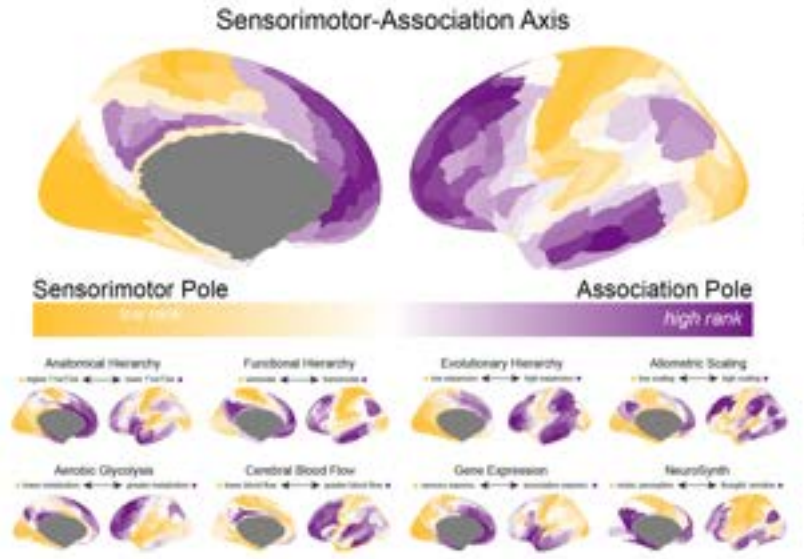
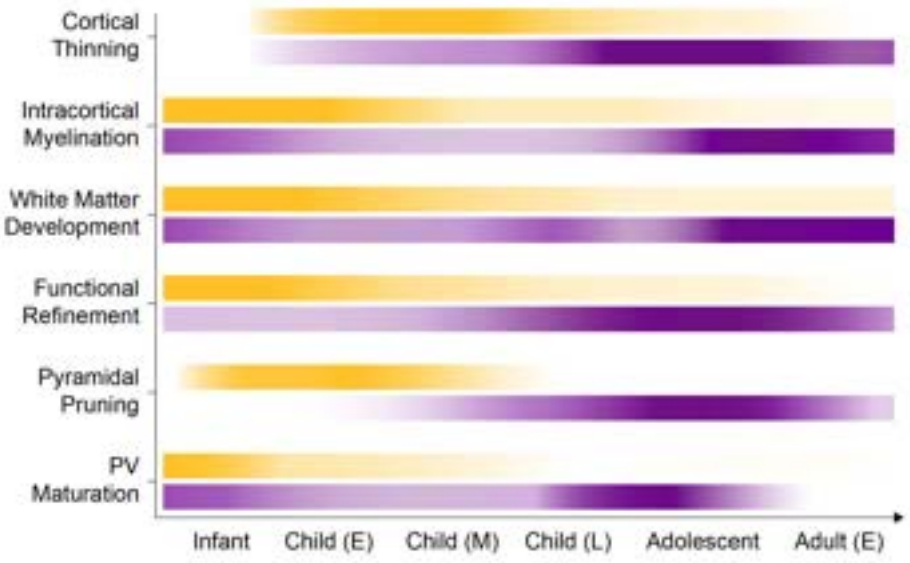
Neurodevelopment of the Association Cortices: Patterns, Mechanisms, and Implications for Psychopathology

