Neuroimaging Profiling of Psychiatric disorders: Insights and Challenges

Sophia Frangou, MD, Ph.D., FRCPsych, FRCPC

Chair in Brain Health and Associate Head
Department of Psychiatry, University of British Columbia
Professor of Psychiatry, Icahn School of Medicine at Mount Sinai

The Quest for Disease-Specific Biomarkers

- **Diagnosis and treatment of psychiatric disorders continue to rely on clinical observation and patient self-report**

- **The lack of biological features associated with psychiatric disorders**
  - **Undermines their biological validity**
  - **Undermines societal confidence in psychiatry**

BEST: Biomarkers, EndpointS, and other Tools Resource
https://www.ncbi.nlm.nih.gov/books/NBK326791/

Developed by the FDA-NIH Joint Leadership Council to harmonize terms used in translational science and medical product development, with a focus on terms related to study endpoints and biomarkers

Biomarker Definition:
A biomarker is a characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or a response to an exposure or intervention, including therapeutic interventions

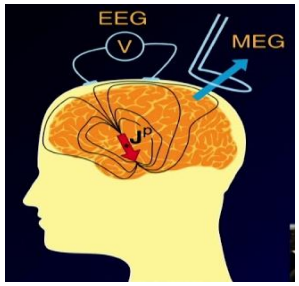
BEST defines 7 biomarker categories: susceptibility/risk, diagnostic, monitoring, prognostic, predictive, pharmacodynamic/response, and safety.

Diagnostic Biomarkers: A biomarker used to detect or confirm the presence of a disease or condition of interest or to identify individuals with a subtype of the disease.

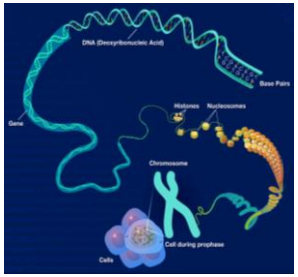
- **Intent-to-diagnose population**
- **Positive Predictive Value, Negative Predictive value [importance of enriched populations]**
- **Analytical performance**

Current State of Affairs

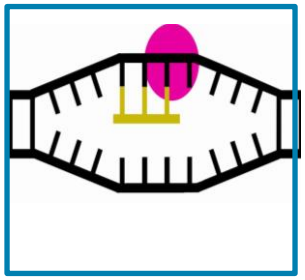
Neuroimaging



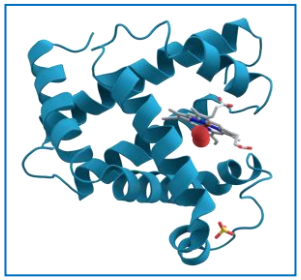
EEG/MEG



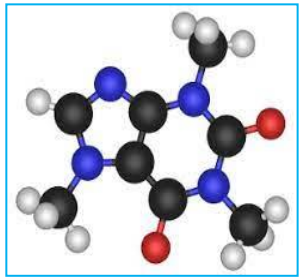
Genomics/Epigenomis



Transcriptomics



Proteomics



Metabolomics

A vast array of candidate biomarkers

Technological advances have increased dramatically
the ability to generate biomarkers

Major investment in the biology of mental disorders

Biological investigations of mental disorders dominate funding awards and publications

Increasing availability of large samples

Major initiatives to create large data repositories of legacy and new data (e.g., UKB, ABCD, AMP SCZ)

Huge literature on case-control differences in biomarkers

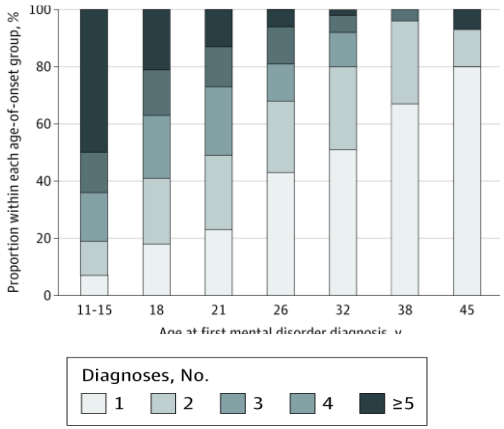
For any given biomarker, there are multiple studies showing “statistically significant” case-control differences

