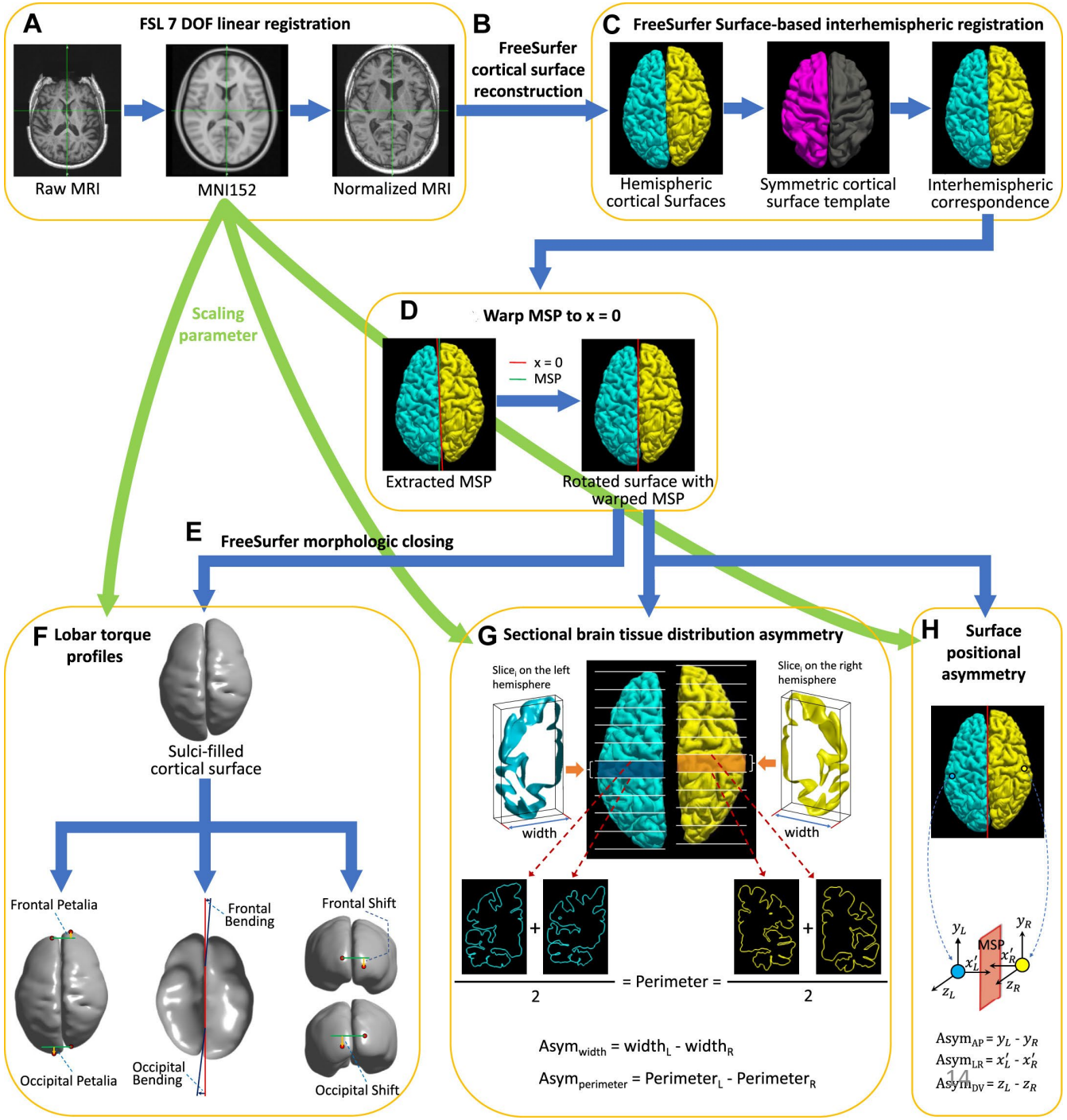
Shift - a relative hemispheric shift along the dorsoventral axis

Brain Torque (Yakovlevian torque) - The most prominent structural brain asymmetry

Brain torque characterization

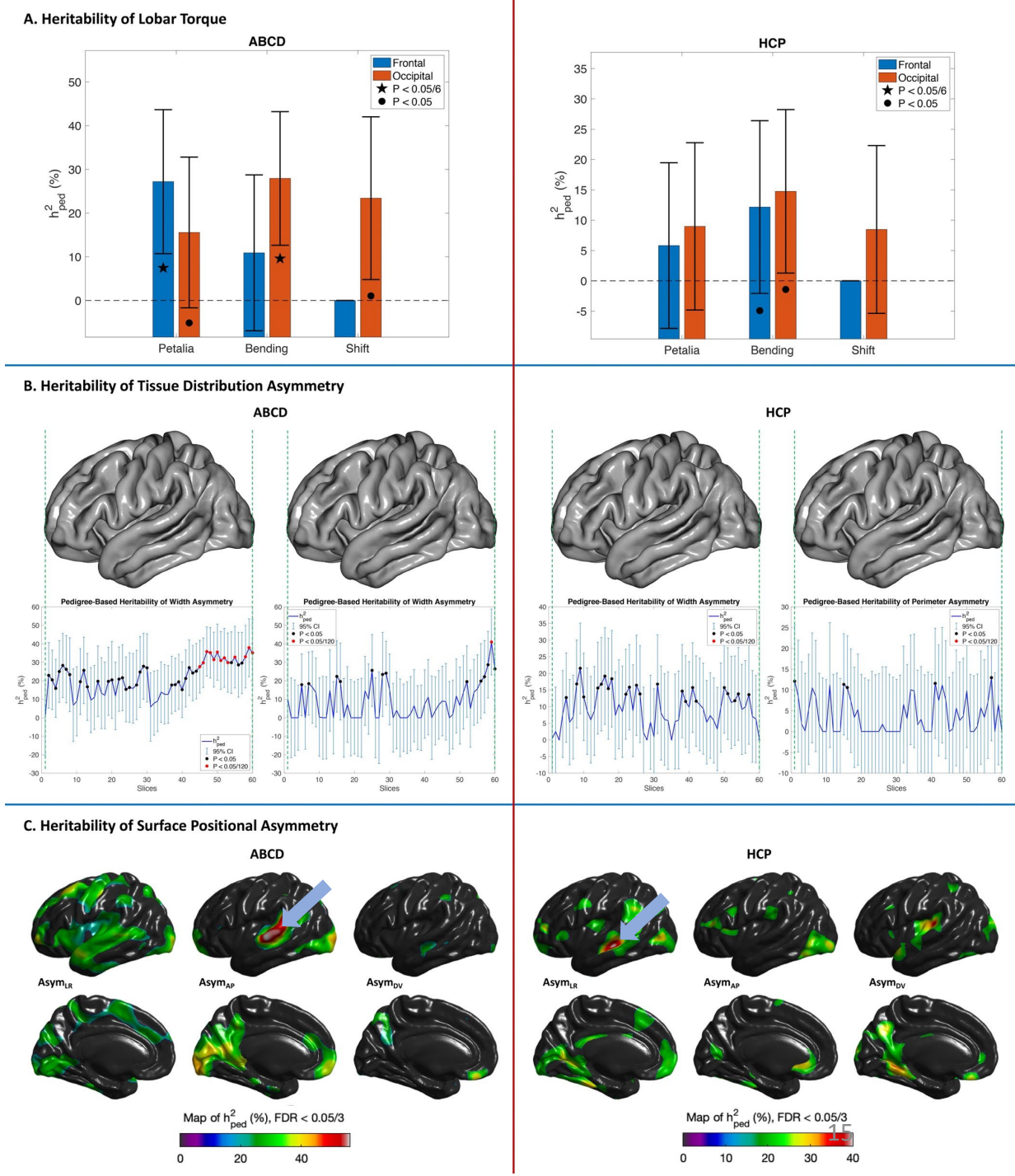
- Automatic, direct modeling
- Lobar measures of fontal/occipital Petalia, Shift and Bending.
- Sectional tissue distribution asymmetry: left-right difference in hemispheric width ($Asym_{width}$) and perimeter ($Asym_{perimeter}$).
- Vertex-wise surface positional asymmetries: along the left-right ($Asym_{LR}$), antero-posterior ($Asym_{AP}$) and dorso-ventral ($Asym_{DV}$) axes