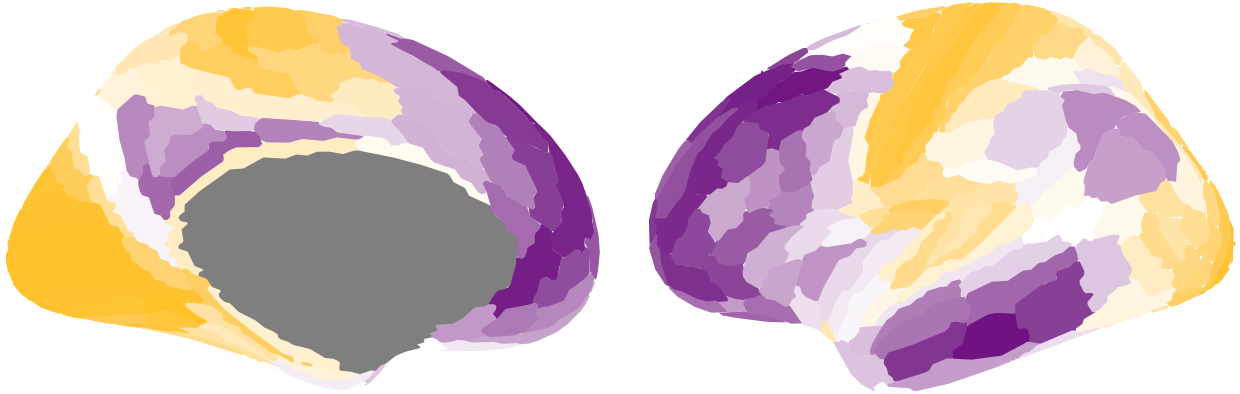




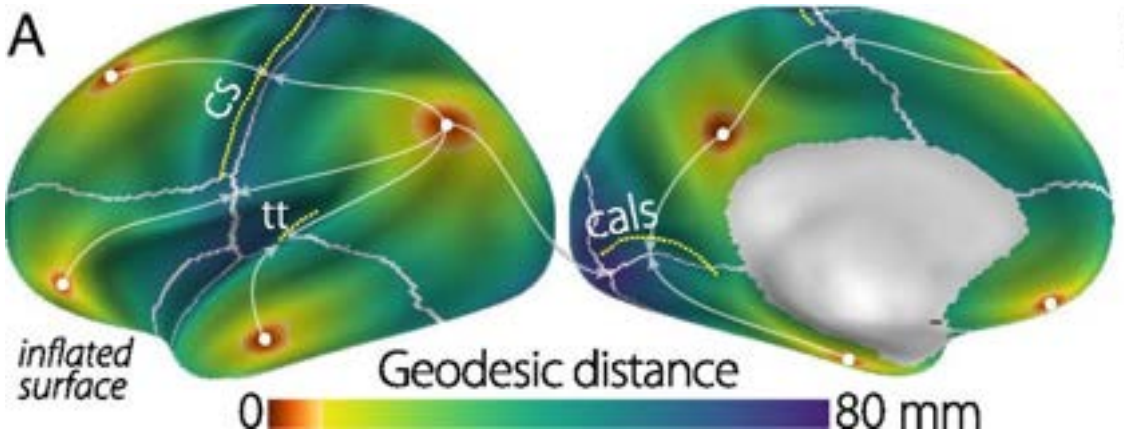
ASSOCIATION CORTICES

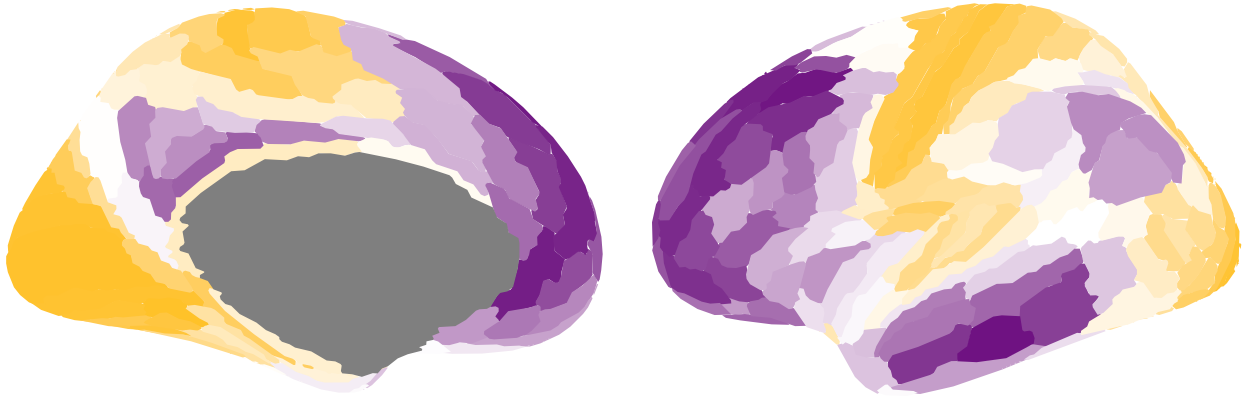
- Heterogeneous, wide-spanning areas of cortex
- Support social, emotional, mentalizing, and executive functions
- Markedly expanded in humans compared to other primates
- Exhibit protracted (multi-decade) development