NO DIAGNOSTIC BIOMARKERS IDENTIFIED YET

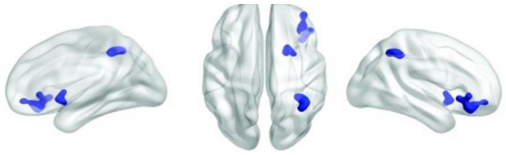
Three Key Challenges

Phenotype

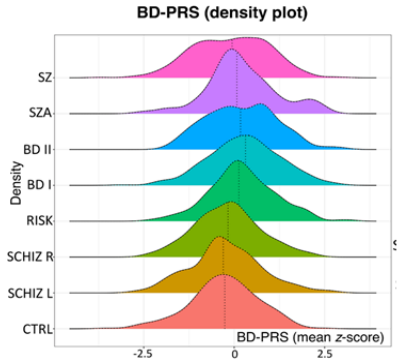
Multimorbidity

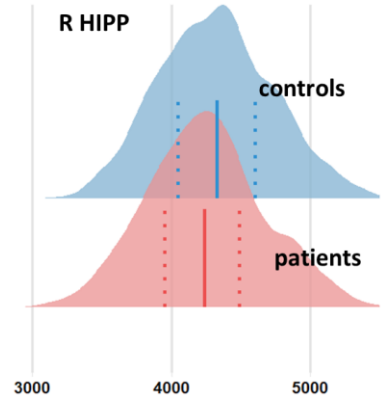


Non-specific Neurosignatures



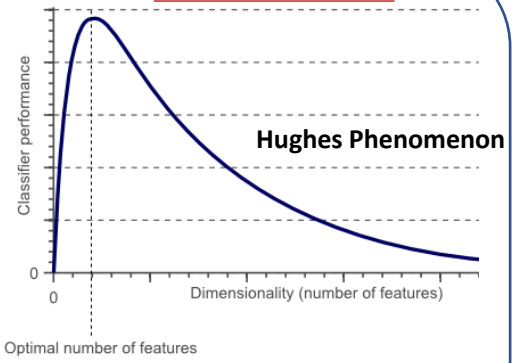
Overlap with healthy variation



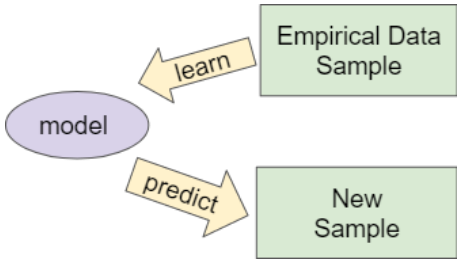


Practical Limitations

Biomarker Selection



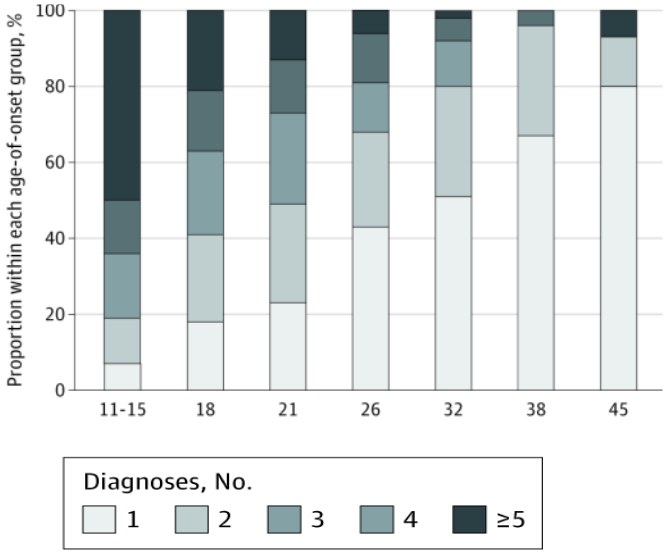
Generalizability



PMID: 34836939; PMID: 32315069; PMID: 31664439

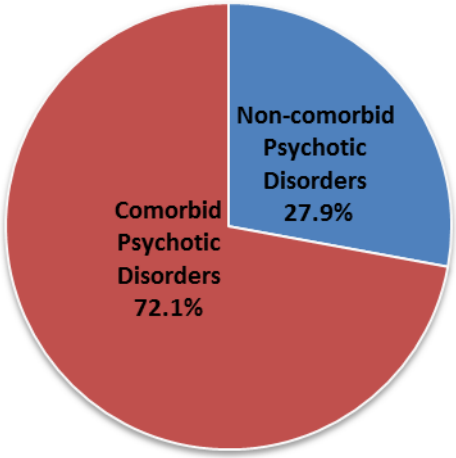
Challenges Related to the Phenotype

Multimorbidity

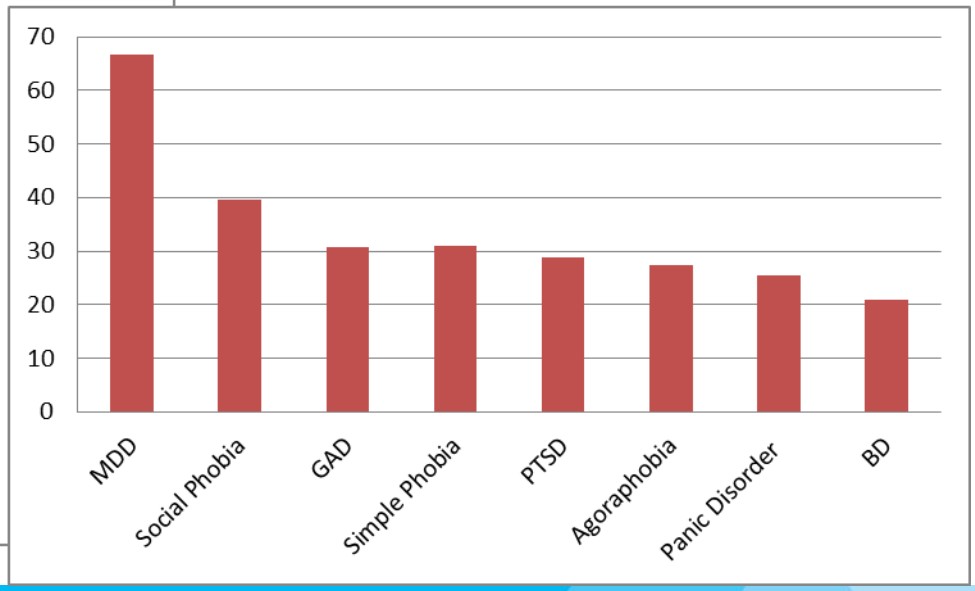


Longitudinal Assessment of Mental Health Disorders and Comorbidities Across 4 Decades Among Participants in the Dunedin Birth Cohort Study

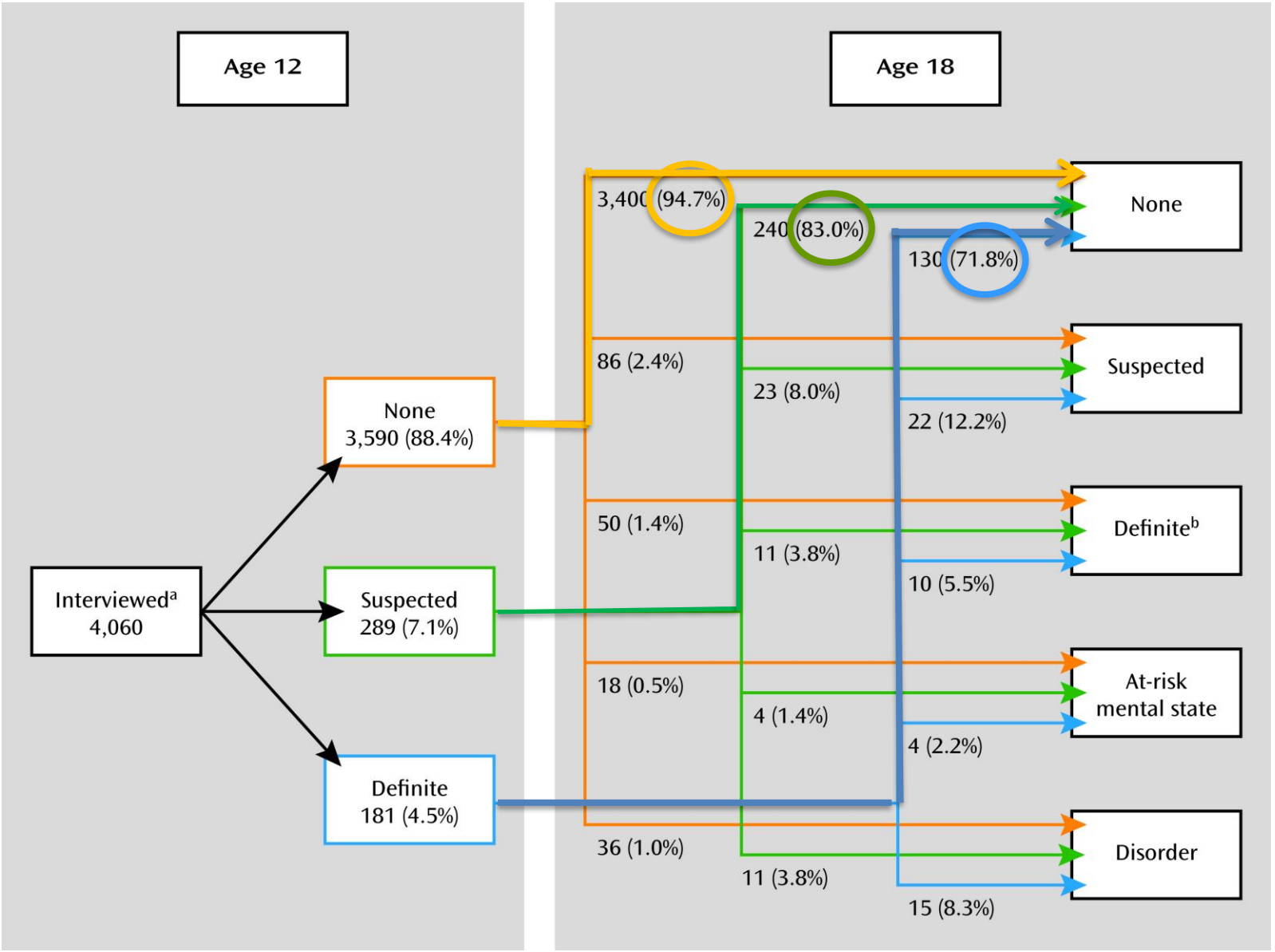
Caspi et al. JAMA Netw Open, 2020



National Comorbidity Survey



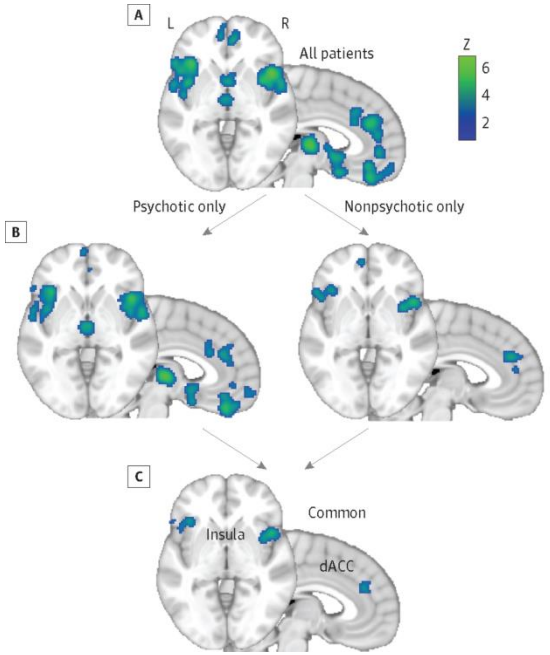
Psychotic experiences and psychotic disorders at age 18 in relation to psychotic experiences at age 12 in a longitudinal population-based cohort study.



Zammit et al. Am J Psychiatry 2013

From: **Identification of a Common Neurobiological Substrate for Mental Illness**

JAMA Psychiatry. Published online February 04, 2015. doi:10.1001/jamapsychiatry.2014.2206



Schizophrenia, Bipolar Disorder, Major Depressive Disorder, Substance Abuse, Obsessive Compulsive Disorder, Anxiety Disorders	
Reduced GM in patients	**Increased GM in patients**
Dorsomedial PFC	striatum
Ventromedial PFC	
Superior Temporal Gyrus	
Parietal Operculum	
Dorsal ACC (all)	
Insula (all)	
Thalamus	
Amygdala	
Hippocampus	

Shared Patterns of Decreased Gray Matter From the Voxel-Based Morphometry Meta-analysis: Results are from patient vs healthy participant comparisons for studies pooled across all diagnoses (A), separately by psychotic or nonpsychotic diagnosis studies (B), and from a conjunction across the psychotic and non-psychotic diagnosis group maps in panel B (C). Results show common gray matter loss across diagnoses in the anterior insula and dorsal anterior cingulate (dACC). The z score is for the activation likelihood estimation analysis for gray matter loss. L indicates left; and r, right.

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Molecular Psychiatry

ARTICLE OPEN

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Neuroimaging profiling identifies distinct brain maturational subtypes of youth with mood and anxiety disorders

