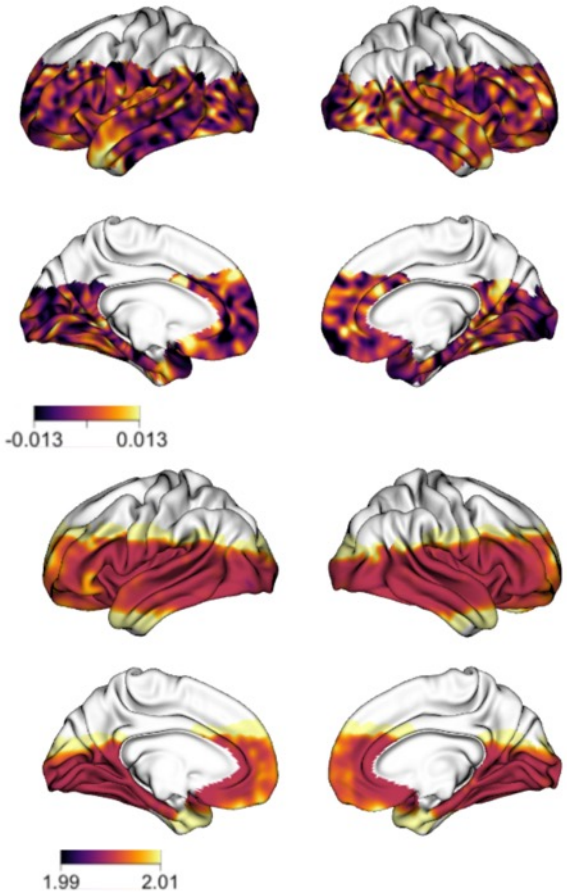
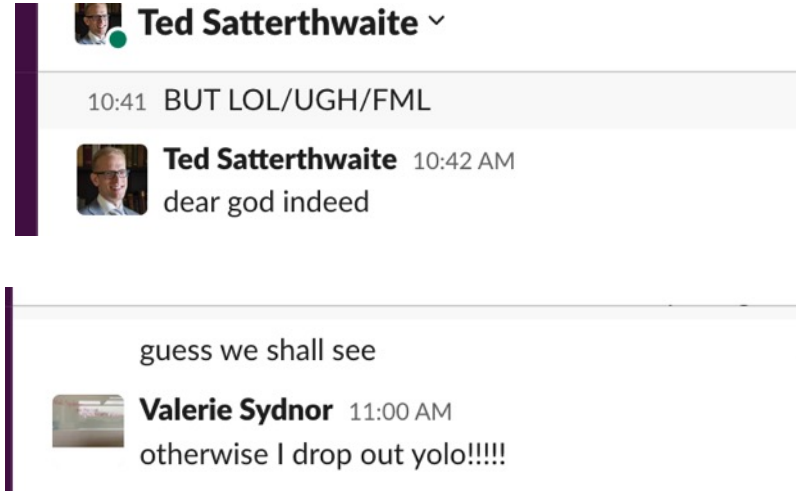
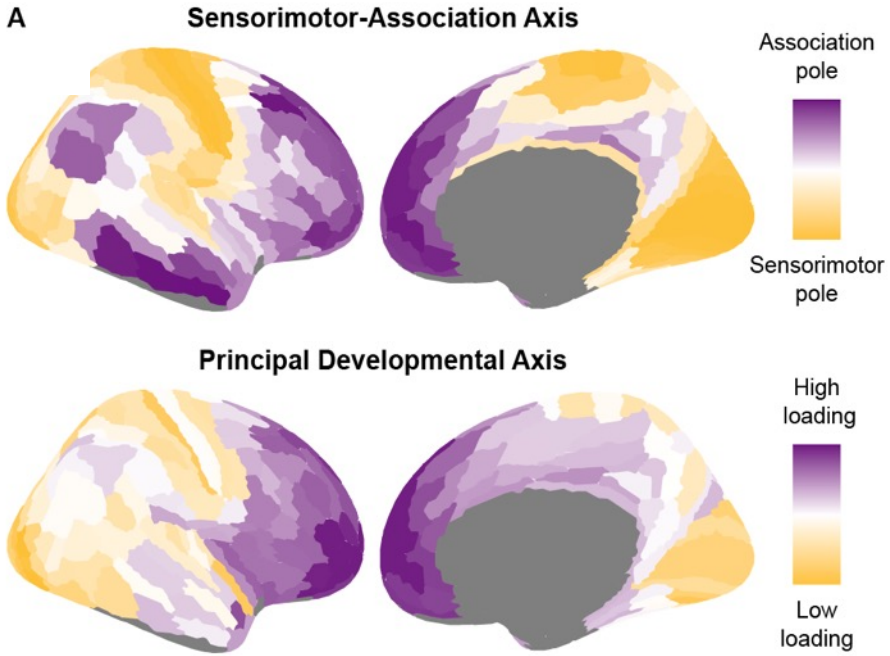
Project Development 🤝 Brain Development

A story in 3 acts







Overarching Project Aim

To characterize the spatiotemporal progression of developmental plasticity across the human cortex during childhood and adolescence.

Principles of Human Cortical Development

Human cortical development is **protracted**

- There are mechanisms that endow the human brain with an extended window of plasticity

Principles of Human Cortical Development

Human cortical development is **protracted**

Human cortical development is **heterochronous**

- Different regions are most plastic at different ages and mature at different rates

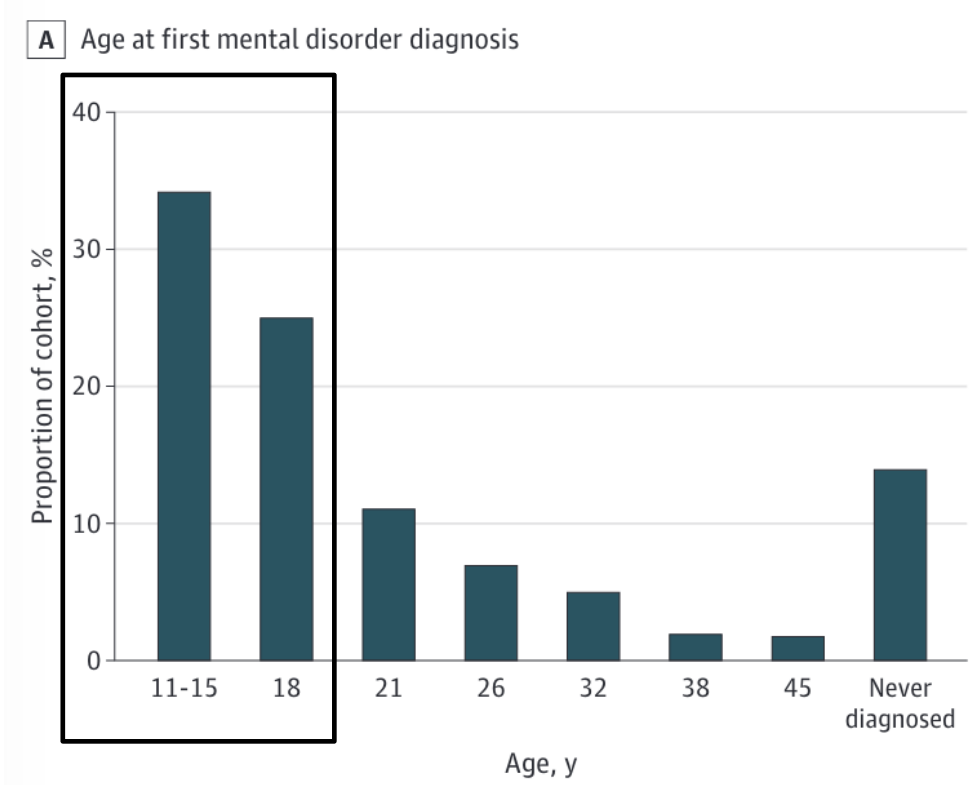
Principles of Human Cortical Development

Human cortical development is **protracted**

Human cortical development is **heterochronous**

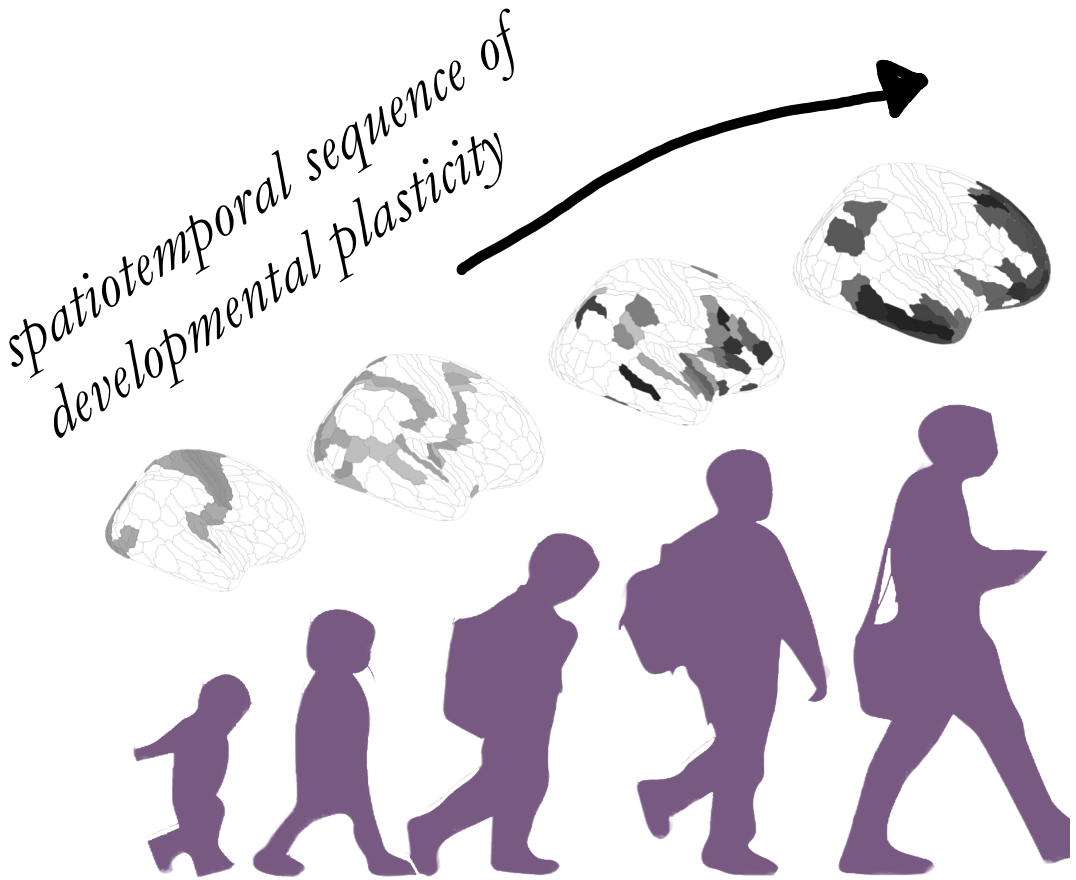
Human cortical development enhances **vulnerability**

- The majority of psychiatric disorders manifest in late childhood or adolescence



Caspi et al., 2020, *JAMA Network Open*

Timing of Human Cortical Development



- Normative patterns of developmental plasticity
- The role of disrupted plasticity mechanisms in youth-onset psychiatric disorders
- Age-dependent brain environment interactions
- Windows where interventions may maximally impact the brain

Timing of Human Cortical Development

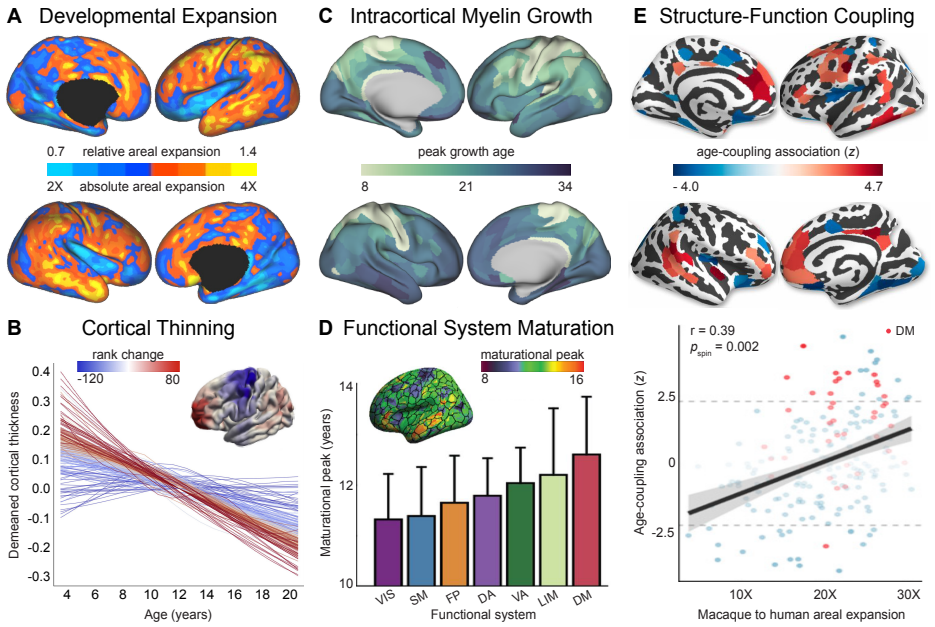
Developmental change happens earlier in **sensorimotor** cortices and later in **association** cortices

Sydnor et al., 2021, *Neuron*

Aim 1:

To characterize the spatiotemporal development of cortical plasticity

Knowledge gap: The precise spatiotemporal sequence of development has yet to be characterized across the cortical mantle.



Sydnor et al., 2021, Neuron

Adapted from Hill et al., 2010 (A), Ball et al., 2020 (B), Grydeland et al., 2019 (C), Dong et al., 2020 (D), Baum et al., 2020 (E)

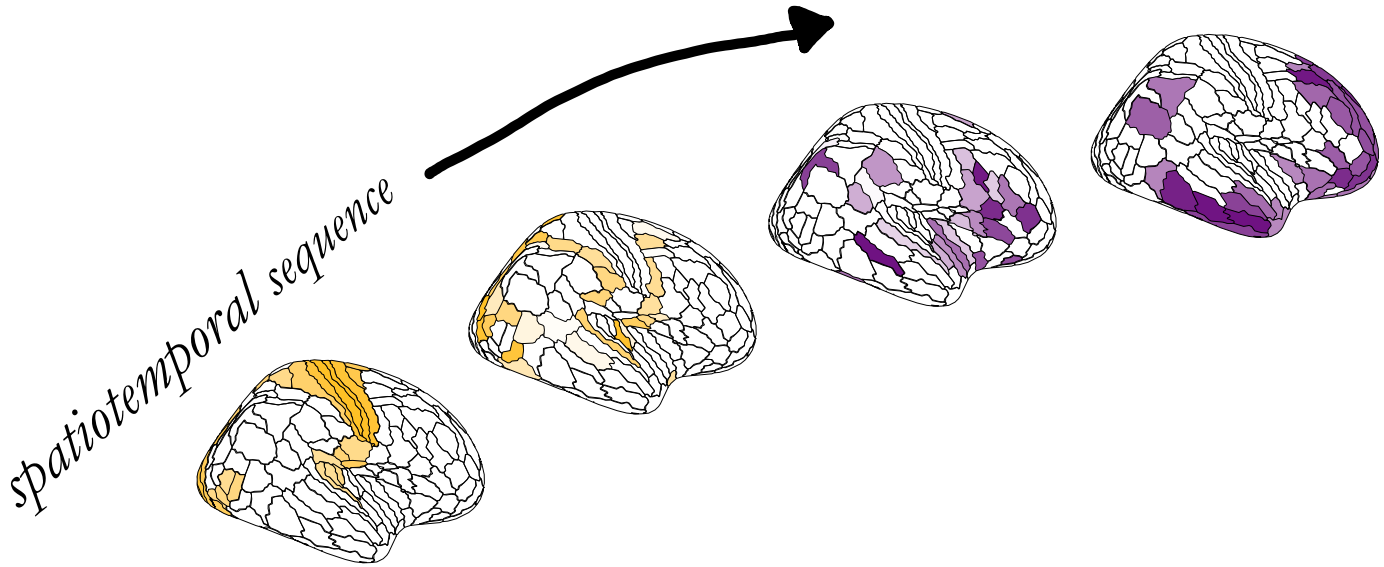
Aim 1:
To characterize the spatiotemporal development of cortical plasticity

Knowledge gap: The precise spatiotemporal sequence of development has yet to be characterized across the cortical mantle.

Imaging and quantifying temporal sequences of cortical plasticity and cortical maturation

Timing of Human Cortical Development

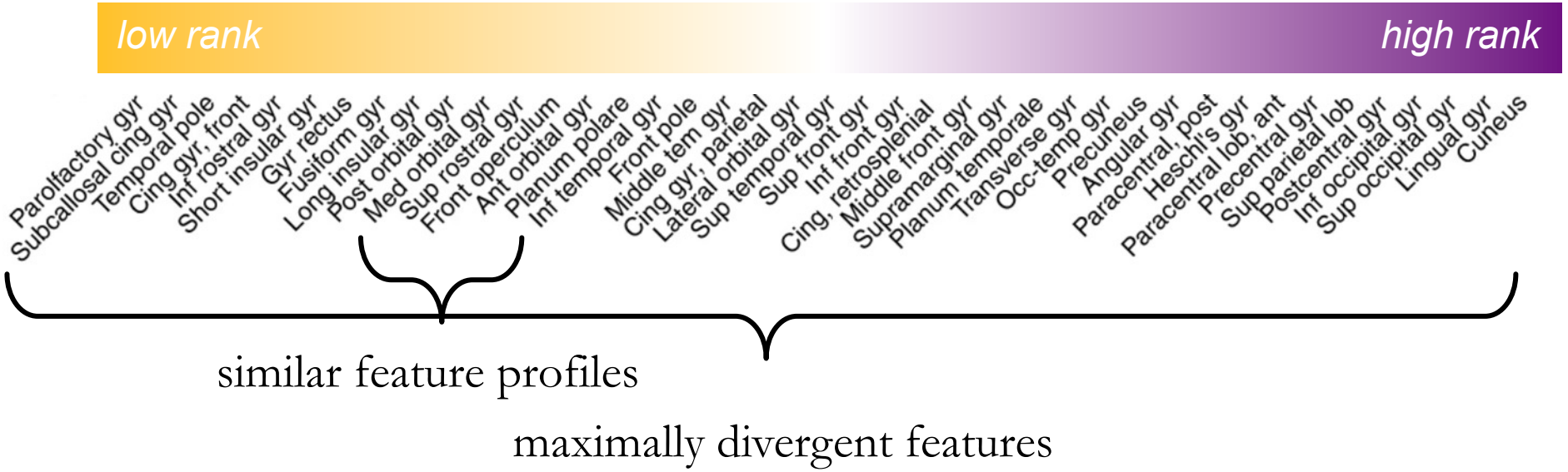
During childhood and adolescence, cortical maturation progresses along a sensorimotor-association axis due to the hierarchical unfolding of plasticity-regulating events



Sydnor et al., 2021, *Neuron*

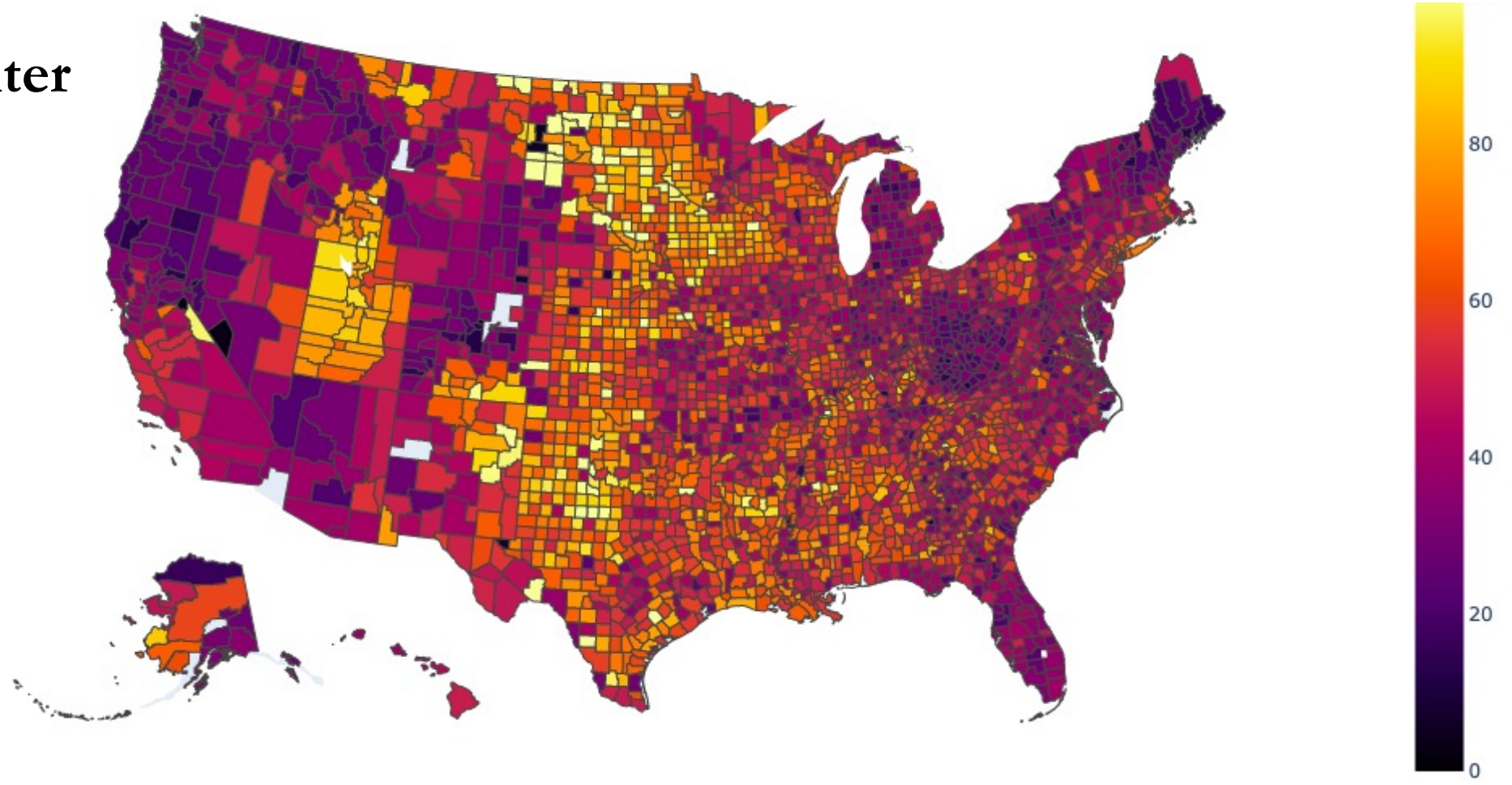
Sensorimotor-Association Axis

Axis: unidimensional ordering (ranking) of cortical regions, defined by patterns of variability in one or more cortical properties