- Most different in form and function from primary visual, auditory, motor, and somatosensory cortices



ASSOCIATION CORTICES





Margulies et al., 2016 PNAS

SENSORIMOTOR-ASSOCIATION AXIS

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

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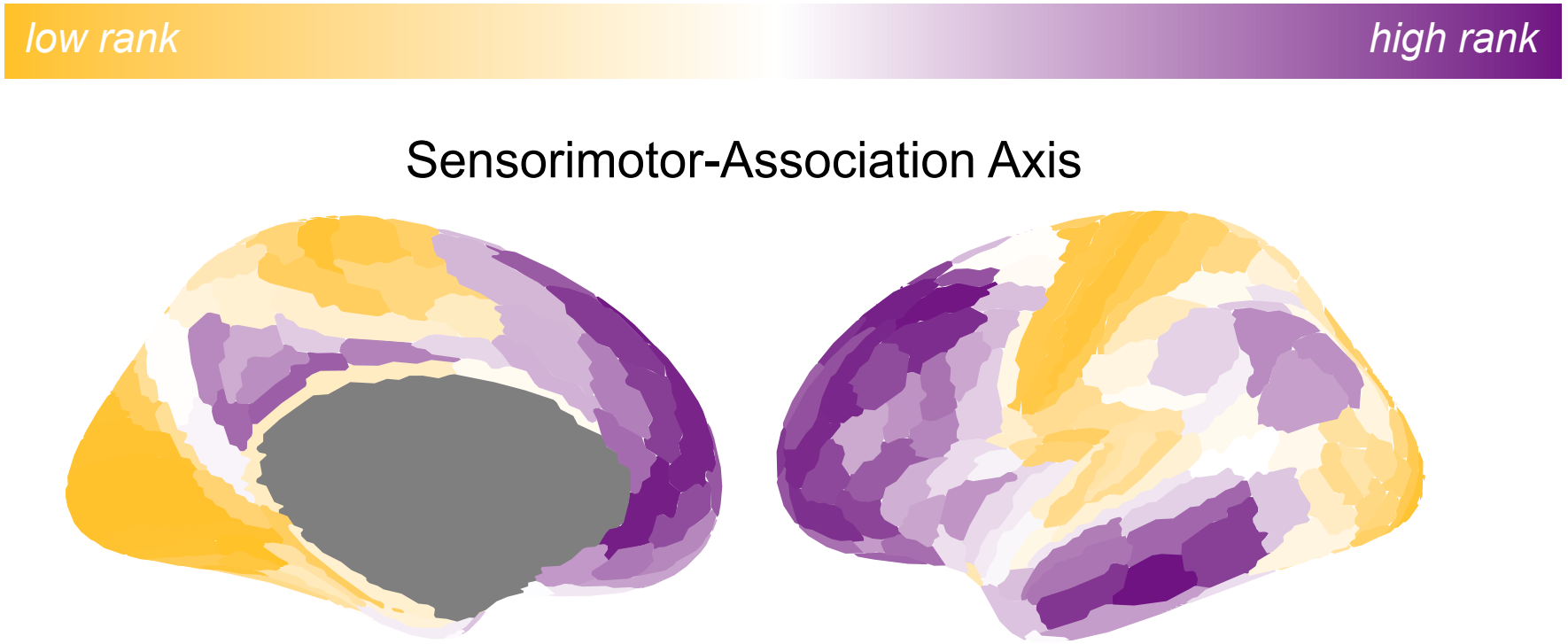
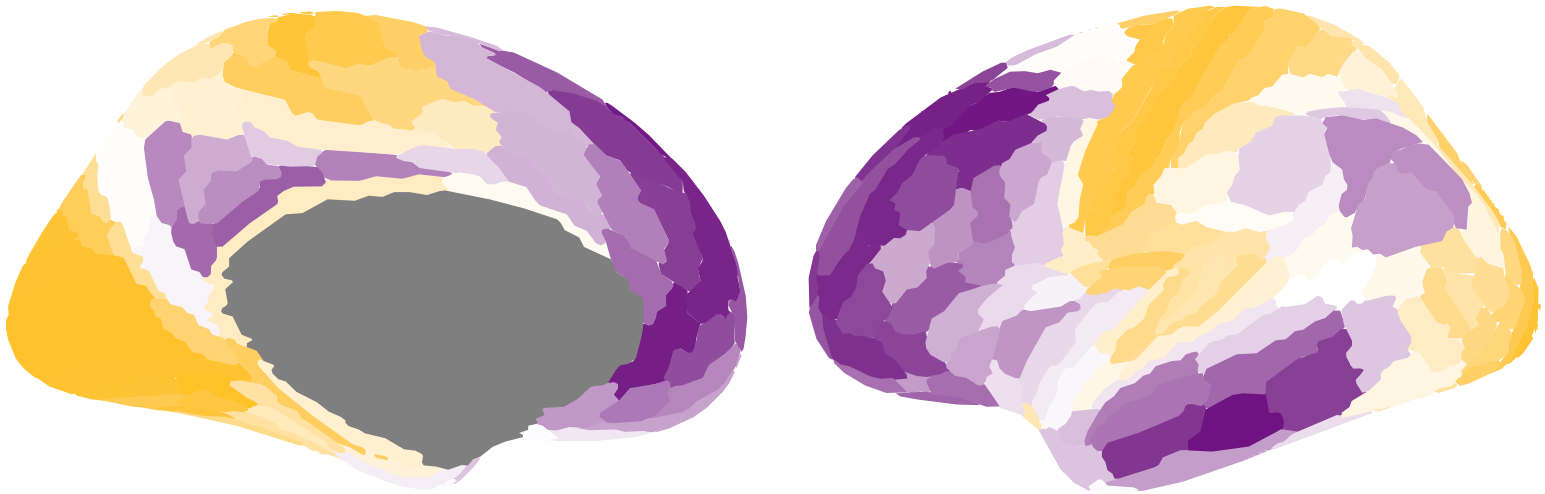