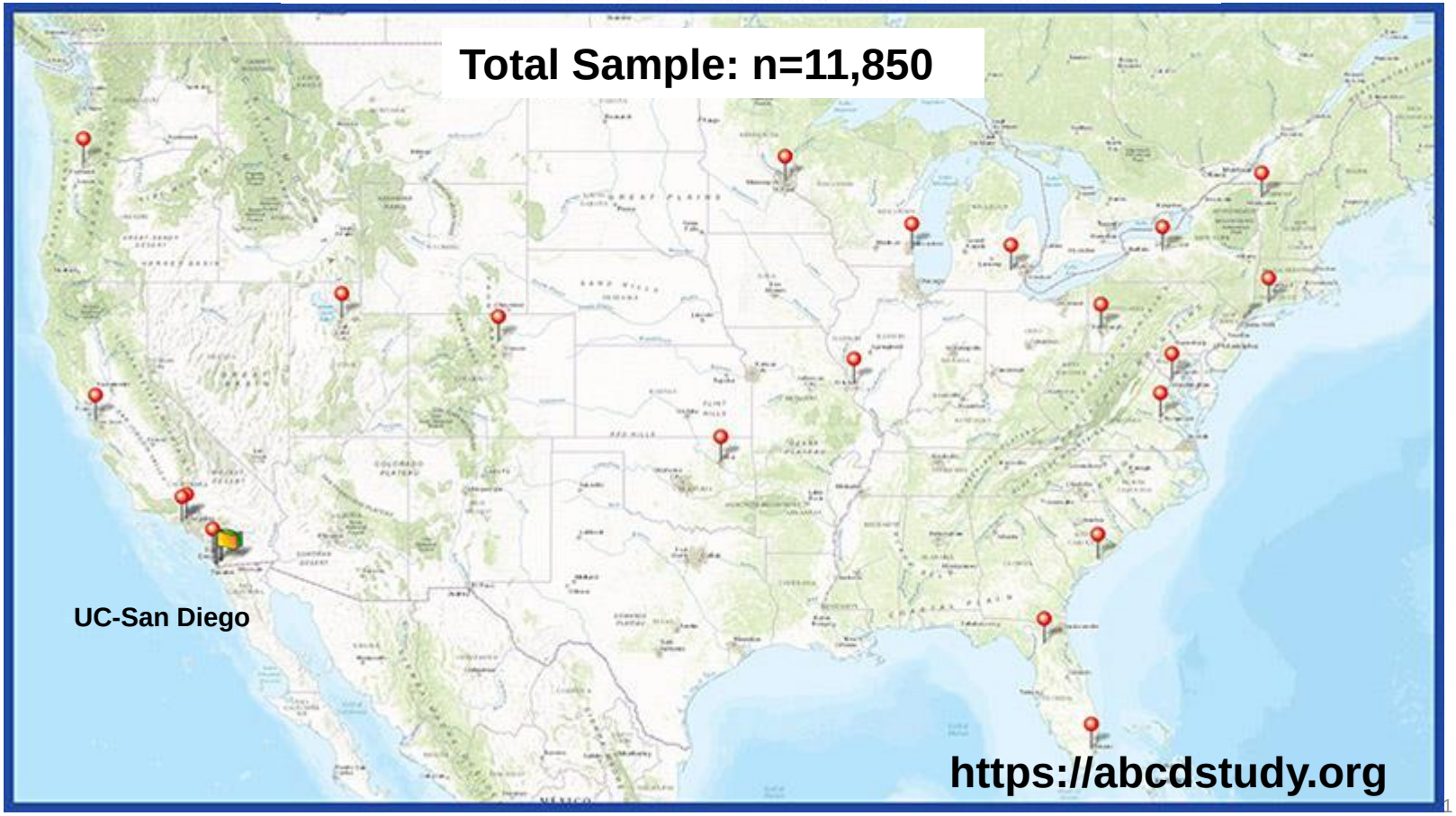
Ruiyang Ge[1,2], Roberto Sassi[1,2,3], Lakshmi N. Yatham[1,2] and Sophia Frangou[1,2,4]✉

Mood and anxiety disorders typically begin in adolescence and have overlapping clinical features but marked inter-individual variation in clinical presentation. The use of multimodal neuroimaging data may offer novel insights into the underlying brain mechanisms. We applied Heterogeneity Through Discriminative Analysis (HYDRA) to measures of regional brain morphometry, neurite density, and intracortical myelination to identify subtypes of youth, aged 9–10 years, with mood and anxiety disorders ($N = 1931$) compared to typically developing youth ($N = 2823$). We identified three subtypes that were robust to permutation testing and sample composition. Subtype 1 evidenced a pattern of imbalanced cortical-subcortical maturation compared to the typically developing group, with subcortical regions lagging behind prefrontal cortical thinning and myelination and greater cortical surface expansion globally. Subtype 2 displayed a pattern of delayed cortical maturation indicated by higher cortical thickness and lower cortical surface area expansion and myelination compared to the typically developing group. Subtype 3 showed evidence of atypical brain maturation involving globally lower cortical thickness and surface coupled with higher myelination and neural density. Subtype 1 had superior cognitive function in contrast to the other two subtypes that underperformed compared to the typically developing group. Higher levels of parental psychopathology, family conflict, and social adversity were common to all subtypes, with subtype 3 having the highest burden of adverse exposures. These analyses comprehensively characterize pre-adolescent mood and anxiety disorders, the biopsychosocial context in which they arise, and lay the foundation for the examination of the longitudinal evolution of the subtypes identified as the study sample transitions through adolescence.

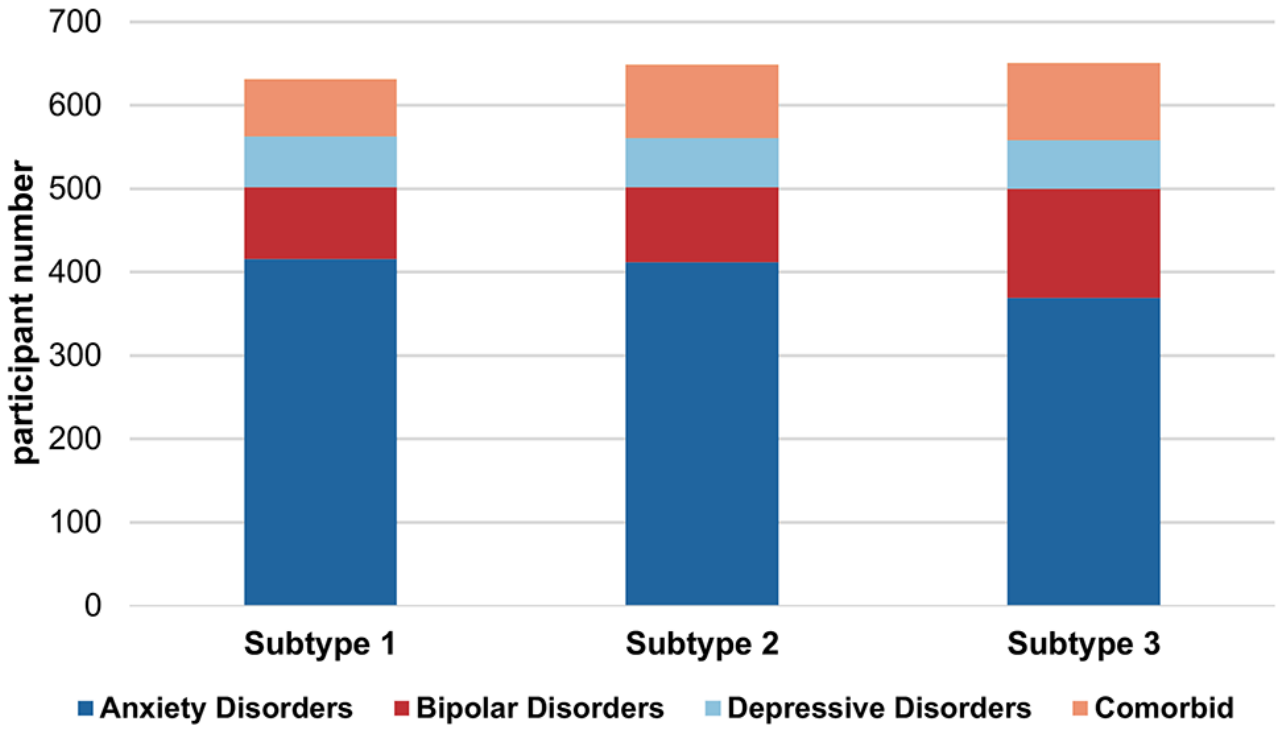
Molecular Psychiatry (2023) 28:1072–1078; https://doi.org/10.1038/s41380-022-01925-9