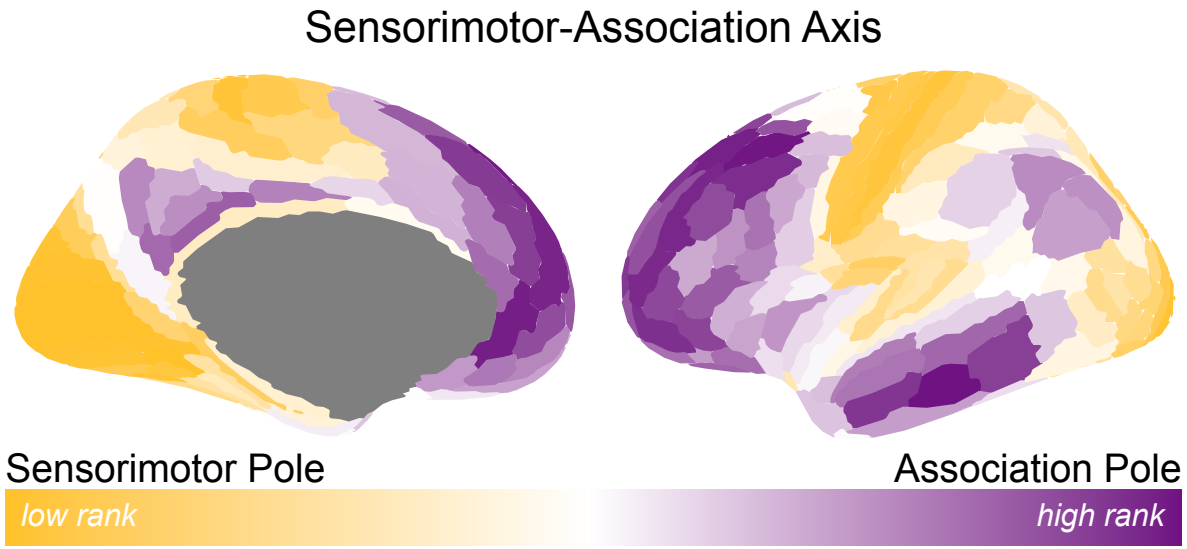


Sensorimotor-Association Axis

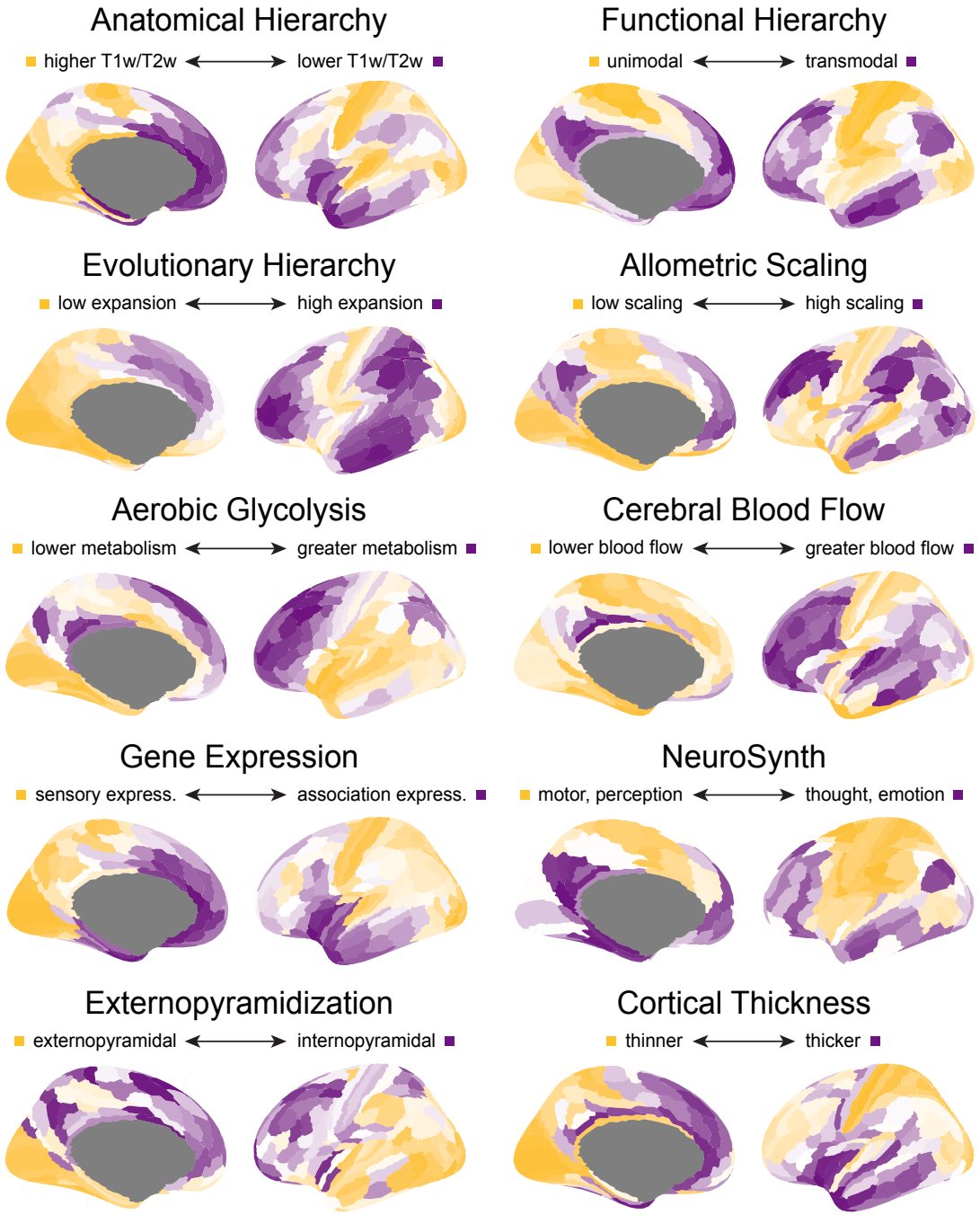
Coast-to-center axis



Sensorimotor-Association (S-A) Axis

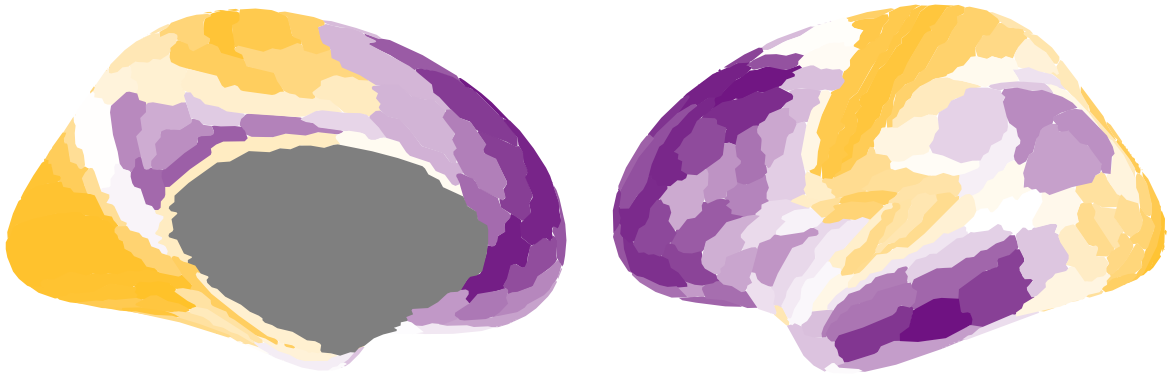


An axis of cortical feature variation



Sydnor et al., 2021, *Neuron*

Sensorimotor-Association Axis

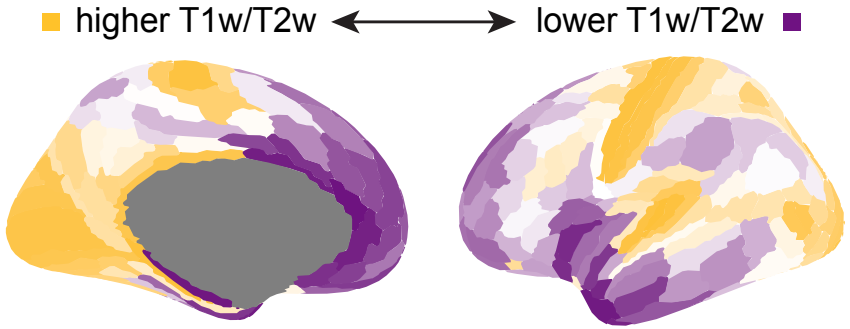


feed-forward connections
low evolution expansion
action, perception, sensation

feed-back connections
high evolution expansion
introspection, socioemotional processing

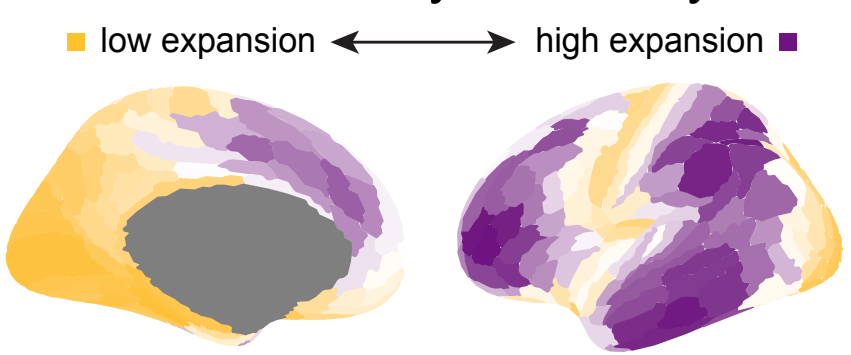
Sydnor et al., 2021, *Neuron*

Anatomical Hierarchy



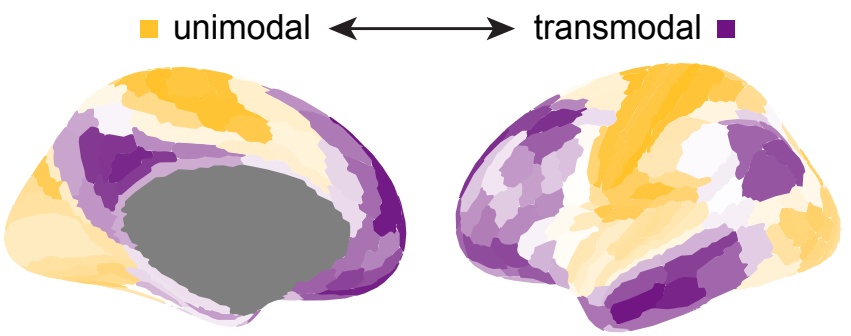
Burt et al., 2018, *Nat Neuro*

Evolutionary Hierarchy



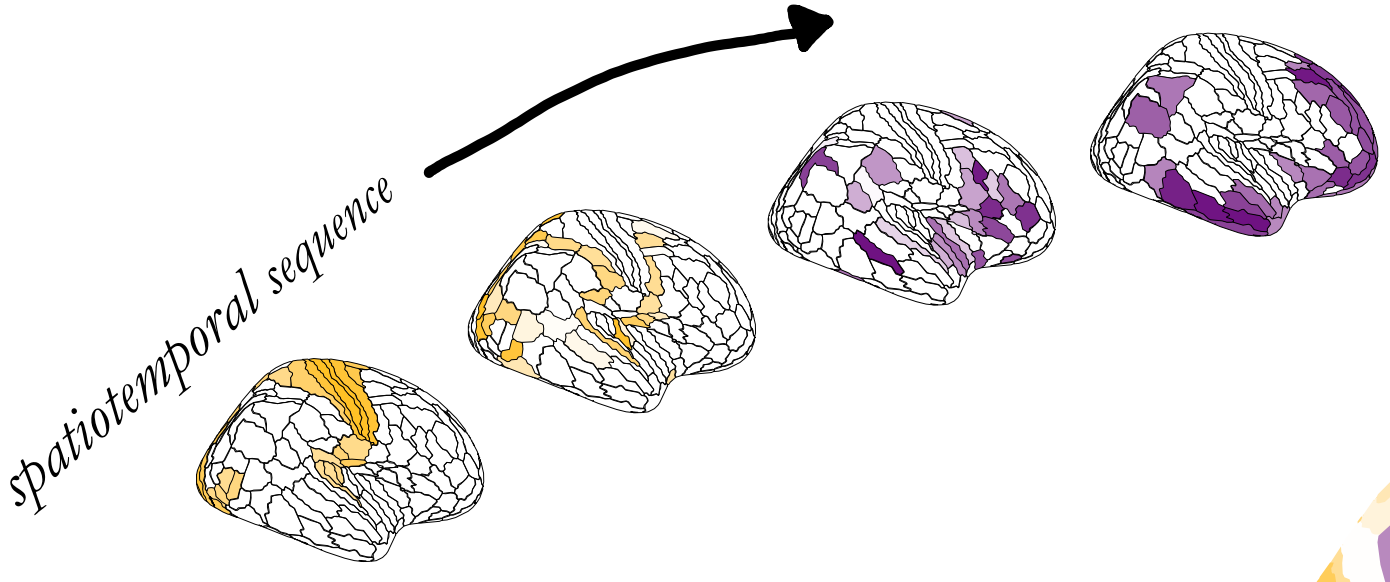
Hill et al., 2010, *PNAS*

Functional Hierarchy

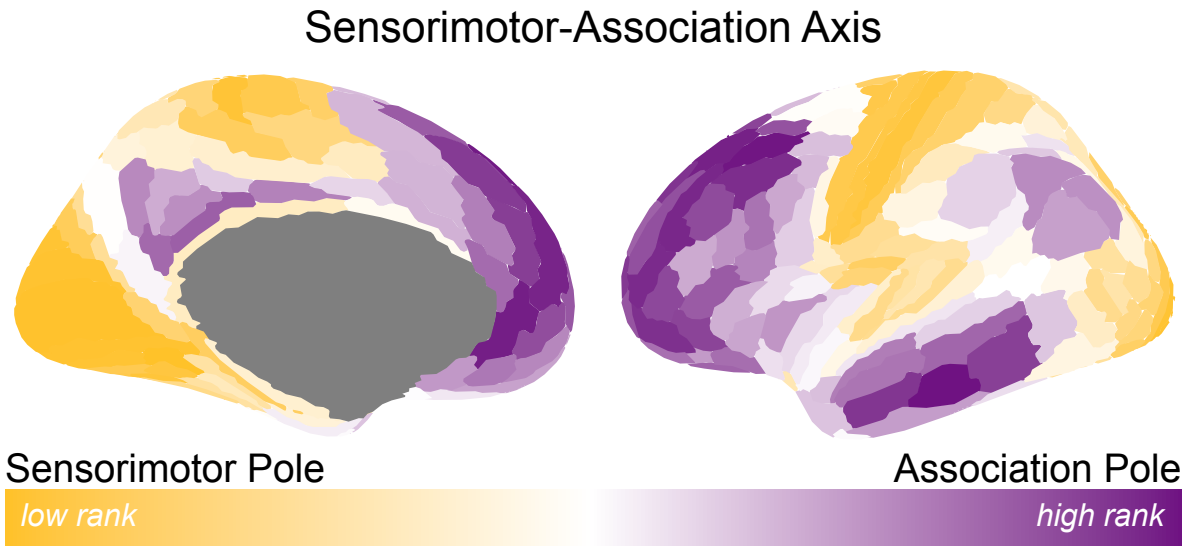


Margulies et al., 2016, *PNAS*

Timing of Human Cortical Development



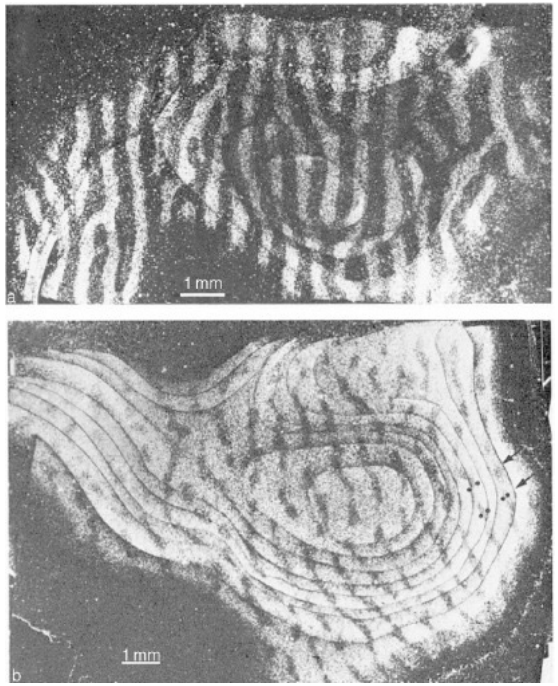
Neurodevelopmental Hierarchy?



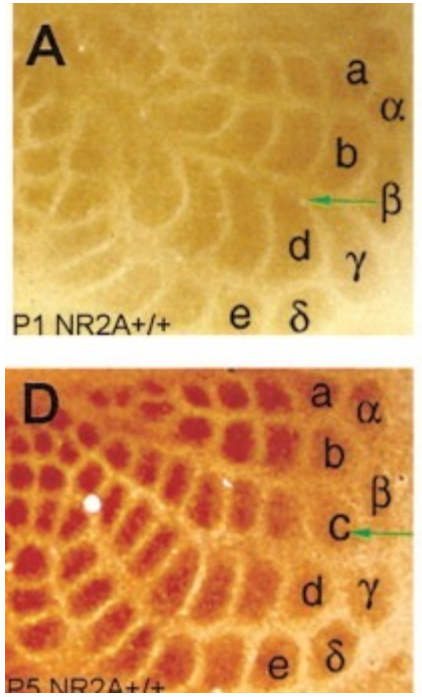
Critical Periods of Plasticity

Temporally constrained developmental windows where experiences have a large and lasting impact on the organization of neural circuits

Visual cortex: ocular dominance columns



Somatosensory cortex: barrel map



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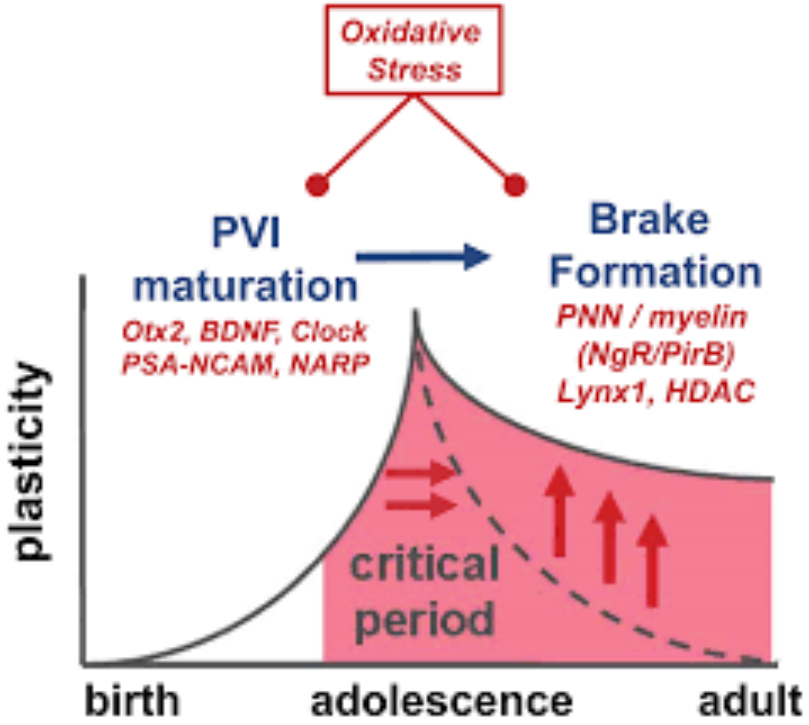
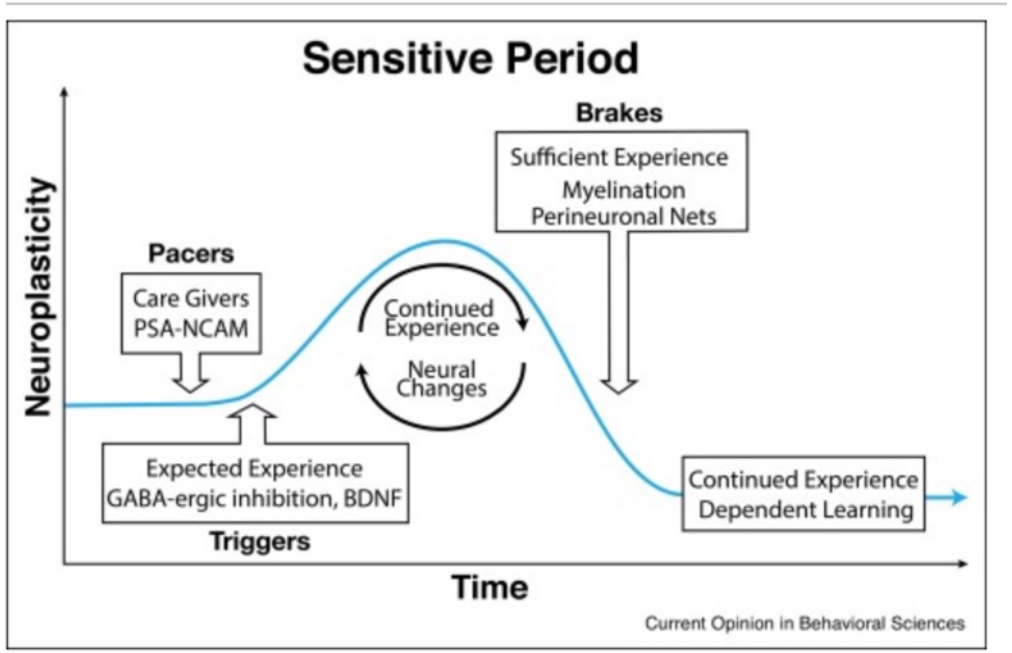
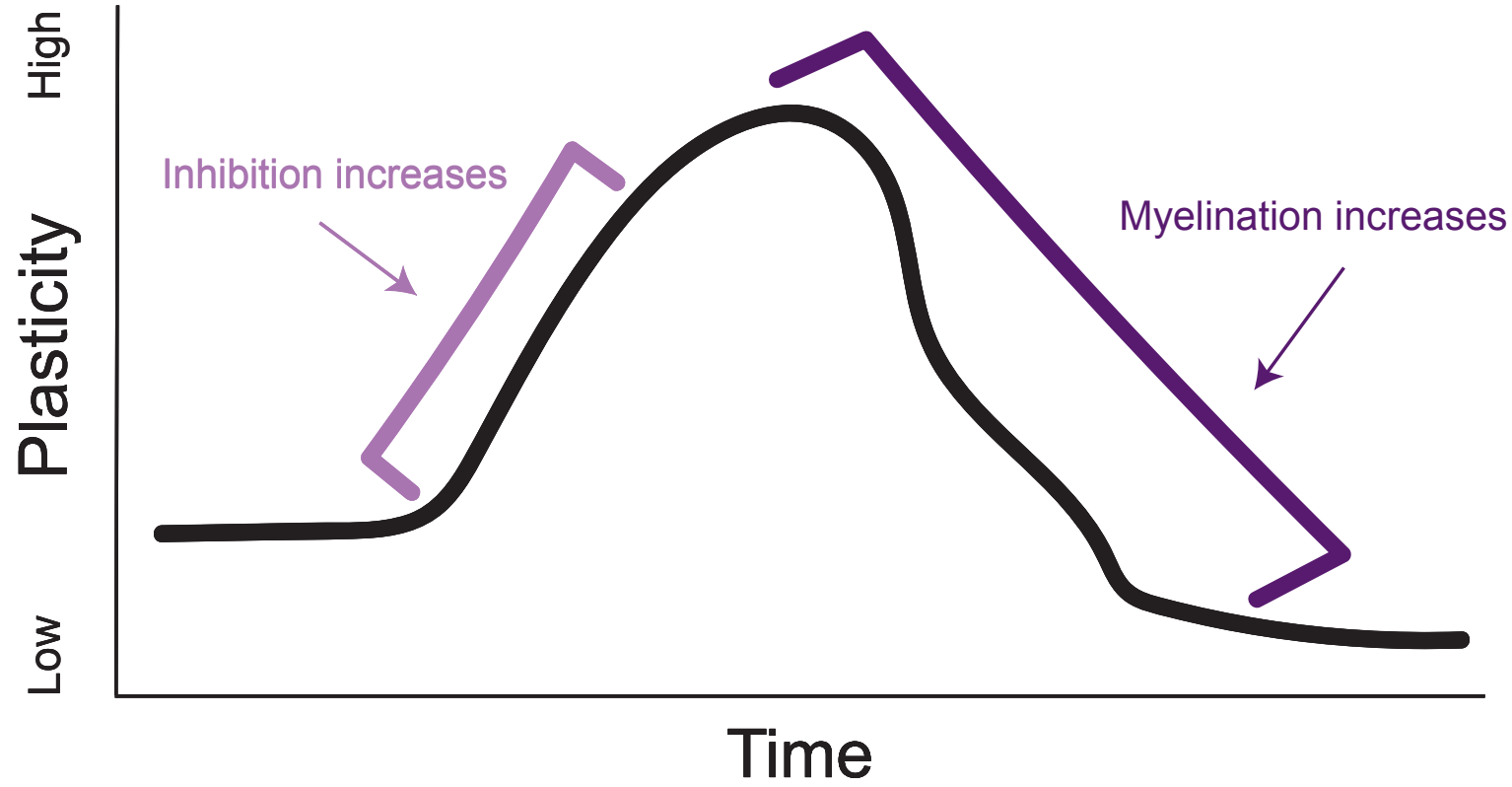




Plasticity Signatures



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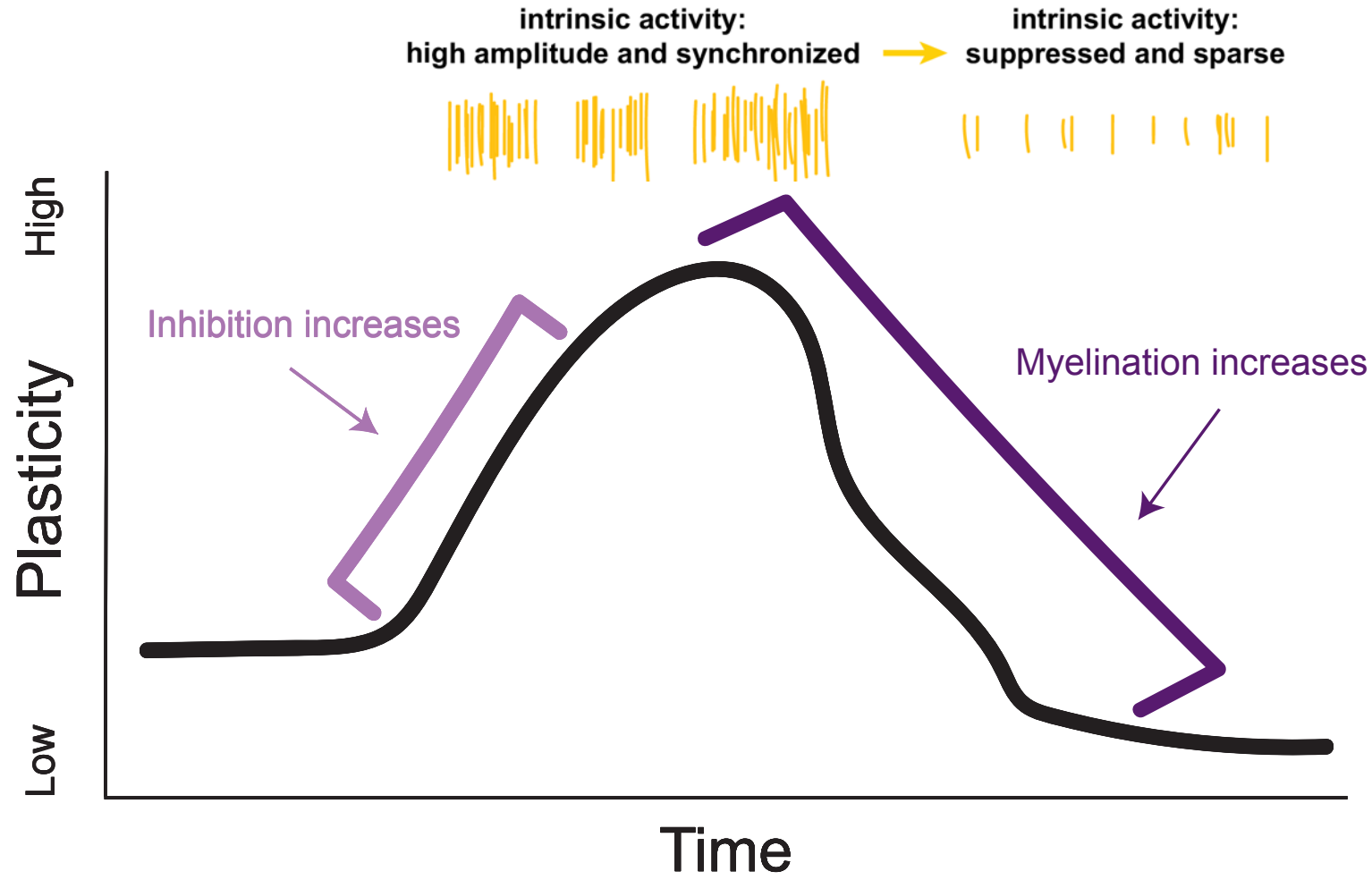
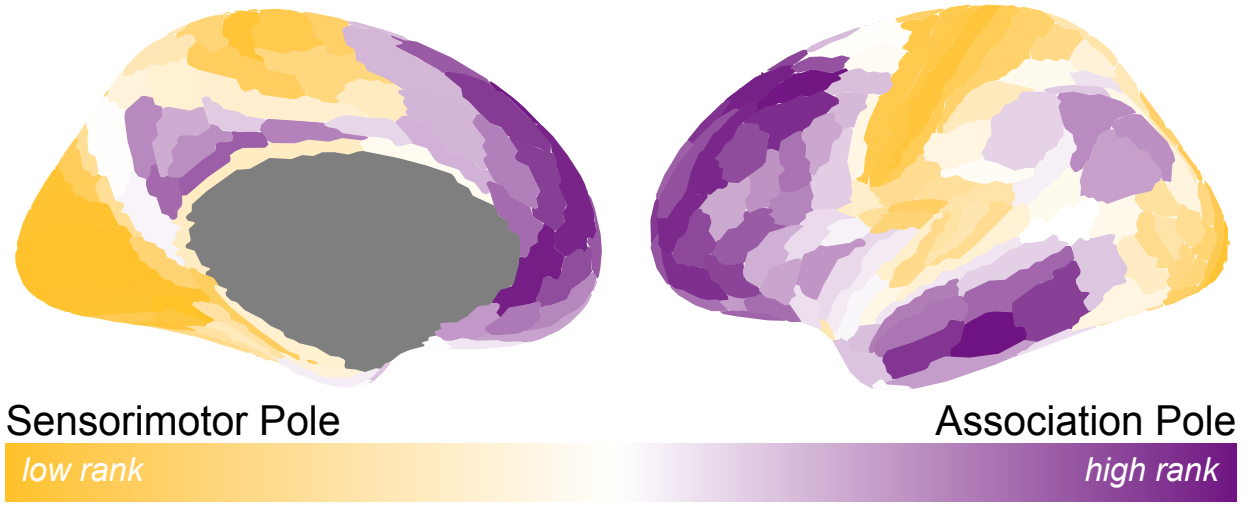


