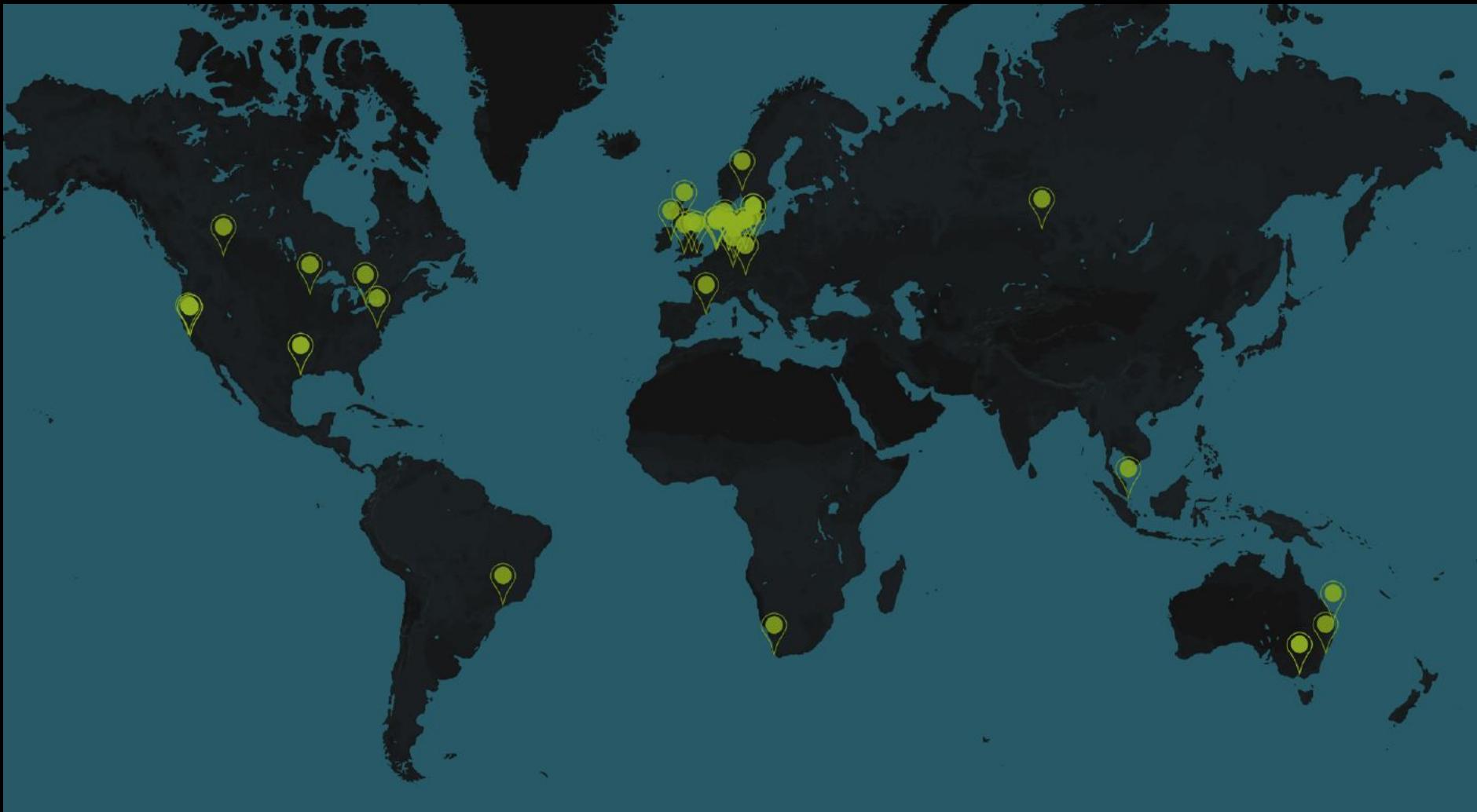


oxyg
gen

NORMATIVE BRAIN DEVELOPMENT AND AGEING IN A LARGE MULTI-SITE DEPRESSION COHORT

A/Prof Lianne Schmaal

NHMRC CDF & Dame Kate Campbell fellow
Head of Mood & Anxiety Disorders Research
Orygen & Centre for Youth Mental Health, The University of Melbourne



ENIGMA Major Depressive Disorder (MDD)
45 participating cohorts
MRI scans from N= 4709 MDD and N= 10,194 Healthy Controls

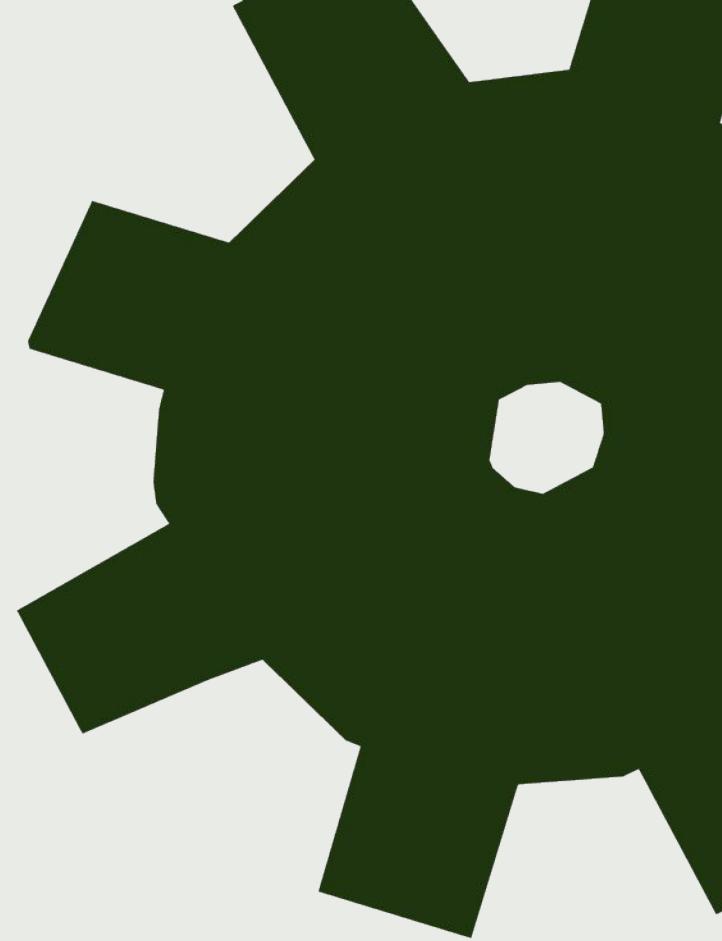
Funding:

NIH Big Data to Knowledge
(BD2K) U54 EB020403
(subcontract, PI Paul
Thompson)

NIH RO1 MH116147
(subcontract, PI Paul
Thompson)

NIH RO1 MH121246
(subcontract, PI Turner)

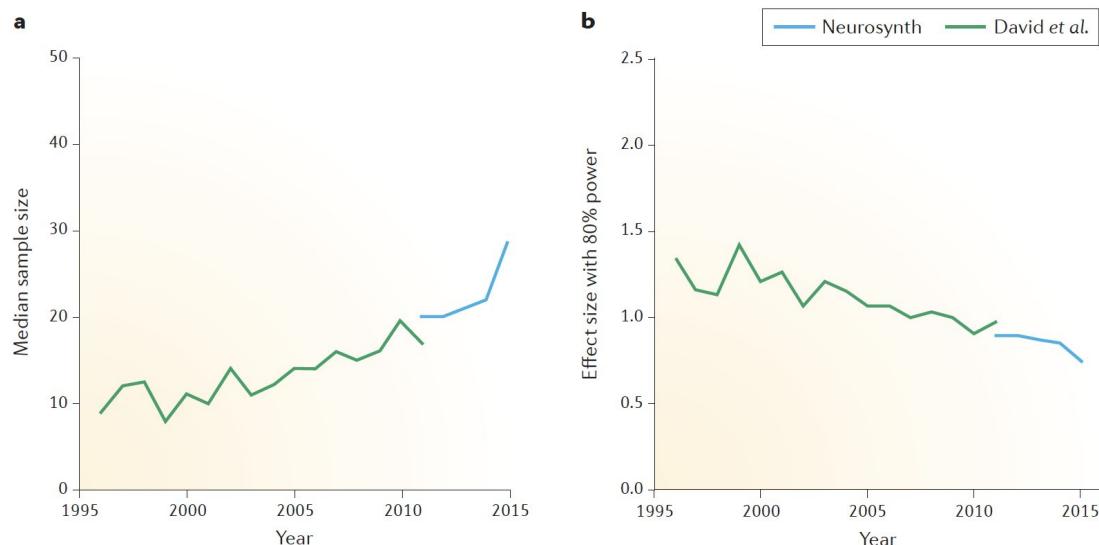




WHY DO WE NEED LARGE SAMPLES?

REPLICATION FAILURE

- Goal of many neuroimaging studies is to link differences in brain structure and function to behavioural, cognitive or clinical phenotypes.
- Given that neuroimaging is expensive and it is not easy to recruit large samples, sample sizes are often <100
- In 2015 the median study (with N=25) was only sufficiently powered to detect relatively large effects of greater than Cohen's d of ~0.75.

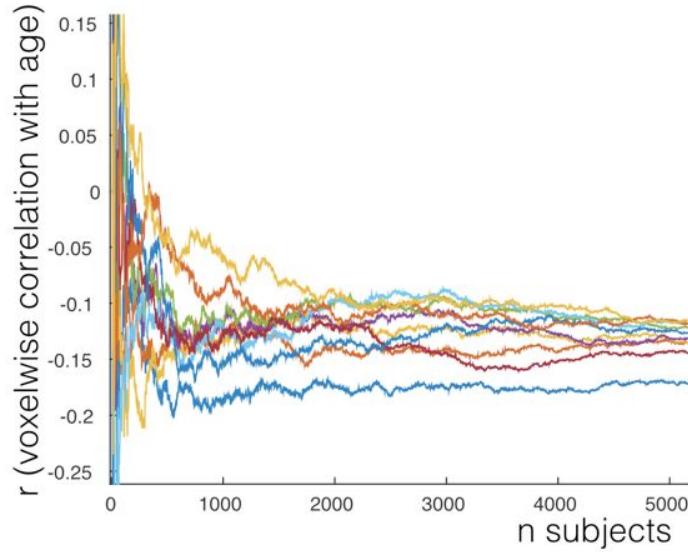


REPLICATION FAILURE

- Actual effect sizes for group differences or brain–behaviour associations are more subtle (small to medium effect sizes)
- Leads to results that are often not replicated.
- Other contributors: methodological variability, p-hacking, confirmation and publication biases