Adolescent Brain Cognitive Development®

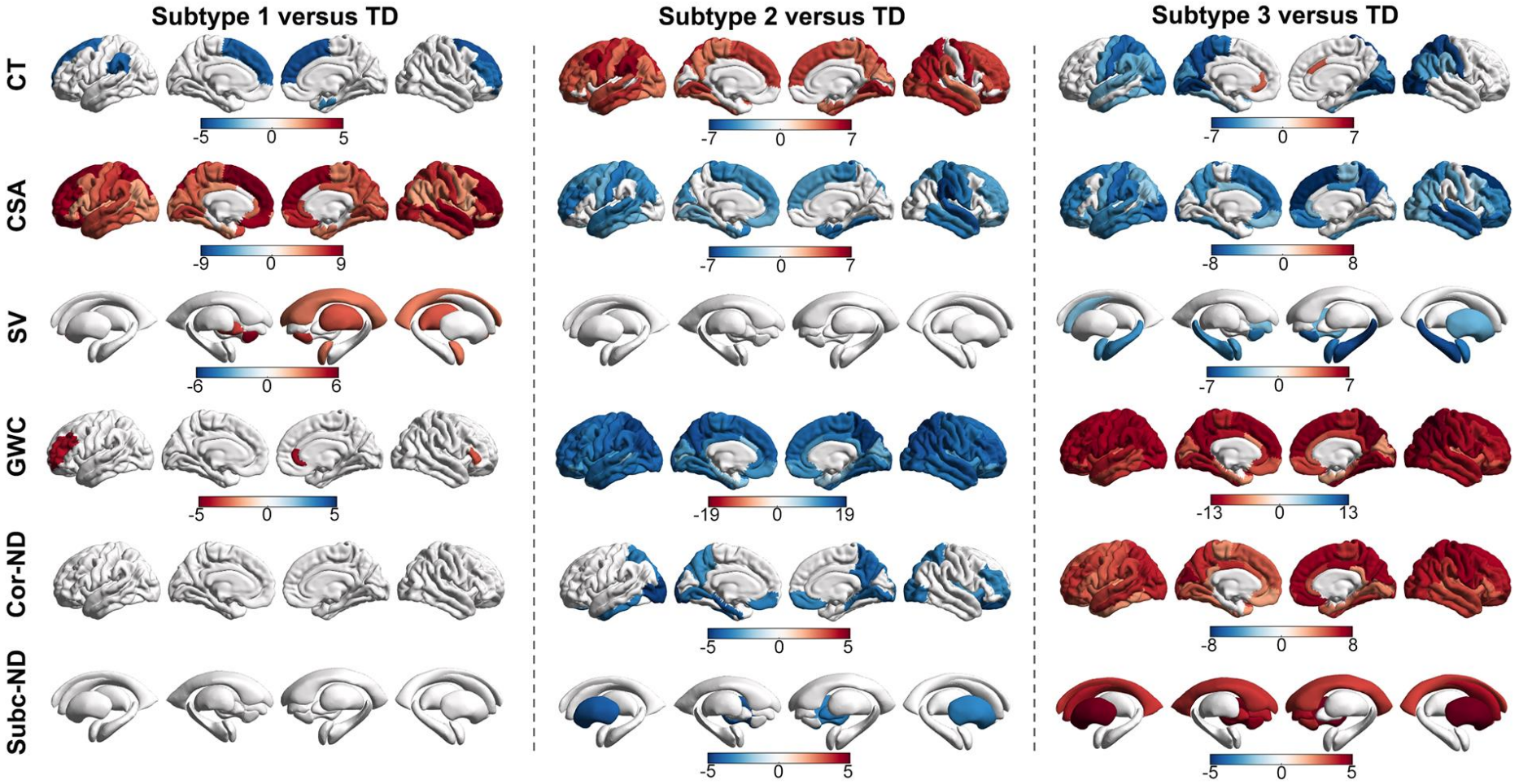
Teen Brains. Today's Science. Brighter Future.



Transdiagnostic Neuroimaging-Derived Profiles in youth with Mood and Anxiety Disorders



Transdiagnostic Neuroimaging Profiles in Childhood Mood and Anxiety Disorders



Ge R, Sassi R, Yatham LN, Frangou S. Mol Psychiatry. 2022; PMID: 36577839

HUMAN BRAIN MAPPING

Research Article | Open Access

Addressing reverse inference in psychiatric neuroimaging: Meta-analyses of task-related brain activation in common mental disorders

Emma Sprooten, Alexander Rasgon, Morgan Goodman, Ariella Carlin, Evan Leibu, Won Hee Lee, Sophia Frangou

https://doi.org/10.1002/hbm.23486

Pairwise Comparisons between Psychiatric Disorders

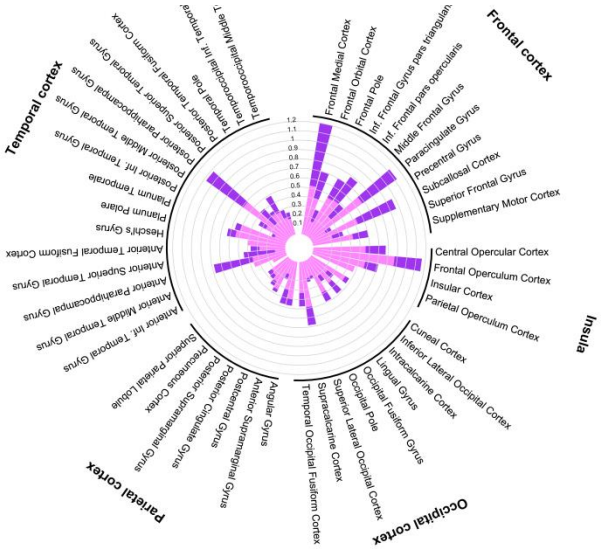
	Correlation Coefficient	Confidence intervals	
		Lower	Upper
MDD-SCZ	0.83	0.71	0.9
MDD-BD	0.9	0.83	0.94
MDD-ANX	0.91	0.84	0.95
MDD-OCD	0.8	0.67	0.88
SCZ-BD	0.91	0.84	0.95
SCZ-ANX	0.88	0.8	0.93
SCZ-OCD	0.72	0.55	0.84
BD-ANX	0.88	0.8	0.93
BD-OCD	0.75	0.6	0.85
ANX-OCD	0.7	0.51	0.82

Sprooten et al. HBM 2017

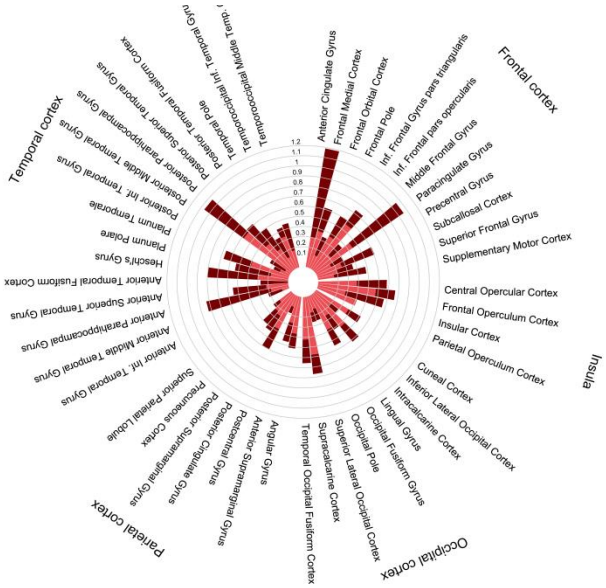
Cortical Regions

% of studies per region (normalized by region size)

Major depression



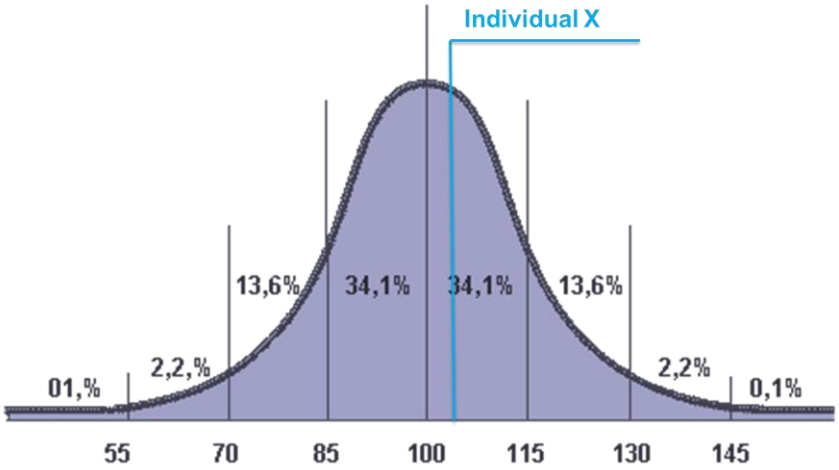
Anxiety disorders

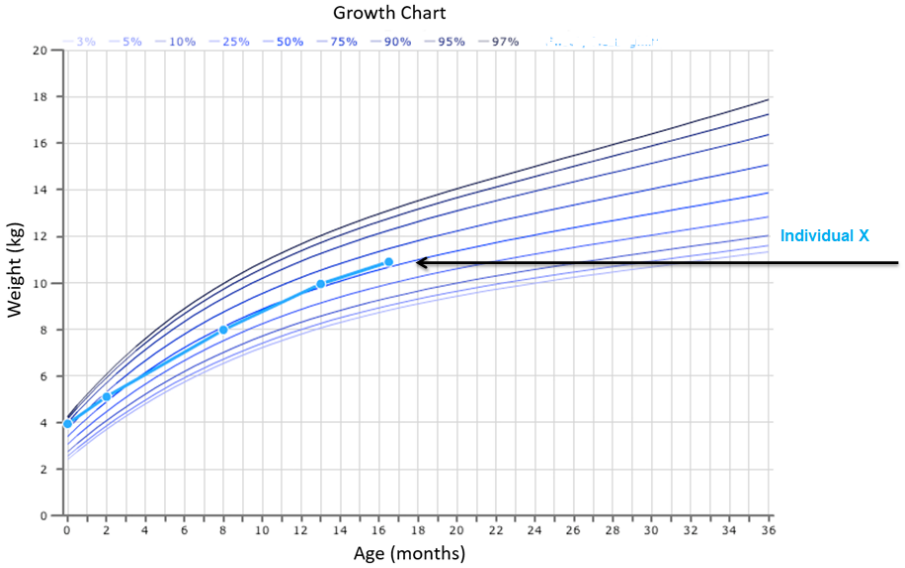


Sprooten et al. HBM 2017

Challenges Related to Overlap with Normal Deviation

Normative Modeling
Individualized measures of deviation from population means





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Normative Modeling of Brain Morphometry Across the Lifespan using CentileBrain:Algorithm Benchmarking and Model Optimization