(*Zhao, Biological Psyhicatry, 2022*)

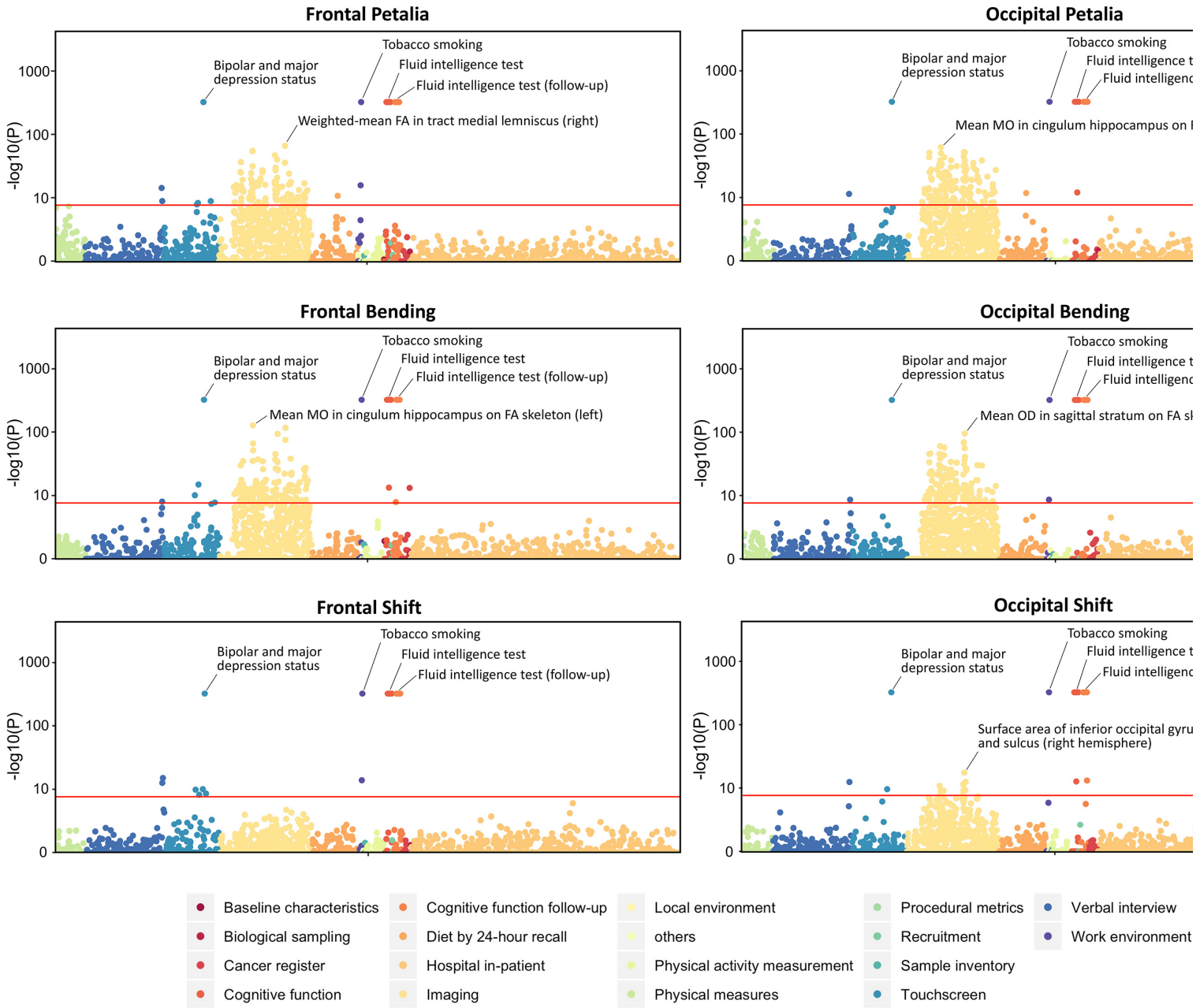


- Heritability
  - Highest heritability in temporal language area (56% in ABCD, 40% in HCP, 21% in UKB)
  - H^2(Children) > H^2(Adults)
  - There exist environmental influences