EFFECT SIZES AS A FUNCTION OF SAMPLE SIZES



Miller et al. 2016 in Nature Neuroscience

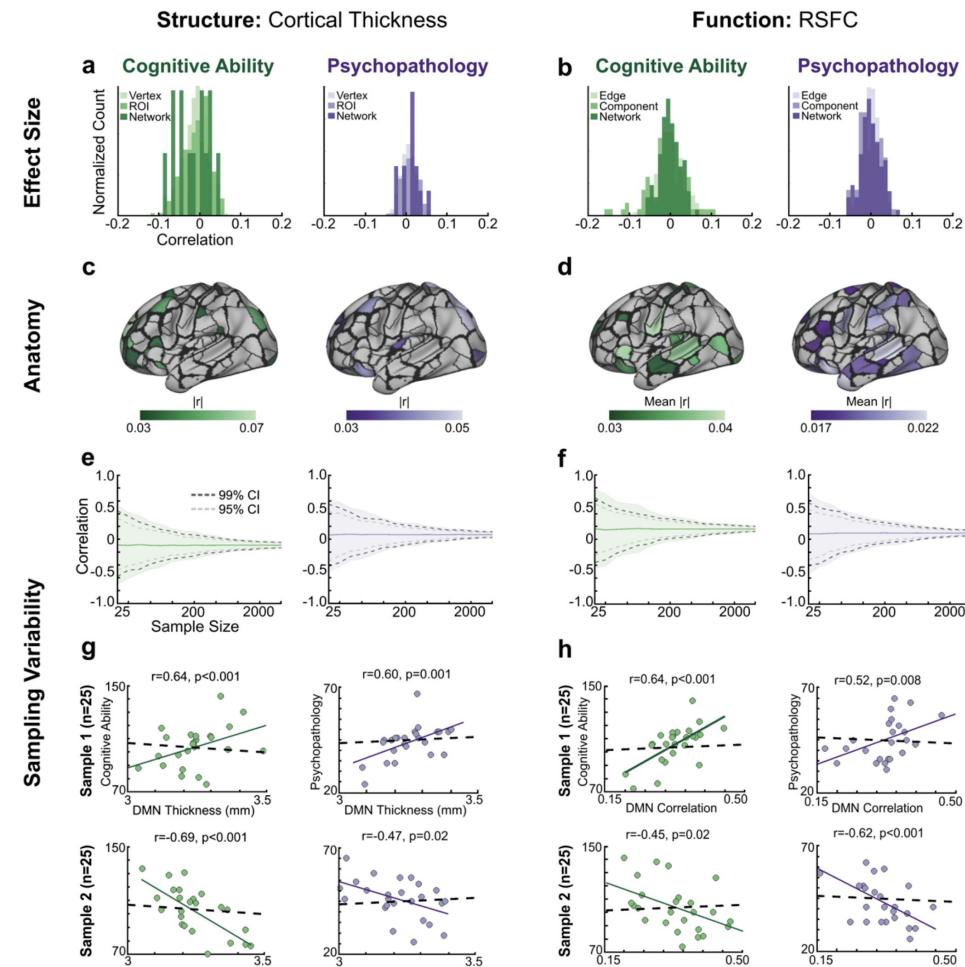
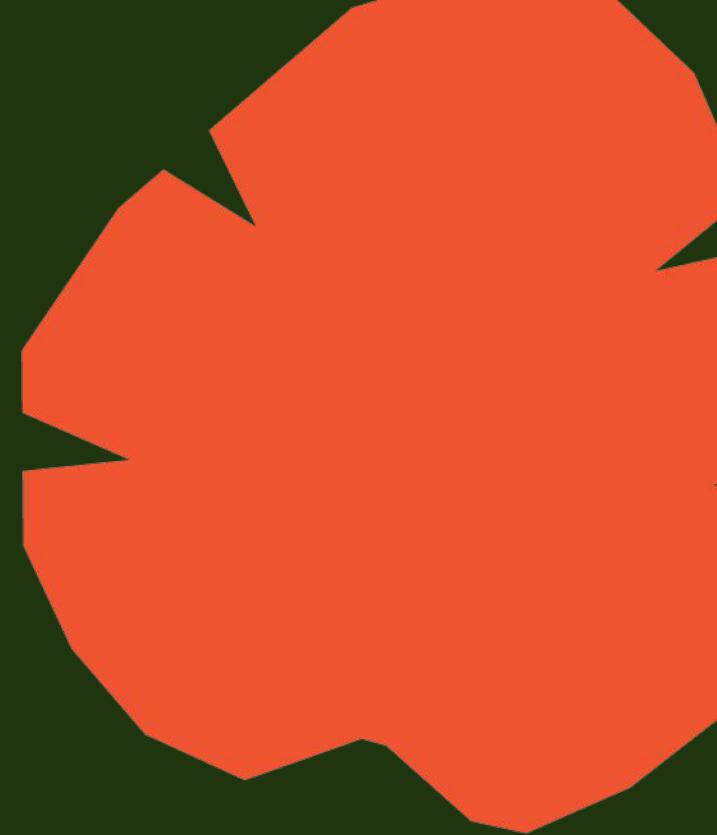
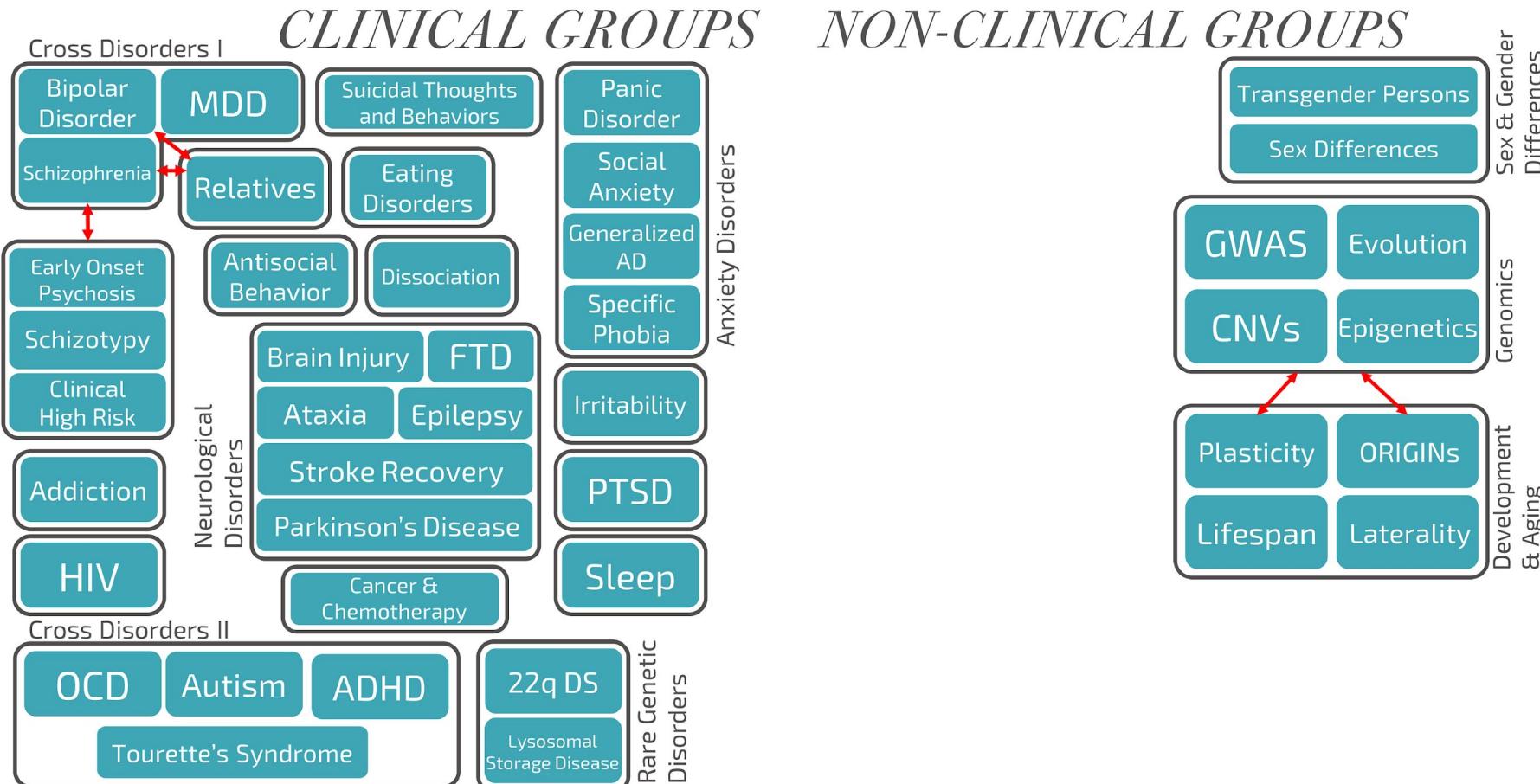


Fig 1. Effect Sizes and Sampling Variability of Univariate Brain-Wide Associations as a Function of Sample



ENHANCING NEUROIMAGING GENETICS THROUGH META-ANALYSIS (ENIGMA) CONSORTIUM

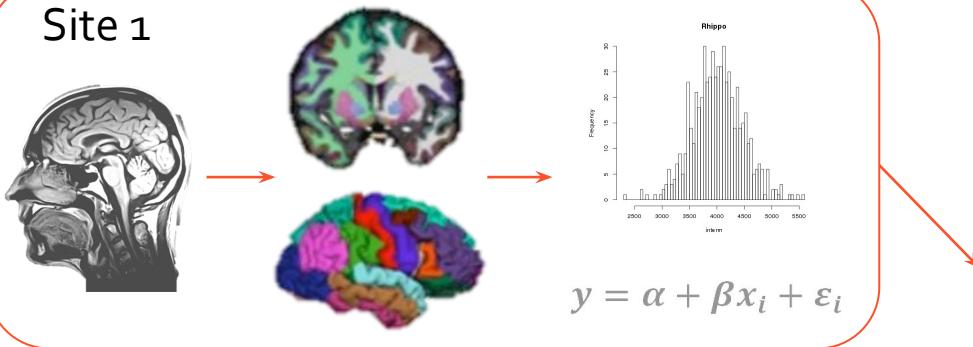
ENIGMA



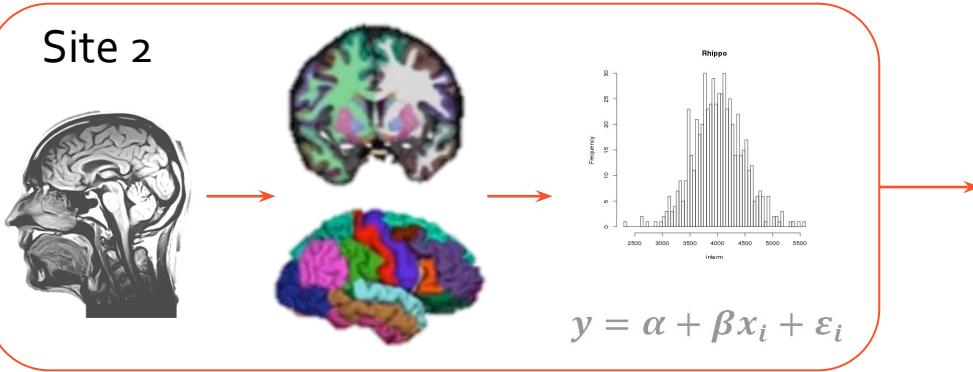
GENERAL AIMS ENIGMA MDD

- Identify imaging markers of MDD that can be **reliable detected and replicated** across many different samples worldwide
- Investigate how factors including **age, sex, and disease characteristics** (disease stage, severity, illness duration, age of onset, medication use) moderate these brain alterations in MDD
- Identify **common and unique patterns of brain alterations** across MDD and other mental disorders

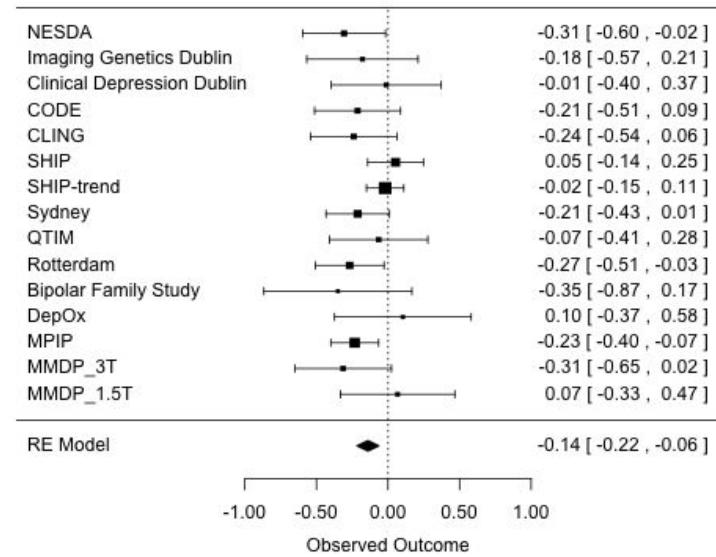
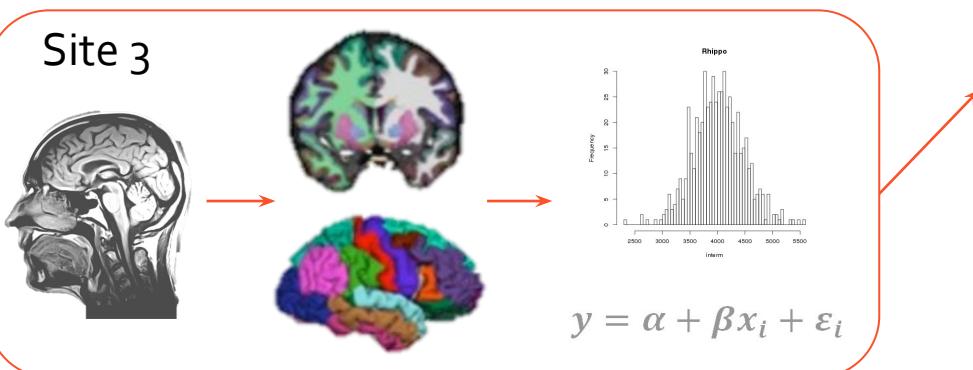
Site 1



Site 2



Site 3



OPEN

Molecular Psychiatry (2015), 1–7
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Molecular Psychiatry
<https://doi.org/10.1038/s41380-020-0774-9>

ARTICLE



Brain structural abnormalities in obesity: relation to age, genetic risk, and common psychiatric disorders

Evidence through univariate and multivariate mega-analysis including 6,120 participants from ENIGMA-MDD

Research

JAMA Psychiatry | Original Investigation

Virtual Histology in 6 Psychiatric Conditions

Writing Committee for the Attention Deficit Hyperactivity Disorder; Major Depressive Disorder; Obsessive Compulsive Disorder; Panic Disorder; Posttraumatic Stress Disorder; Schizophrenia

THREE
TWO

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Leerssen et al. *Translational Psychiatry* (2020) 10:425
<https://doi.org/10.1038/s41398-020-01109-5>

ARTICLE

Translational Psychiatry

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Molecular Psychiatry (2016), 1–10
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REVIEW ARTICLE

Open Access

ENIGMA MDD: seven years of global neuroimaging studies of major depression through worldwide data sharing