Ruiyang Ge, Yuetong Yu, Yi Xuan Qi, Yunan Vera Fan, Shiyu Chen, Chuntong Gao, Shalaila S Haas, Amirhossein Modabbernia, Faye New, Ingrid Agartz, Philip Asherson, Rosa Ayesa-Arriola, Nerisa Banaj, Tobias Banaschewski, Sarah Baumeister, Alessandro Bertolino, Dorret I Boomsma, Stefan Borgwardt, Josiane Bourque, Daniel Brandeis, Alan Breier, Henry Brodaty, Rachel M Brouwer, Randy Buckner, Jan K Buitelaar, Dara M Cannon, Xavier Caseras, Simon Cervenka, Patricia J Conrod, Benedicto Crespo-Facorro, Fabrice Crivello, Eveline A Crone, Liewe de Haan, Greig I de Zubicaray, Annabella Di Giorgio, Susanne Erk, Simon E Fisher, Barbara Franke, Thomas Frodl, David C Glahn, Dominik Grotegerd, Oliver Gruber, Patricia Gruner, Raquel E Gur, Ruben C Gur, Ben J Harrison, Sean N Hatton, Ian Hickie, Fleur M Howells, Hilleke E Hulshoff Pol, Chaim Huyser, Terry L Jernigan, Jiyang Jiang, John A Joska, René S Kahn, Andrew J Kalnin, Nicole A Kochan, Sanne Koops, Jonna Kuntsi, Jim Lagopoulos, Luisa Lazaro, Irina S Lebedeva, Christine Lochner, Nicholas G Martin, Bernard Mazoyer, Brenna C McDonald, Colm McDonald, Katie L McMahon, Tomohiro Nakao, Lars Nyberg, Fabrizio Piras, Maria J Portella, Jiang Qiu, Joshua L Roffman, Perminder S Sachdev, Theodore D Satterthwaite, Andrew J Saykin, Gunter Schumann, Carl M Sellgren, Kang Sim, Jordan W Smoller, Jair Soares, Iris E Sommer, Gianfranco Spalletta, Dan J Stein, Christian K Tamnes, Sophia I Thomopolous, Alexander S Tomyshev, Diana Tordesillas-Gutiérrez, Julian N Trollor, Dennis van 't Ent, Odile A van den Heuvel, Theo GM van Erp, Neeltje EM van Haren, Daniela Vecchio, Dick J Veltman, Henrik Walter, Yang Wang, Bernd Weber, Dongtao Wei, Wei Wen, Lars T Westlye, Lara M Wierenga, Steven CR Williams, Margaret J Wright, Sarah Medland, Mon-Ju Wu, Neda Jahanshad, Paul M Thompson, Sophia Frangou

doi: https://doi.org/10.1101/2023.01.30.523509

CentileBrain (www.centilebrain.org)

- An empirically benchmarked framework for normative modeling in brain morphometry
- Offers the opportunity to generate metrics for typical brain structural trajectories for research purposes
- Normative models were generated using data from over 37,000 healthy individuals aged 3-90 years
- An ENIGMA Lifespan working group initiative

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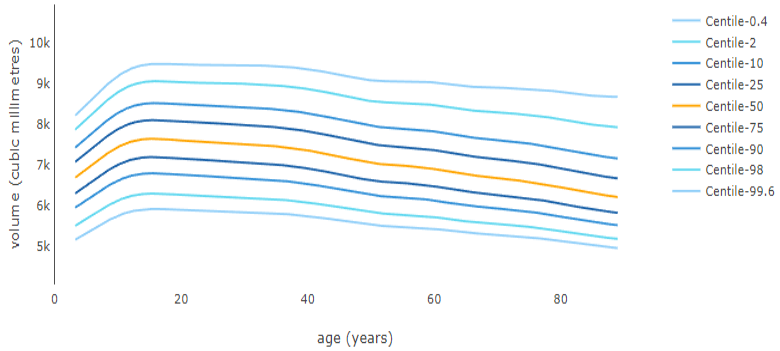
CentileBrain Data Vault | Visualize Regional Age-Related Curves

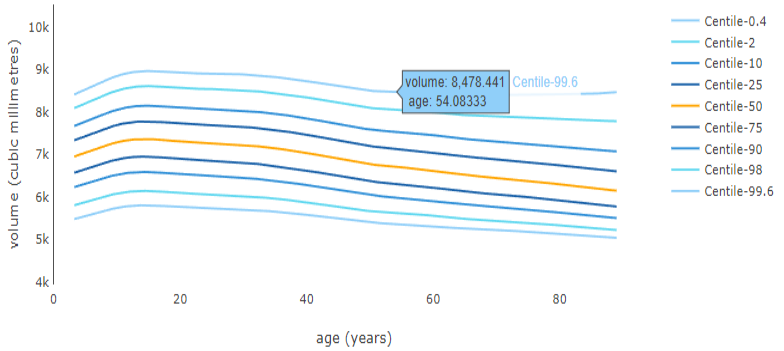
Select Sex: Female

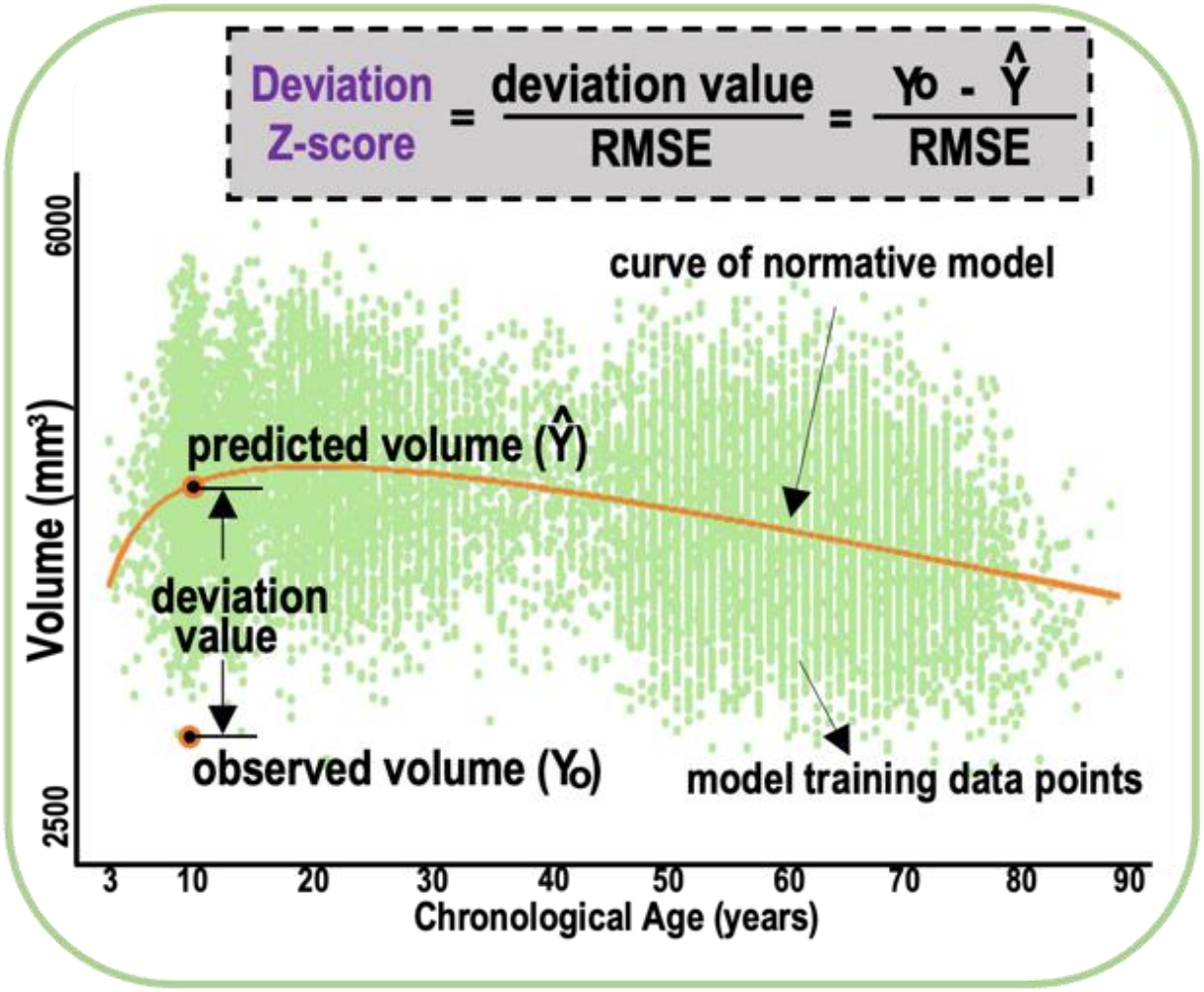
Select Morphometric Measure: Regional Subcortical Volumes