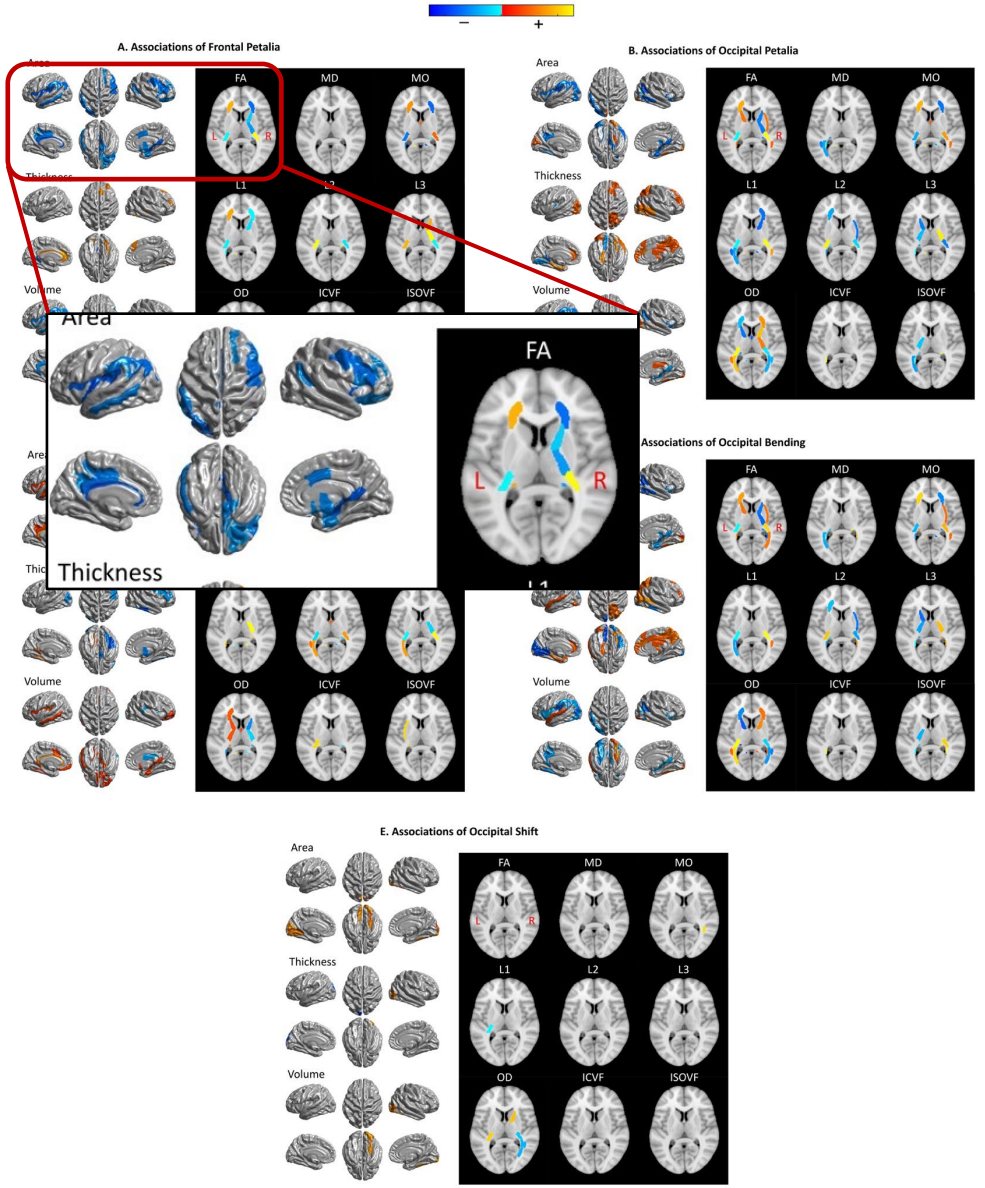
(*Zhao, Biological Psyhicatry, 2022*)



Phenome scans: 942 BT-related phenotypes (P < 2.16e-8)



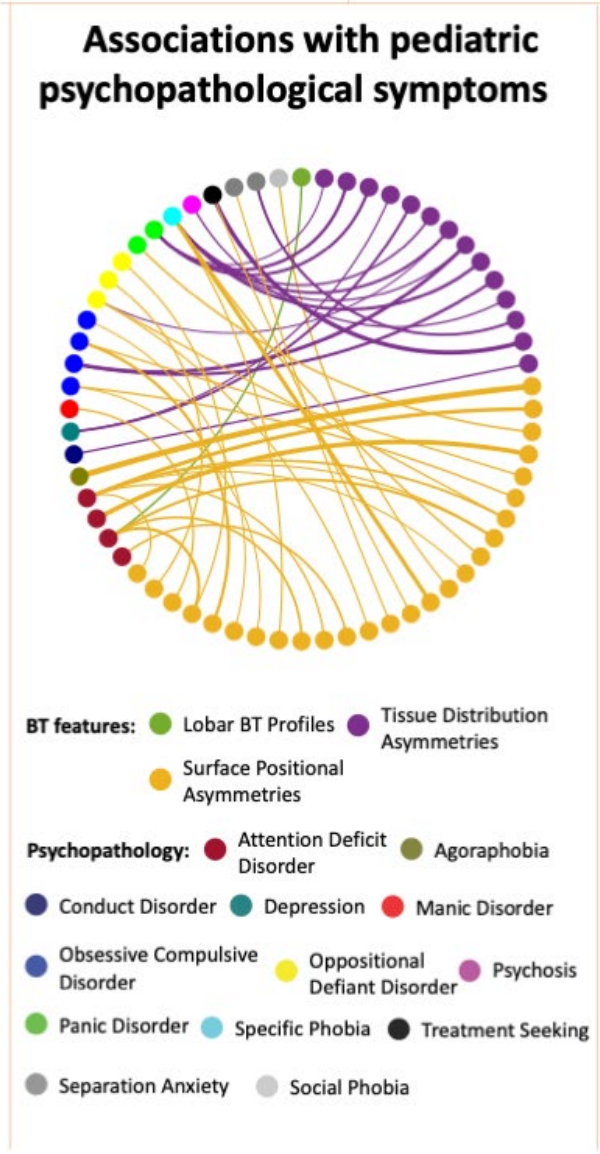
Asymmetric and twisted associations with MRI metrics in GM, WM and ventricles