Aim 1:

To characterize the spatiotemporal development of cortical plasticity

Methods gap: most prior developmental imaging studies have not aimed to examine metrics that are sensitive to biological features that influence cortical plasticity



Aim 1:

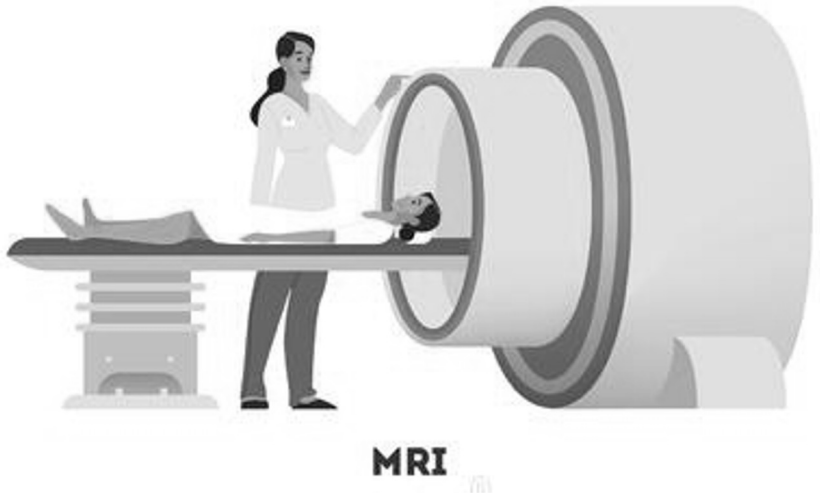
To characterize the spatiotemporal development of cortical plasticity

Plasticity-Regulating Features

Increases in inhibition

Increases in intracortical myelination

Alterations in spontaneous activity patterns



Aim 1:

To characterize the spatiotemporal development of cortical plasticity

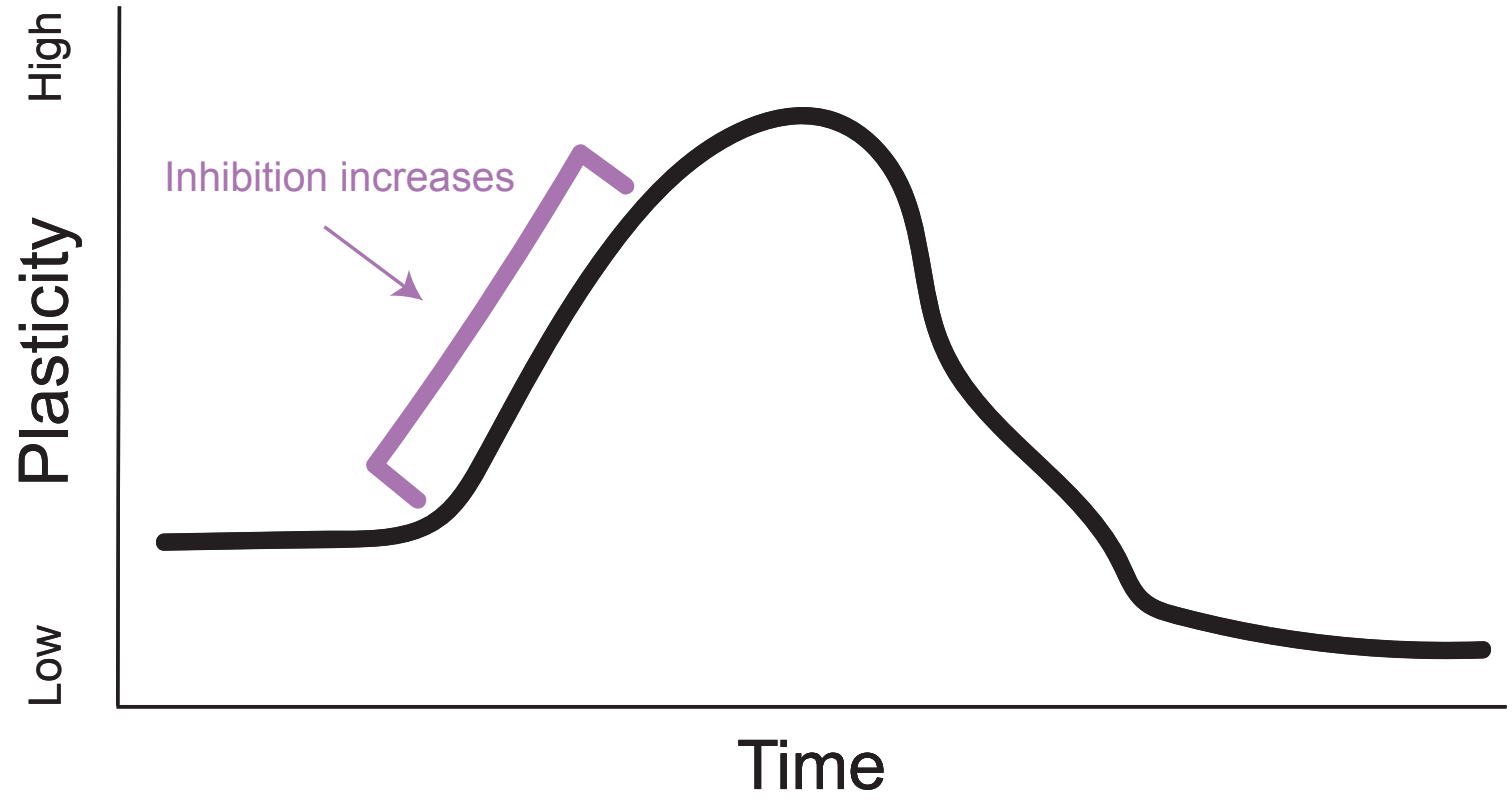
Plasticity-Regulating Features

Increases in inhibition: **REHO, Catch22**

Increases in intracortical myelination: **GWC**

Alterations in spontaneous activity patterns: **ALFF**

Plasticity Signatures: Act 1



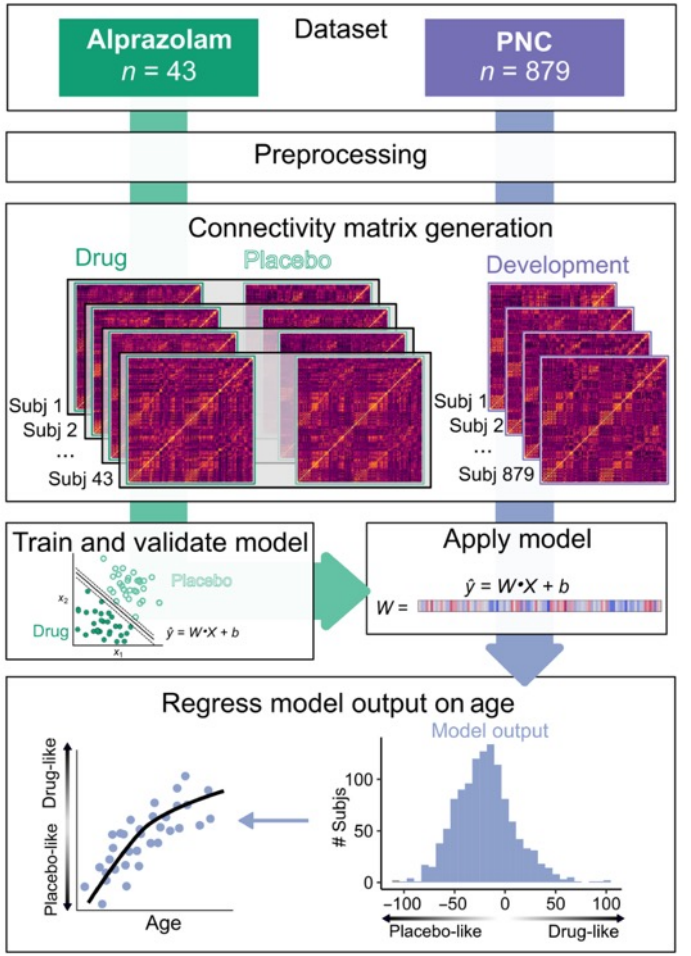
In Vivo Imaging of Inhibition

SCIENCE ADVANCES | RESEARCH ARTICLE

DEVELOPMENTAL NEUROSCIENCE

A developmental reduction of the excitation:inhibition ratio in association cortex during adolescence

Bart Larsen[1,2,3]*, Zaixu Cui[1,2,3,4], Azeez Adebimpe[1,2,3], Adam Pines[1,2,3], Aaron Alexander-Bloch[2,3], Max Bertolero[1,2,3], Monica E. Calkins[2,3], Raquel E. Gur[2,3,5], Ruben C. Gur[2,3,5], Arun S. Mahadevan[6], Tyler M. Moore[2,3], David R. Roalf[2,3], Jakob Seidlitz[2,3], Valerie J. Sydnor[1,2,3], Daniel H. Wolf[2,3]†, Theodore D. Satterthwaite[1,2,3]†



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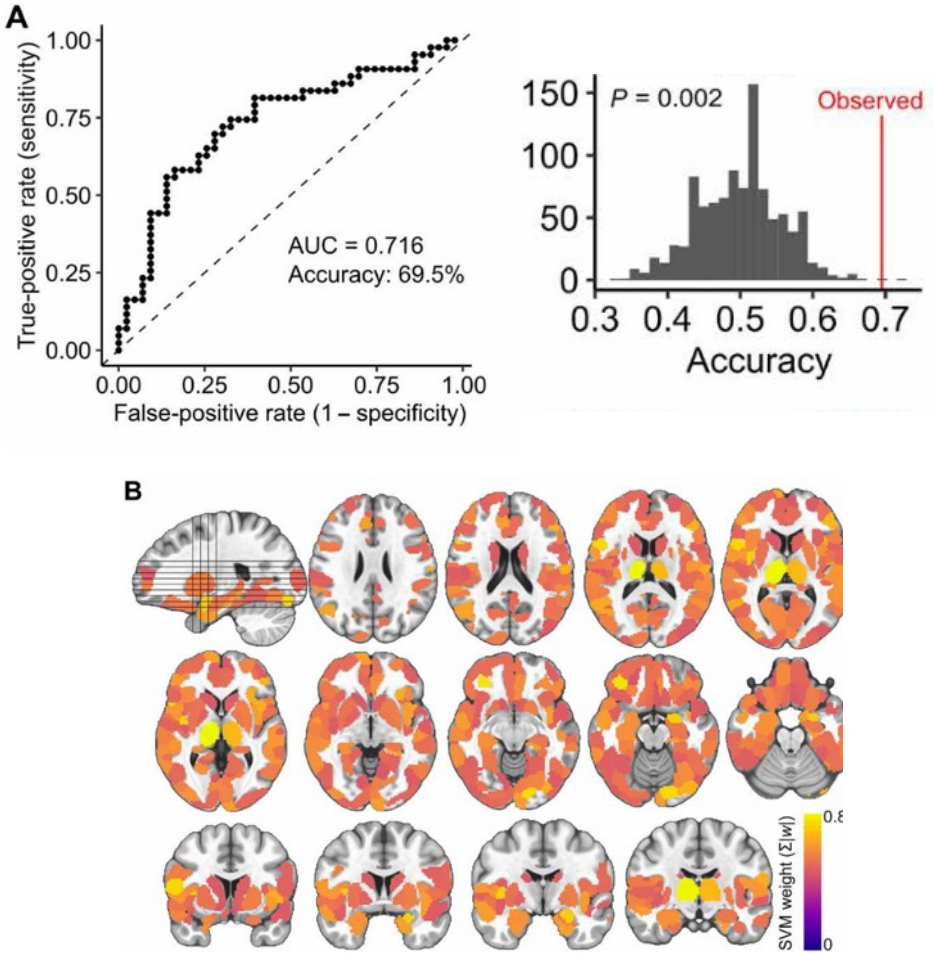
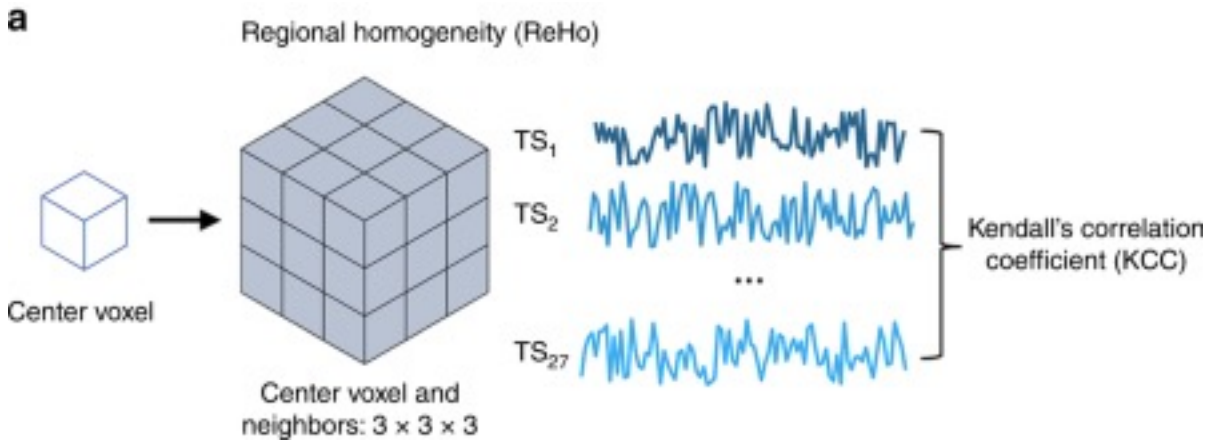


Aim 1:

To characterize the spatiotemporal development of cortical plasticity

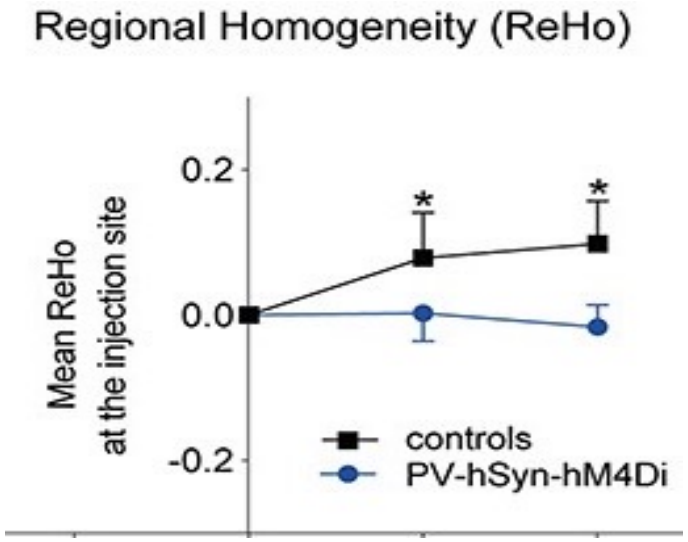
Imaging Cortical Inhibition

REHO



Chemogenetic manipulation of excitation and inhibition with simultaneous fMRI

Markicevic et al., 2020



Aim 1:

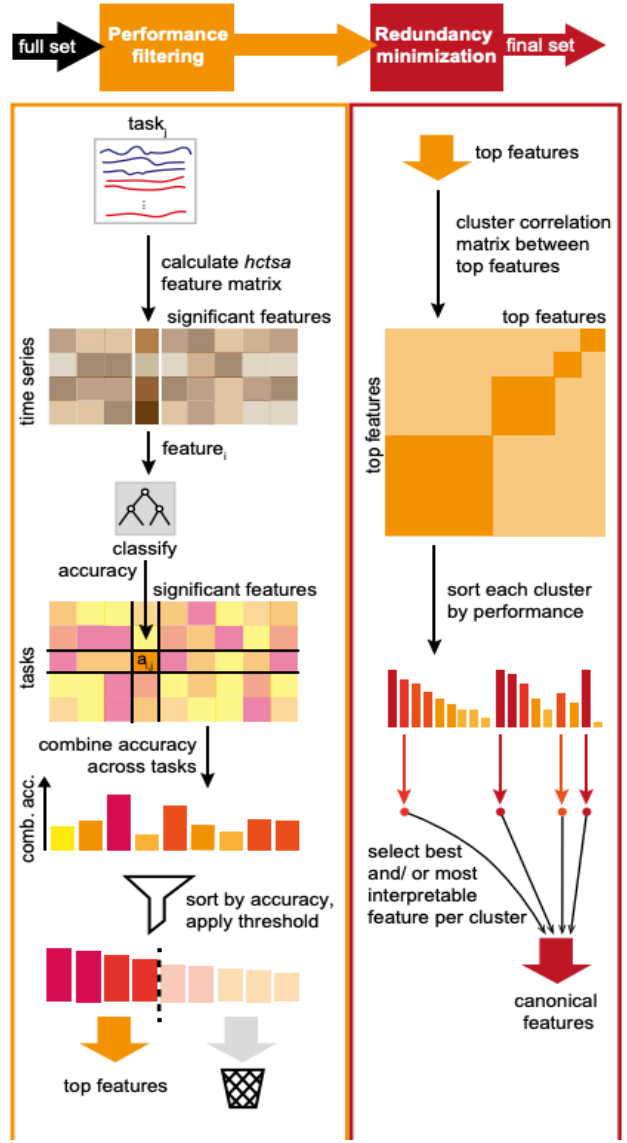
To characterize the spatiotemporal development of cortical plasticity

Imaging Cortical Inhibition

REHO, Catch22

***catch22*: CAnonical Time-series CHaracteristics**

Selected through highly comparative time-series analysis

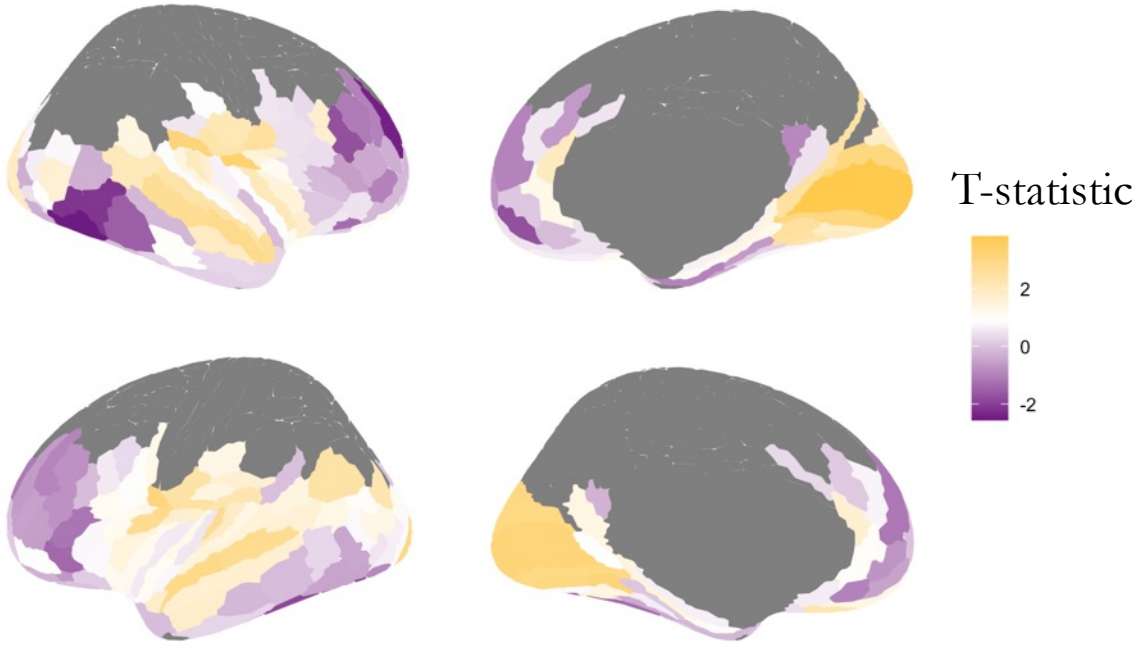


In Vivo Imaging of Inhibition: REHO

Surface (2D) regional functional homogeneity

GABA agonist v. placebo t-tests
Yellow: GABA agonist = higher REHO
Purple: GABA agonist = lower REHO

Correlation of t-statistic with
S-A axis: r = -0.4



N = 42 subjects (84 scans)

In Vivo Imaging of Inhibition: REHO

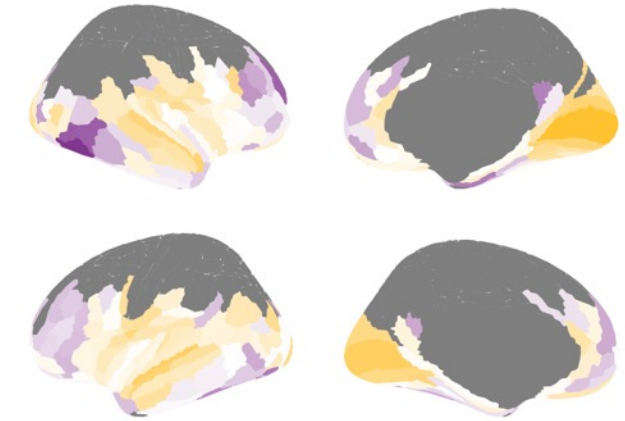
Surface (2D) regional functional homogeneity

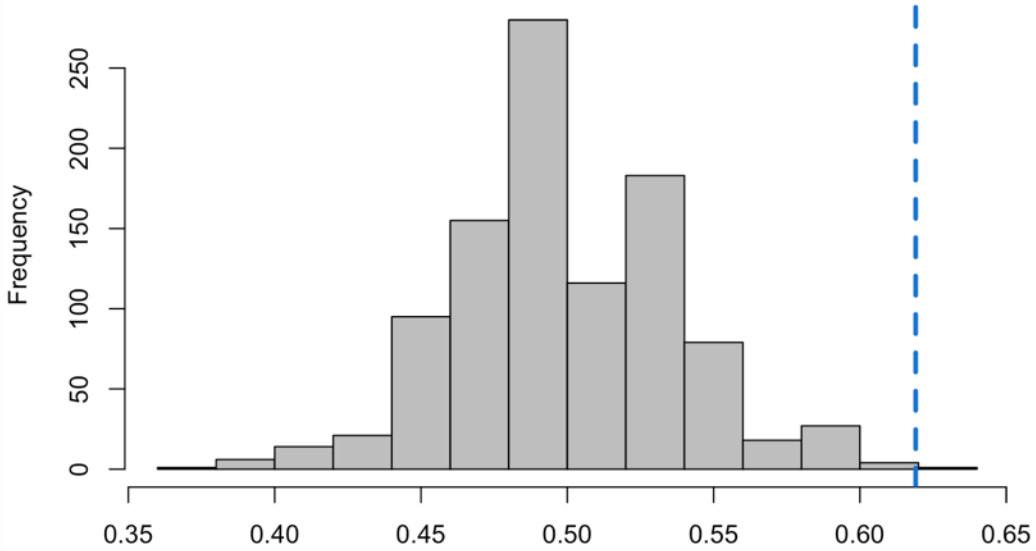
Permutation p-value = 0.001

SVM Results:

Accurately classified 52/84 scans

Accuracy: 62%





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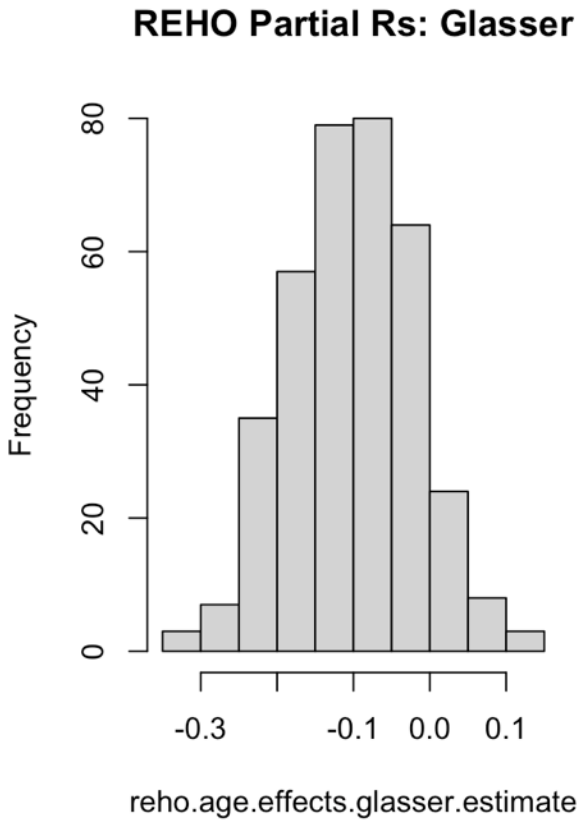
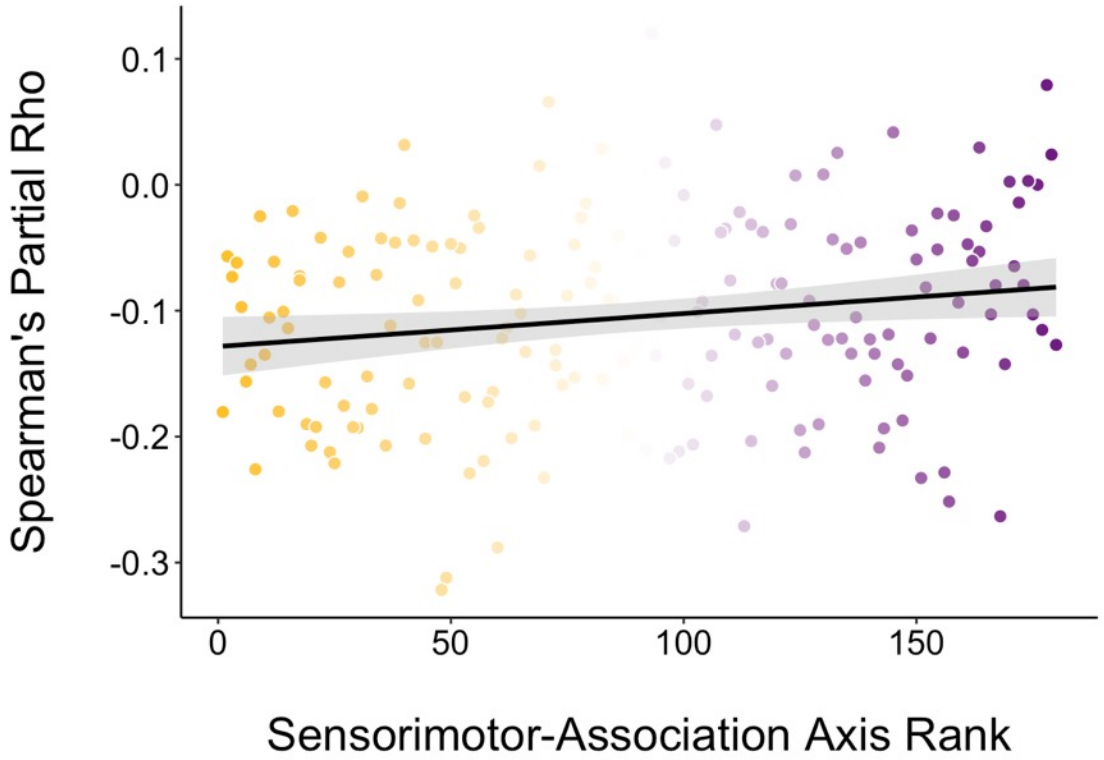
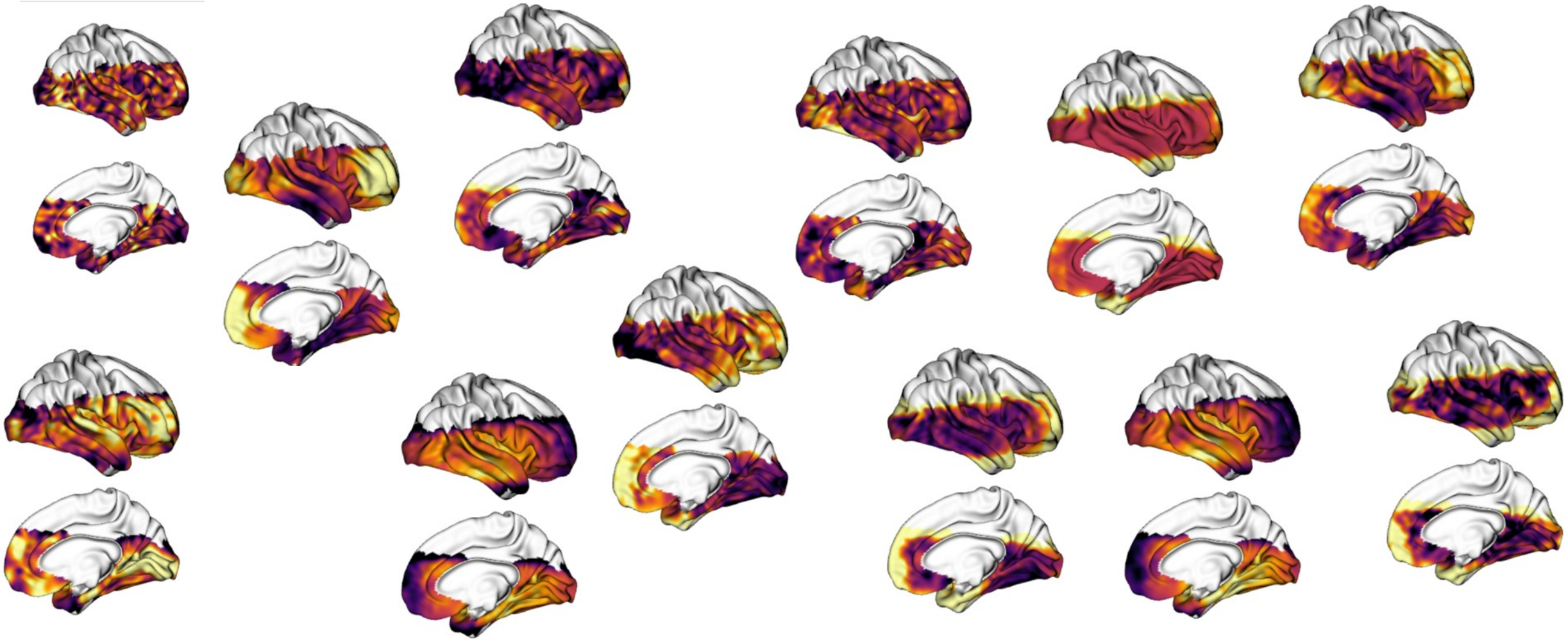
In Vivo Imaging of Inhibition: REHO DEV

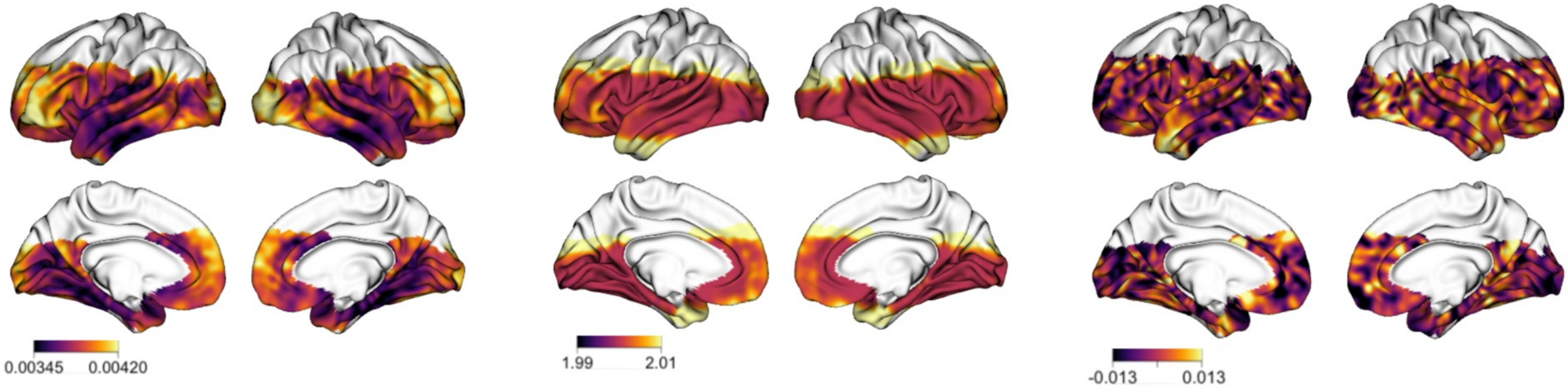




In Vivo Imaging of Inhibition: CATCH 22

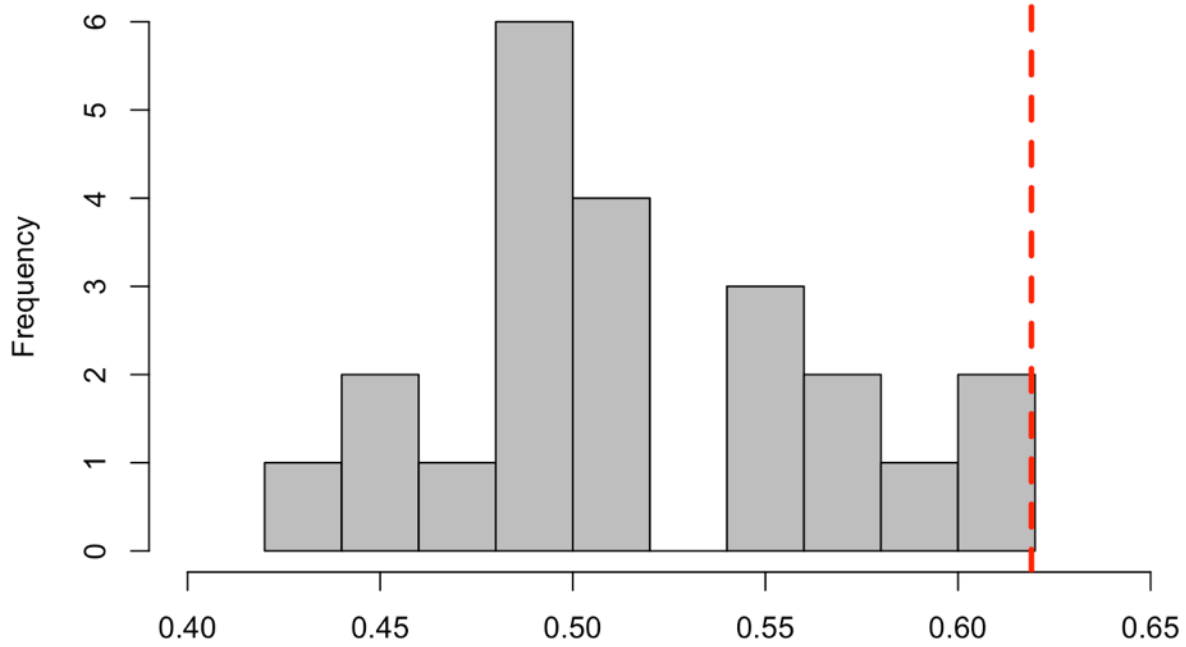


In Vivo Imaging of Inhibition: CATCH 22

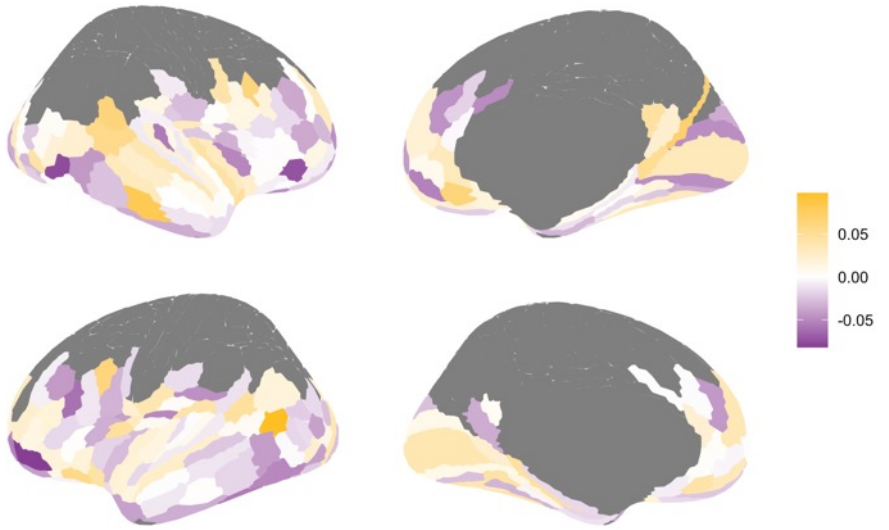


In Vivo Imaging of Inhibition: CATCH 22

Functional Homogeneity
SB_TransitionMatrix_3ac_sumdiagcov



Model Accuracy (Catch22 Features)

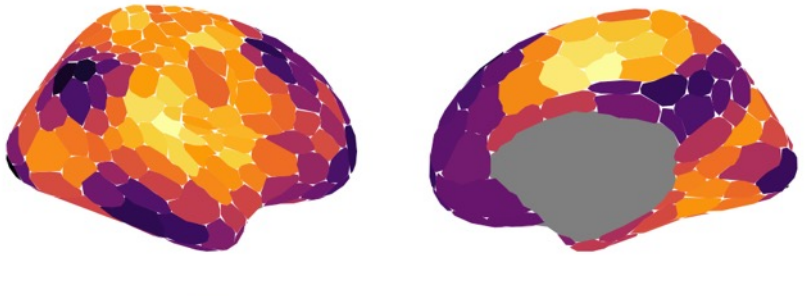


N = 42 subjects (84 scans)

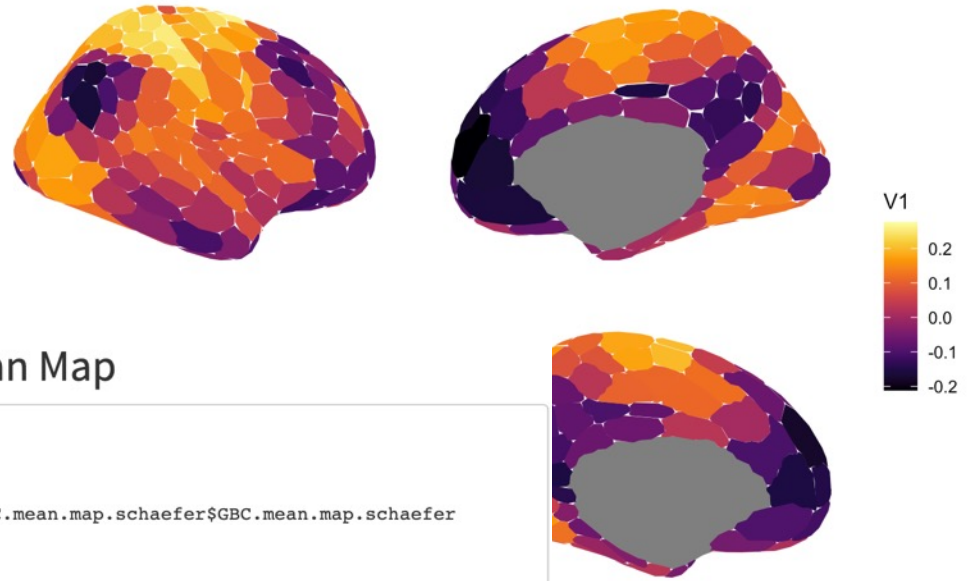
In Vivo Imaging of Inhibition: GBC (lol)

Regional global brain connectivity development

Average GBC



GBC Development Effects



Correlation of Age Effects with Mean Map

```
##
##  Spearman's rank correlation rho
##
## data:  GBC.age.effects.schaefer.estimate$V1 and GBC.mean.map.schaefer$GBC.mean.map.schaefer
## S = 2318794, p-value < 2.2e-16
## alternative hypothesis: true rho is not equal to 0
## sample estimates:
##       rho
## 0.7826117
```

INHIBITION: FAILED!

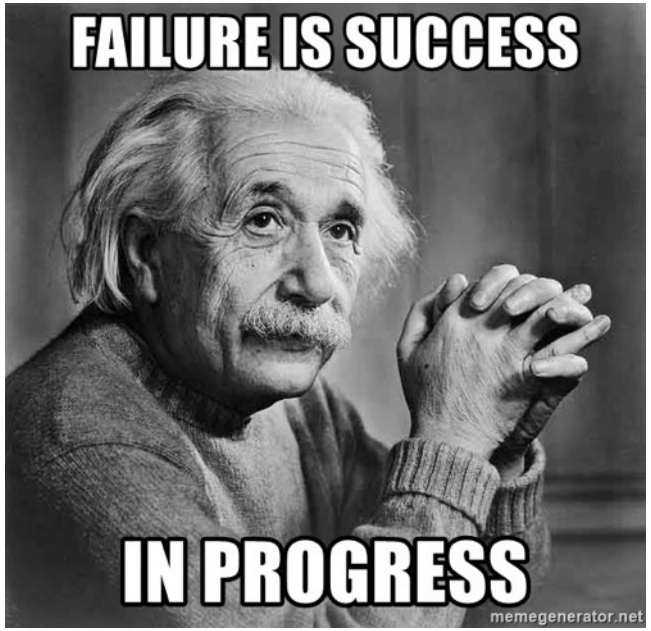
What I learned:

- Dream big, let your PI and thesis committee be the realistic ones

INHIBITION: FAILED!

What I learned:

- Dream big, let your PI and thesis committee be the realistic ones
- When to let go of a failed analysis/approach



INHIBITION: FAILED!

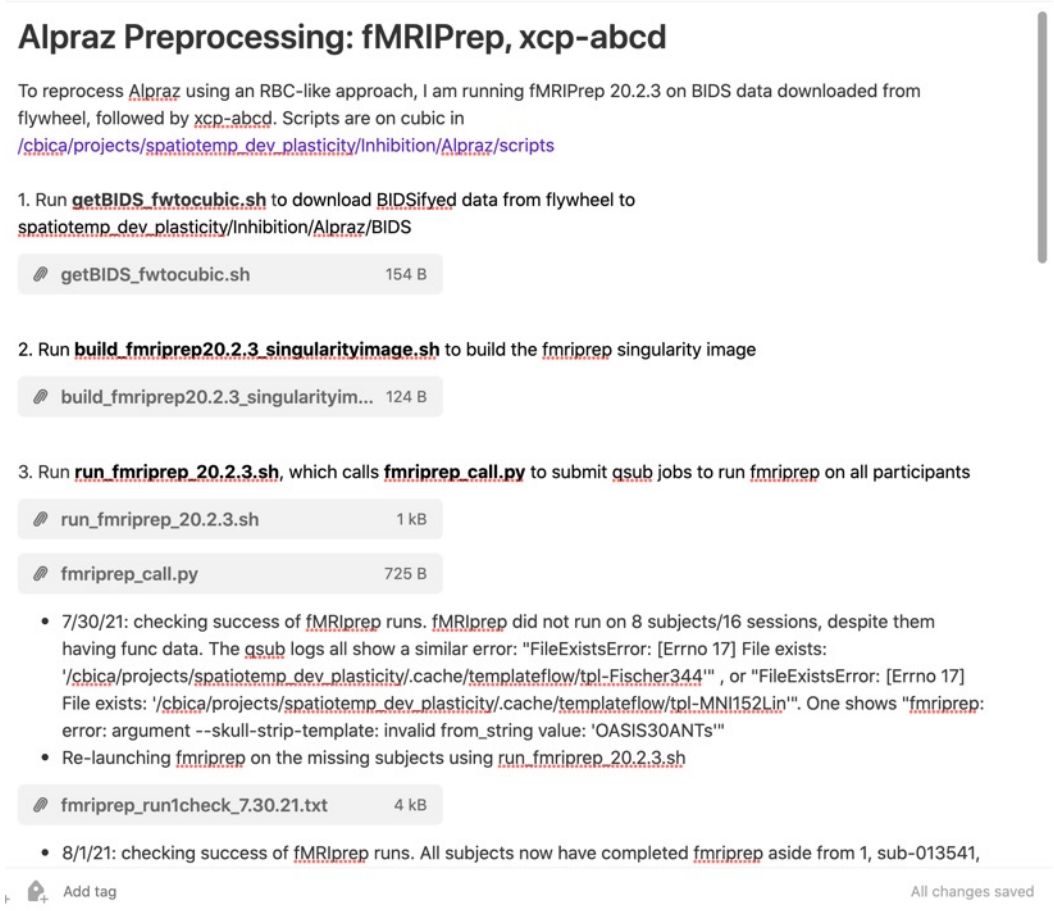
What I learned:

- Dream big, let your PI and thesis committee be the realistic ones
- When to let go of a failed analysis/approach
- GBC, a diamond in the rough

INHIBITION: FAILED!

What I learned:

- How to run fmriprep and xcp (with task regres



Alpraz Preprocessing: fMRIPrep, xcp-abcd

To reprocess Alpraz using an RBC-like approach, I am running fMRIPrep 20.2.3 on BIDS data downloaded from flywheel, followed by xcp-abcd. Scripts are on cubic in /cbica/projects/spatiotemp_dev_plasticity/Inhibition/Alpraz/scripts

1. Run **getBIDS_fwtocubic.sh** to download BIDSifyed data from flywheel to spatiotemp_dev_plasticity/Inhibition/Alpraz/BIDS

getBIDS_fwtocubic.sh 154 B

2. Run **build_fmriprep20.2.3_singularityimage.sh** to build the fmriprep singularity image

build_fmriprep20.2.3_singularityim... 124 B

3. Run **run_fmriprep_20.2.3.sh**, which calls **fmriprep_call.py** to submit qsub jobs to run fmriprep on all participants

run_fmriprep_20.2.3.sh 1 kB

fmriprep_call.py 725 B

- 7/30/21: checking success of fMRIprep runs. fMRIprep did not run on 8 subjects/16 sessions, despite them having func data. The qsub logs all show a similar error: "FileExistsError: [Errno 17] File exists: '/cbica/projects/spatiotemp_dev_plasticity/.cache/templateflow/tpl-Fischer344'" , or "FileExistsError: [Errno 17] File exists: '/cbica/projects/spatiotemp_dev_plasticity/.cache/templateflow/tpl-MNI152Lin'". One shows "fmriprep: error: argument --skull-strip-template: invalid from_string value: 'OASIS30ANTs'"
- Re-launching fmriprep on the missing subjects using run_fmriprep_20.2.3.sh

fmriprep_run1check_7.30.21.txt 4 kB

- 8/1/21: checking success of fMRIprep runs. All subjects now have completed fmriprep aside from 1, sub-013541,

Add tag All changes saved

INHIBITION: FAILED!

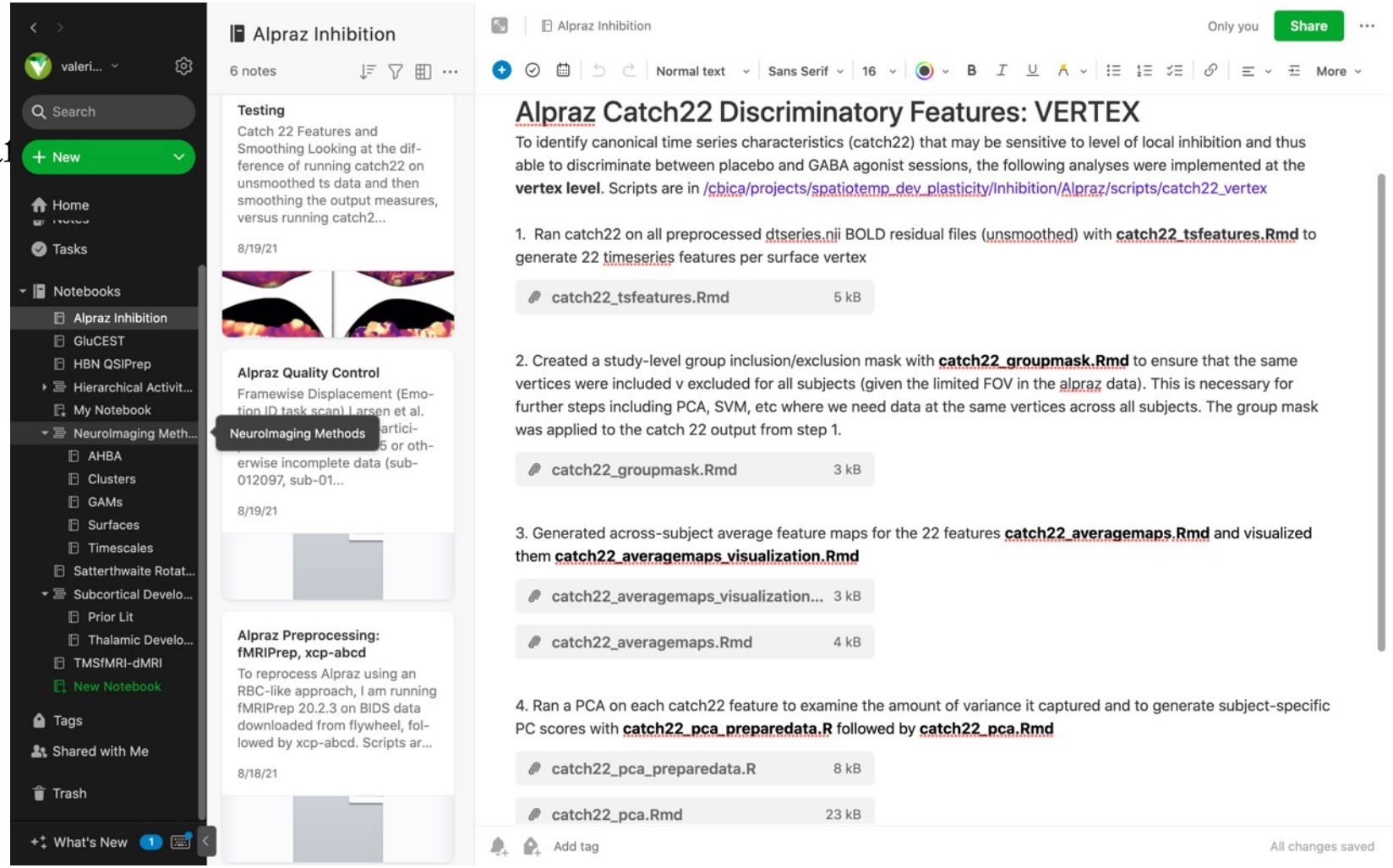
What I learned:

- How to run fmriprep and xcp (with task regression)
- SVM basics

INHIBITION: FAILED!