Regional Subcortical Volumes: Thalamus

Curves
MFP Regression
Centile Curves

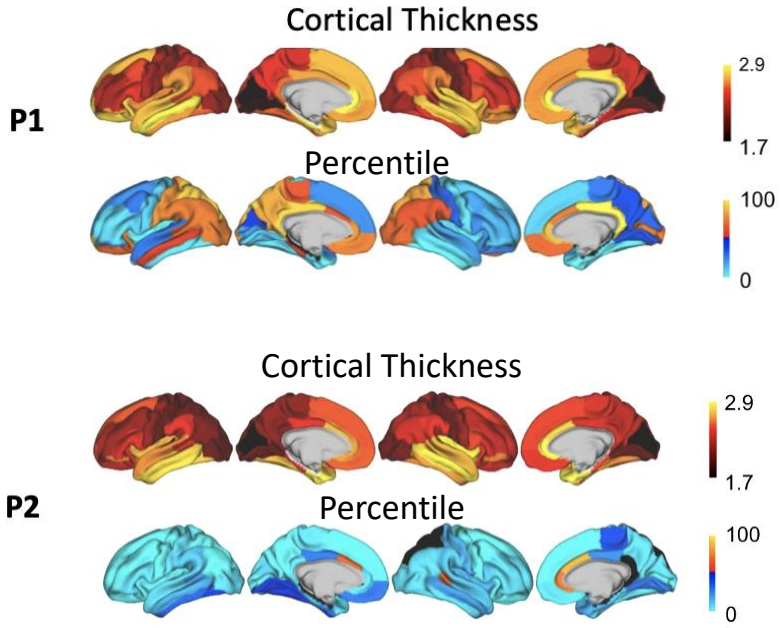




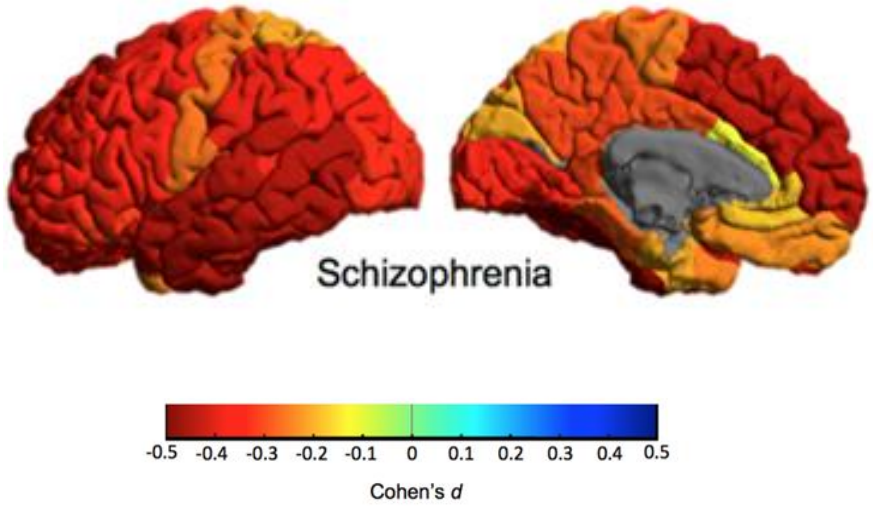

Deviation Z-score = deviation value / RMSE = Yo - Ŷ / RMSE
curve of normative model
predicted volume (Ŷ)
deviation value
observed volume (Yo)
model training data points
Volume (mm³)
6000
2500
3
10
20
30
40
50
60
70
80
90
Chronological Age (years)

Individual-level Deviations vs Average "Disease" Maps

Individual-level Percentile Deviation in Regional CT



Case-Control Differences in Regional CT



Lv et al. Mol Psychiatry 2020;

Ching et al. HBM 2020

Normative Modeling in Psychiatric Populations

Wolfers T, Doan NT, Kaufmann T, Alnæs D, Moberget T, Agartz I, et al. Mapping the heterogeneous phenotype of schizophrenia and bipolar disorder using normative models. JAMA Psychiatry. 2018;75:1146–1155.

Zabihi M, Oldehinkel M, Wolfers T, Frouin V, Goyard D, Loth E, Charman T, Tillmann J, Banaschewski T, Dumas G, Holt R, Baron-Cohen S, Durston S, Bölte S, Murphy D, Ecker C, Buitelaar JK, Beckmann CF, Marquand AF. Dissecting the Heterogeneous Cortical Anatomy of Autism Spectrum Disorder Using Normative Models. Biol Psychiatry Cogn Neurosci Neuroimaging. 2019;4(6):567-578.

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Zabihi M, Floris DL, Kia SM, Wolfers T, Tillmann J, Arenas AL, Moessnang C, Banaschewski T, Holt R, Baron-Cohen S, Loth E, Charman T, Bourgeron T, Murphy D, Ecker C, Buitelaar JK, Beckmann CF, Marquand A; EU-AIMS LEAP Group. Fractionating autism based on neuroanatomical normative modeling. Transl Psychiatry. 2020;10(1):384.

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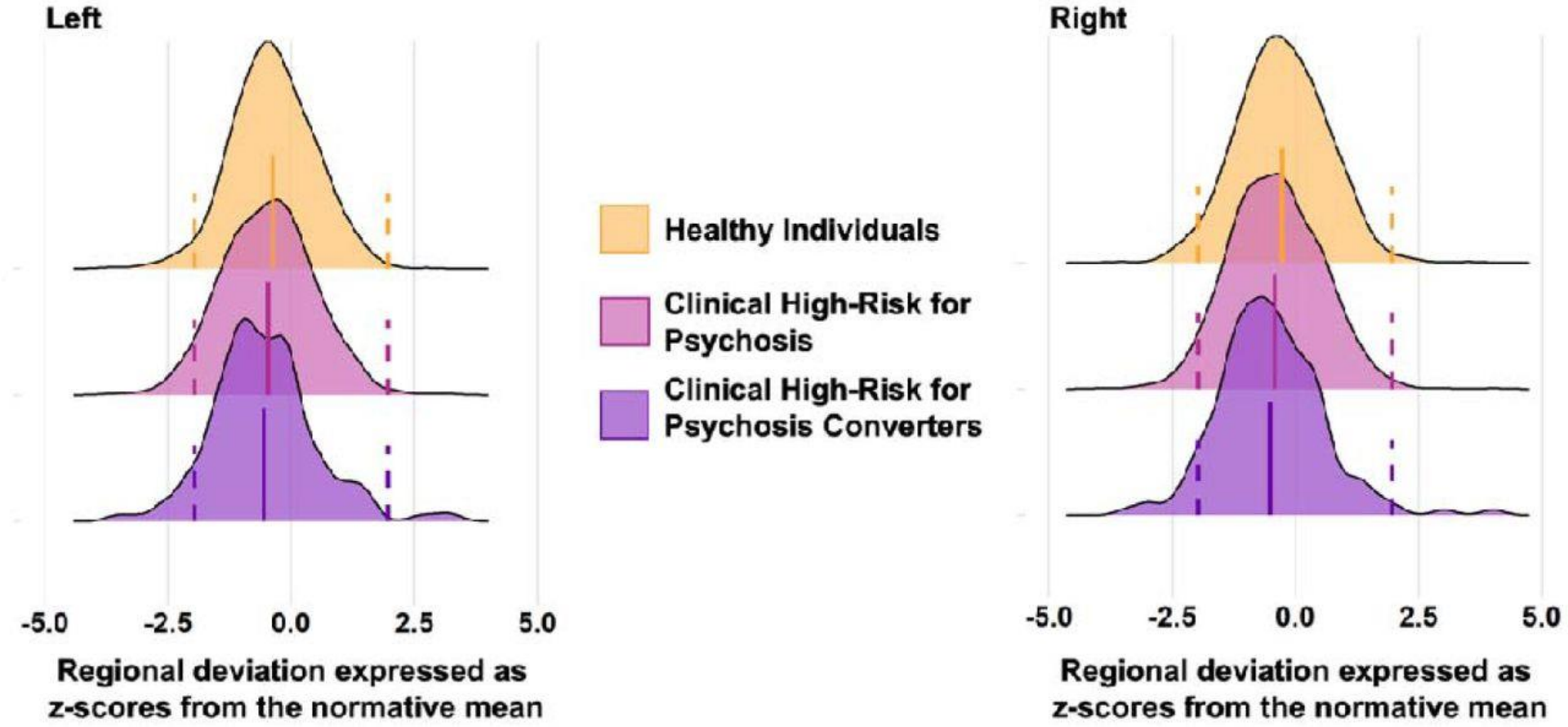
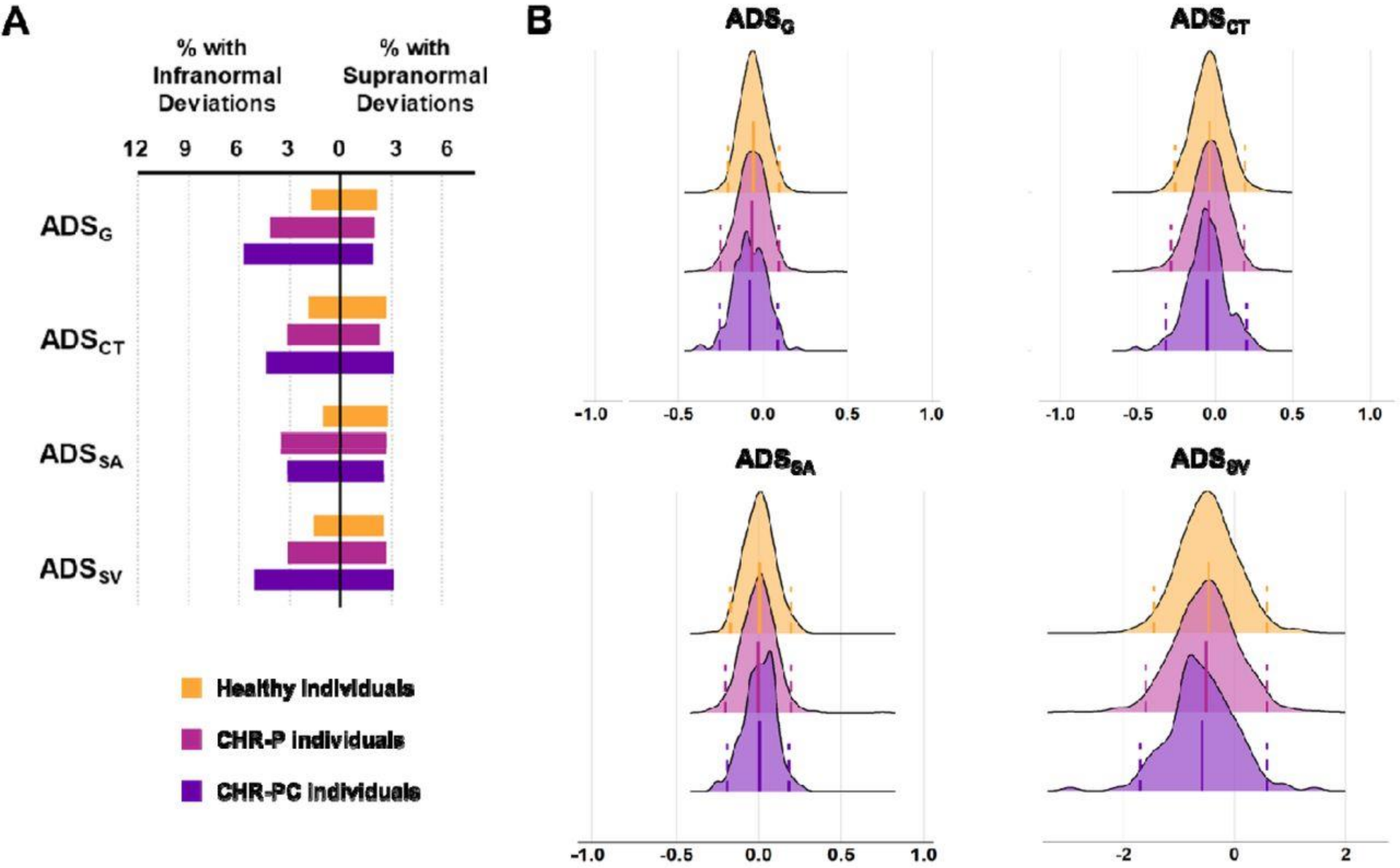
Normative modeling of brain morphometry in Clinical High-Risk for Psychosis