Lianne Schmaal^{1,2}, Elena Pozzi^{1,2}, Tiffany C. Ho^{3,4,5}, Laura S. van Velzen^{1,2}, Ilya M. Veer⁶, Nils Opel⁷, Eus J. W. Van Someren^{8,9,10}, Laura K. M. Han¹⁰, Lybomir Aftanas^{11,12}, André Aleman¹³, Bernhard T. Baune^{7,14,15}, Klaus Berger¹⁶, Tessa F. Blanken^{8,9}, Liliana Capitão^{17,18}, Baptiste Couvy-Duchesne¹⁹, Kathryn R. Cullen²⁰, Udo Dannlowski⁷, Christopher Davey¹⁴, Tracy Erwin-Grabner²¹, Jennifer Evans²², Thomas Frodl²³, Cynthia H. Y. Fu^{24,25}, Beata Godlewska¹⁷, Ian H. Gotlib³, Roberto Goya-Maldonado²¹, Hans J. Grabe^{16,27}, Nynke A. Groenewold²⁸, Dominik Grotegerd⁷, Oliver Gruber²⁹, Boris A. Gutman³⁰, Geoffrey B. Hall³¹, Ben J. Harrison³², Sean N. Hatton³³, Marco Hermesdorf¹⁶, Ian B. Hickie³³, Eva Hilland^{34,35,36}, Benson Irungu³⁷, Rune Jonassen³⁸, Sinead Kelly³⁹, Tilo Kircher⁴⁰, Bonnie Klimes-Dougan²⁰, Axel Krug¹⁶, Nils Inge Landrø^{34,35}, Jim Lagopoulos⁴¹, Jeanne Leerssen^{8,9}, Meng Li²³, David E. J. Linden^{10,42,43,44}, Frank P. MacMaster⁴⁵, Andrew M. McIntosh¹⁶, David M. A. Mehler^{7,43,44}, Igor Nenadic^{40,47}, Brenda W. J. H. Penninx¹⁰, Maria J. Portella^{48,49,50}, Liesbeth Reneman⁵¹, Miguel E. Rentería⁵², Matthew D. Sacchet⁵³, Philipp G. Sämann⁵⁴, Anouk Schraanee⁵¹, Kang Sim^{10,55,56}, Jair C. Soares³⁷, Dan J. Stein¹⁶, Leonardo Tozzi¹⁴, Nic J. A. van Der Wee^{58,59}, Marie-José van Tol¹³, Robert Vermeiren⁶⁰, Yolanda Vives-Gilabert⁶¹, Henrik Walter¹⁶, Martin Walter^{62,63}, Heather C. Whalley¹⁶, Katharina Wittfeld^{10,55,56}, Sarah Whittle³², Margaret J. Wright^{16,64,65}, Tony T. Yang⁵, Carlos Zarate Jr⁶⁶, Sophia I. Thomopoulos⁶⁷, Neda Jahanshad¹⁶, Paul M. Thompson⁶⁷ and Dick J. Veltman¹⁰

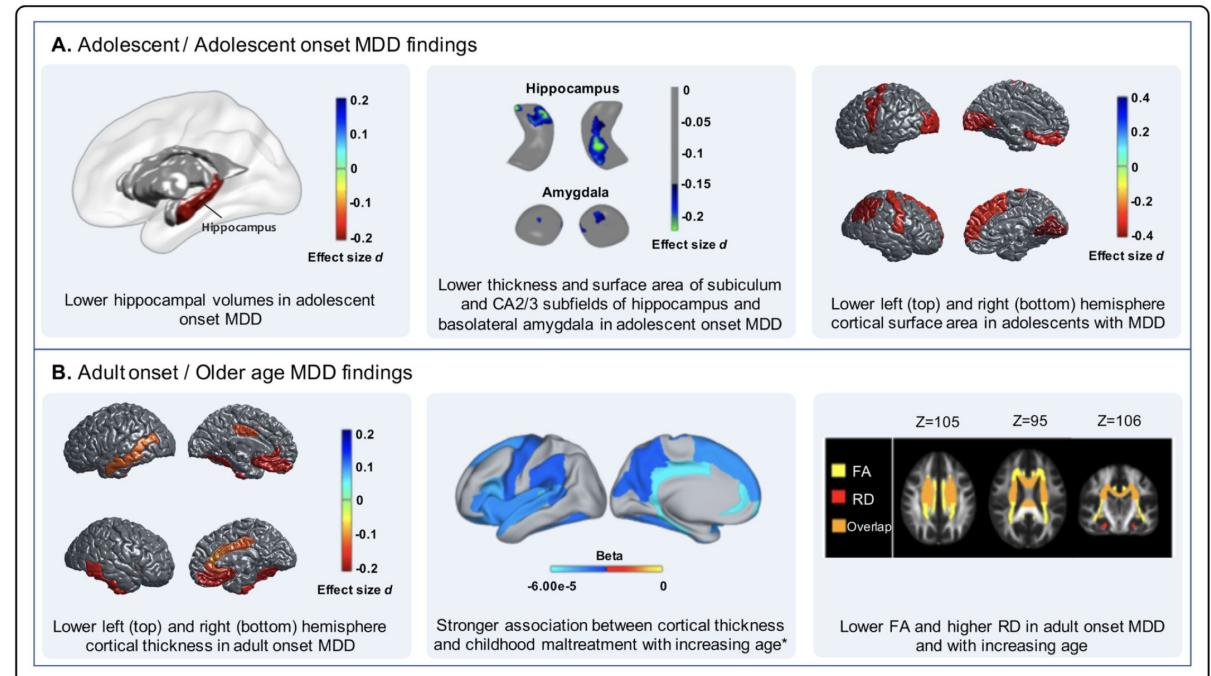


Fig. 3 Converging findings across ENIGMA MDD studies. Specific characteristics of brain structure are differentially affected by MDD (or vice versa) at different stages of life. **a** Alterations in hippocampal and amygdala volumes and shapes are observed in adolescent-onset MDD and lower cortical surface area in adolescents with MDD. **b** Cortical thickness alterations and white matter abnormalities are specifically associated with adult-onset MDD and older age in individuals with MDD and/or childhood maltreatment. *This association was independent of MDD diagnosis. MDD major depressive disorder, FA fractional anisotropy, RD radial diffusivity.

MDD & AGING



Psychological & biological stress

Increased risk:

- Aging-related diseases
- Mortality

Decreased health, decreased quality of life, and increased healthcare costs



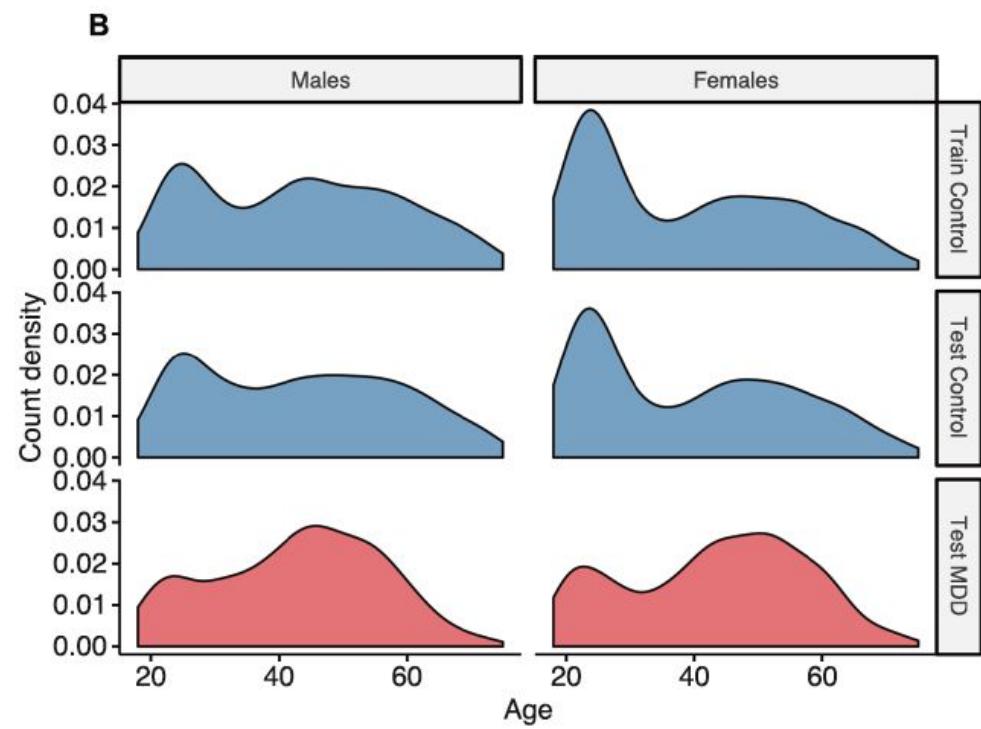
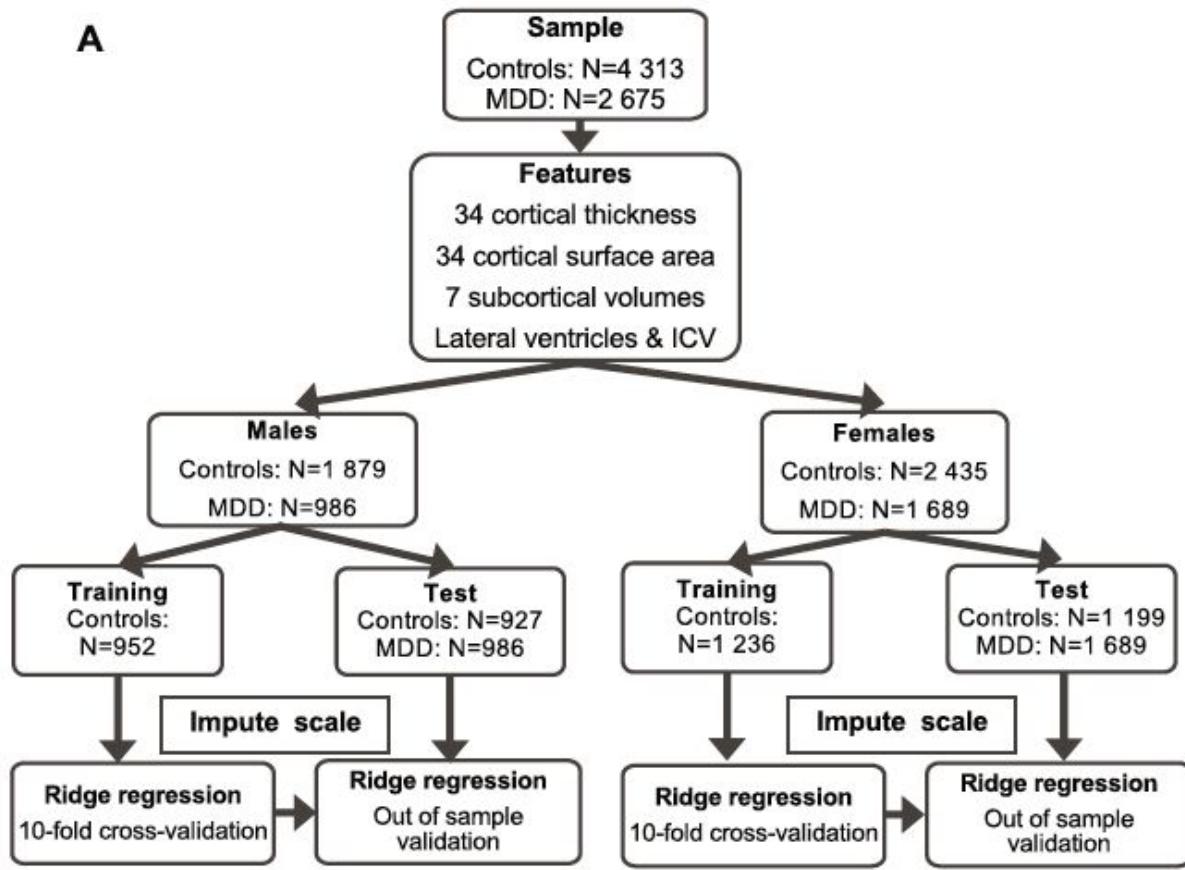
Brain aging in major depressive disorder: results from the ENIGMA major depressive disorder working group

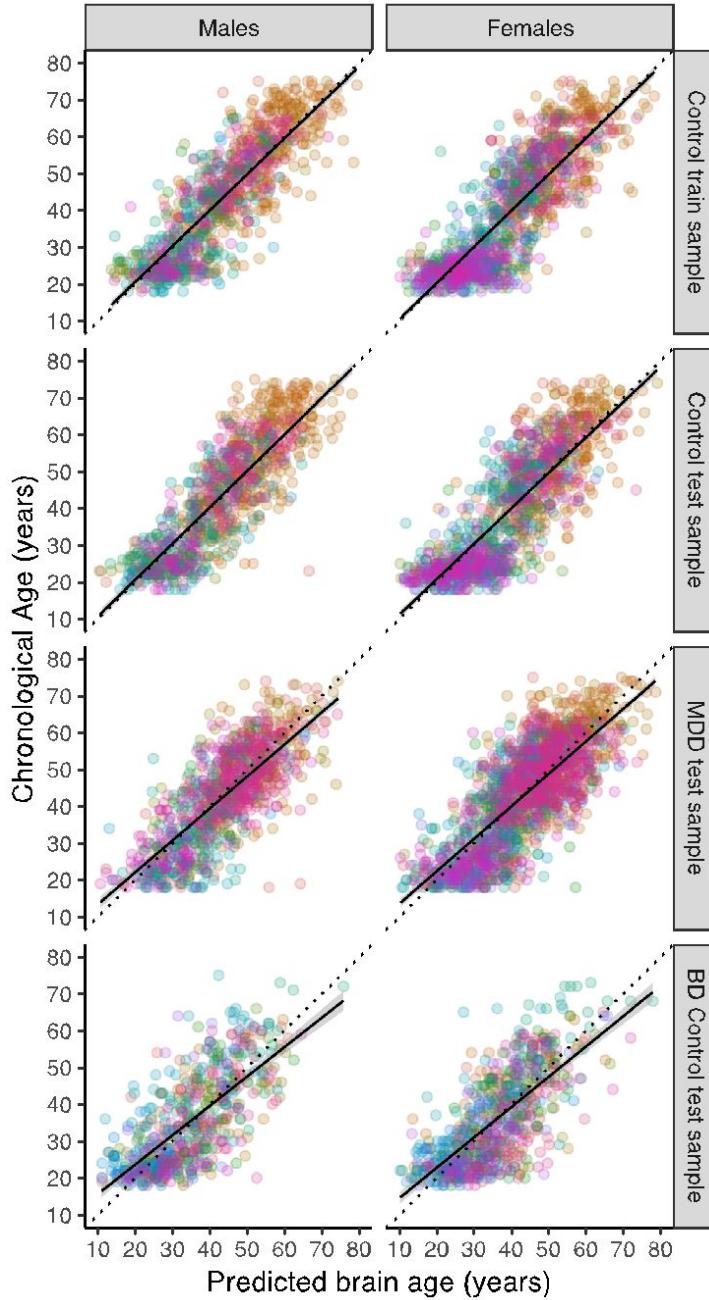
Laura K. M. Han^{ID}¹ et al.