What I learned:

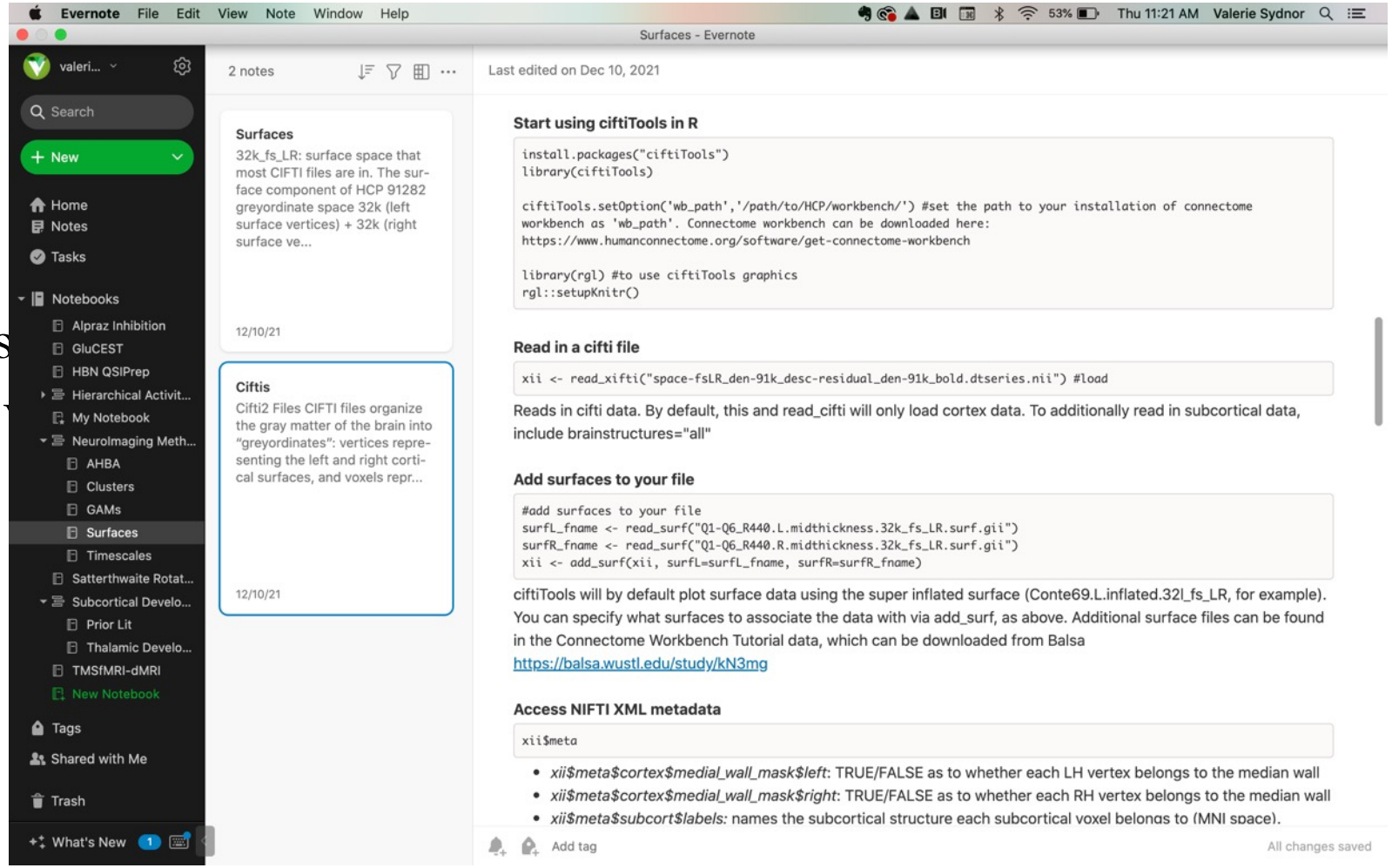
- How to run fmriprep a
- SVM basics
- Catch22



INHIBITION: FAILED!

What I learned:

- How to run fmriprep and
- SVM basics
- Catch22
- How surface data is repres
  manipulate, visualize, and
  and giftis) in R

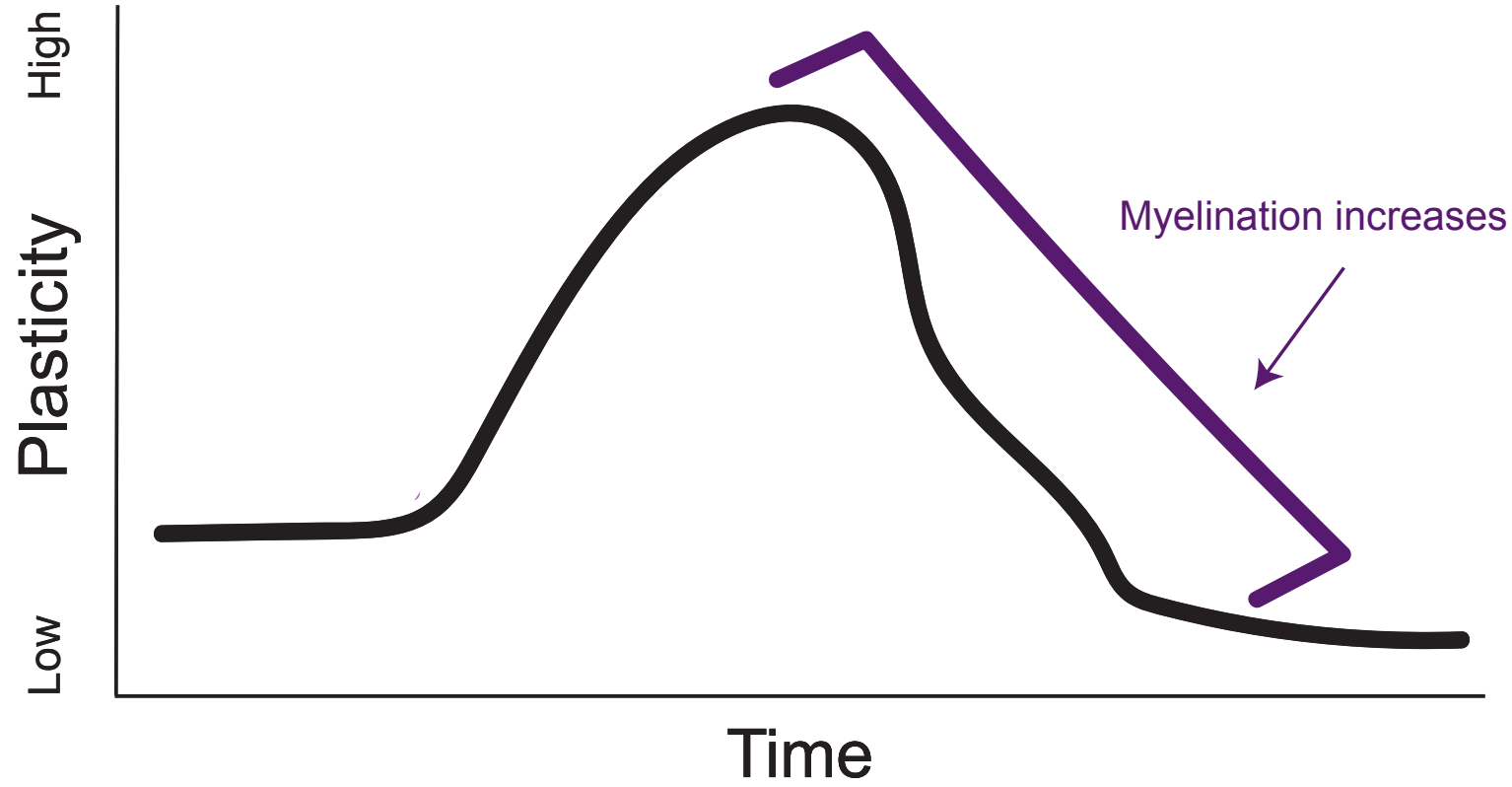


INHIBITION: FAILED!

What I learned:

- How to run fmriprep and xcp (with task regression)
- SVM basics
- Catch22
- How surface data is represented and how to read, manipulate, visualize, and write surface data (cifits and giftis) in R
- Writing better R functions

Plasticity Signatures: Act 2



Aim 1:

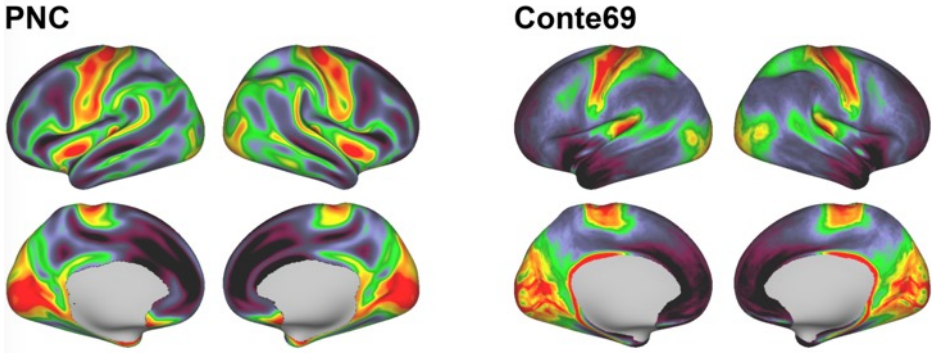
To characterize the spatiotemporal development of cortical plasticity

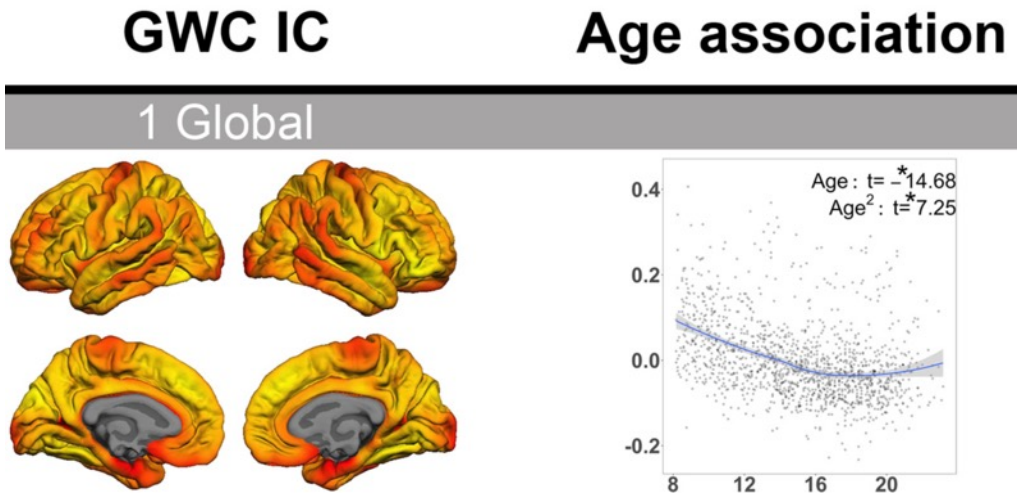
Imaging Intracortical Myelination

GRAY WHITE CONTRAST (GWC)

GWC

T1w/T2w Ratio



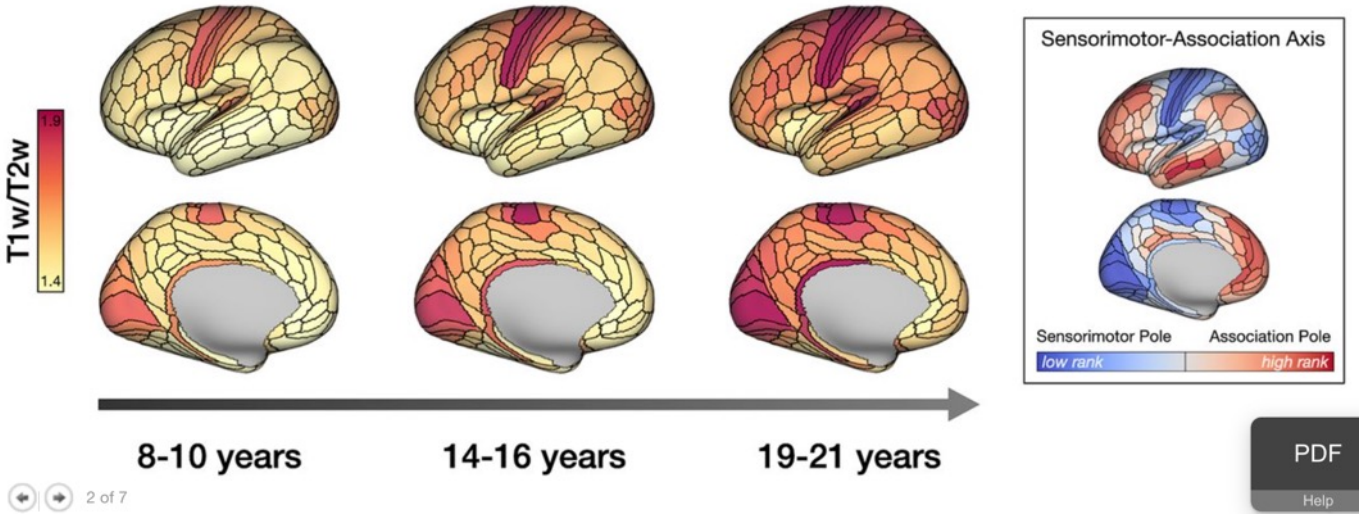


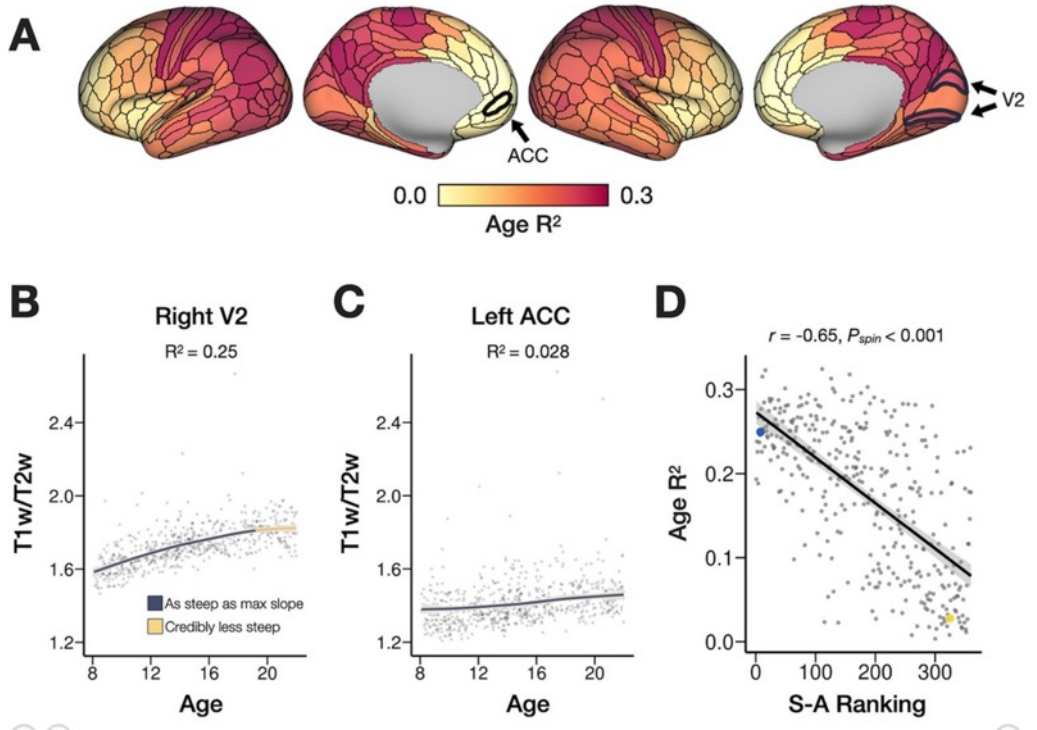
Norbom et al., 2019

MYELIN:

What I learned:

- Having other people believe in and test your ideas is cooler than you doing it





MYELIN: 

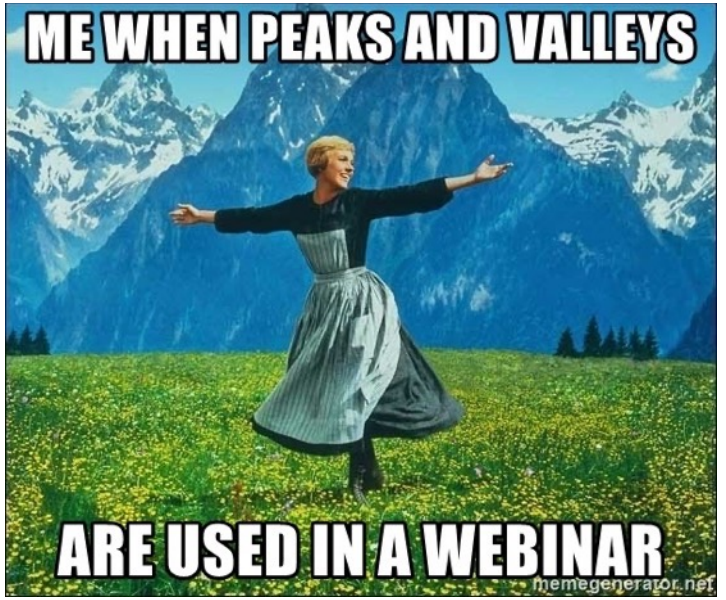
What I learned:

- Having other people believe in and test your ideas is cooler than you doing it
- Turn scoops (or project overlap) into collaborations!

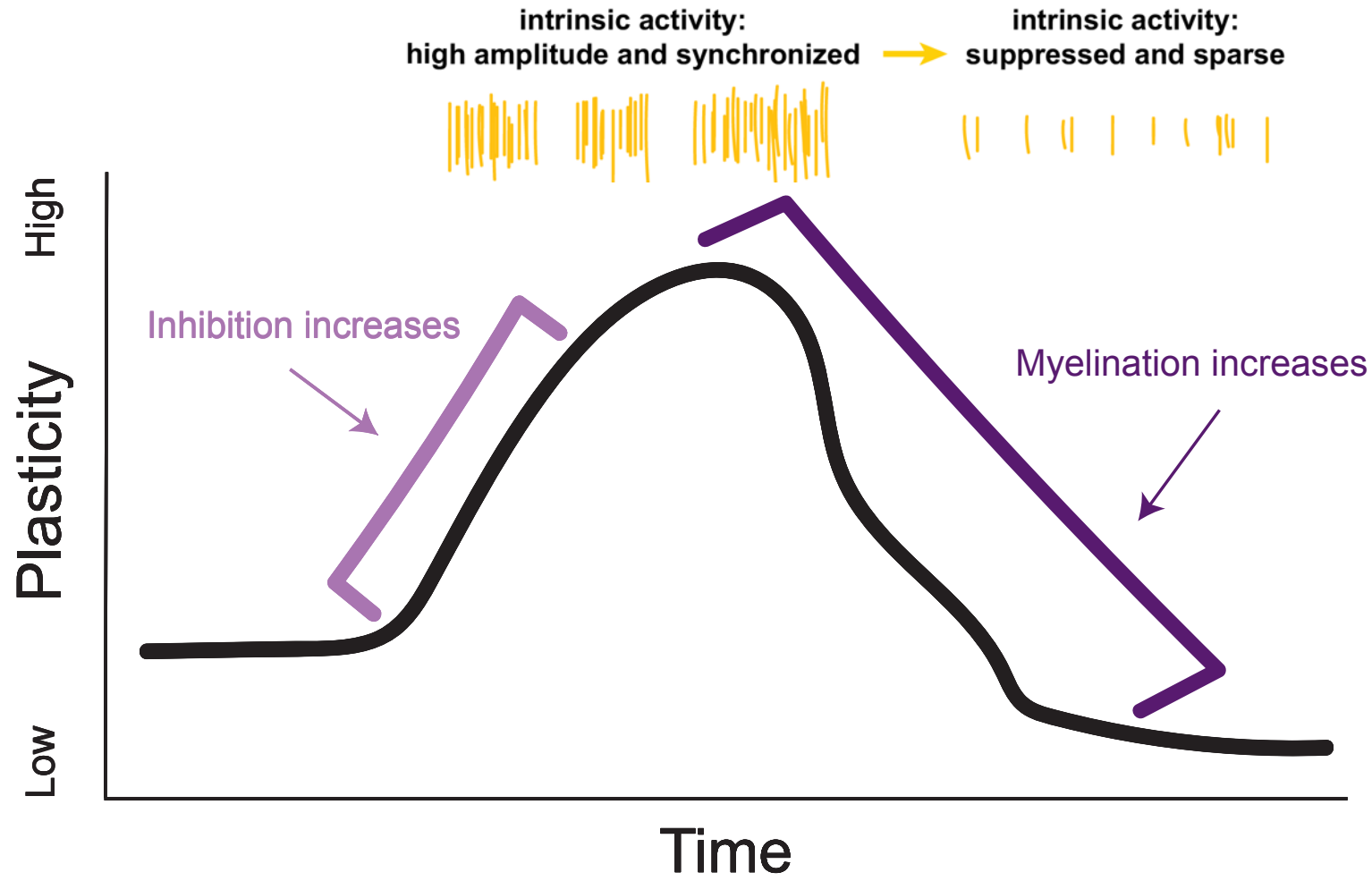
MYELIN: 

What I learned:

- Having other people believe in and test your ideas is cooler than you doing it
- Turn scoops (or project overlap) into collaborations!
- Its going to be okay, fam



Plasticity Signatures: Act 3

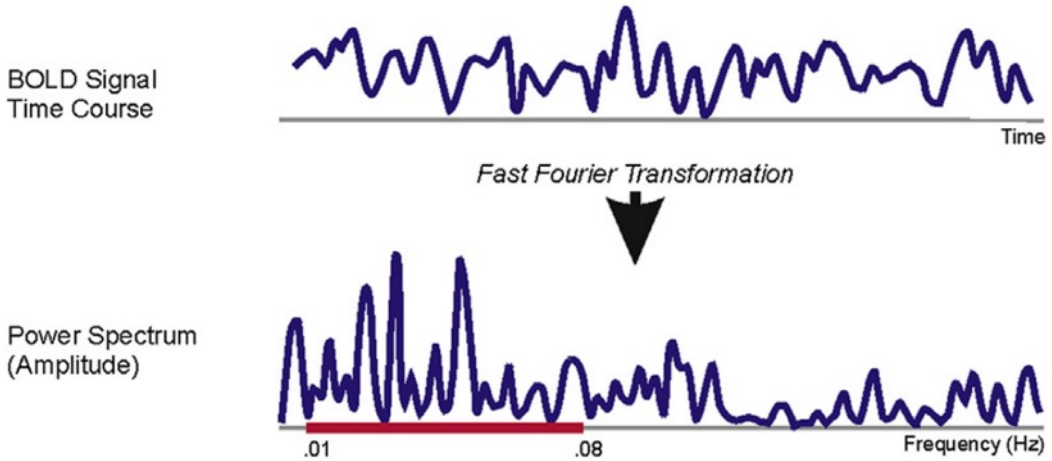


Aim 1:

To characterize the spatiotemporal development of cortical plasticity

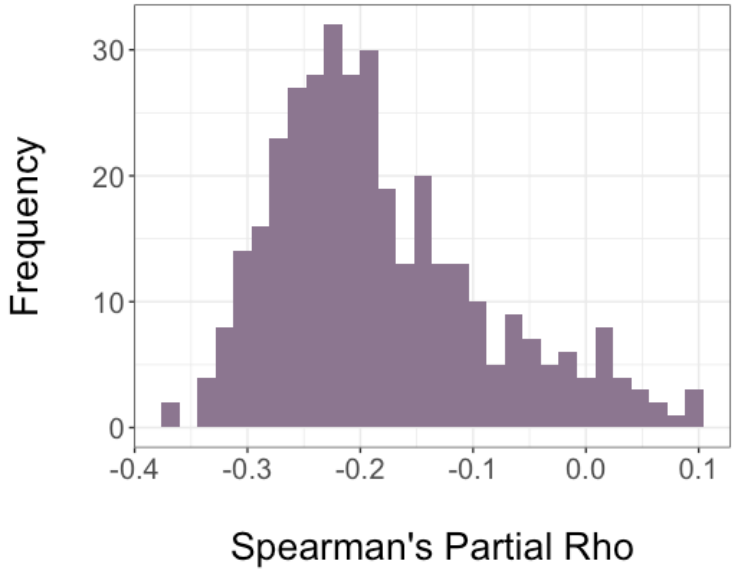
Imaging Spontaneous Activity Patterns

Fluctuation Amplitude



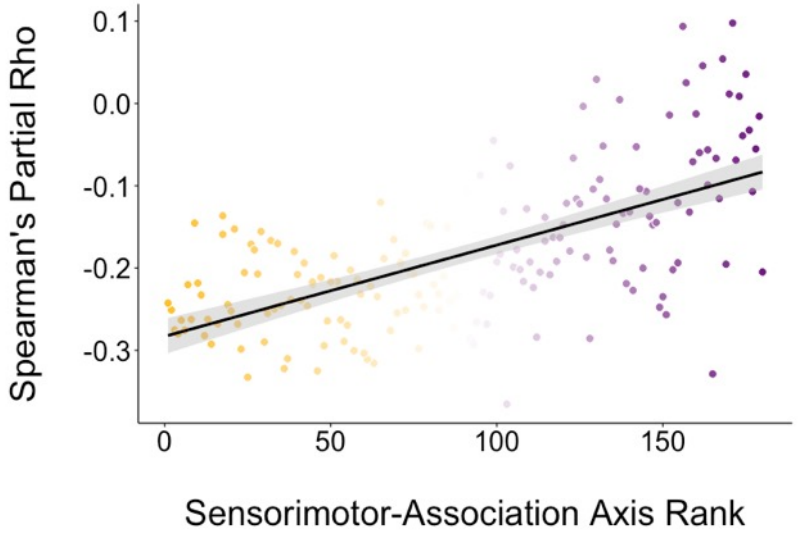
Preliminary Data: Development of ALFF

Associations Between Fluc. Amp. and Age



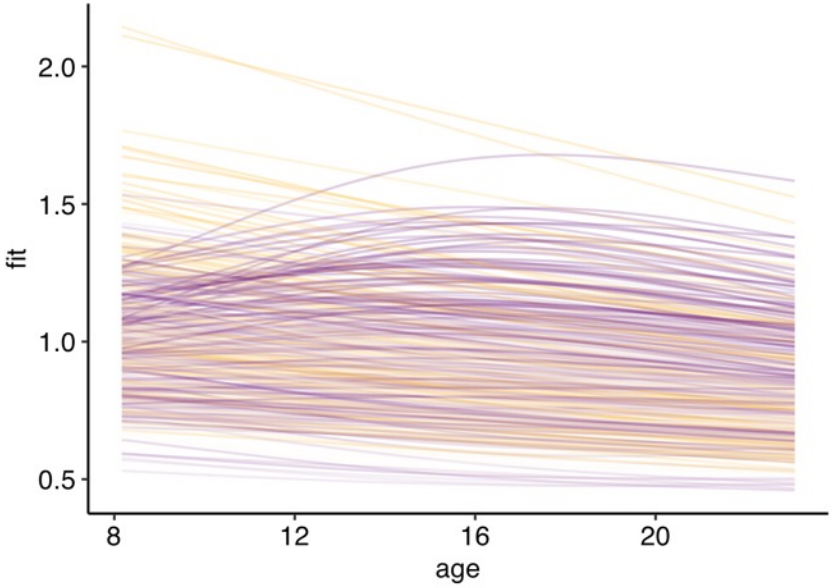
**significant in 314/360 parcels (FDR corrected)*

Correlation Between Age Effect and S-A Axis Rank



Spearman's Rho = 0.61, p = < 2.2e-16

Regional Developmental Trajectories



ALFF: IS BACK!