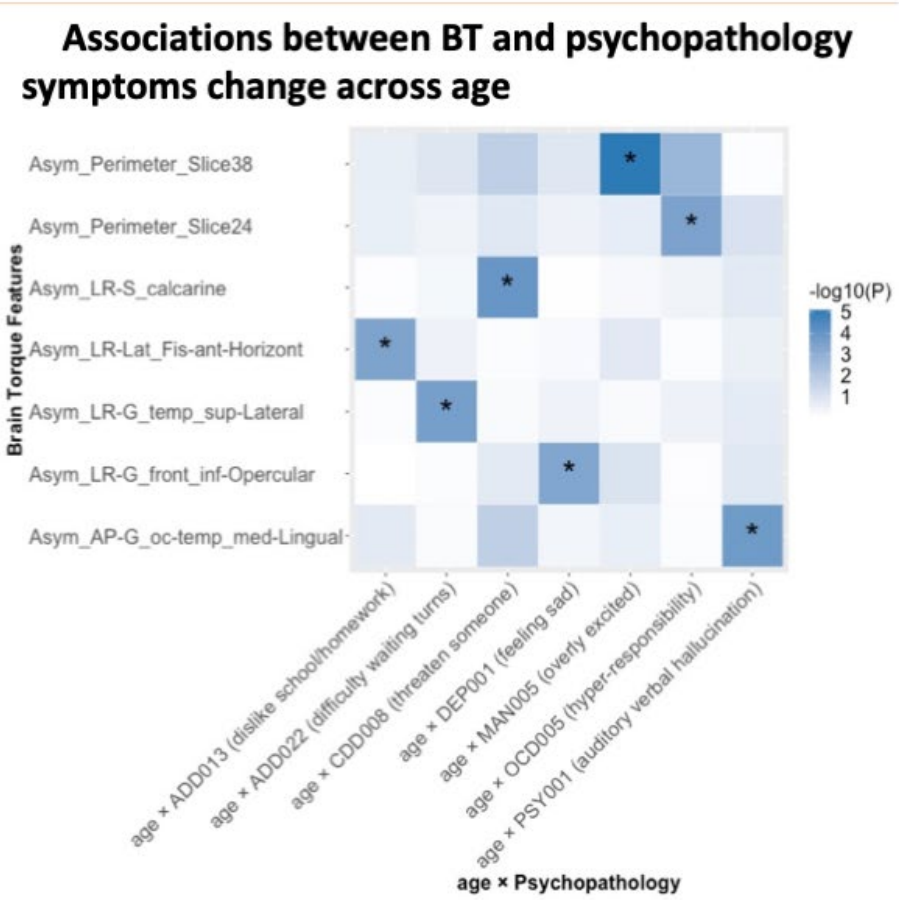


(*Zhao, Biological Psyhicatry, 2022*)

Phenome scans (children)

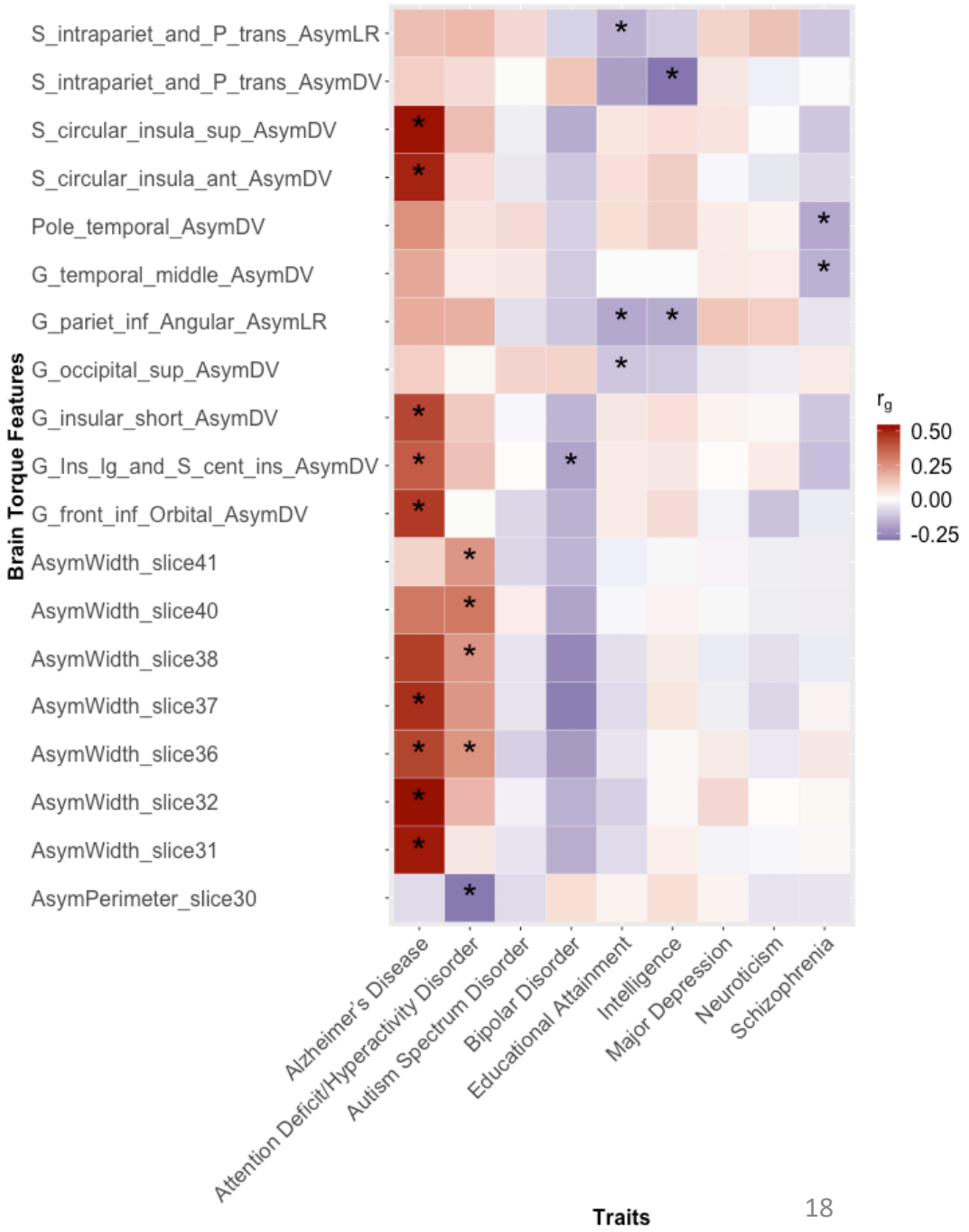
- multiple pediatric psychopathological symptoms/behaviors were associated with brain torque features and their age trajectories from childhood to adolescence





(*Zhao, Biological Psyhicatry, 2022*)

- Genetic correlations
  - Genetic correlations with educational attainment, intelligence, attention-deficit/hyperactivity disorder, Alzheimer's disease, schizophrenia and bipolar disorder ($|r_g|$ = 0.12 to 0.55)
- Brain torque may present an important intermediate phenotype between genes, neurodevelopment and diagnosis