Received: 10 October 2019 / Revised: 1 April 2020 / Accepted: 23 April 2020
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Abstract

Major depressive disorder (MDD) is associated with an increased risk of brain atrophy, aging-related diseases, and mortality. We examined potential advanced brain aging in adult MDD patients, and whether this process is associated with clinical characteristics in a large multicenter international dataset. We performed a mega-analysis by pooling brain measures derived from T1-weighted MRI scans from 19 samples worldwide. Healthy brain aging was estimated by predicting chronological age (18–75 years) from 7 subcortical volumes, 34 cortical thickness and 34 surface area, lateral ventricles and total intracranial volume measures separately in 952 male and 1236 female controls from the ENIGMA MDD working group. The learned model coefficients were applied to 927 male controls and 986 depressed males, and 1199 female controls and 1689 depressed females to obtain independent unbiased brain-based age predictions. The difference between predicted “brain age” and chronological age was calculated to indicate brain-predicted age difference (brain-PAD). On average, MDD patients showed a higher brain-PAD of +1.08 (SE 0.22) years (Cohen’s $d = 0.14$, 95% CI: 0.08–0.20) compared with controls. However, this difference did not seem to be driven by specific clinical characteristics (recurrent status, remission status, antidepressant medication use, age of onset, or symptom severity). This highly powered collaborative effort showed subtle patterns of age-related structural brain abnormalities in MDD. Substantial within-group variance and overlap between groups were observed. Longitudinal studies of MDD and somatic health outcomes are needed to further assess the clinical value of these brain-PAD estimates.

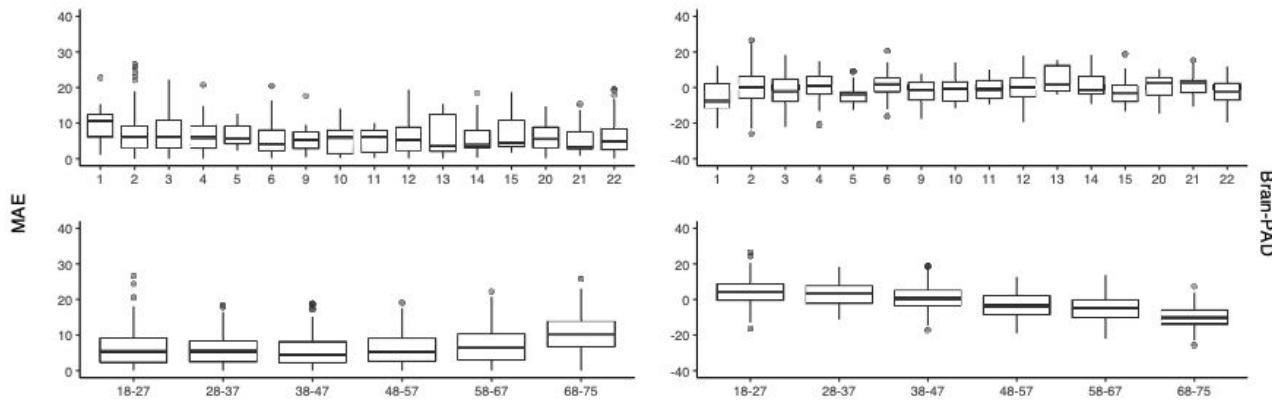




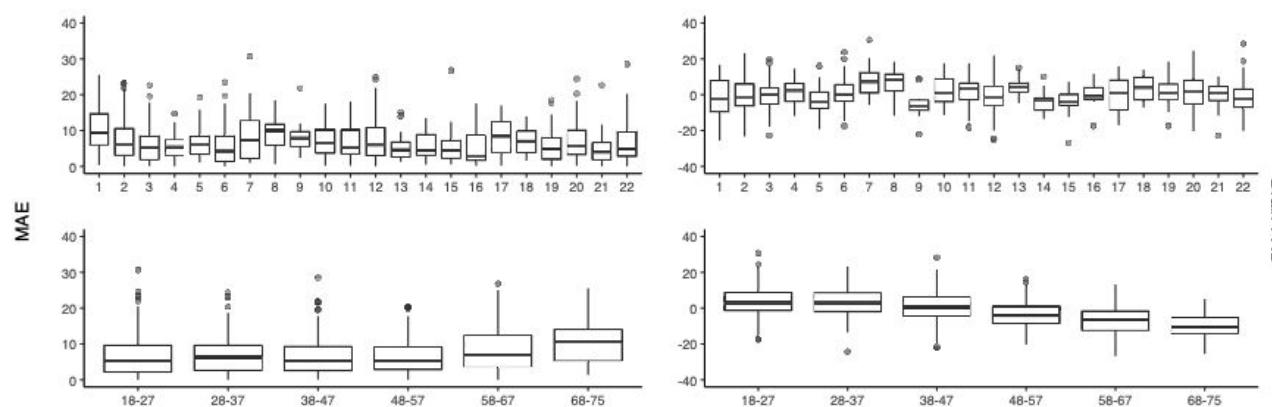
Supplementary Table S6. Alternative machines, kernels, and feature engineering in the brain age prediction framework.

Alternative method	R		R^2		MAE	
	Male training sample	Female training sample	Male training sample	Female training sample	Male training sample	Female training sample
1 Ridge regression	0.85	0.85	0.72	0.72	6.32	6.59
2 SVR linear	0.85	0.84	0.72	0.71	6.86	6.91
3 SVR RBF	0.85	0.87	0.73	0.75	6.50	6.09
4 RFR	0.79	0.80	0.67	0.64	6.81	7.22
5 ROIs regressed on ICV	0.83	0.84	0.68	0.70	6.67	6.81
6 Left and right hemi	0.85	0.84	0.72	0.70	6.37	6.75

Performance metrics in the training samples of males and females across different machine learning algorithms/kernels and feature engineering are displayed here. Models 1-4 show alternative machines and kernels that included the same 77 features. Model 5 features included 76 individual ROIs regressed on ICV, instead of having ICV included as a separate feature. Model 6 included separate features for left and right hemispheres, instead of an average across hemispheres. R, Pearson's correlation; R^2 , explained variance; MAE, mean absolute error; SVR, support vector regression; RBF, radial basis function; RFR, Random Forest Regression; ROI, regions of interest; ICV, intracranial volume; hemi, hemisphere.



Supplementary Figure S2. Mean absolute error (MAE) and brain predicted age difference (brain-PAD) across scanning site and age group for the male control test samples. Top row figures illustrate scanning sites on the x-axis. Prediction errors were examined across 16 different scanning sites and six different age groups of ten-year bins.

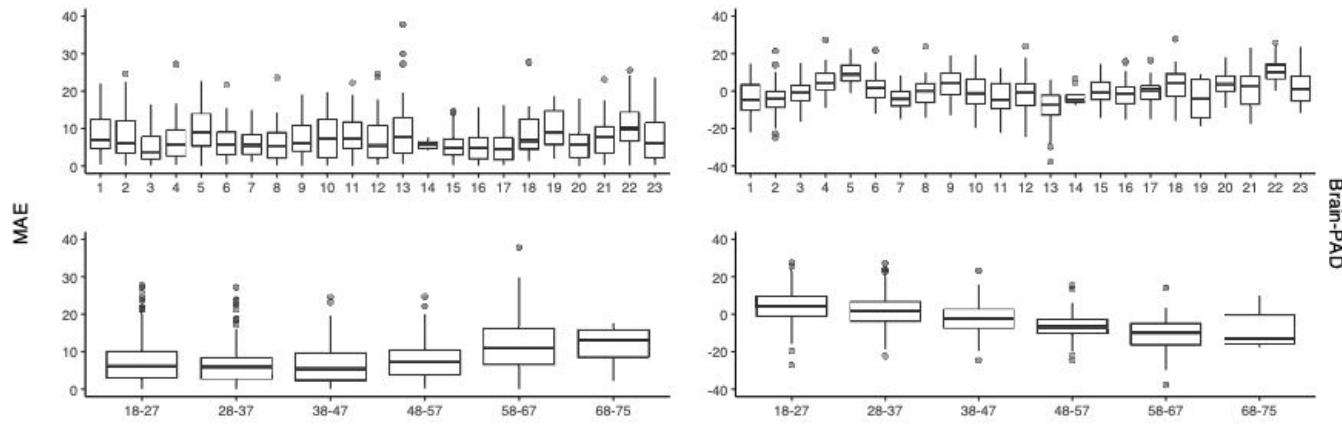


Supplementary Figure S4. Mean absolute error (MAE) and brain predicted age difference (brain-PAD) across scanning site and age group for the female control test samples. Top row figures illustrate scanning sites on the x-axis. Prediction errors were examined across 22 different scanning sites and six different age groups of ten-year bins.

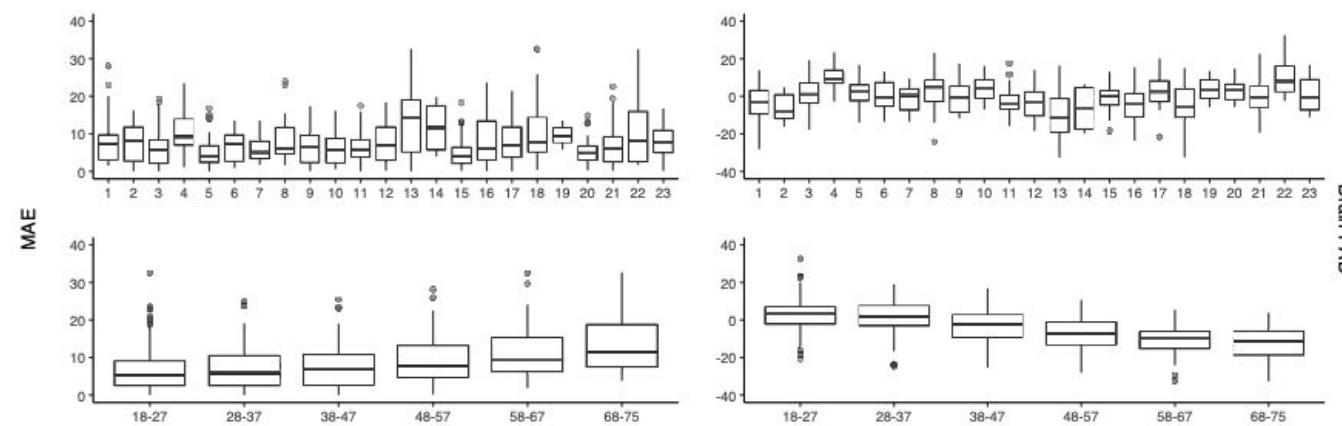
Generalization to independent test controls:

Males: MAE=6.5 , r=0.85,
 $P<0.001$; $R^2=0.72$

Females: MAE=6.8 ,
 $r=0.83, p<0.001$; $R^2=0.69$



Supplementary Figure S7. Mean absolute error (MAE) and brain predicted age difference (brain-PAD) across scanning site and age group for the female control test sample from the ENIGMA Bipolar Disorder (BD) working group. Top row figures illustrate scanning sites on the x-axis. Prediction errors were examined across 23 different scanning sites and six different age groups of ten-year bins.