SENSORIMOTOR-ASSOCIATION AXIS

Primary axis of brain organization and development

low rank — *high rank*

Sensorimotor-Association Axis



- **The brains exhibits a dominant, hierarchical sensorimotor-to-association axis of cortical topography**

- Cortical maturation progresses along this axis from childhood to adulthood, as revealed by neuroimaging and underlied by the hierarchical unfolding of plasticity-related events

- This spatiotemporal pattern of brain development:
  - Enhances variation across the cortical mantle, refining association cortex features and functions
  - Contributes to heightened association cortex inter-individual variability
  - Informs about the emergence of transdiagnostic psychopathology and windows of intervention

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HIERARCHICAL CORTICAL TOPOGRAPHY

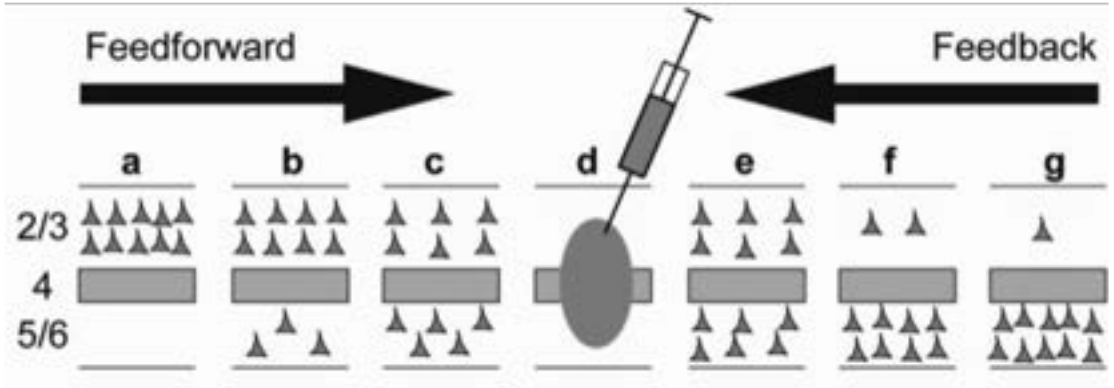
Cortical topography: the spatial distribution of functional areas across the cortical mantle