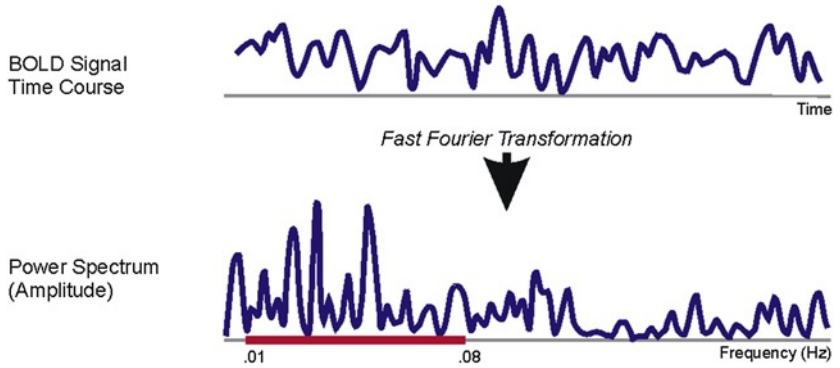
What I learned:

- Have mentors who lift you up
- Get other people's perspectives on your data
- Follow the data brick road

Study Design

N = 1033
Ages 8-23 years
PNC

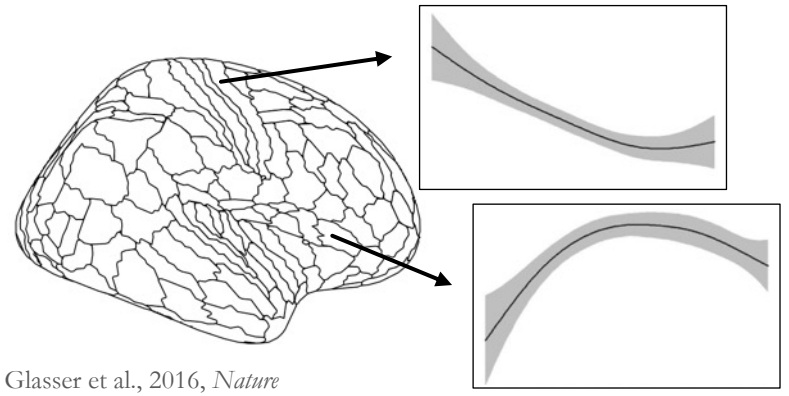
Satterthwaite et al., 2016, *Neuroimage*



Haag et al., 2015, *Cortex*

fMRI BOLD
fluctuation amplitude

Zang et al., 2007, *Brain Dev*



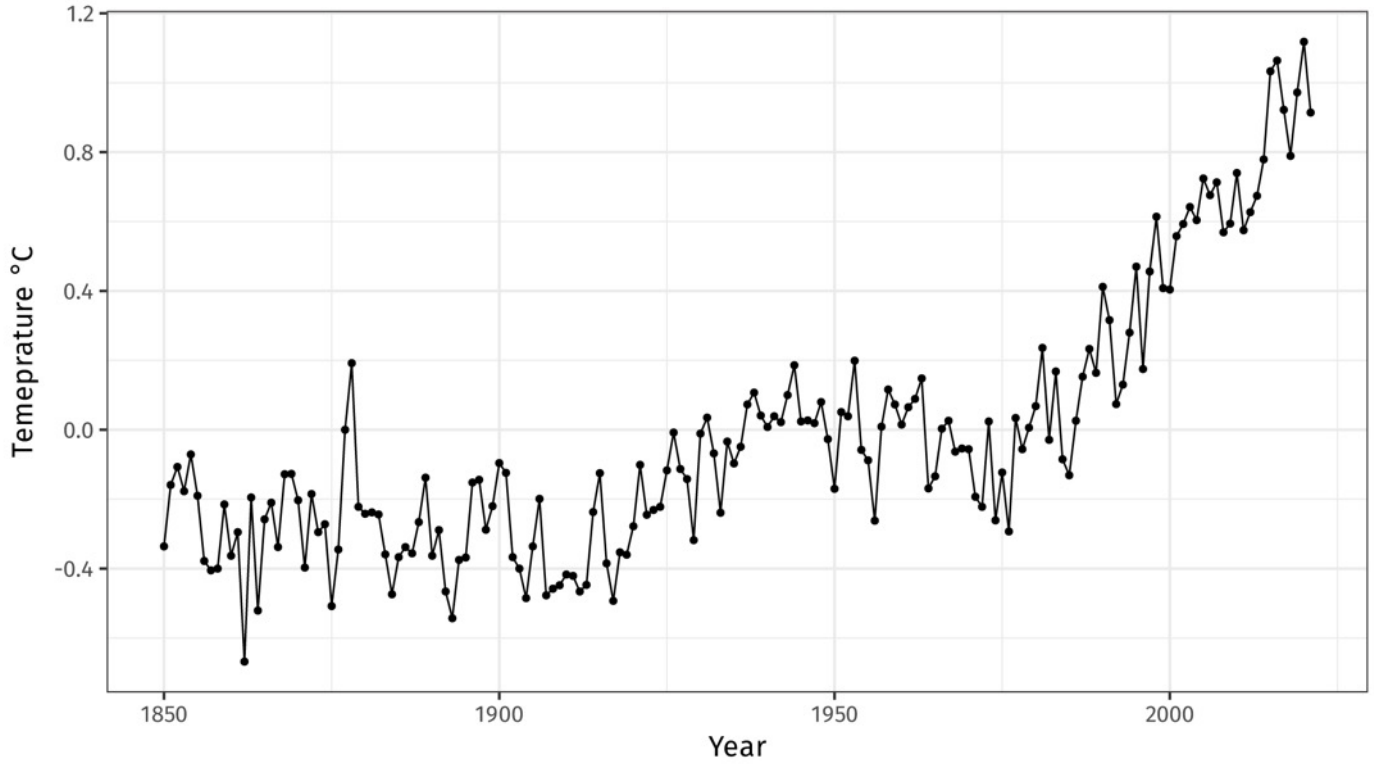
Glasser et al., 2016, *Nature*

Region-specific
generalized additive
models
(age splines)

Study Design

Generalized Additive Models (GAMs)

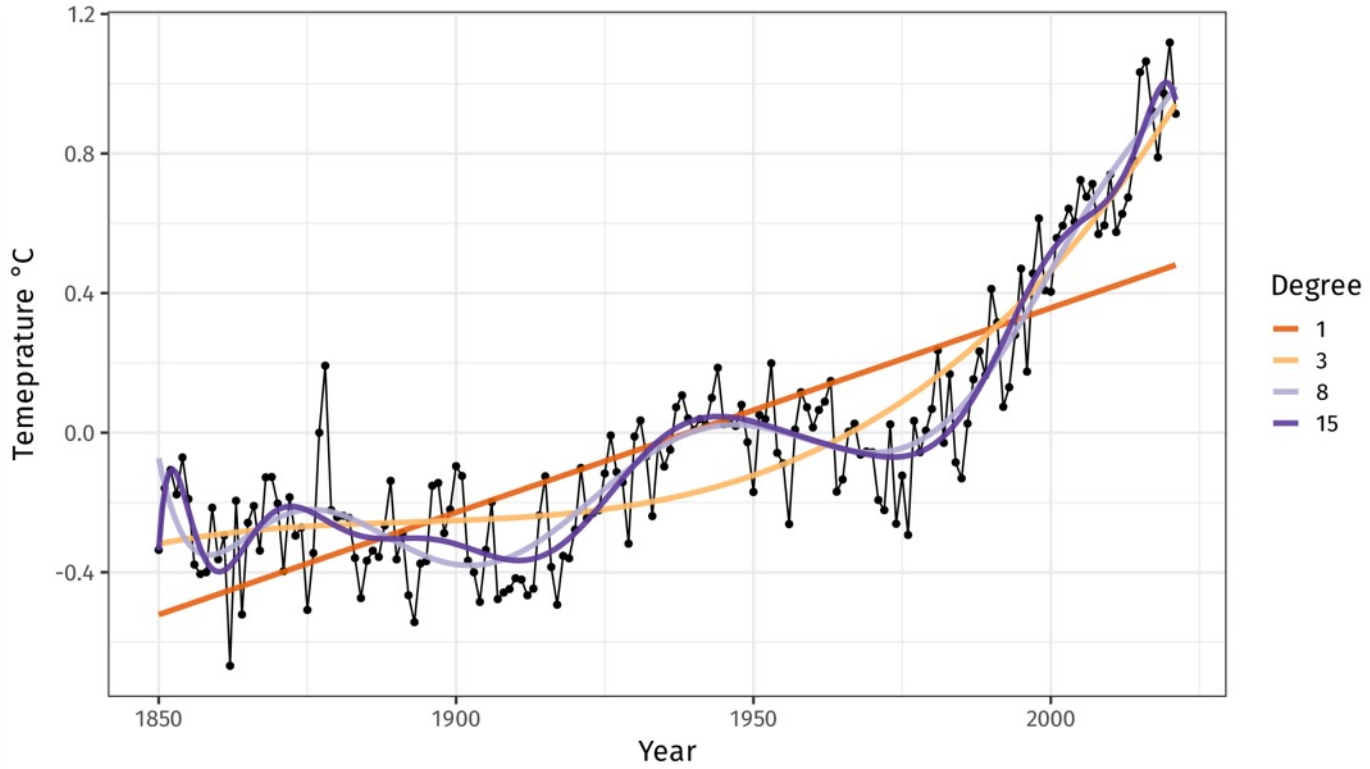
Is this linear?



Study Design

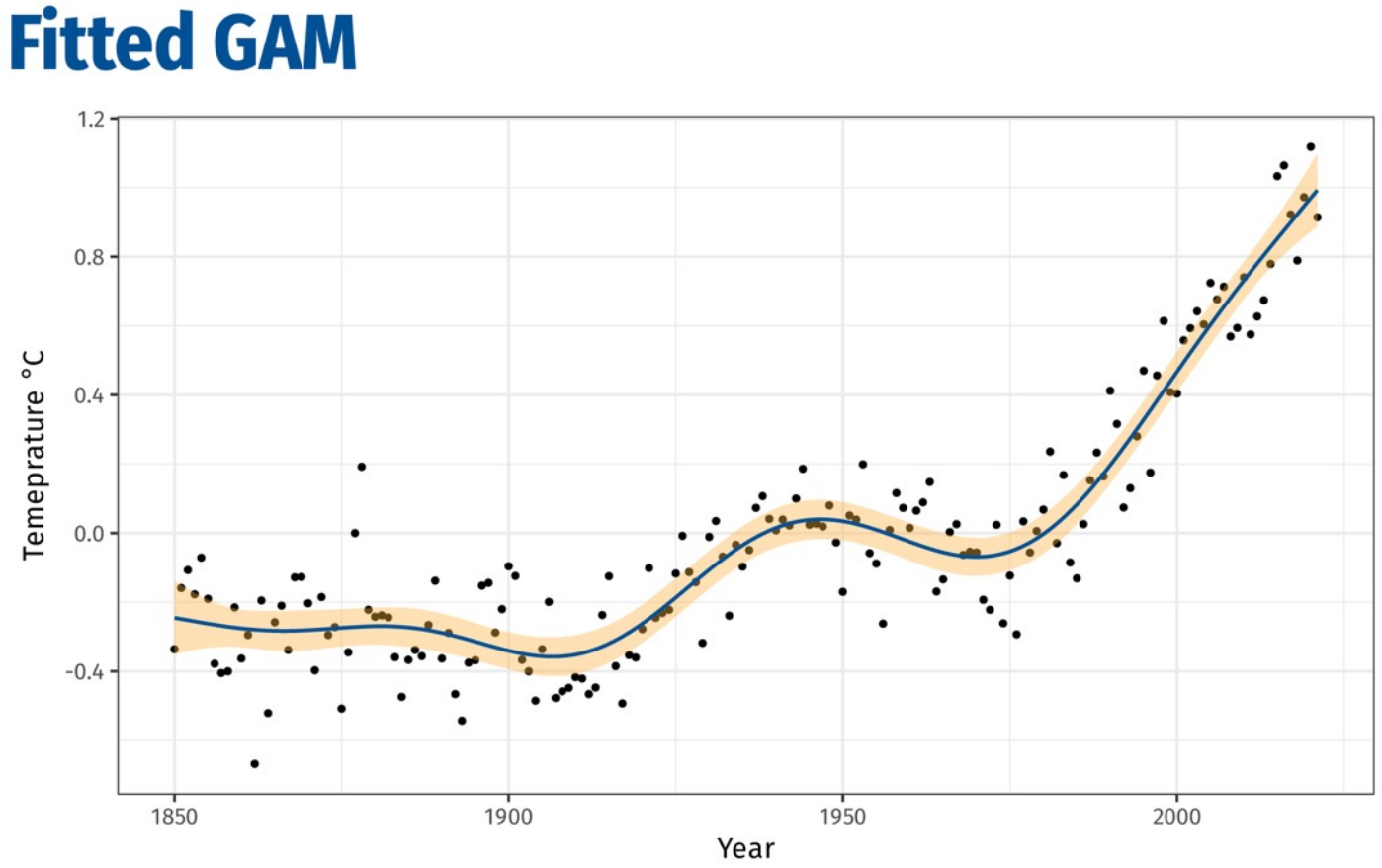
Generalized Additive Models (GAMs)

Polynomials perhaps...



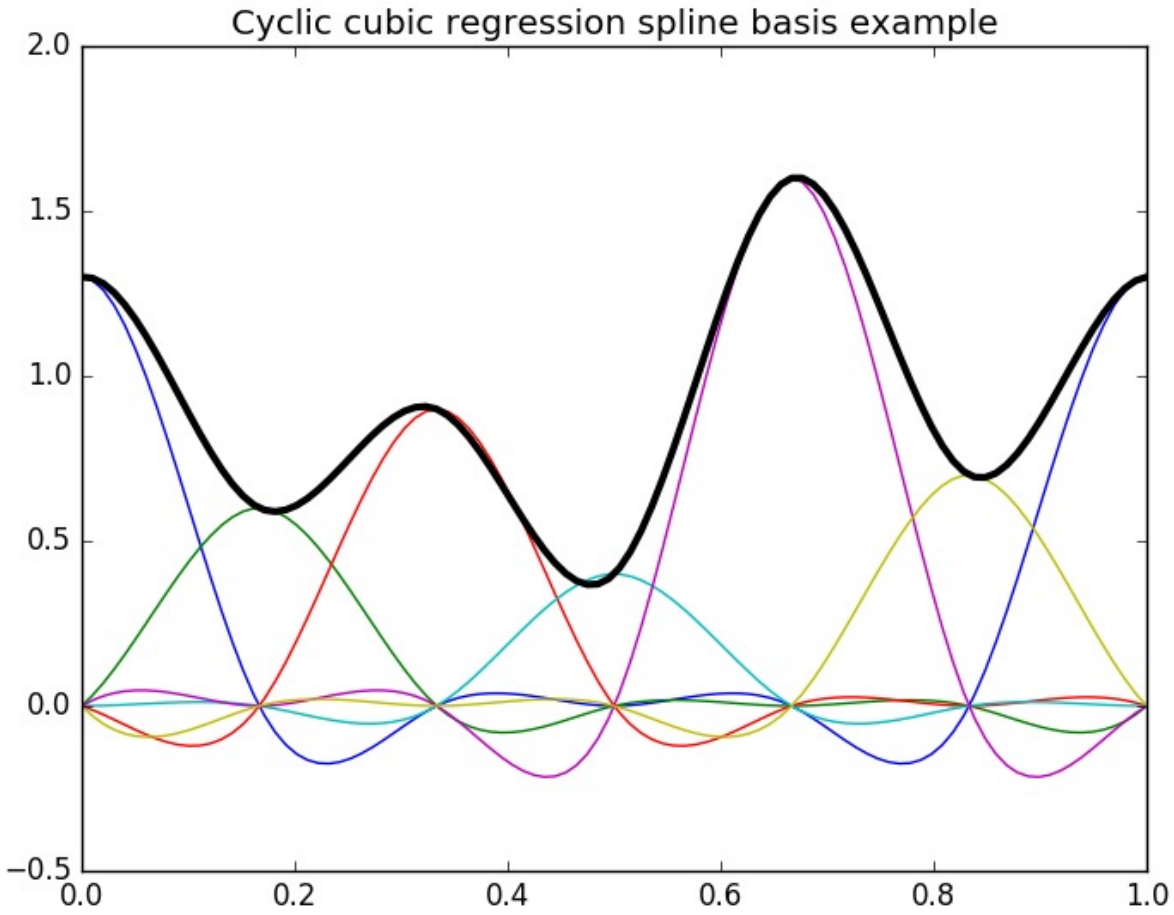
Study Design

Generalized Additive Models (GAMs)



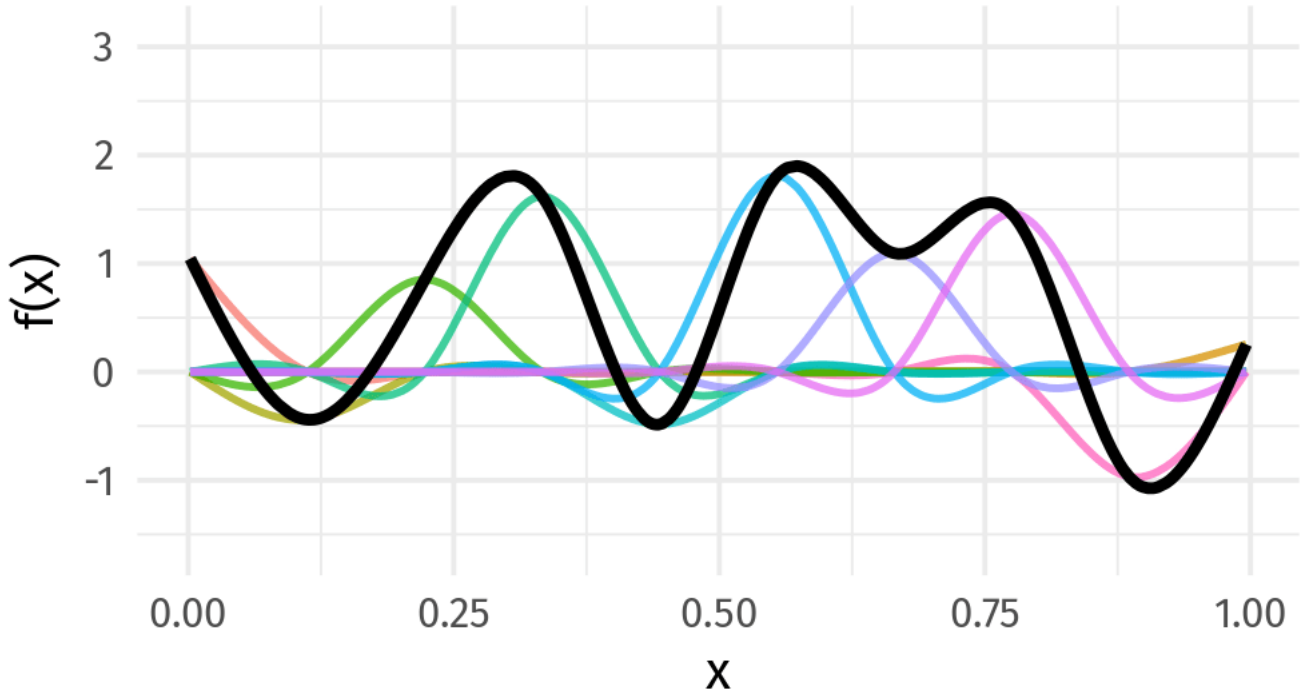
Study Design

Generalized Additive Models (GAMs)



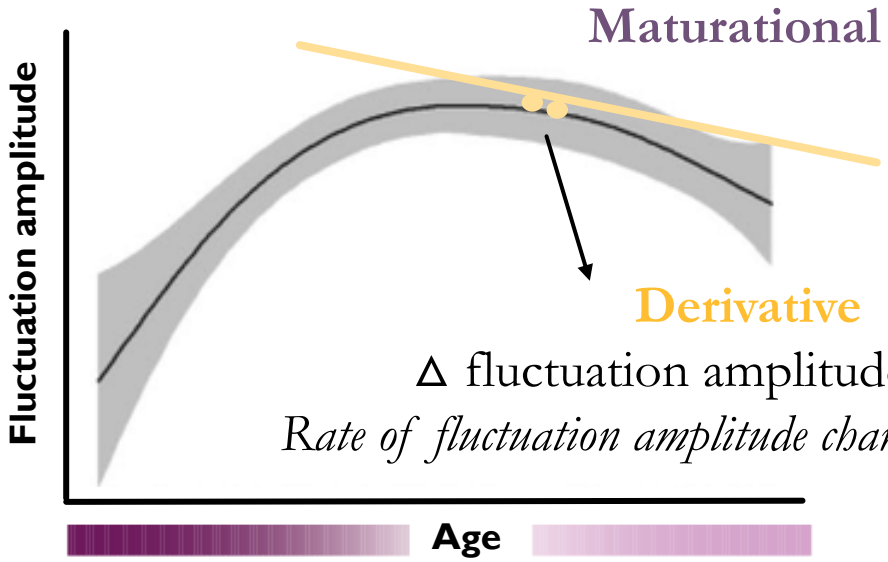
Study Design

Generalized Additive Models (GAMs)