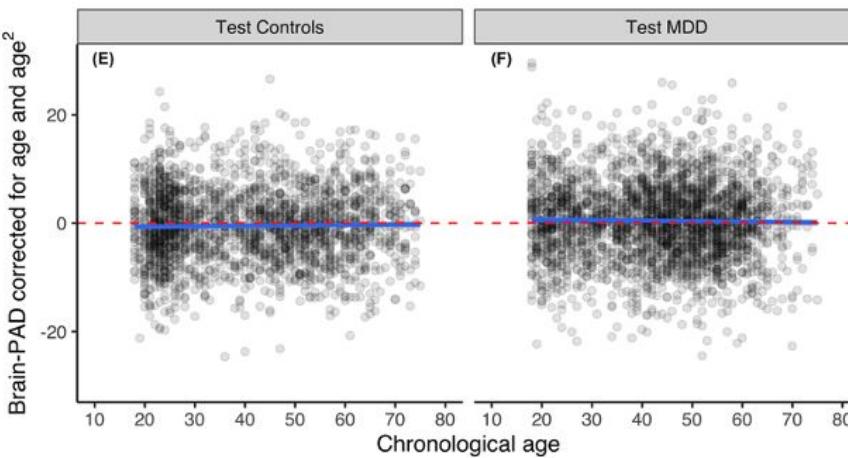
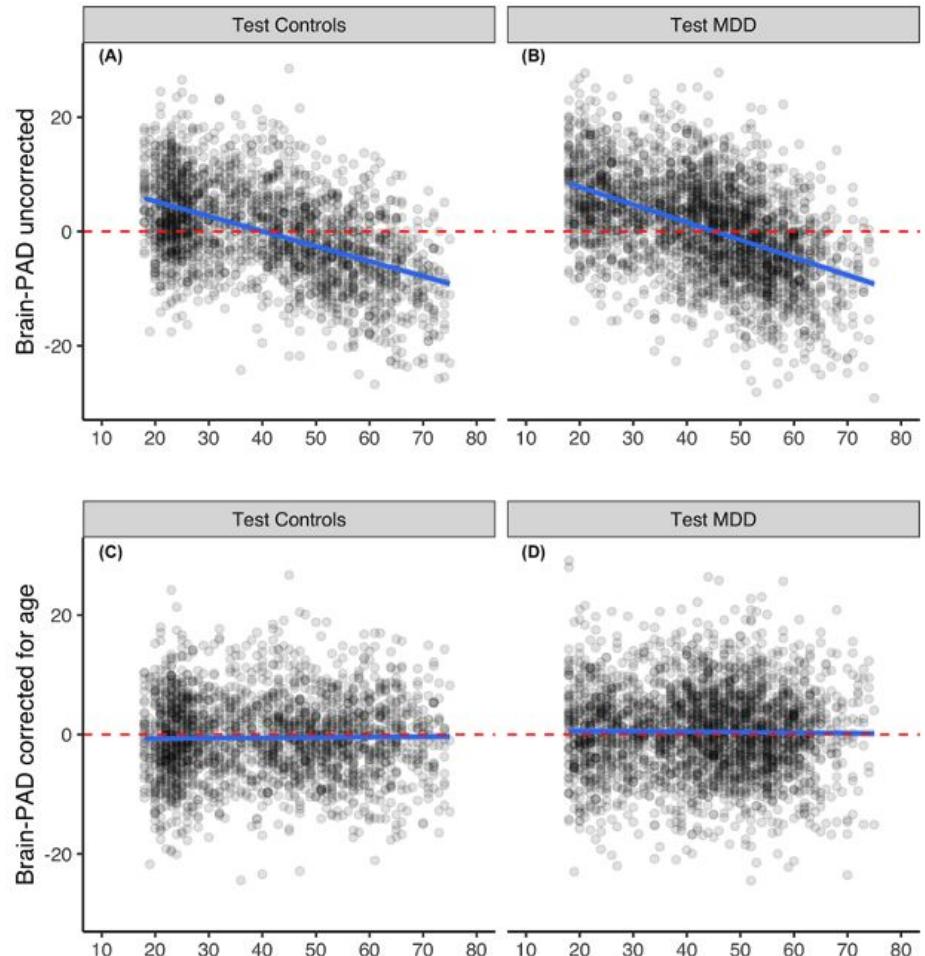
Supplementary Figure S6. Mean absolute error (MAE) and brain predicted age difference (brain-PAD) across scanning site and age group for the male control test sample from the ENIGMA Bipolar Disorder (BD) working group. Top row figures illustrate scanning sites on the x-axis. Prediction errors were examined across 23 different scanning sites and six different age groups of ten-year bins.

Generalization to independent controls from ENIGMA BD (N=1330):

Males: MAE=7.49 , r=0.71, P<0.001;
 $R^2=0.45$

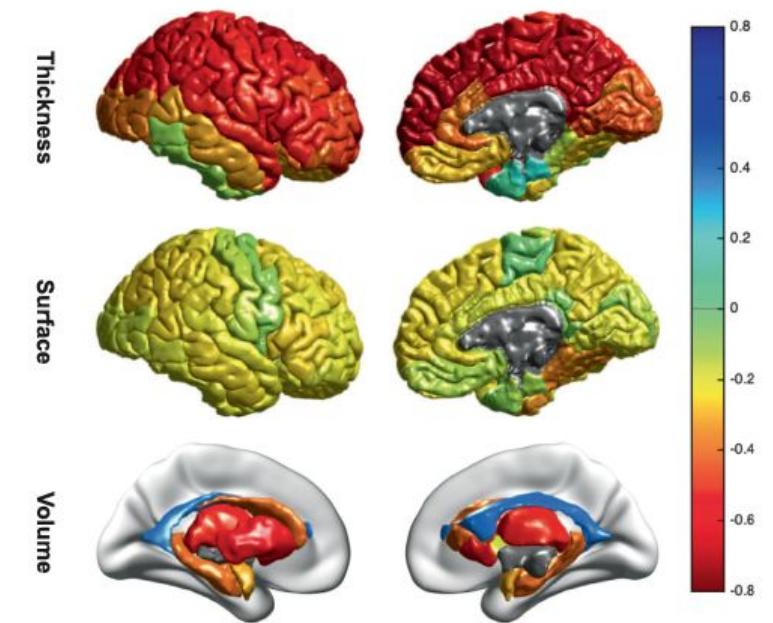
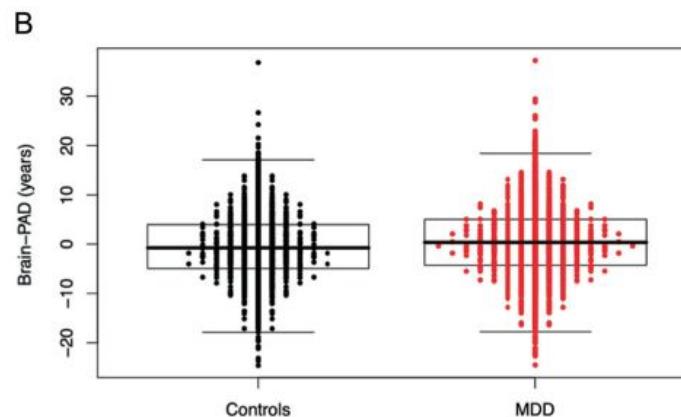
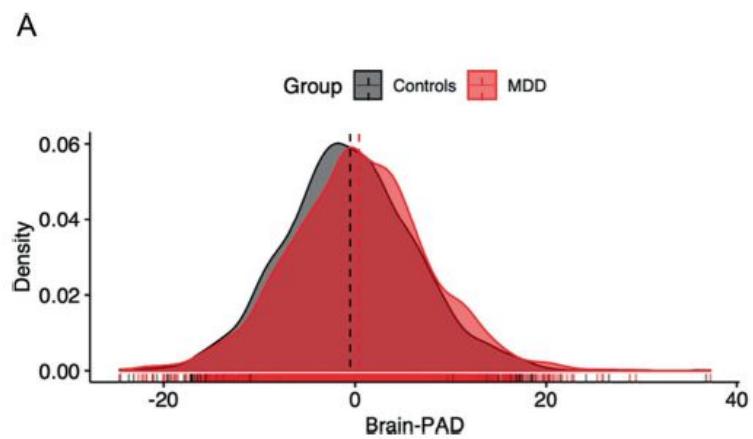
Females: MAE=7.26 , r=0.72,p<0.001;
 $R^2=0.6948$

CORRELATION BETWEEN AGE AND BRAIN-PAD



Le et al. 2018 in Front Aging Neurosci
Liang, Zhang and Niu 2018 in Hum Brain Mapp
Smith et al. 2019 in Neuroimage

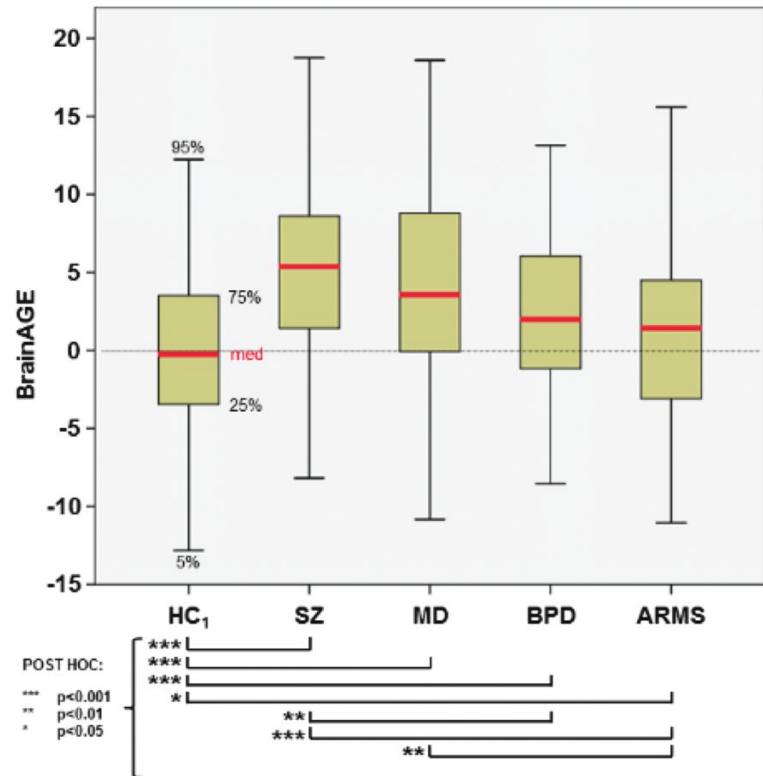
BRAINS OF INDIVIDUALS WITH MDD ESTIMATED TO BE 1.08 YEARS OLDER THAN BRAINS OF CONTROLS



CONCLUSIONS

- ❖ Subtle higher brain aging in MDD patients ($\sim + 1$ year)
- ❖ Higher brain-PAD in antidepressant users (+1.4 years)
- ❖ However, small effects; most MDD patients do not show significant brain ageing
- ❖ Similar or smaller aging magnitude as reported brain aging in MDD in previous studies

CONCLUSIONS



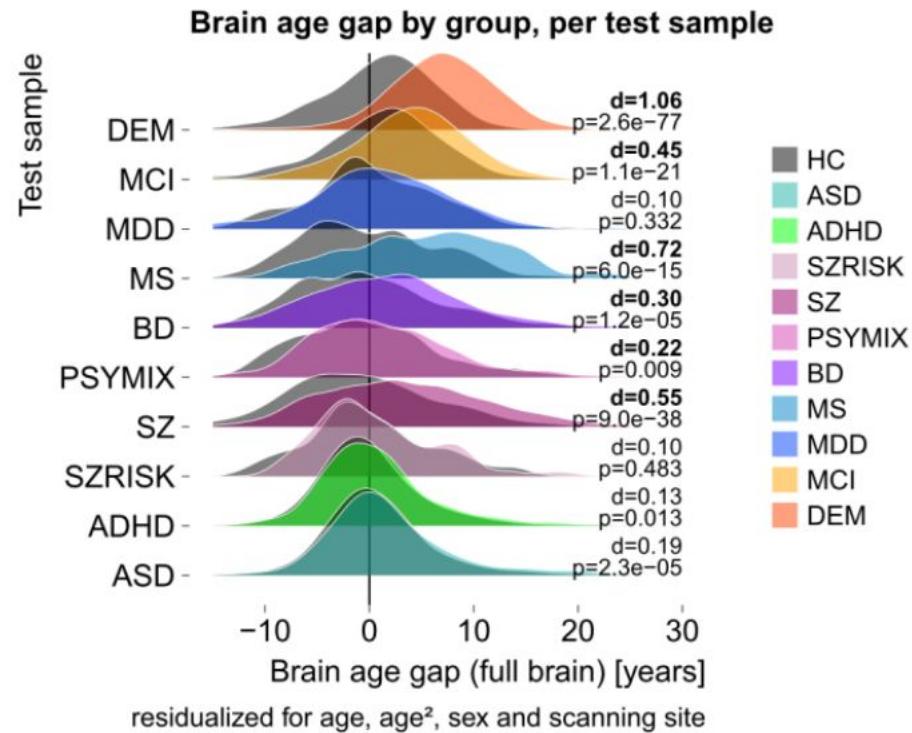
Koutsouleris et al. (2014), Schizophr Bull

HC train set ($n= 800$; 18-65 years)
MAE: 4.6 years

MDD test set ($n = 104$)
HC test set ($n = 127$)

BrainAGE gap MDD: 4 years older

CONCLUSIONS



Kaufmann et al. (2018), bioRxiv

Training set controls: $n = 30,967$
3-95 years

MDD ($n = 211$; 18-71 years)

BrainAGE gap MDD: 0.8 years

MAE?

CONCLUSIONS

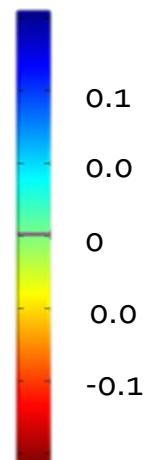
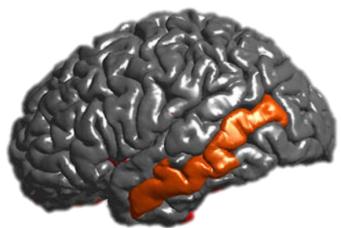
- ❖ Subtle higher brain aging in MDD patients ($\sim + 1$ year)
- ❖ Higher brain-PAD in antidepressant users (+1.4 years)
- ❖ However, small effects; most MDD patients do not show significant brain ageing
- ❖ Similar or smaller aging magnitude as reported brain aging in MDD in previous studies
- ❖ Underlying mechanisms? Inflammation? Shared underlying (epi)genetic mechanisms?
- ❖ Model publicly available: https://www.photon-ai.com/enigma_brainage

LIMITATIONS

- ❖ Limited availability of clinical characterization and longitudinal data
- ❖ No access to raw imaging data (high dimensional features, multimodal)
- ❖ Clinical use at individual patient level limited given large within-group variance of brain-PAD outcome in both controls and MDD compared with the small between-group variance