Shalaila S Haas, Ruiyang Ge, Ingrid Agartz, G. Paul Amminger, Ole A Andreassen, Peter Bachman, Inmaculada Baeza, Sunah Choi, Tiziano Colibazzi, Vanessa L Cropley, Camilo de la Fuente-Sandoval, Bjørn H Ebdrup, Adriana Fortea, Paolo Fusar-Poli, Birte Yding Glenthøj, Louise Birkedal Glenthøj, Kristen M Haut, Rebecca A Hayes, Karsten Heekeren, Christine I Hooker, Wu Jeong Hwang, Neda Jahanshad, Michael Kaess, Kiyoto Kasai, Naoyuki Katagiri, Minah Kim, Jochen Kindler, Shinsuke Koike, Tina D Kristensen, Jun Soo Kwon, Stephen M Lawrie, Jimmy Lee, Imke LJ Lemmers-Jansen, Ashleigh Lin, Xiaoqian Ma, Daniel H Mathalon, Philip McGuire, Chantal Michel, Romina Mizrahi, Masafumi Mizuno, Paul Møller, Ricardo Mora-Durán, Barnaby Nelson, Takahiro Nemoto, Merete Nordentoft, Dorte Nordholm, Maria A Omelchenko, Christos Pantelis, Jose C Pariente, Jayachandra M Raghava, Francisco Reyes-Madrigal, Jan I Røssberg, Wulf Rössler, Dean F Salisbury, Daiki Sasabayashi, Ulrich Schall, Lukasz Smigielski, Gisela Sugranyes, Michio Suzuki, Tsutomu Takahashi, Christian K Tamnes, Anastasia Theodoridou, Sophia I Thomopoulos, Paul M Thompson, Alexander S Tomyshev, Peter J Uhlhaas, Tor G Værnes, Therese AMJ van Amelsvoort, Theo GM van Erp, James A Waltz, Christina Wenneberg, Lars T Westlye, Stephen J Wood, Juan H Zhou, Dennis Hernaus, Maria Jalbrzikowski, René S Kahn, Cheryl M Corcoran, Sophia Frangou, the ENIGMA Clinical High Risk for Psychosis Working Group

doi: https://doi.org/10.1101/2023.01.17.523348

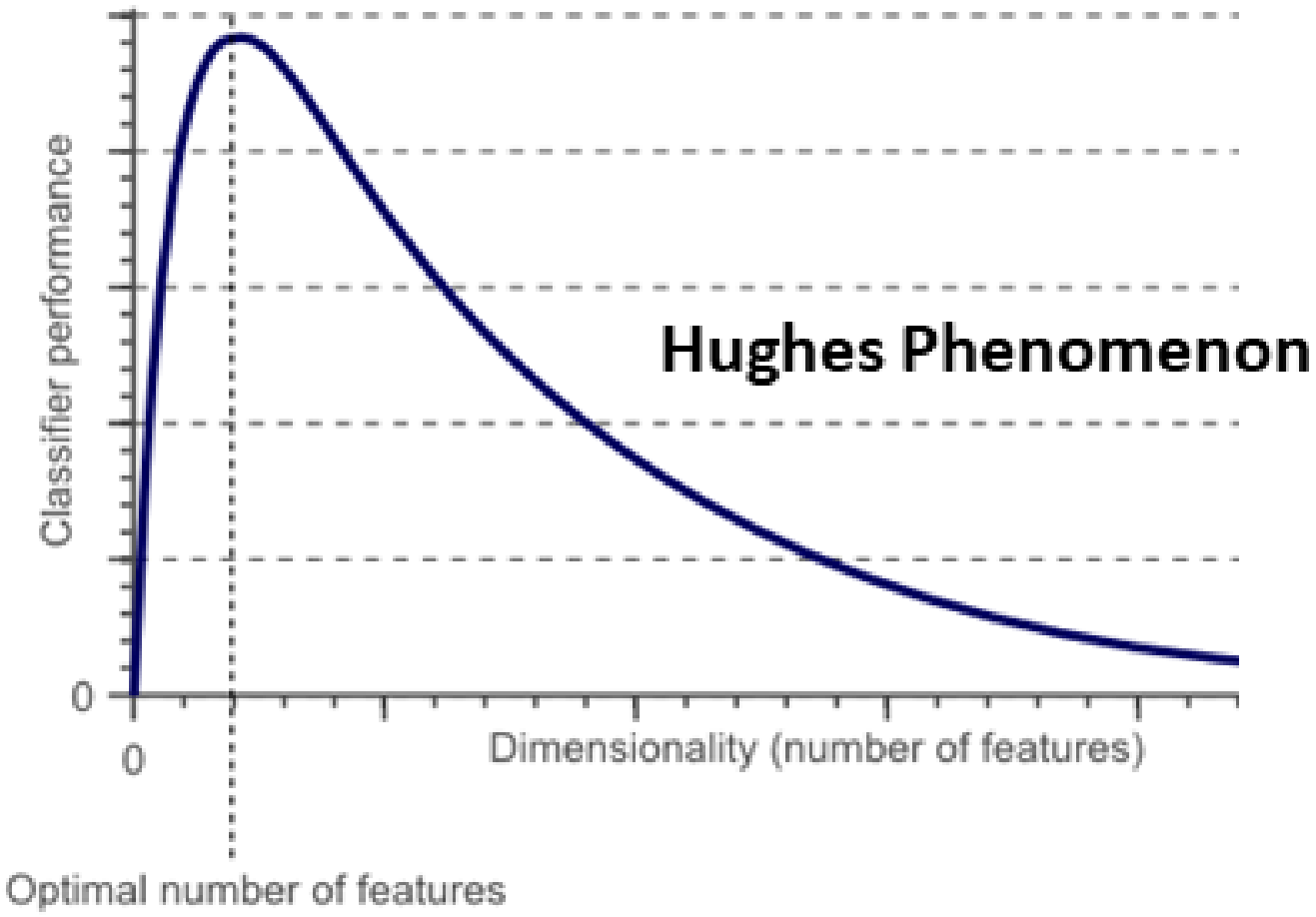
Distribution of hippocampal subcortical volume normative z-scores in the study sample



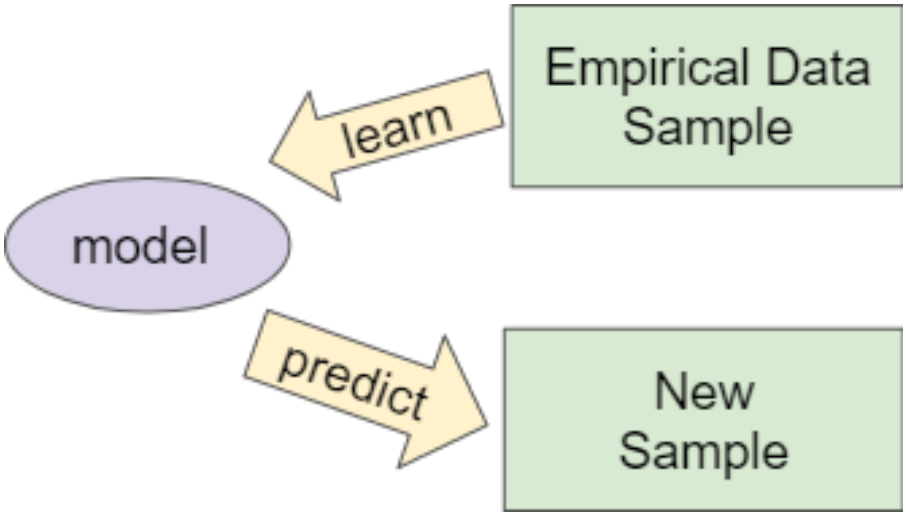

A
% with Infranormal Deviations
% with Supranormal Deviations
12 9 6 3 0 3 6
ADS_G
ADS_CT
ADS_SA
ADS_SV
Healthy Individuals
CHR-P Individuals
CHR-PC Individuals
B
ADS_G
ADS_CT
ADS_SA
ADS_SV
-1.0 -0.5 0.0 0.5 1.0
-2 0 2