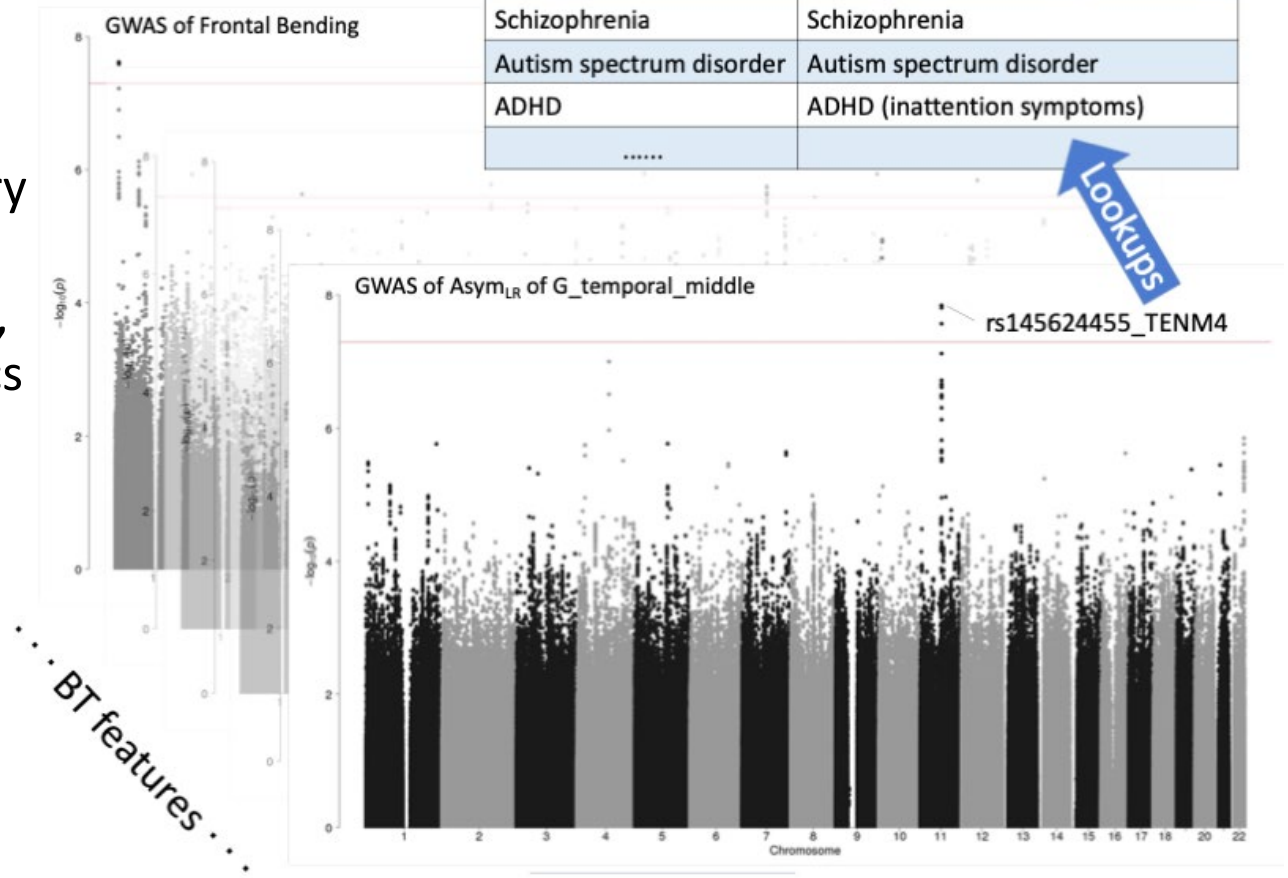
(*Zhao, Biological Psyhicatry, 2022*)

Genetic architecture

- Meta-GWAS: 86 independent lead SNPs (P < 5e-8)
  - Implicated in:
    - GM/WM/ventricular structures
    - Cognitive abilities and intelligence
    - Neurological and psychiatric disorders
    - Cardiovascular, autoimmune and inflammatory diseases
    - Educational attainment, alcohol consumption, smoking, sleep, anthropometric characteristics and physical appearance
  - Genetic basis for phenome associations
  - 3 lead variants (LMOD1, CHMP1A and MAPK3) in cytoskeletal organization and its regulation
    - Cytoskeleton for embryonic development of organ laterality in other species (*Ray, PNAS, 2018; Tee, Nat Cell Biol, 2015*)
    - A cytoskeleton-mediated mechanism for human brain asymmetry development