DEVIATIONS FROM NORMATIVE BRAIN STRUCTURE MODELS IN MDD

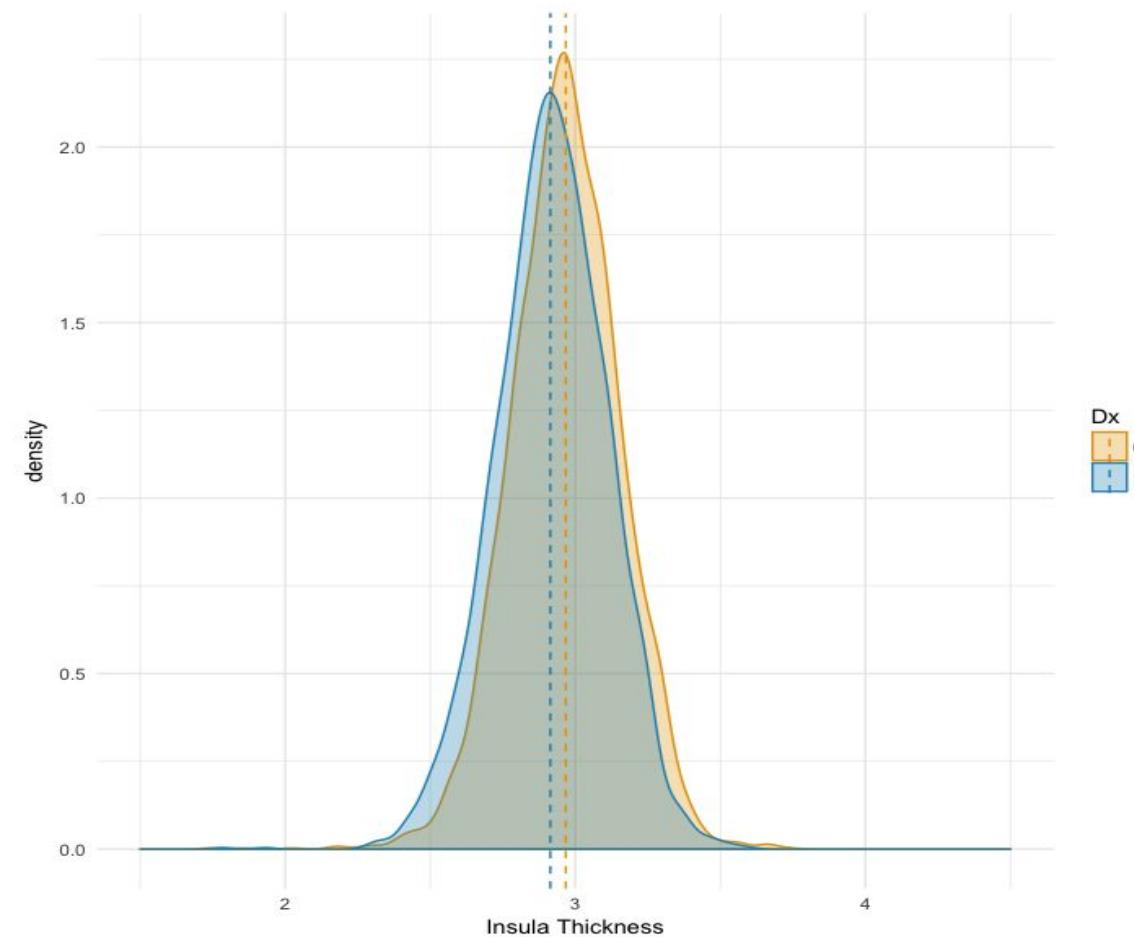
SMALL EFFECT
SIZES

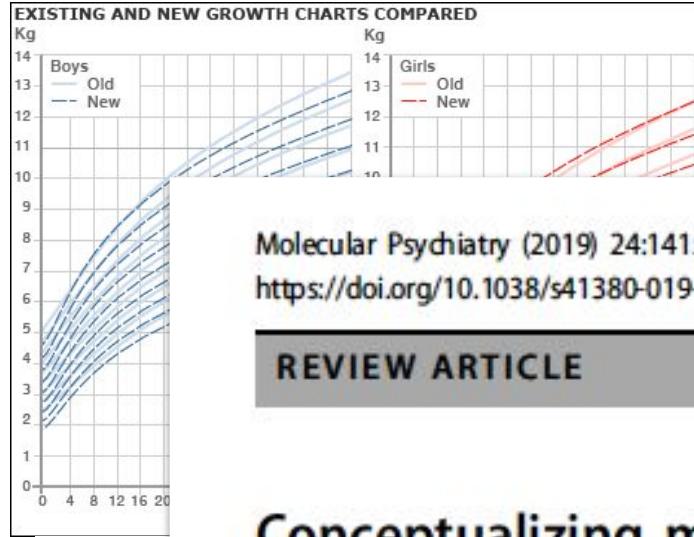


Thickness



Schmaal et al., *Molecular Psychiatry* 2017





Molecular Psychiatry (2019) 24:1415–1424
<https://doi.org/10.1038/s41380-019-0441-1>

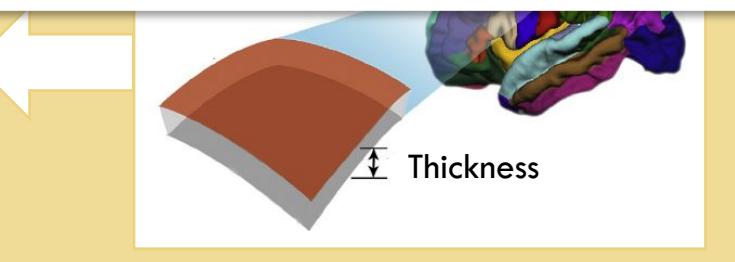
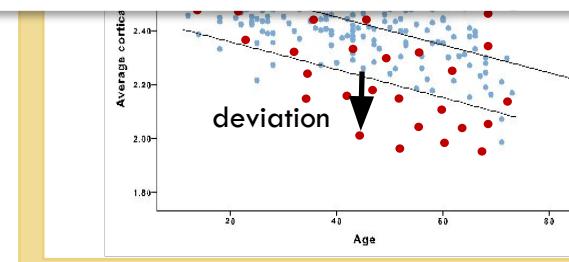
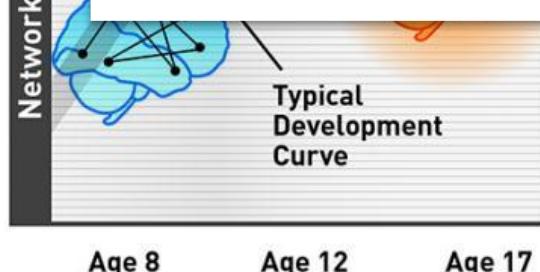
REVIEW ARTICLE



Conceptualizing mental disorders as deviations from normative functioning

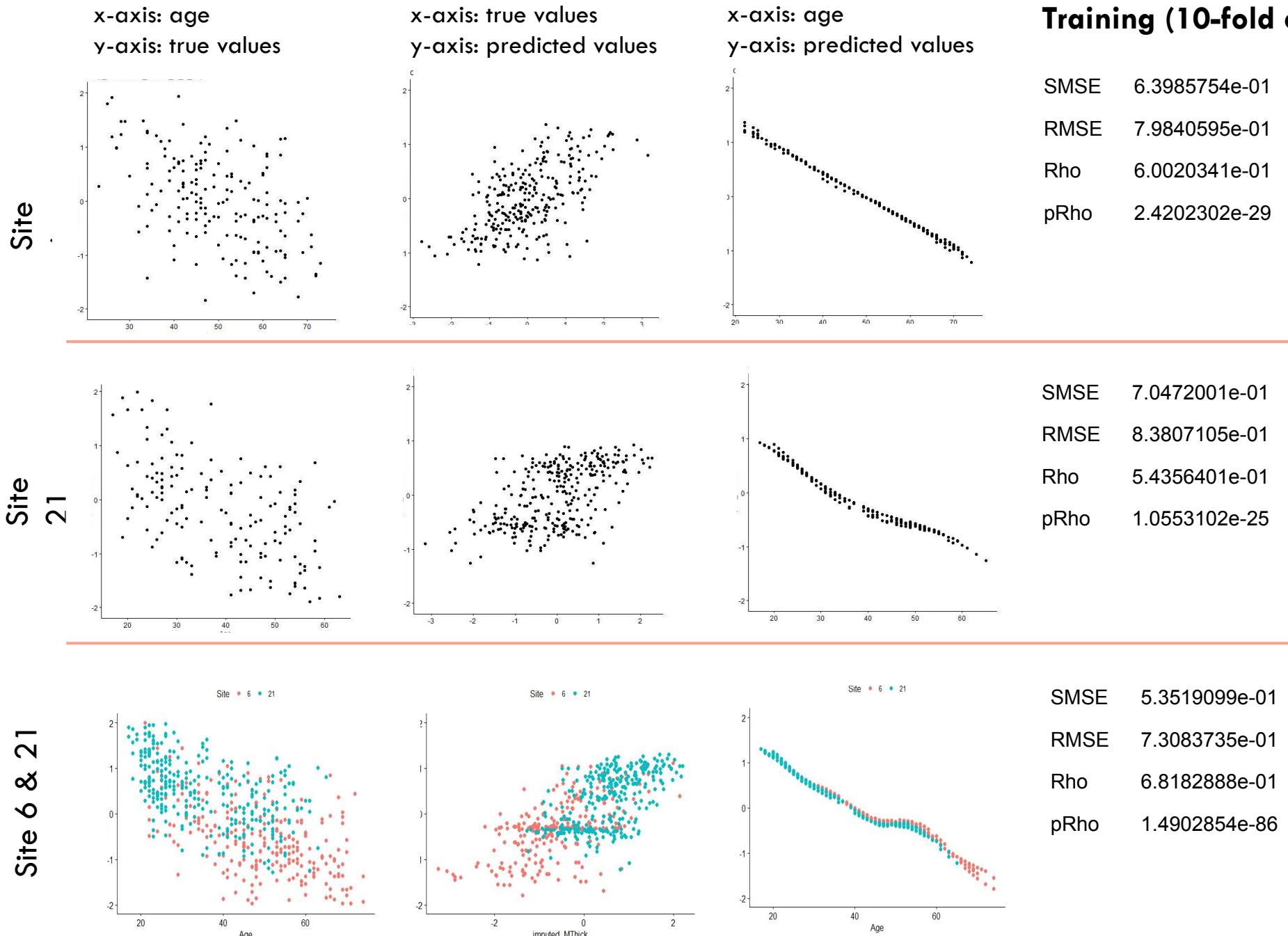
This article has been corrected since Advance Online Publication and a correction is also printed in this issue

Andre F. Marquand^{1,2,3} · Seyed Mostafa Kia^{1,2} · Mariam Zabihí^{1,2} · Thomas Wolfers^{1,2} · Jan K. Buitelaar^{1,2,4} · Christian F. Beckmann^{1,2,5}



Normative modeling

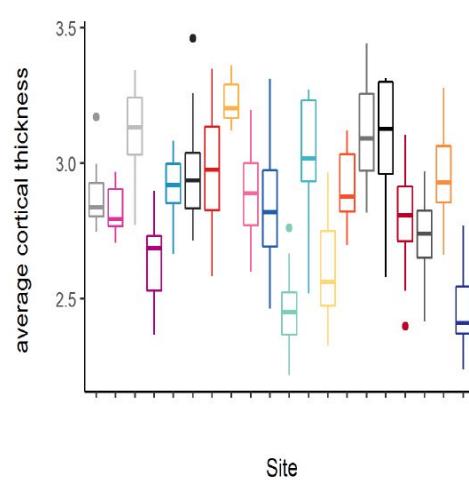




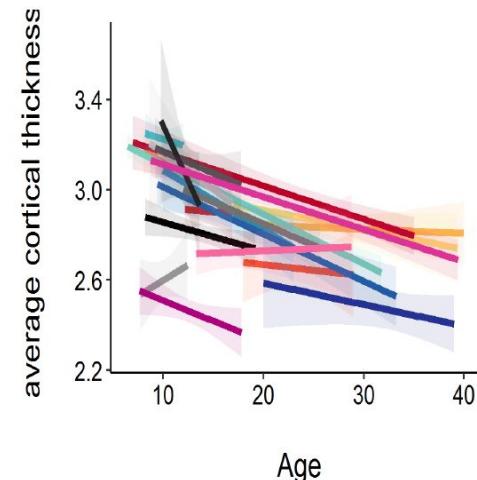
HIERARCHICAL BAYESIAN MODEL



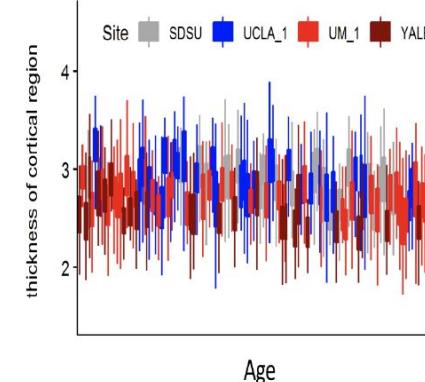
Bayer et al. 2020
BioRxiv



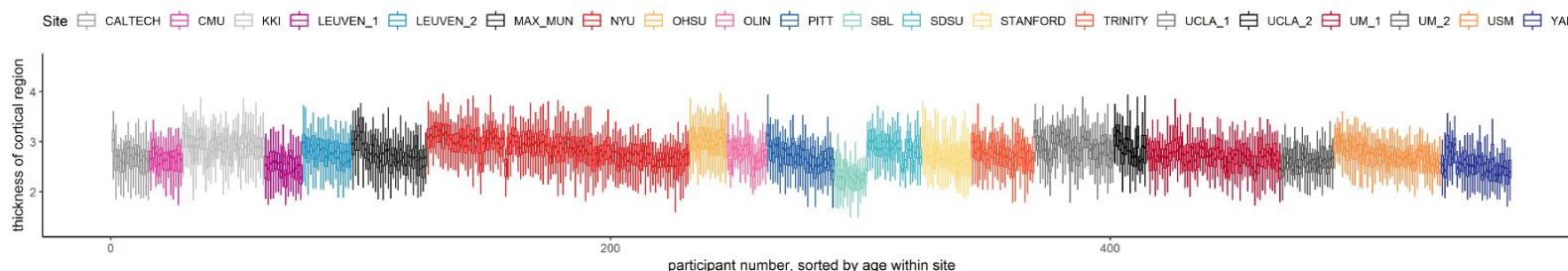
(a) Distribution of average cortical thickness measures of 573 individuals, grouped by the 20 acquisition sites the data were collected at (each boxplot describes the distribution of one site).