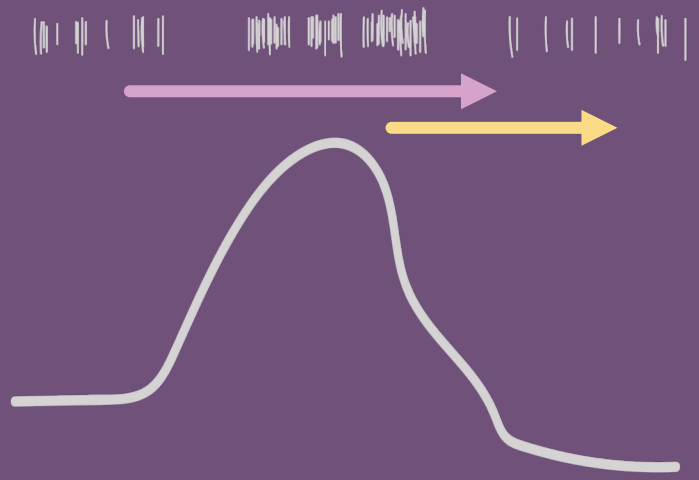


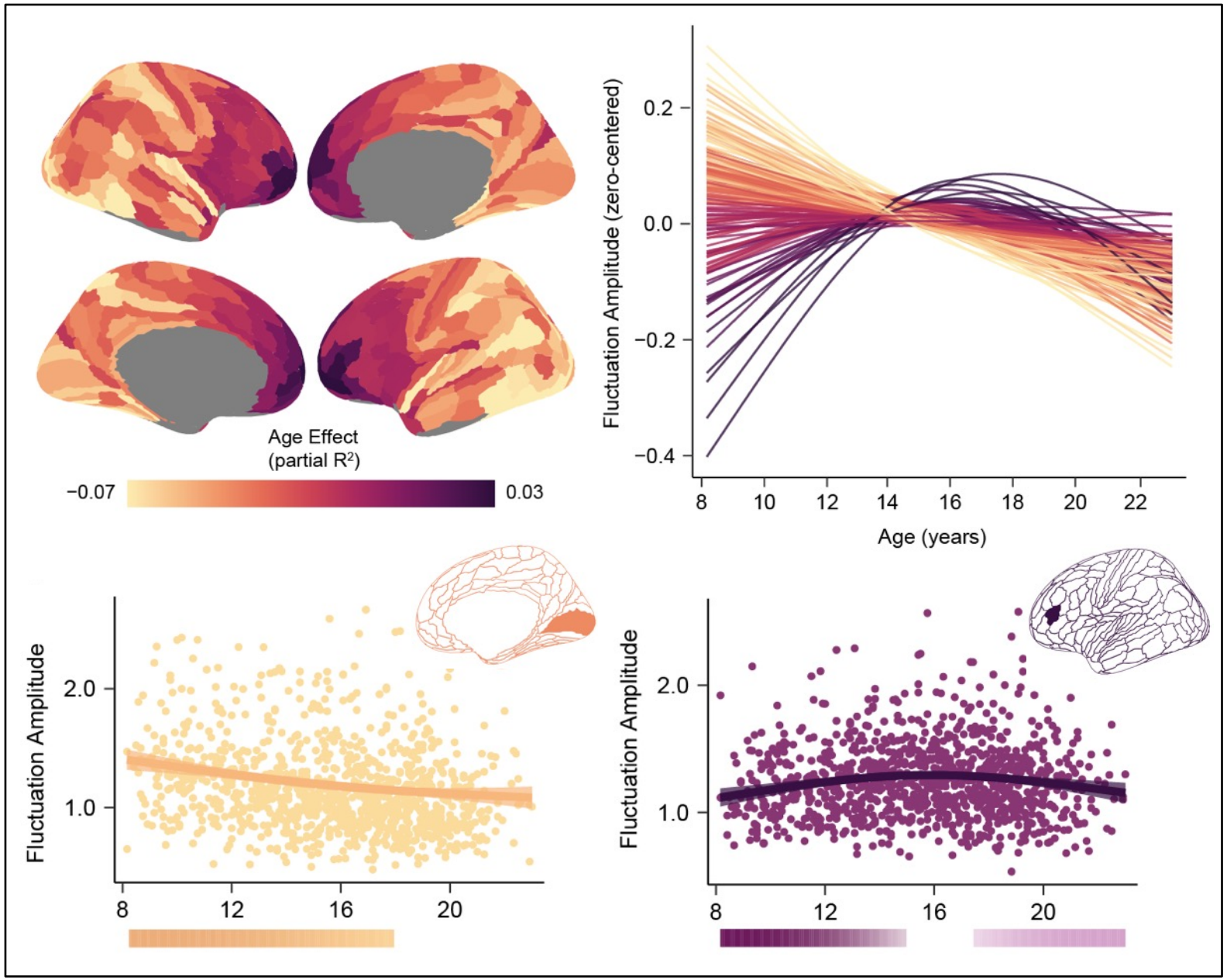
Study Design

Generalized Additive Models (GAMs)

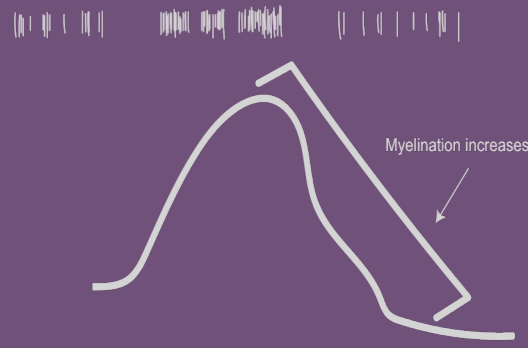


Fluctuation Amplitude Development Varies Across the Cortex

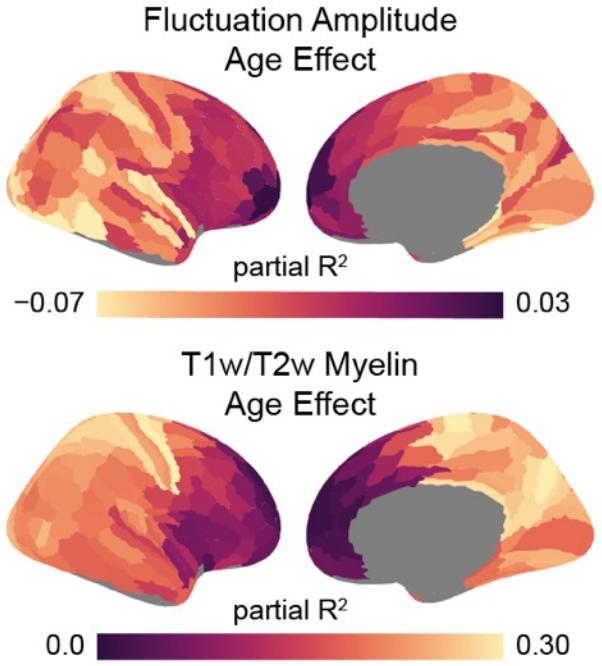


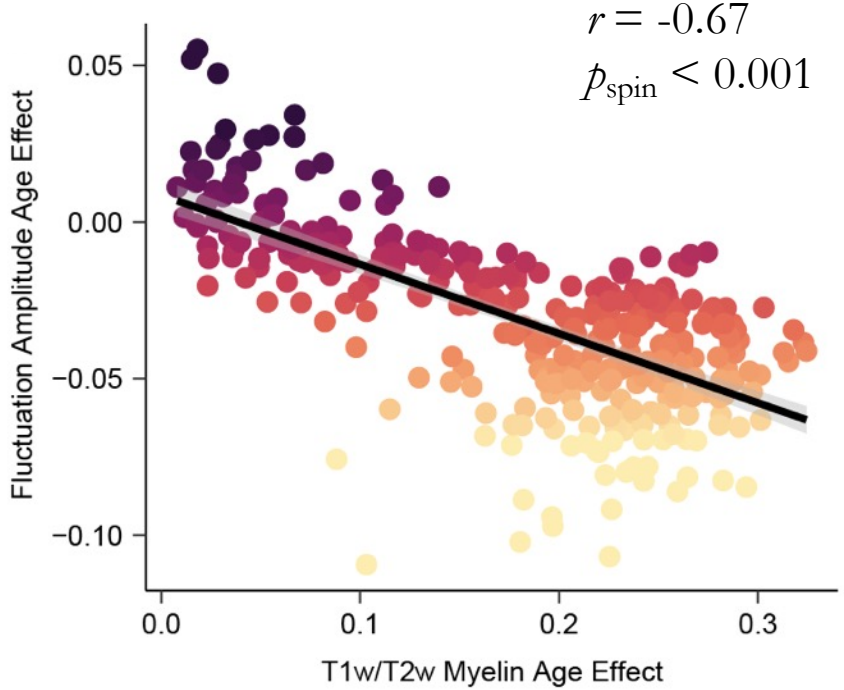


Fluctuation Amplitude Development Parallels Myelin Maturation



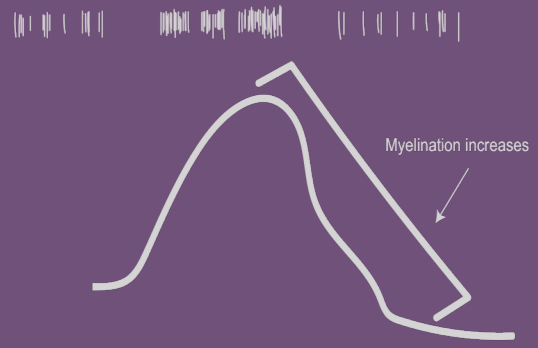
Larger increases in myelin content were associated with larger decreases in BOLD fluctuation amplitude



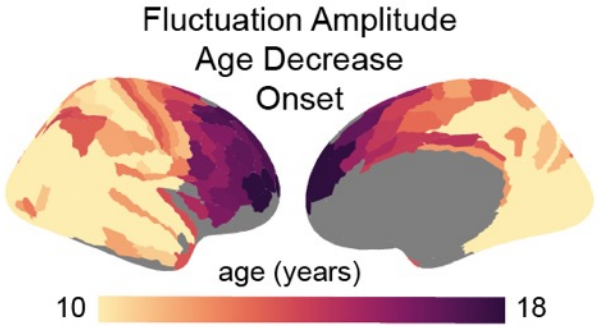


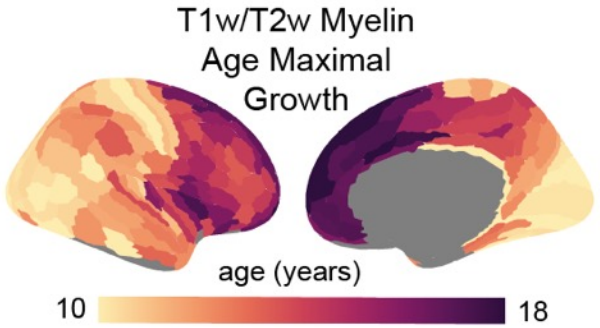
T1w/T2w data from Baum et al., 2022

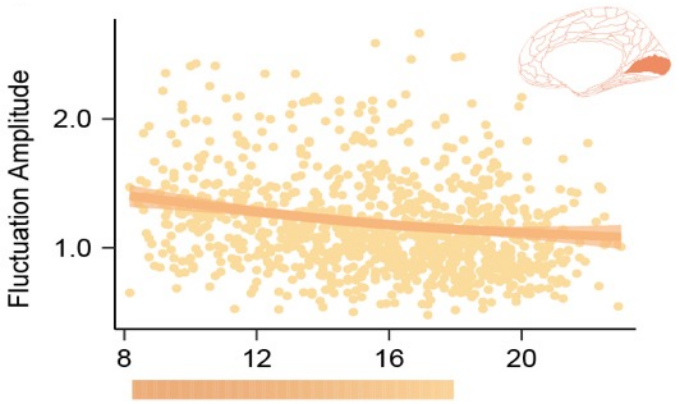
Fluctuation Amplitude Development Parallels Myelin Maturation

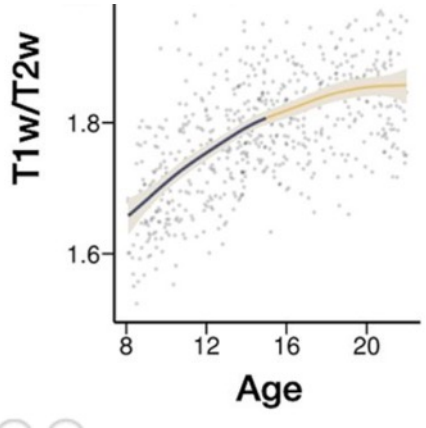


Later increases in myelin content were associated with later decreases in BOLD fluctuation amplitude



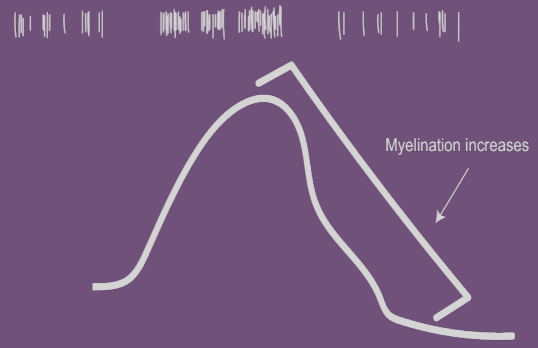




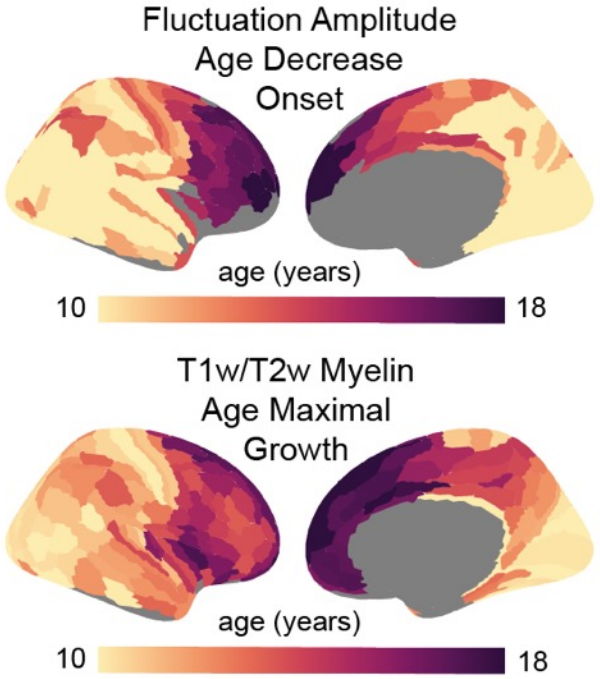


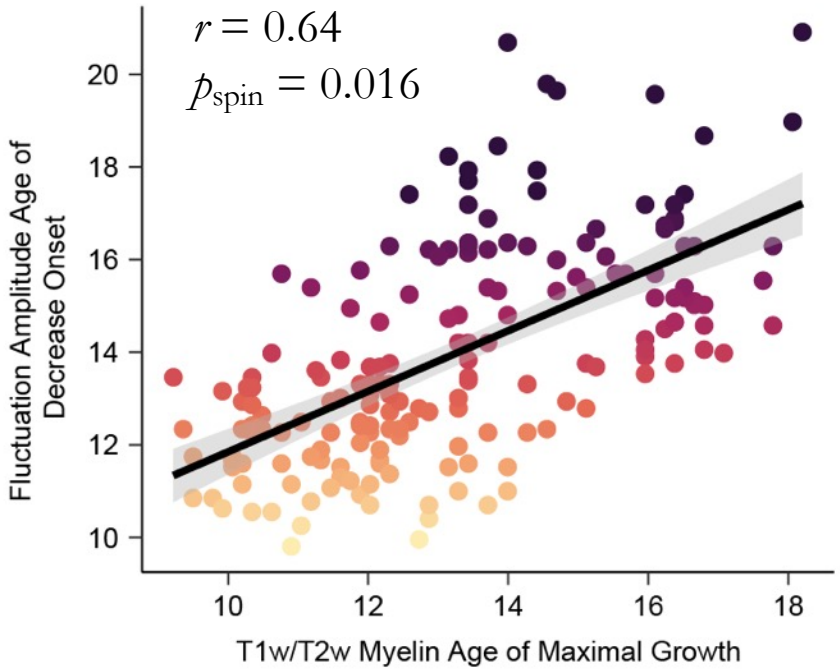
T1w/T2w data from Baum et al., 2022

Fluctuation Amplitude Development Parallels Myelin Maturation



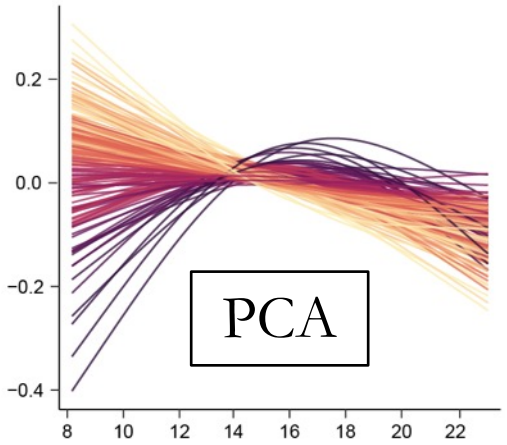
Later increases in myelin content were associated with later decreases in BOLD fluctuation amplitude





T1w/T2w data from Baum et al., 2022

The Principal Developmental Axis is Sensorimotor to Associative



87% of variance

Filter Cols: « < 1 - 50 > »

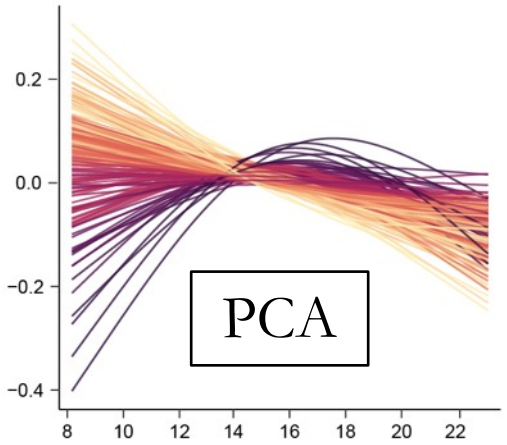
	rh_R_V1	rh_R_MST	rh_R_V6	rh_R_V2	rh_R_V3	rh_R_V4	rh_R_V8	rh_R_4
1	2.033030e−01	0.1179170186	0.0985694235	0.1780745959	1.970712e−01	0.2095216127	0.1607135694	0.1191682380
2	2.008926e−01	0.1166356797	0.0971965841	0.1759761476	1.948175e−01	0.2071876924	0.1588626685	0.1181422875
3	1.984822e−01	0.1153543466	0.0958237649	0.1738777163	1.925638e−01	0.2048537854	0.1570117807	0.1171163292
4	1.960719e−01	0.1140730251	0.0944509860	0.1717793190	1.903102e−01	0.2025199047	0.1551609193	0.1160903553
5	1.936616e−01	0.1127917212	0.0930782684	0.1696809737	1.880566e−01	0.2001860641	0.1533100981	0.1150643578
6	1.912515e−01	0.1115104439	0.0917056432	0.1675827064	1.858030e−01	0.1978522841	0.1514593374	0.1140383244
7	1.888414e−01	0.1102292064	0.0903331567	0.1654845565	1.835496e−01	0.1955185949	0.1496086676	0.1130122374
8	1.864316e−01	0.1089480263	0.0889608697	0.1633865752	1.812963e−01	0.1931850363	0.1477581284	0.1119860733
9	1.840220e−01	0.1076669250	0.0875888567	0.1612888255	1.790432e−01	0.1908516570	0.1459077686	0.1109598032
10	1.816128e−01	0.1063859275	0.0862172052	0.1591913816	1.767904e−01	0.1885185145	0.1440576457	0.1099333933
11	1.792041e−01	0.1051050629	0.0848460155	0.1570943281	1.745380e−01	0.1861856742	0.1422078251	0.1089068048
12	1.767960e−01	0.1038243631	0.0834753997	0.1549977598	1.722860e−01	0.1838532096	0.1403583804	0.1078799944
13	1.743885e−01	0.1025438635	0.0821054799	0.1529017800	1.700345e−01	0.1815212008	0.1385093915	0.1068529148
14	1.719819e−01	0.1012635999	0.0807363815	0.1508064949	1.677836e−01	0.1791897297	0.1366609407	0.1058255175
15	1.695762e−01	0.0999836106	0.0793682370	0.1487120162	1.655335e−01	0.1768588832	0.1348131145	0.1047977513
16	1.671716e−01	0.0987039362	0.0780011882	0.1466184639	1.632842e−01	0.1745287539	0.1329660059	0.1037695613

Regions (n = 336)

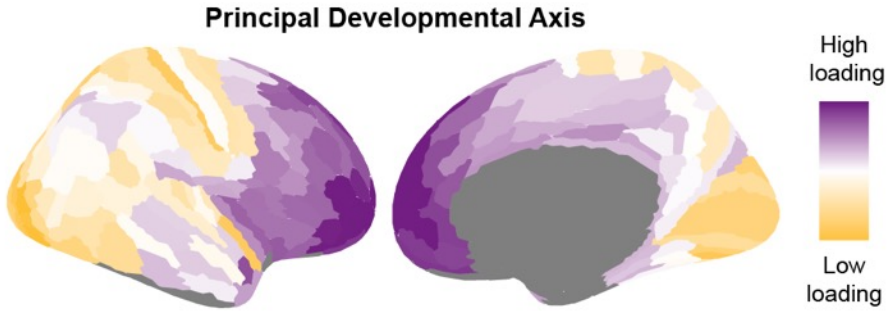
Age
n = 200

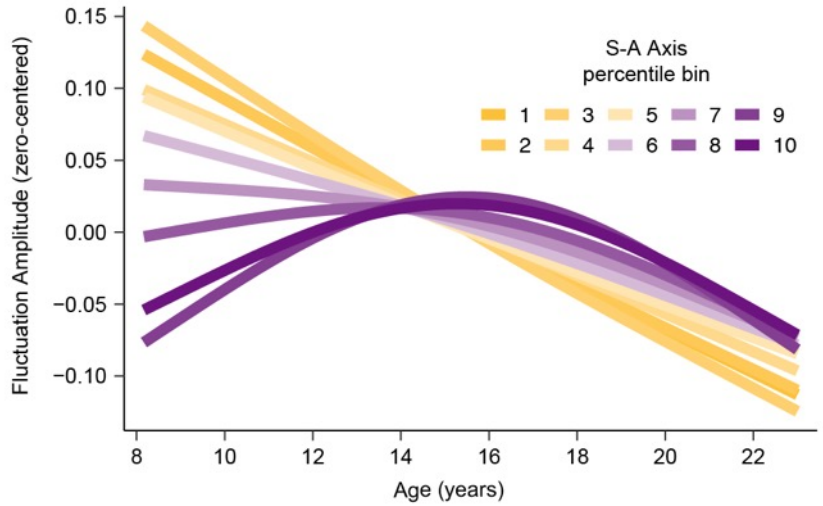
Loadings (regions)
Scores (ages)