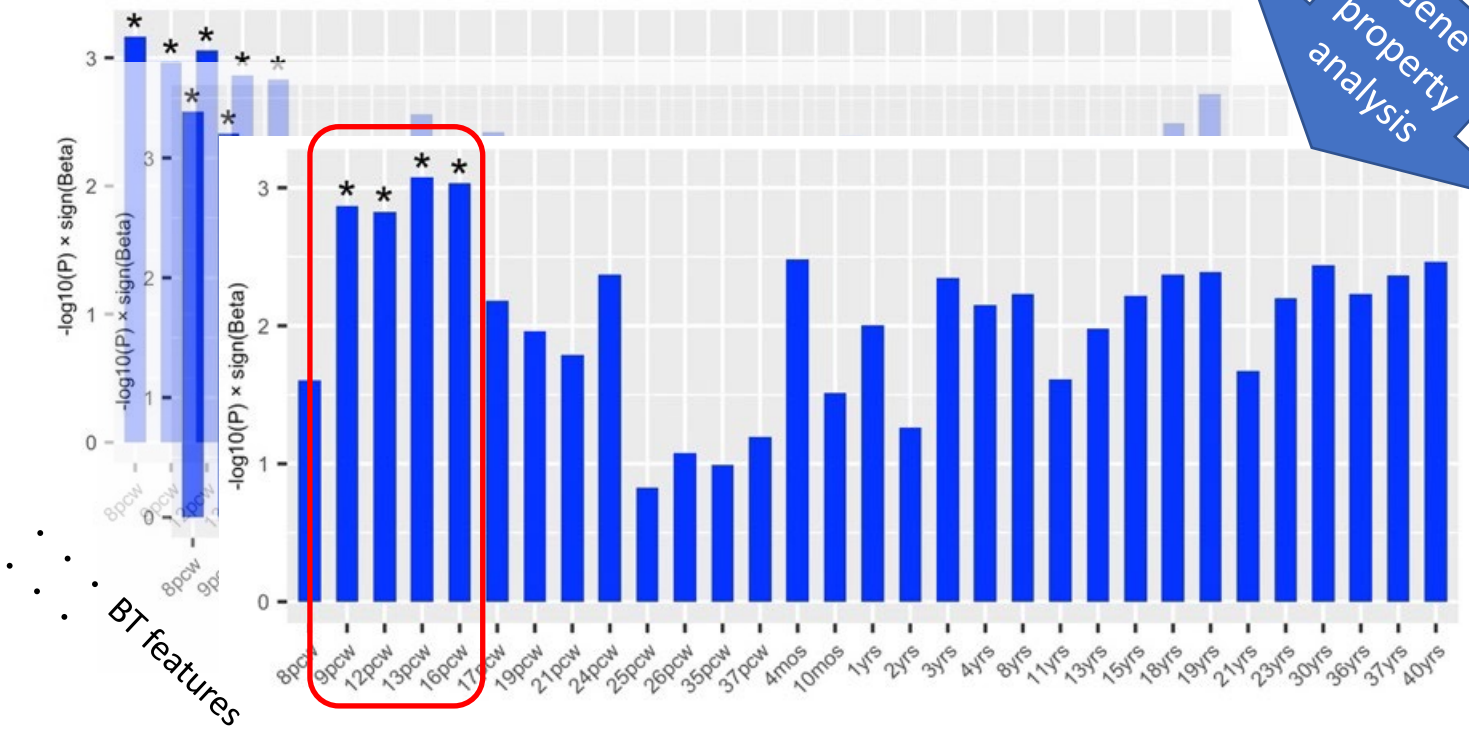
GWAS Catalog

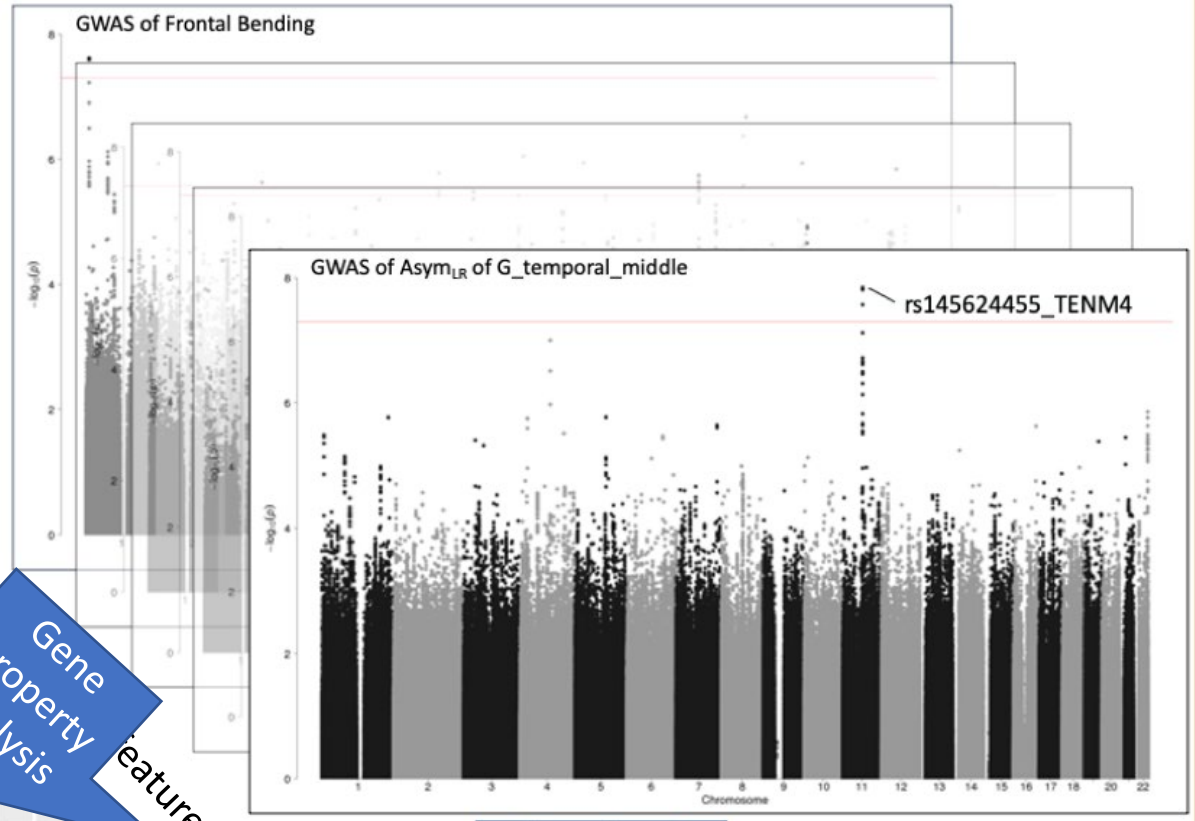
Trait label(s)	Reported trait(s)
Bipolar disorder	Bipolar disorder
Educational attainment	Educational attainment
Intelligence	Intelligence, General cognitive ability
Schizophrenia	Schizophrenia
Autism spectrum disorder	Autism spectrum disorder
ADHD	ADHD (inattention symptoms)
.....	



(*Zhao, Biological Psyhicatry, 2022*)

- Gene-set enrichment
  - 75 biological pathways (P < 6.61E-6)
    - BP: neuronal development and CNS myelin maintenance
    - Mechanisms of synaptic pruning and axon tension in the development of brain torque
- Gene-property analysis
  - genetic associations of BT were correlated with higher gene expression levels during the gestational stages





Functional Enrichment

et	NGENES	BETA	P
REGULATION_OF_NEURON_PROJECTION_DEVELOPMENT	485	0.15	3.72E-06
NEURON_DIFFERENTIATION	1337	0.094	2.36E-06
NEURON_DEVELOPMENT	1084	0.11	3.71E-07
CELL_MORPHOGENESIS_INVOLVED_IN_NEURON_DIFFERENTIATION	574	0.14	4.60E-06
POSITIVE_REGULATION_OF_DEVELOPMENTAL_PROCESS	1331	0.093	3.34E-06
.....			

(*Zhao, Biological Psyhicatry, 2022*)

Open-source, web-based GWAS/PheWAS catalogs

- Oxford *BIG40* Brain Imaging Genetics webserver (https://open.win.ox.ac.uk/ukbiobank/big40/)
- PheWAS catalog (https://phewascatalog.org)
- Pheweb (https://pheweb.sph.umich.edu)
- LONI online resource (http://phewas.loni.usc.edu/data/contents.php)

Detailed tables of all phenotypes/SNPs

PheWeb | Search for a variant, gene, or phenotype | Phenotypes | Top Hits | Random | About