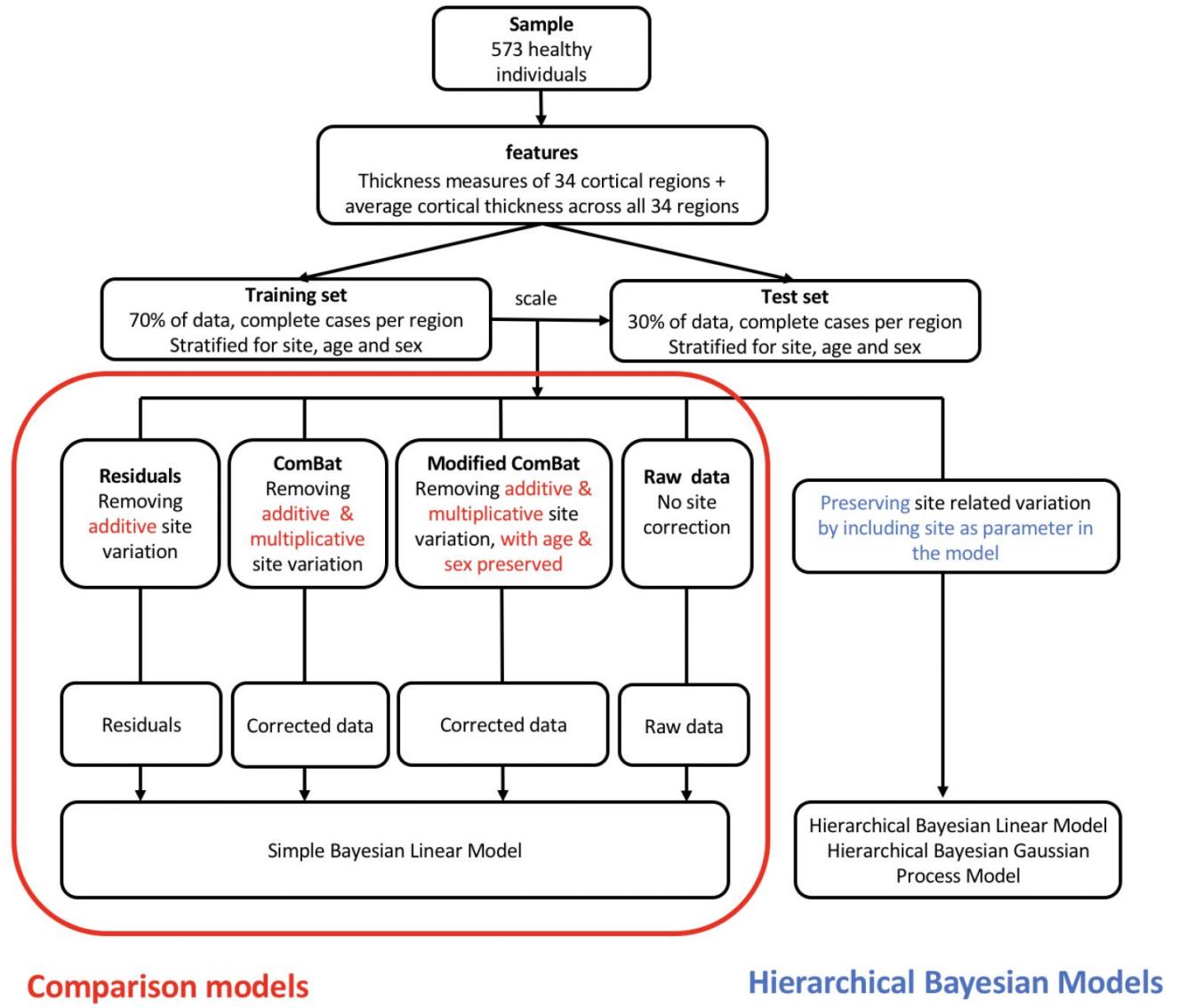
(b) Average cortical thickness of 573 individuals regressed onto age, grouped by site (each regression line describes one site).



(c) Thickness measures of all 34 cortical regions average cortical thickness grouped by individual, colored by site, sorted by age (each boxplot represents one individual). Displayed are 4 out of 20 sites from the ABIDE data set



(d) Distribution of all 34 cortical regions average cortical thickness per individual, summarized as boxplot (each boxplot represents one individual). Boxplots are coloured by site and ordered by age within site.



Comparison models

Hierarchical Bayesian Models

ρ	Mean Correlation (STD)		Post-hoc comparison					
	training set	test set	HBLM	HBGPM	mod. ComBat	ComBat	residuals	raw data
HBLM	0.734 (0.06)	0.694 (0.06)		ns.	***	***	***	***
HBGPM	0.752 (0.05)	0.705 (0.06)	ns.		***	***	***	***
mod. ComBat	0.541 (0.15)	0.568 (0.16)	***	***		***	***	***
ComBat	0.289 (0.09)	0.343 (0.11)	***	***	***		ns.	***
residuals	0.267 (0.08)	0.329 (0.12)	***	***	***	ns.		***
raw data	0.435 (0.14)	0.435 (0.16)	***	***	***	*	**	

Table 2: Post-hoc tests of correlations between true and predicted values. Cell values indicate post-hoc comparison significance values (adjusted by tukey method for a comparing a family of 6 estimates). Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1 ns. blue: test set. yellow: training set.

SRMSE	Mean SRMSE (STD)		Post-hoc comparison					
	training set	test set	HBLM	HBGPM	mod. ComBat	ComBat	residuals	raw data
HBLM	0.0608 (0.006)	0.066 (0.005)		n.s.	***	***	***	***
HBGPM	0.0587 (0.006)	0.064 (0.006)	ns.		***	***	***	***
mod. ComBat	0.0763 (0.007)	0.075 (0.008)	***	***		***	n.s.	ns.
ComBat	0.0872 (0.003)	0.085 (0.005)	***	***	***		***	***
residuals	0.0865 (0.003)	0.085 (0.004)	***	***	n.s.	***		ns.
raw data	0.0808 (0.006)	0.085 (0.008)	***	***	***	***	***	

Table 3: Post-hoc tests of SRMSE between true and predicted values. Cell values indicate post-hoc comparison significance values (adjusted by tukey method for a comparing a family of 6 estimates). Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1 ns. blue: test set. yellow: training set.

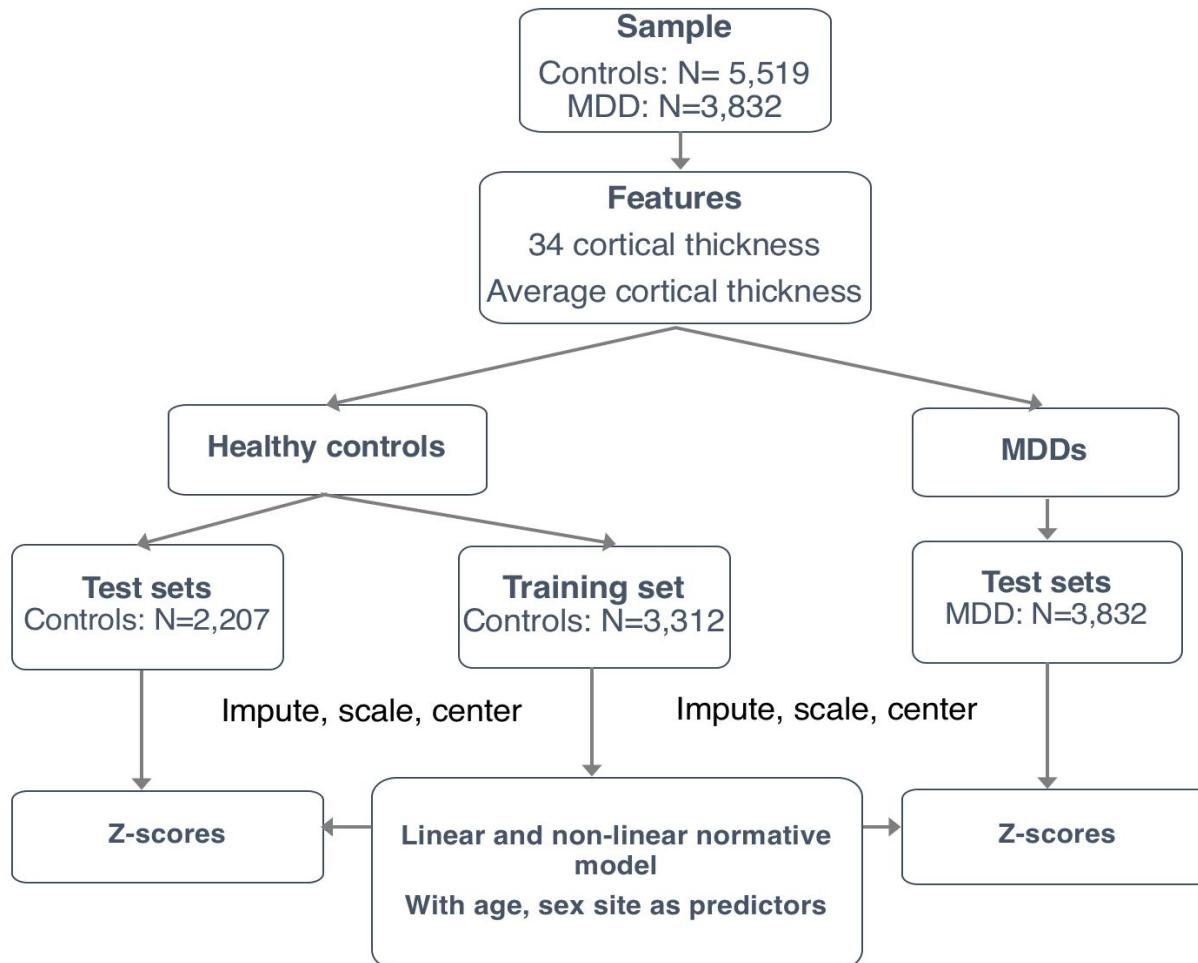
LL	training set	test set
HBLM	-1.050	-1.121
HBGPM	-1.020	-1.109
ComBat mod.	-1.225	-1.193
ComBat	-1.374	-1.336
residuals	-1.381	-1.394
raw	-1.299	-1.335

Table 4: Averaged log loss for training and test set.

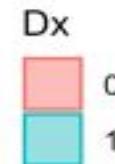
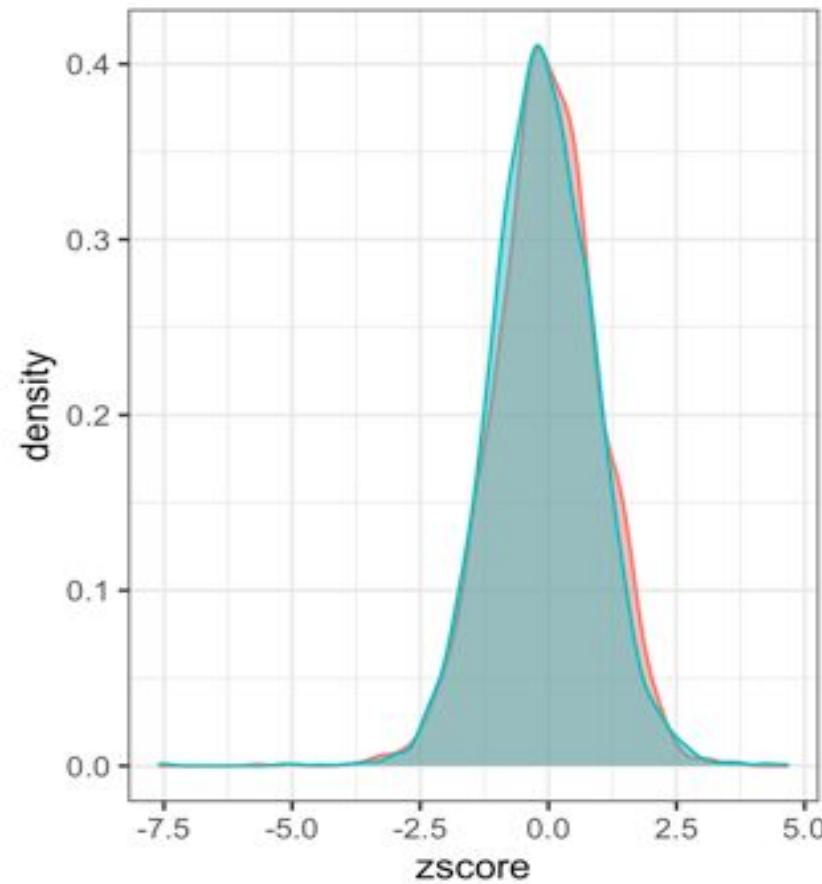
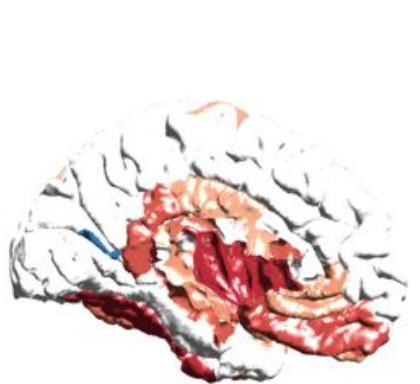
EV	training set	test set
HBLM	0.5674	0.5
HBGPM	0.5397	0.485
ComBat mod.	0.3146	0.338
ComBat	0.0918	0.122
residuals	0.0778	0.114
raw	0.2091	0.208

Table 5: Averaged explained variance for training and test set.