The Principal Developmental Axis is Sensorimotor to Associative

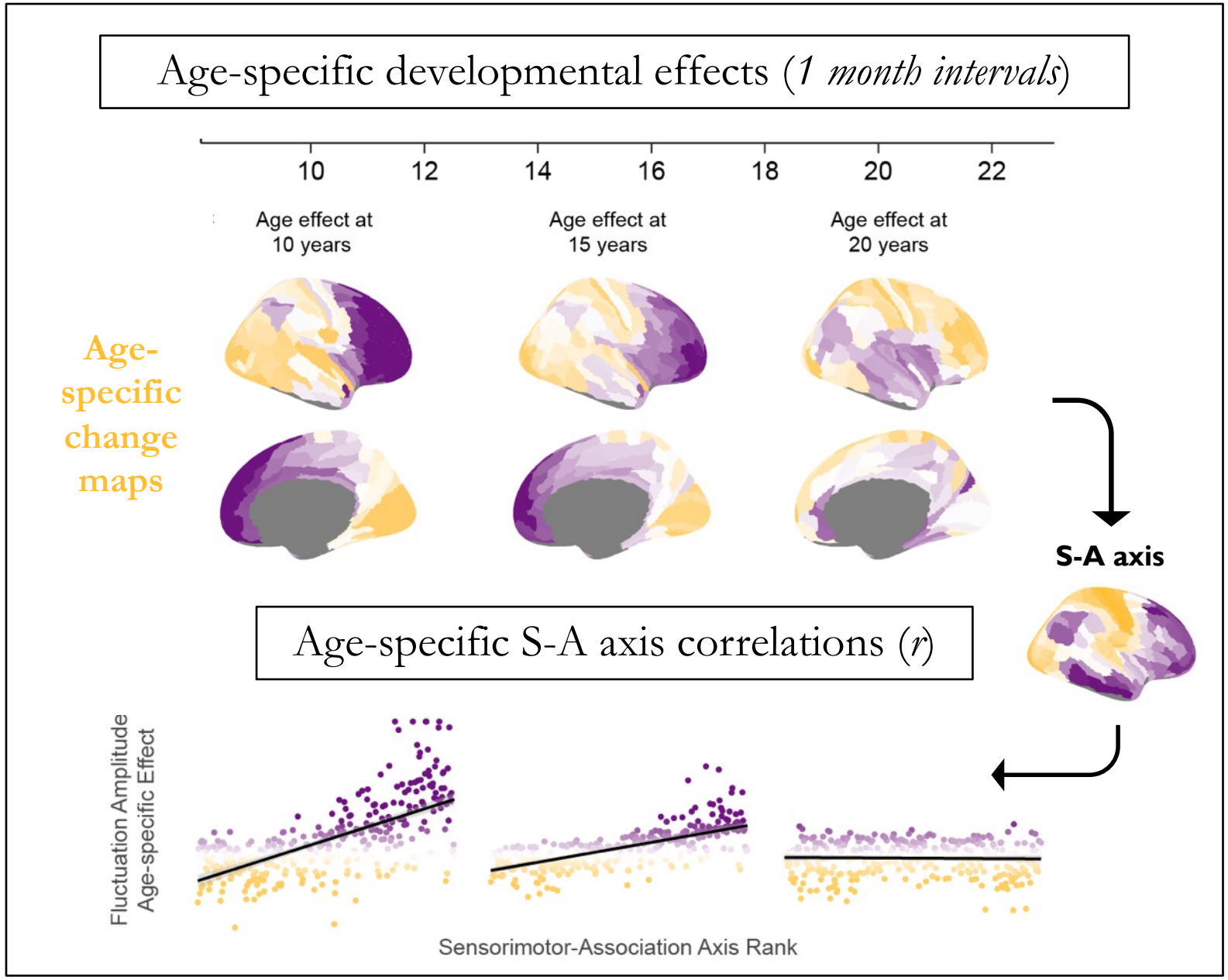


87% of variance

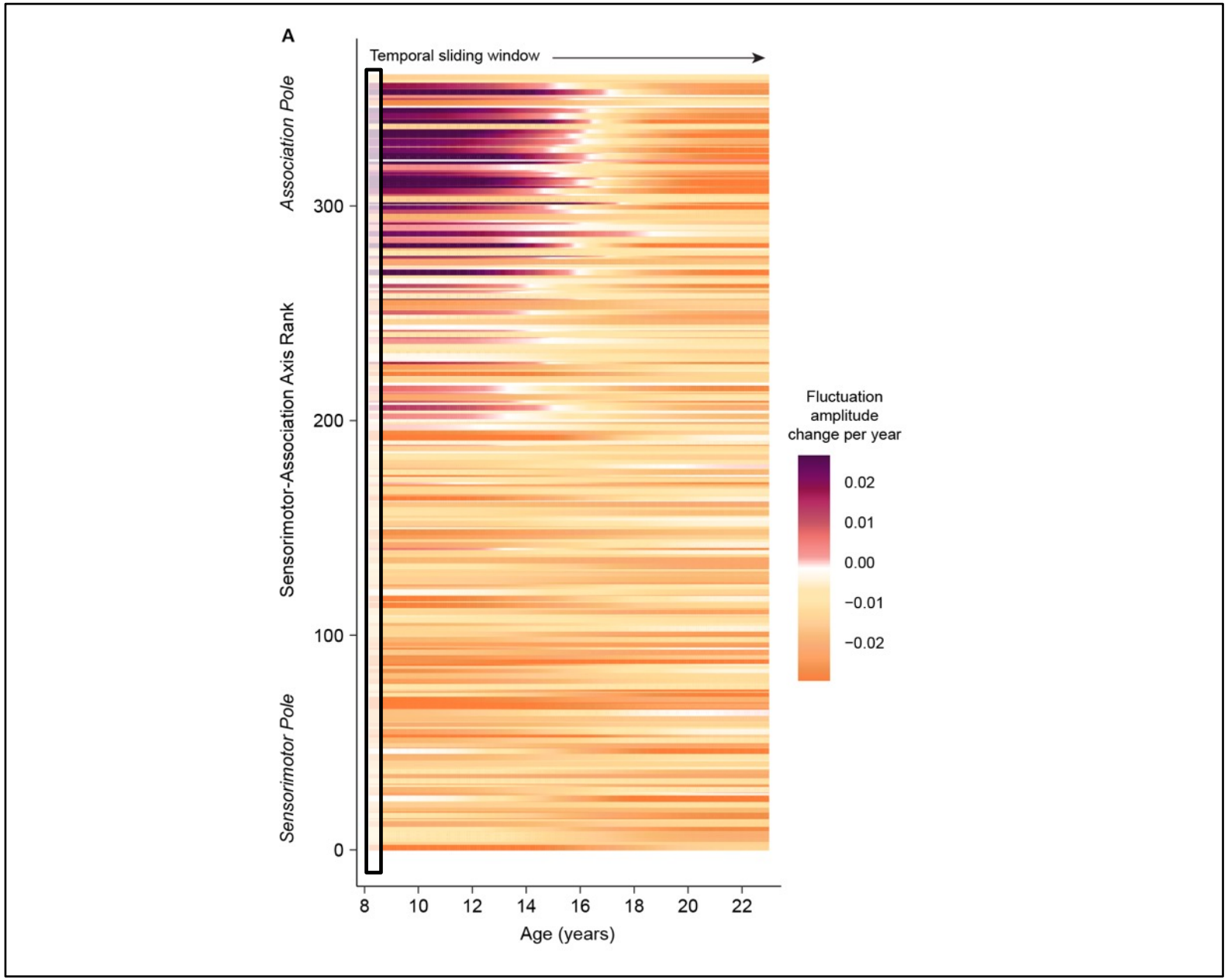




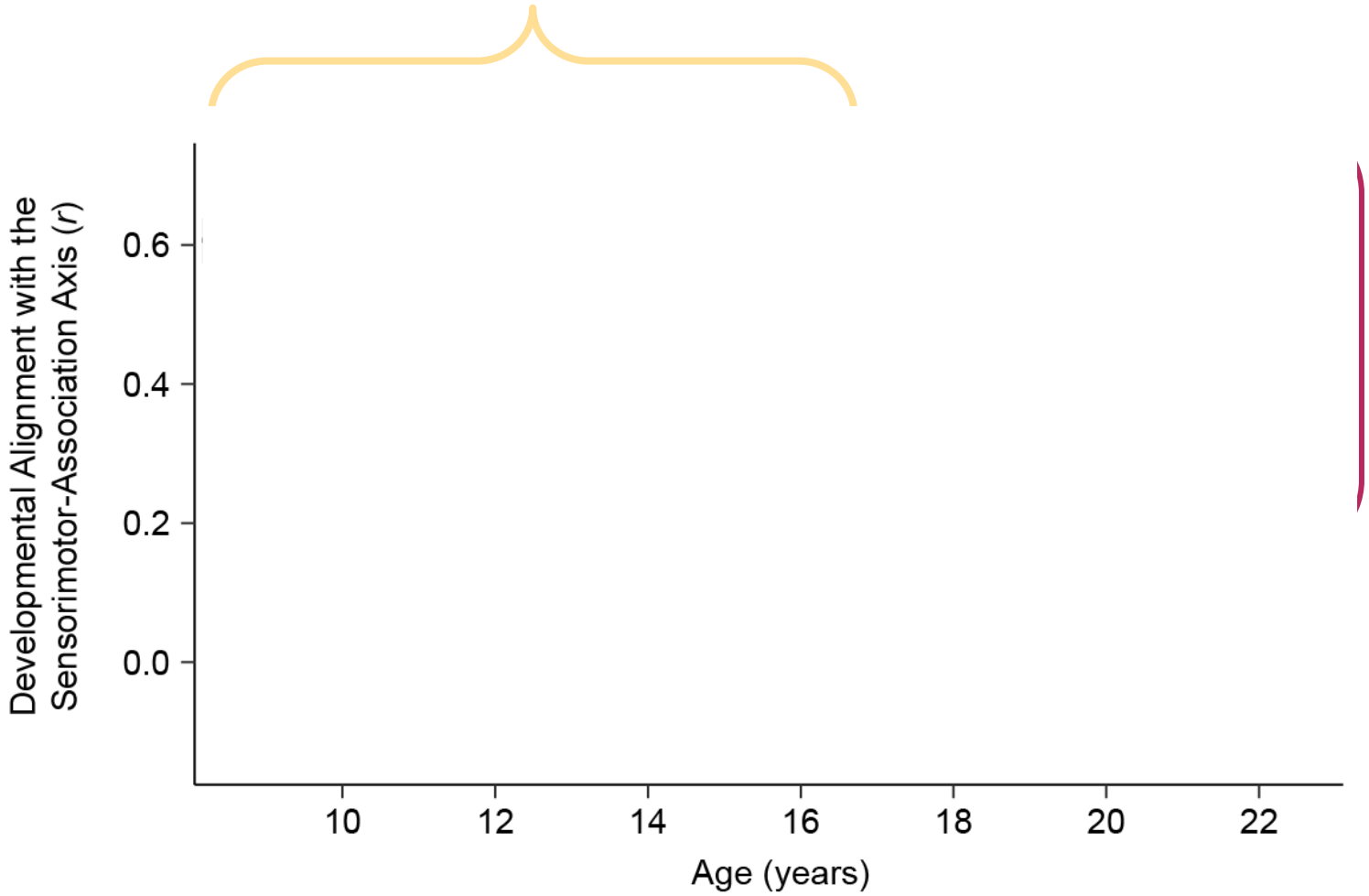
Development Aligns with the S-A Axis through Adolescence



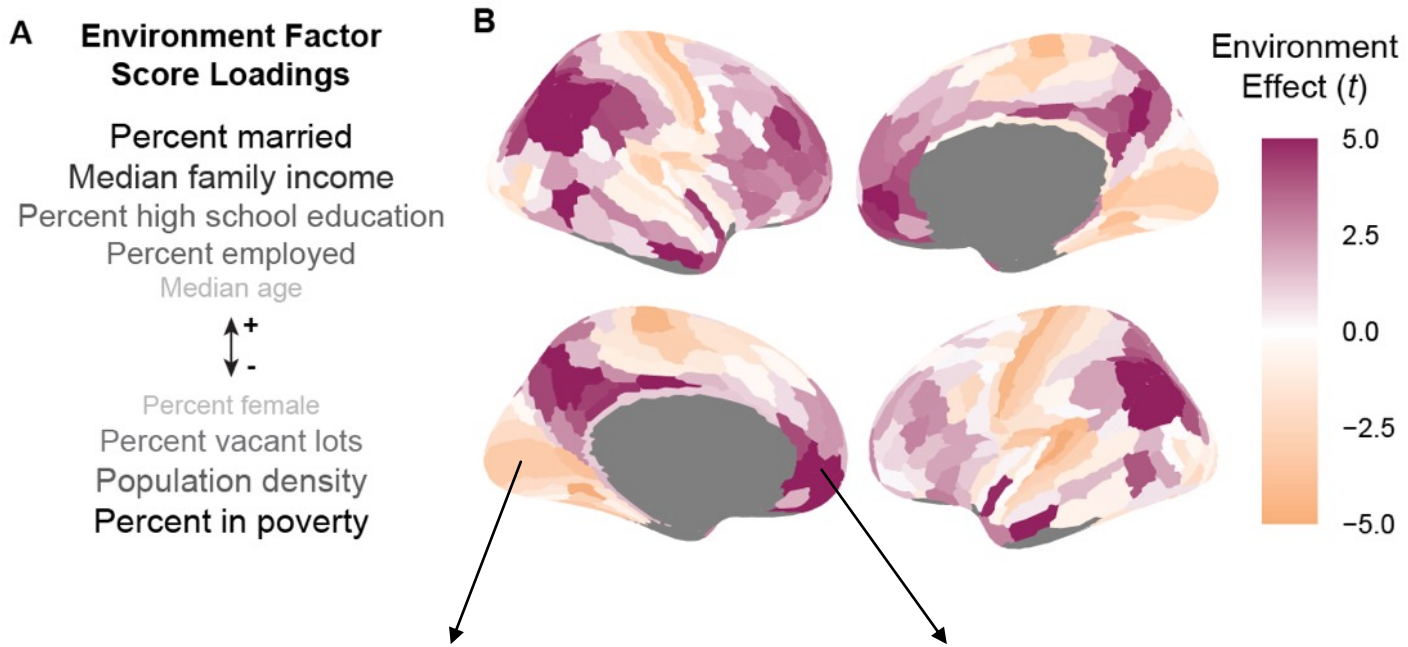
Development Aligns with the S-A Axis through Adolescence



Development Aligns with the S-A Axis through Adolescence



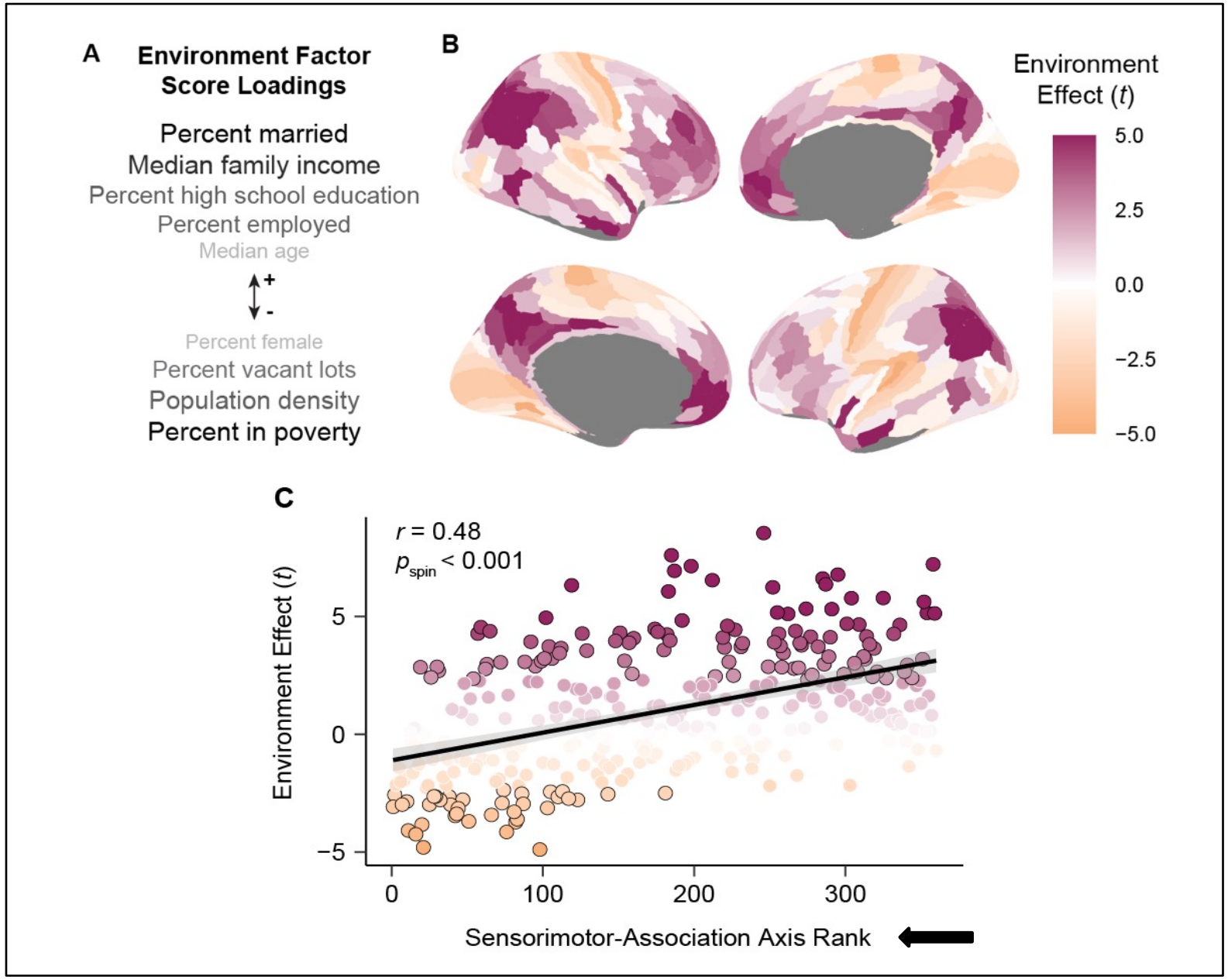
Environmental Effects on Cortical Spontaneous Activity



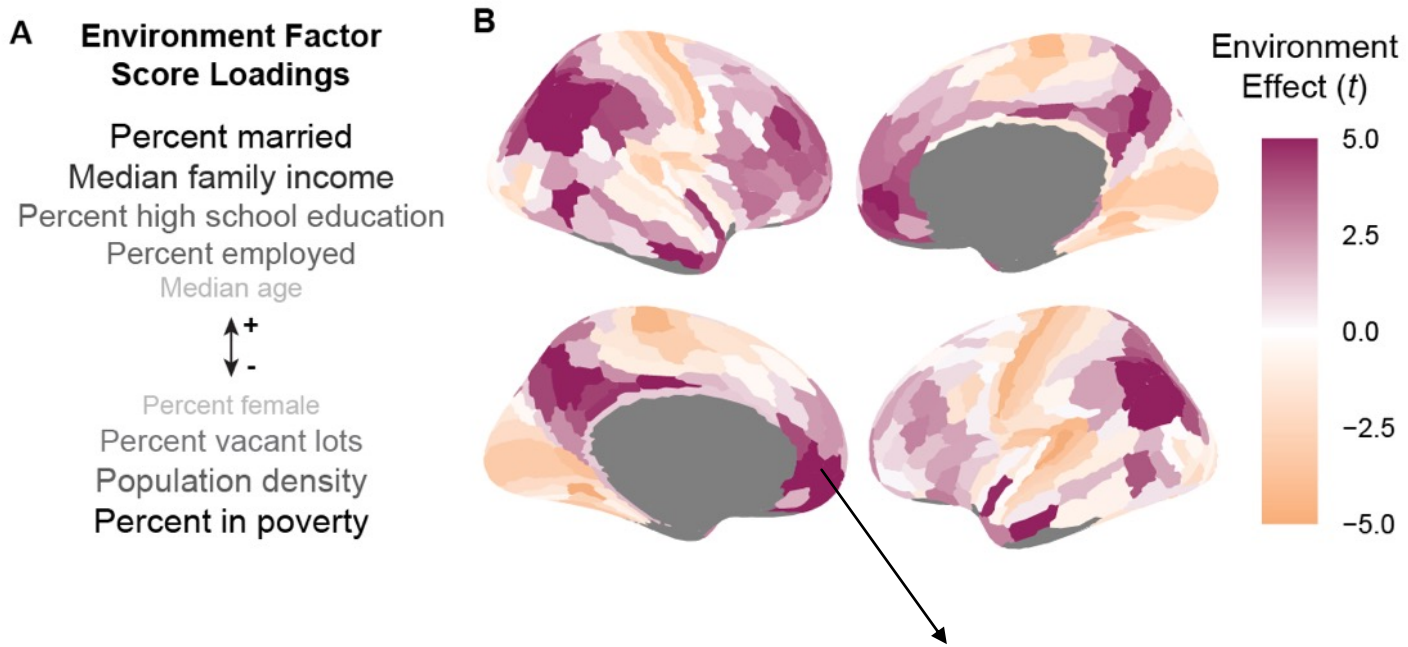
Lower factor scores, higher fluctuation amplitude

Lower factor scores, lower fluctuation amplitude

Environmental Effects on Cortical Spontaneous Activity



Environmental Effects on Cortical Spontaneous Activity

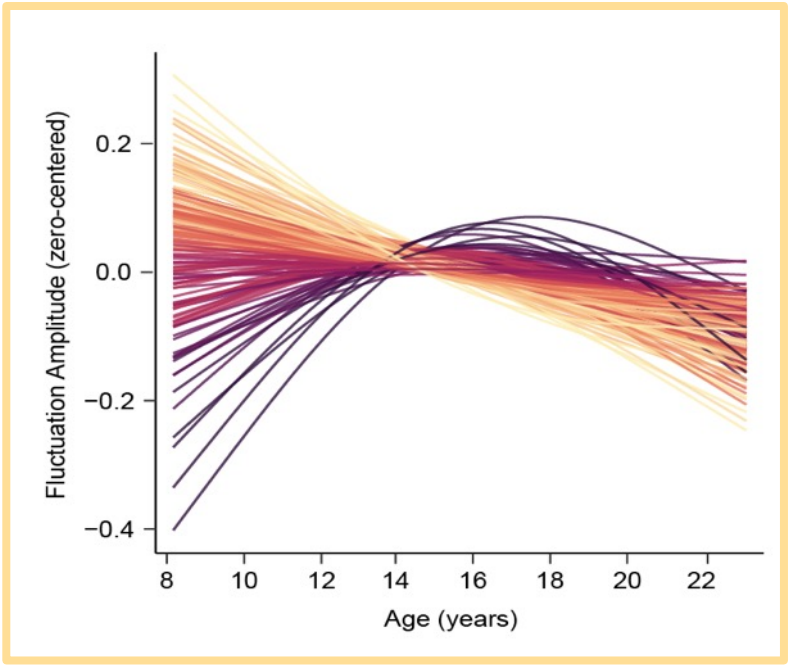


Lower factor scores, lower fluctuation amplitude

more mature cortex
a reduced potential for plasticity
accelerated development

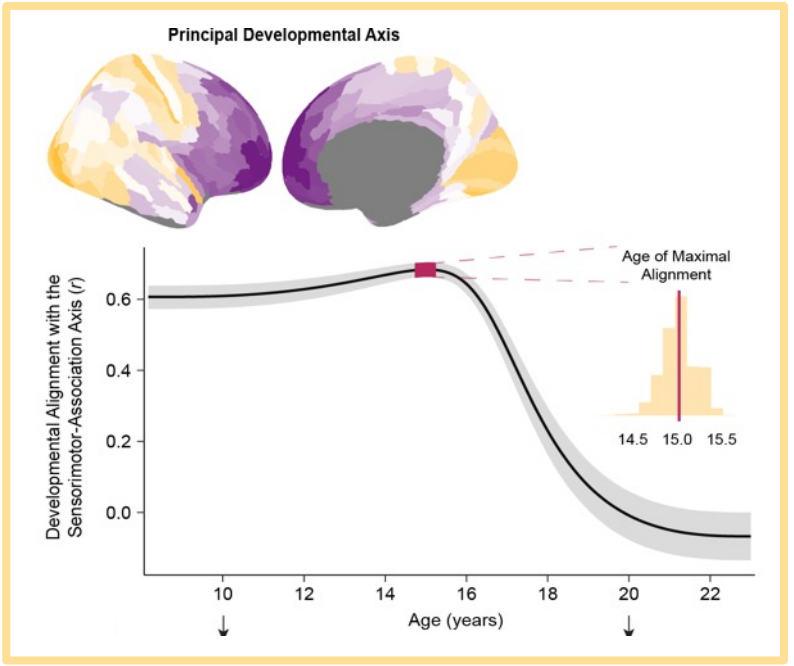
Study Conclusions

- A non-invasive functional marker of activity-indexed plasticity heterochronously declines across the cortex during childhood and adolescence



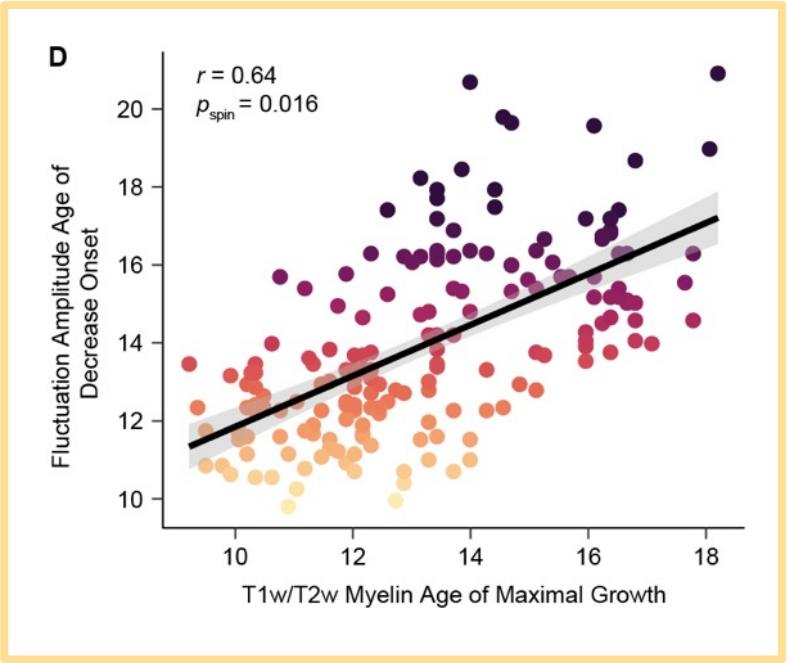
Study Conclusions

- A non-invasive functional marker of activity-indexed plasticity heterochronously declines across the cortex during childhood and adolescence
- Variance in developmental trajectories can be parsimoniously explained by the S-A axis until the end of adolescence



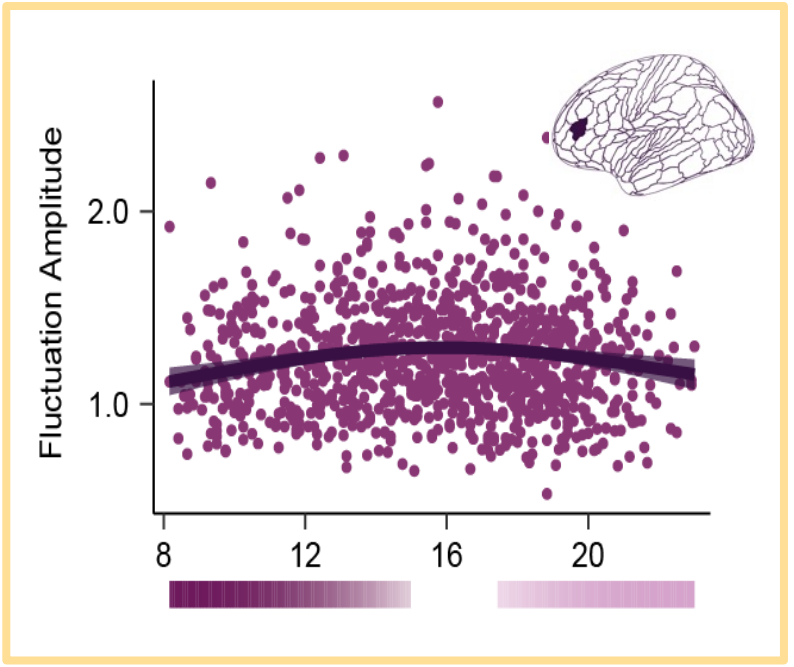
Study Conclusions

- A non-invasive functional marker of activity-indexed plasticity heterochronously declines across the cortex during childhood and adolescence
- Variance in developmental trajectories is parsimoniously explained by the S-A axis
- Reductions in plasticity are patterned hierarchically across the cortex



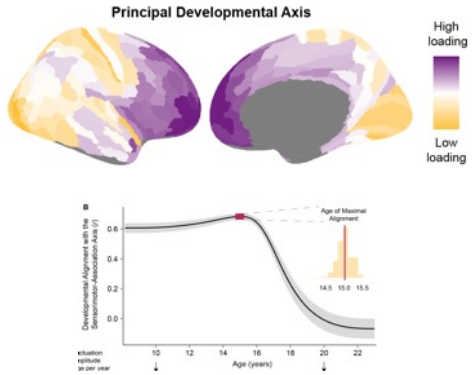
Study Conclusions

- A non-invasive functional marker of activity-indexed plasticity heterochronously declines across the cortex during childhood and adolescence
- Variance in developmental trajectories is parsimoniously explained by the S-A axis
- Reductions in plasticity are patterned hierarchically across the cortex
- Adolescence may be a sensitive period for development of transmodal association cortex



Future Directions

PATTERNS

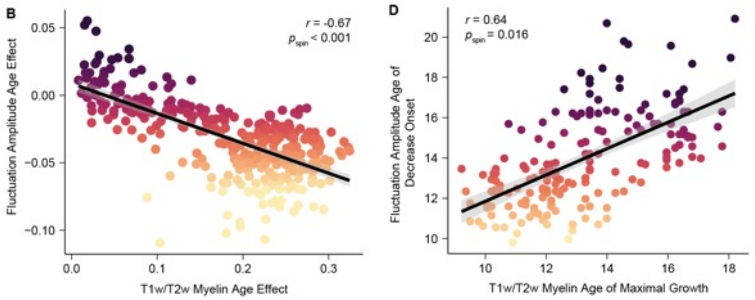


Developmental axes from infancy to adulthood

Subcortical developmental hierarchy

Alignment to gradients of patterning molecules and circadian genes

PLASTICITY

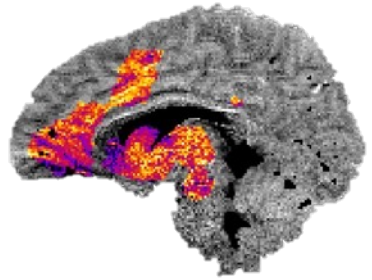


Neuroimaging of plasticity mechanisms

Sensitive periods (mechanisms and experiences)

Effect of interventions on plasticity-associated features

PSYCHO-PATHOLOGY



Studying psychiatric symptoms for a developmental plasticity perspective

Associations between developmental timing, psychiatric symptoms, and environment/experience