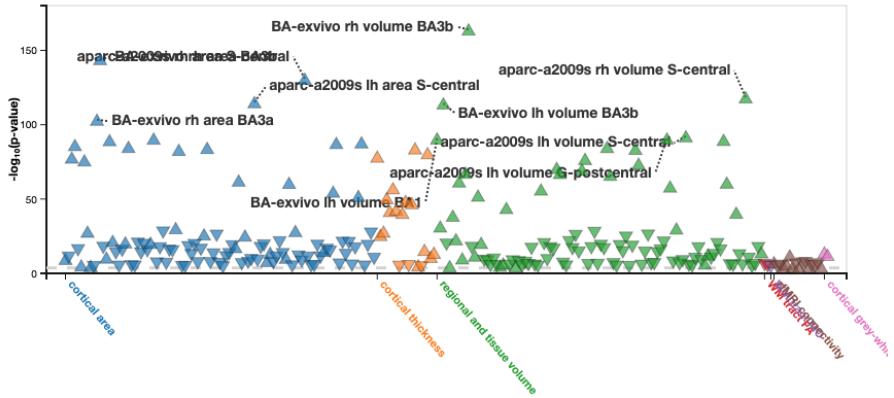
All Phenotypes

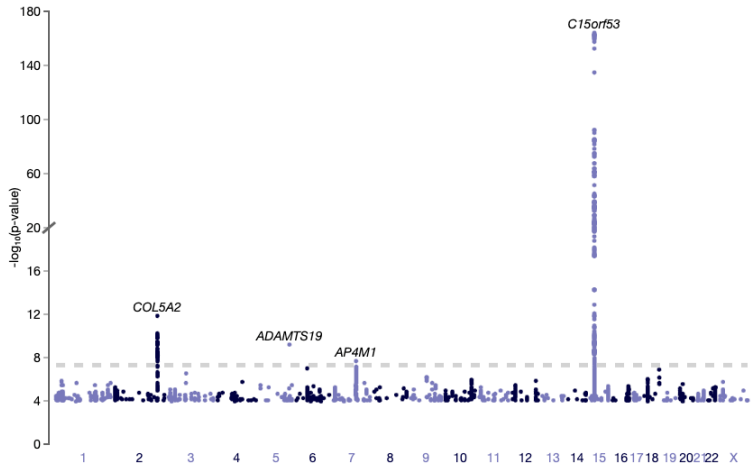
Search... "TCF7L2", "rs1861867", etc.

3935 phenotypes

Category	Phenotype	Loci < 10^{-6}	Top variant	Top p-value	Nearest Gene(s)
regional and tissue volume	BA-exvivo rh volume BA3b	9	15:39,634,222 A / G (rs1080066)	7.8e-165	*C15orf53*
cortical area	BA-exvivo rh area BA3b	15	15:39,634,222 A / G (rs1080066)	6.2e-145	*C15orf53*
cortical area	aparc-a2009s rh area S-central	10	15:39,634,222 A / G (rs1080066)	1.2e-131	*C15orf53*
regional and tissue volume	IDP T1 FAST ROIs L ventral striatum	32	4:103,188,709 C / T (rs13107325)	1.4e-119	*SLC39A8*
regional and tissue volume	aparc-a2009s rh volume S-central	10	15:39,634,222 A / G (rs1080066)	3.5e-119	*C15orf53*
cortical area	aparc-a2009s lh area S-central	14	15:39,633,877 A / AG (rs5812099)	3.3e-116	*C15orf53*
regional and tissue volume	BA-exvivo lh volume BA3b	6	15:39,639,898 A / C (rs4924345)	3.8e-116	*C15orf53*
regional and tissue volume	IDP T1 FAST ROIs R ventral striatum	25	4:103,188,709 C / T (rs13107325)	1.8e-115	*SLC39A8*
regional and tissue volume	IDP T1 FAST ROIs R putamen	34	4:103,188,709 C / T (rs13107325)	2.8e-104	*SLC39A8*
cortical area	BA-exvivo rh area BA3a	12	15:39,634,222 A / G (rs1080066)	4.1e-104	*C15orf53*
regional and tissue volume	IDP T1 FAST ROIs L putamen	36	4:103,188,709 C / T (rs13107325)	2.2e-103	*SLC39A8*
regional and tissue intensity	aseg rh intensity Accumbens-area	39	4:103,188,709 C / T (rs13107325)	5.3e-97	*SLC39A8*
regional and tissue volume	IDP T1 FAST ROIs V cerebellum IX	31	4:103,188,709 C / T (rs13107325)	1.2e-93	*SLC39A8*
regional and tissue volume	aparc-a2009s lh volume S-central	6	15:39,634,222 A / G (rs1080066)	5.3e-93	*C15orf53*
regional and tissue volume	BA-exvivo lh volume BA1	7	15:39,634,222 A / G (rs1080066)	1.6e-91	*C15orf53*
regional and tissue volume	aparc-a2009s lh volume G-postcentral	8	15:39,634,222 A / G (rs1080066)	1.8e-91	*C15orf53*