Practical Limitations

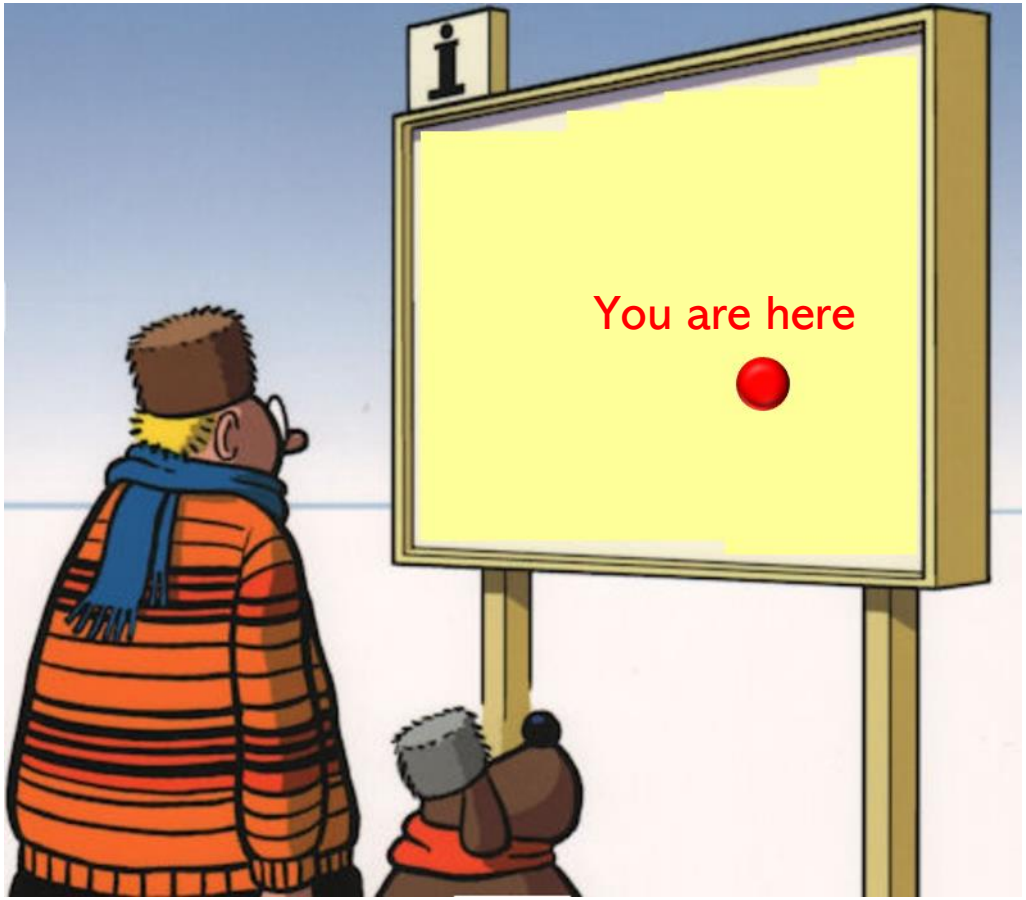
Biomarker Number and Selection



Generalizability



- **Model dependence on**
  - **Algorithm**
  - **Sample Composition**
  - **Training features**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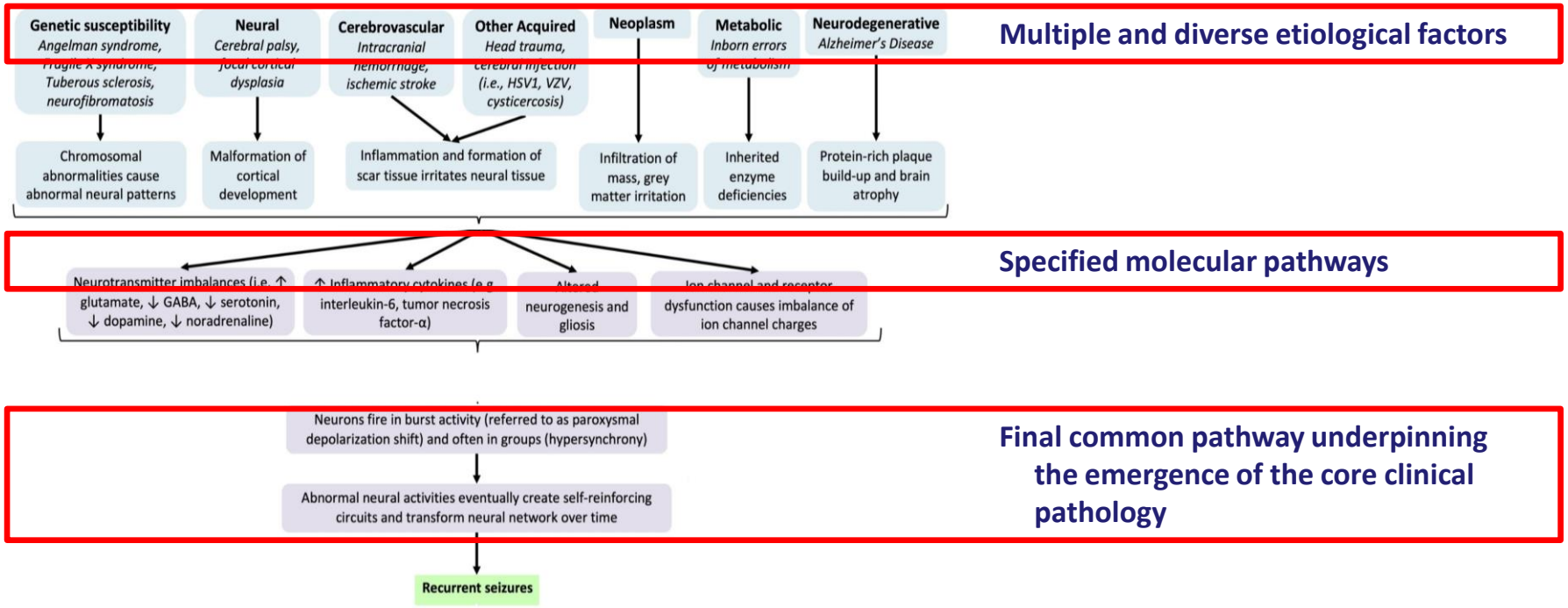
Lessons from Epilepsy

Complex clinical presentations of seizures (peri-ictal; ictal; post-ictal) with significant inter-individual and intra-individual variation

Multidomain impairment in neurocognition and affective cognition with significant intra-individual variation

Psychiatric comorbidities in up to a third of patients

Multidimensional psychosocial disadvantage/impairment



Multiple and diverse etiological factors

Specified molecular pathways

Final common pathway underpinning the emergence of the core clinical pathology

Epilepsy is defined as a disorder of the brain characterized by an enduring disposition towards recurrent seizures with associated cognitive, psychological, and social dysfunction.

This definition identifies a "core" clinical feature while recognizing other domains of impairment that are not diagnostically necessary or sufficient

Schizophrenia can be defined as a disorder of the brain characterized by an enduring disposition towards recurrent positive psychotic symptoms, associated with cognitive, psychological, and social dysfunction.

Persistent and recurrent perceptual distortions (i.e., hallucinations) could be proposed as the most distinct clinical feature of schizophrenia

Hallucinations as a window into mechanistic underpinnings of schizophrenia

Attractor cortical neurodynamics in schizophrenia
Rolls E. Transl Psychiatry 2021
Modeling the transition between the healthy state and the hallucinatory state using maps of brain dynamics

Dynamic Causal Modeling for fMRI With Wilson-Cowan-Based Neuronal Equations Sadeghi et al Front Neurosci 2020
This approach which describes the evolution of excitatory and inhibitory activity in a population of neurons can be implemented in DCM, yielding parameters that can be directly interpreted physiologically

Neurite and Synaptic density in schizophrenia
Onwordi et al Nat Comm 2020; Kraculjac et al 2021
Estimates of synaptic and neurite density in schizophrenia (e.g., NODDI; SV2A ligands) can inform neural firing and system-level dynamic models

Quantification of the dynamic aspects of neurotransmission in the human brain in vivo
This is an area that requires further methodological development as current approaches (e.g., functional MRS) probably lack the necessary essay sensitivity

Liquid biopsy: CNS-derived but peripherally harvested extracellular vesicles (EVs)
Goetzl et al FASEB 2022
Nanosized bilayer particles circulating in the blood that carry cargoes such as lipids, proteins, and nucleic acids that can be assigned neuronal or central glial origin; potential to provide a handle into molecular pathways

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