NORMATIVE MODELLING IN ENIGMA MDD



GROUP DIFFERENCES IN Z-SCORES



INDIVIDUAL LEVEL DEVIATIONS

Negative deviations:

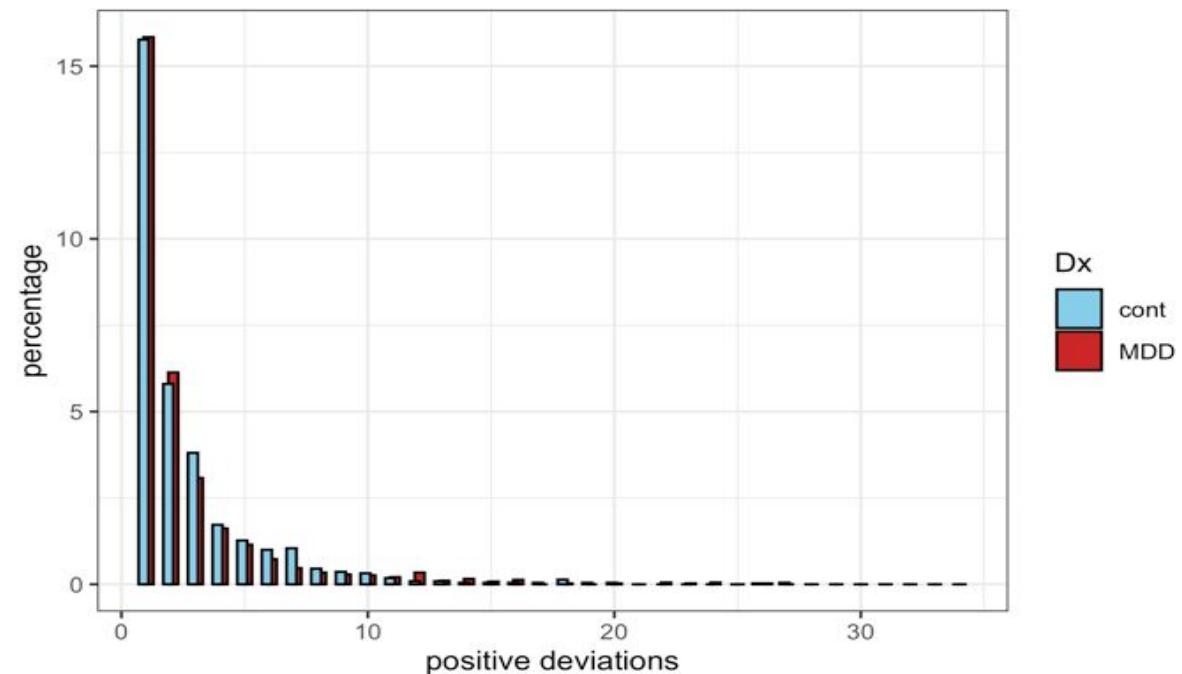
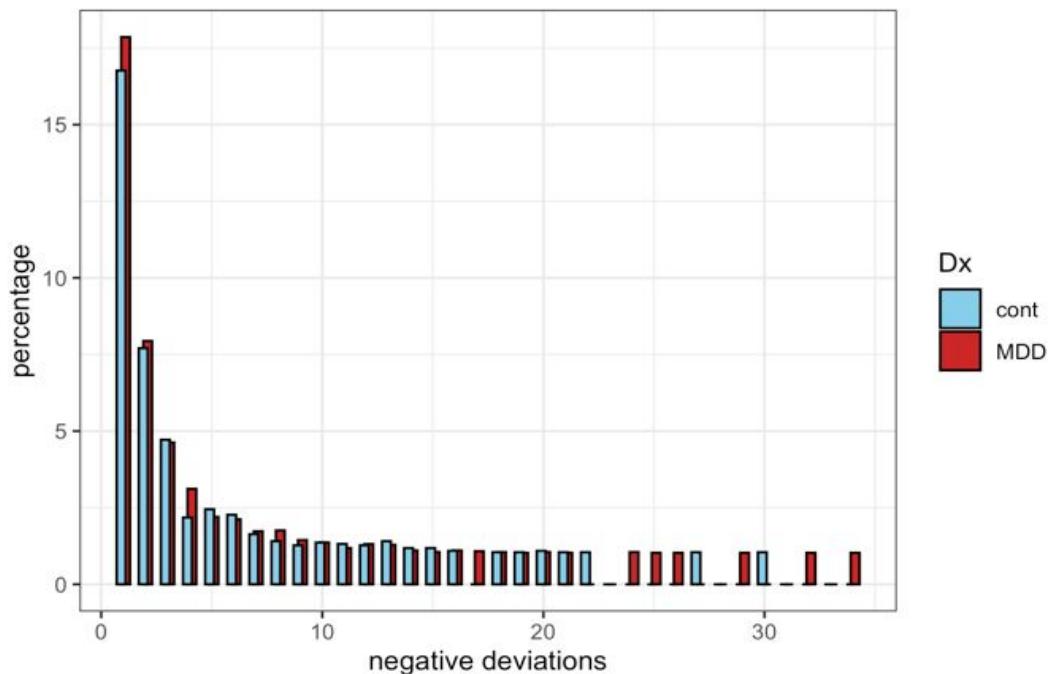
MDD: 35.6% at least one extreme negative deviation

HC: 33.8% at least one extreme negative deviation

Positive deviations:

31.1% at least one extreme positive deviation

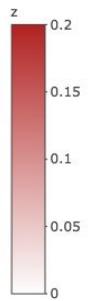
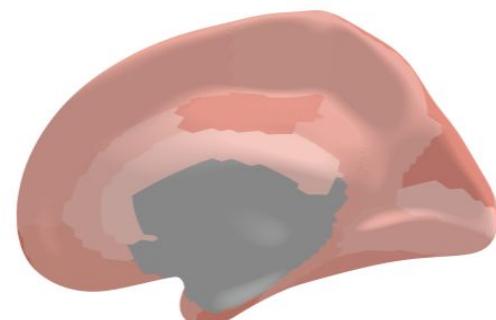
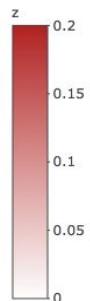
32.4% at least one extreme positive deviation



INDIVIDUAL LEVEL DEVIATIONS

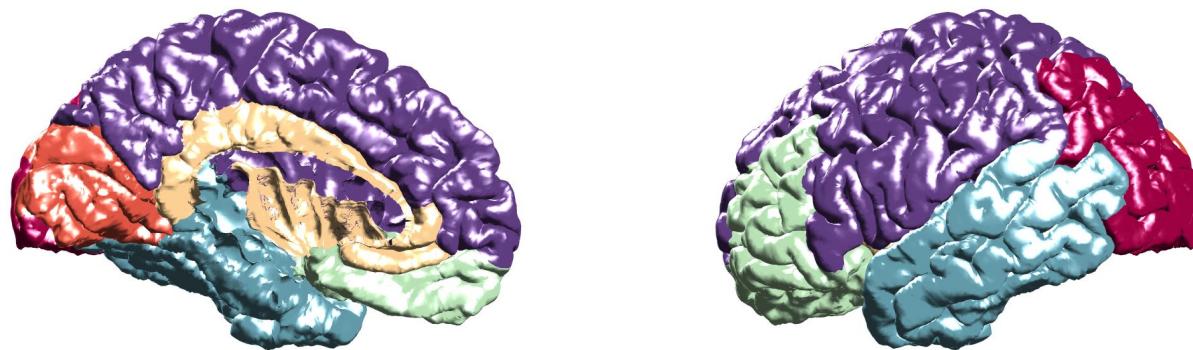
Maximum percentage of MDD patients that showed extreme negative deviations in the same region was **12.0%**

Maximum percentage of MDD patients that showed extreme positive deviations in the same region was **13.1%**



INDIVIDUAL LEVEL DEVIATIONS

Factor analysis on z-scores



Occipital (red), temporal (blue), (orbito)-frontal (green), limbic (yellow), fronto-parietal (purple), cuneus (orange)

CLINICAL ASSOCIATIONS

MDD patients with extreme negative deviations compared to MDD patients in normative range:

- ❖ Were younger (temporal, orbito-frontal, occipital, fronto-parietal and cuneus areas)
- ❖ Less likely to use antidepressant medication at time of scan (orbito-frontal and occipital regions)
- ❖ More likely to be first episode patients (orbito-frontal)
- ❖ Had an earlier age of onset (cuneus)
- ❖ Lower symptom severity on HDRS (fronto-parietal)

MDD patients with extreme positive deviations compared to MDD patients in normative range:

- ❖ Less likely to use antidepressant medication at time of scan (temporal)
- ❖ Had an earlier age of onset (temporal)
- ❖ Lower symptom severity on BDI and HDRS (fronto-parietal)
- ❖ Less likely to report childhood trauma (fronto-parietal)

CONCLUSIONS

- ❖ Cortical thickness of most individuals with MDD fall within the normative range
- ❖ Heterogeneity in regional pattern of deviations
- ❖ MDD individuals with extreme negative deviations were younger (not observed in HC)
- ❖ Complex associations with clinical characteristics
- ❖ Normative modeling can provide more insight into the heterogeneity, individual differences and the extent of cortical thickness alterations in people with MDD
- ❖ Future local longitudinal studies could clarify whether people with extreme deviations have worse outcomes or respond differently to treatment

FUTURE DIRECTIONS ENIGMA MDD

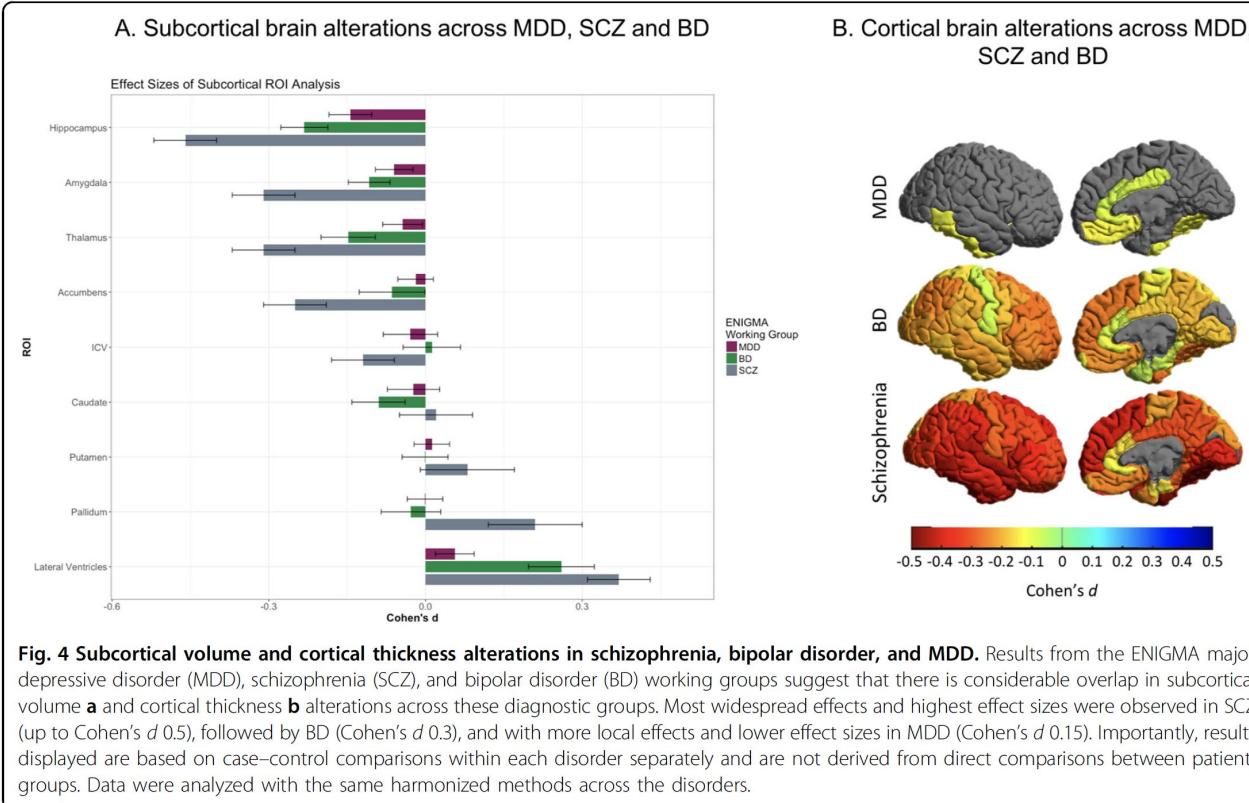
- Include higher dimensional structural brain measures and multivariate techniques
- Include resting state and task based functional MRI measures

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ENIGMA HALFpipe: Interactive, reproducible, and efficient analysis for resting-state and task-based fMRI data

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FUTURE DIRECTIONS ENIGMA MDD



es and multivariate

ential mechanisms

logical subtypes,

CHALLENGES LARGE SCALE CONSORTIA

- Ethical, computational and privacy law issues with regard to data sharing
- No harmonization in neuroimaging and clinical data collection
- Unavailability of deeply characterized phenotypes and longitudinal data
- Some relevant neurobiological mechanisms of MDD may not be obtained by analysis of ever larger existing samples; need for alternative methods of data collection or new data types

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Translational Psychiatry

REVIEW ARTICLE

Open Access

ENIGMA MDD: seven years of global neuroimaging studies of major depression through worldwide data sharing

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REVOLUTION IN MIND

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THANK YOU