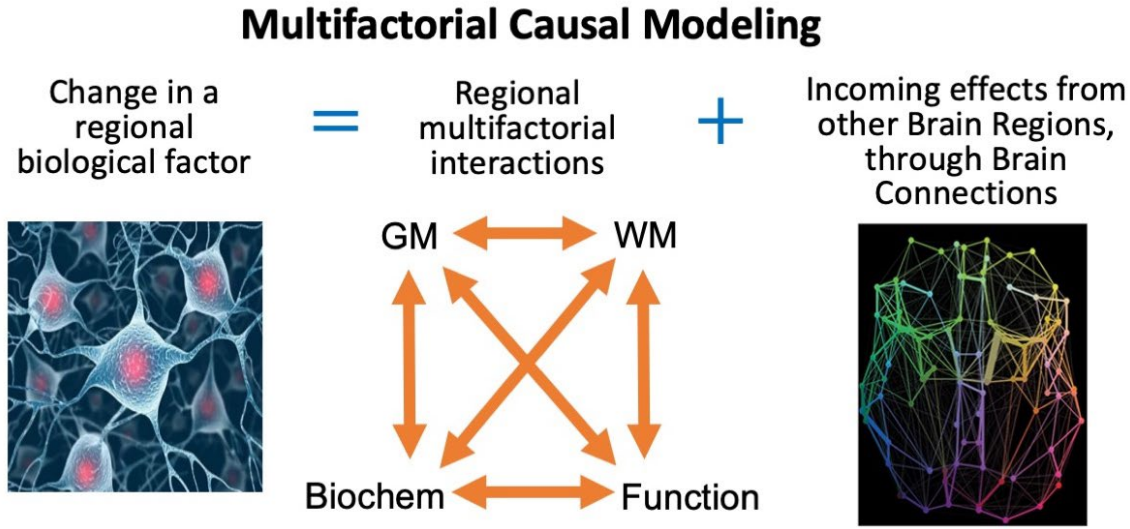
Interactive viewers

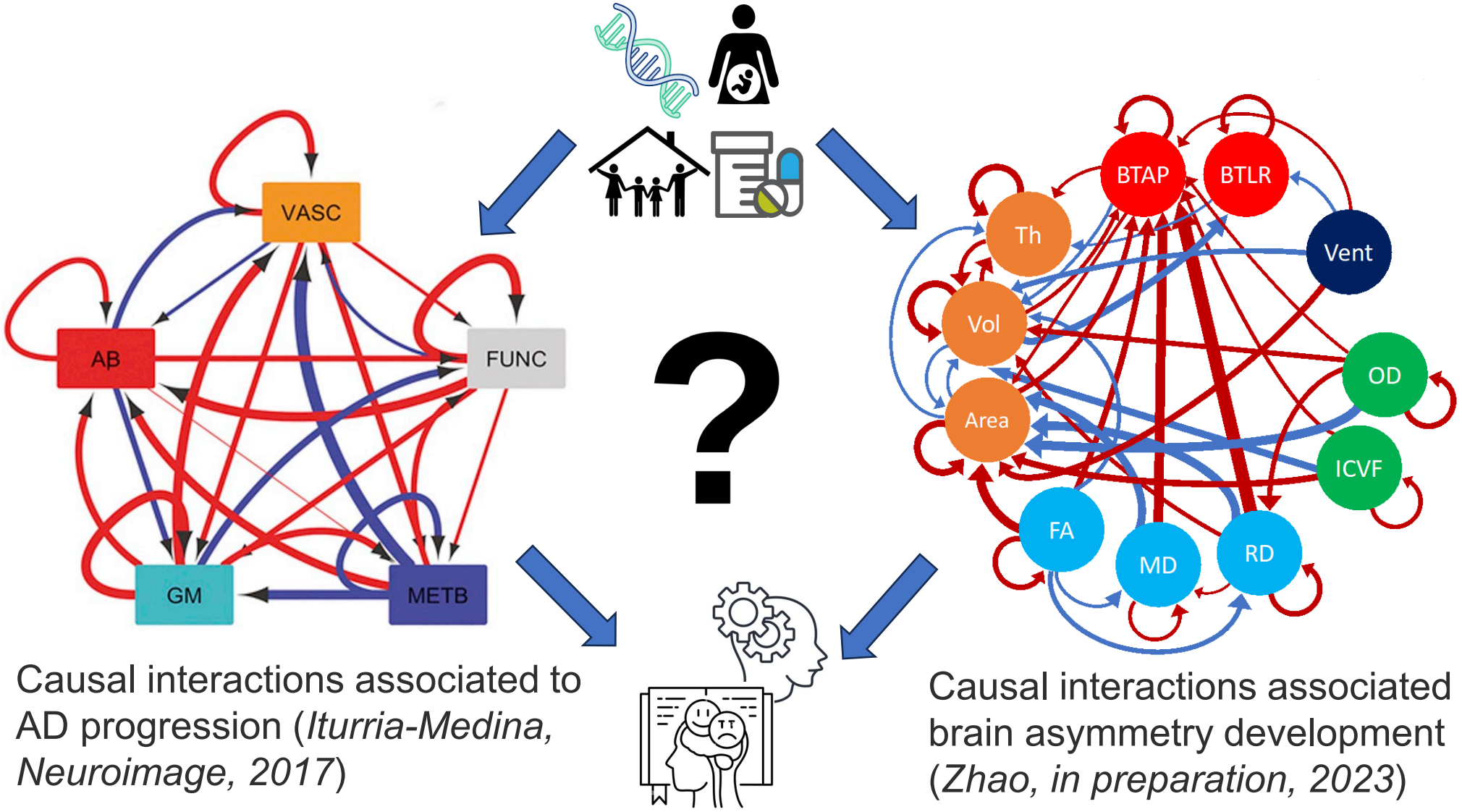




What's the next?

- Current results are limited by the univariate and cross-sectional study design
- The dynamic causal interactions across brain imaging profiles, genetic, environmental and clinical factors are unknown
- Systems biology aims to generate spatiotemporal mechanistic models (*Hampel, Prog. Neurobiol. 2019; Hampel, J. Alzheimer's Dis., 2019*)



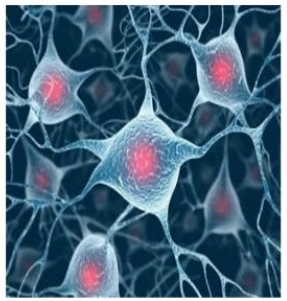


Causal interactions associated to AD progression (*Iturria-Medina, Neuroimage, 2017*)

Causal interactions associated to brain asymmetry development (*Zhao, in preparation, 2023*)

Multifactorial Causal Modeling

Change in a regional biological factor



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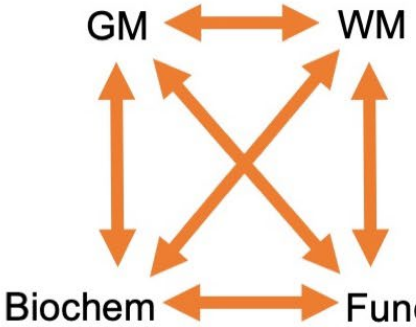
Regional multifactorial interactions



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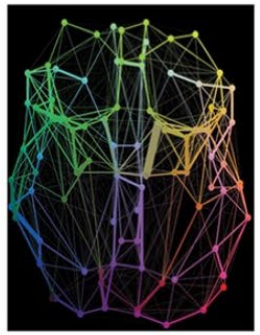
Incoming effects from other Brain Regions, through Brain Connections



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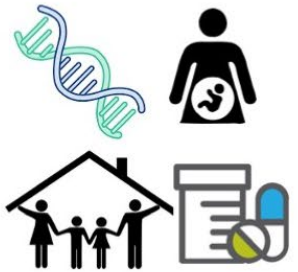
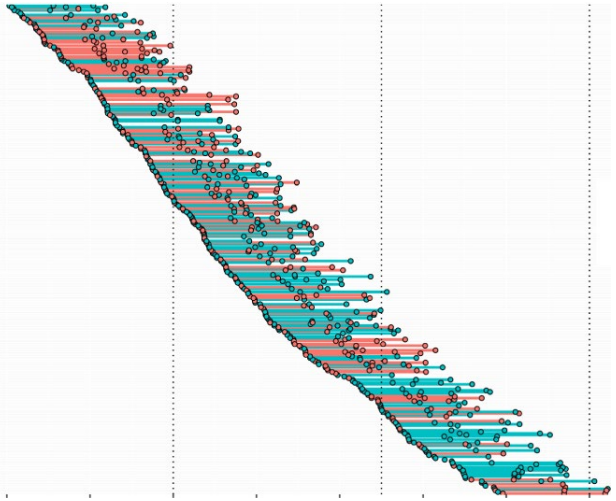
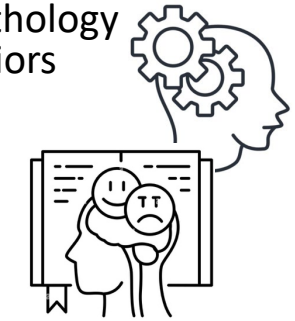
External Influences



Longitudinal omics data



Cognition/ Psychopathology behaviors



Thank you for your attention!