Investigations into cortical topography have revealed how the organization of the brain can be understood in terms of **anatomical, functional, and evolutionary cortical hierarchies**

HIERARCHICAL CORTICAL TOPOGRAPHY

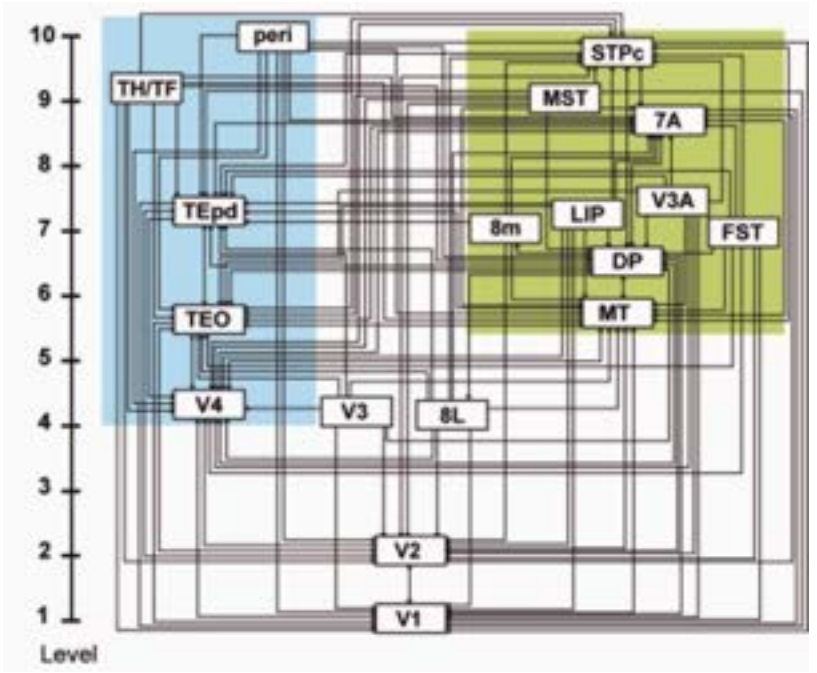
supragranular

infragranular



Markov et al., 2013

infragranular connections
distributed connectivity
feed-back

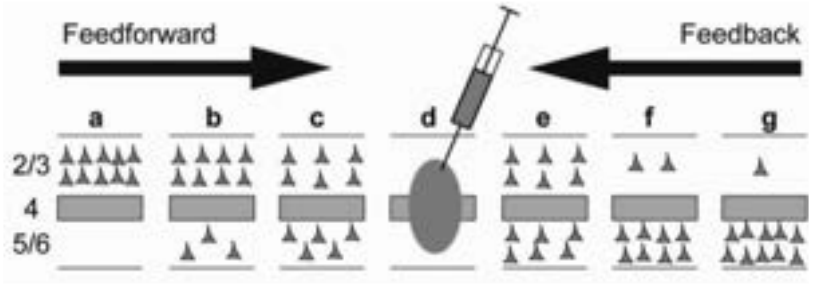


supragranular connections
local connectivity
feed-forward

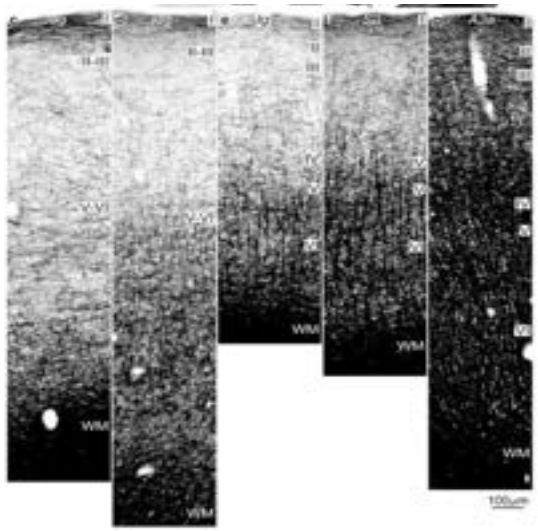
Pandya and Kuypers, 1969; Jones and Powell, 1970; Felleman and Van Essen, 1991

HIERARCHICAL CORTICAL TOPOGRAPHY

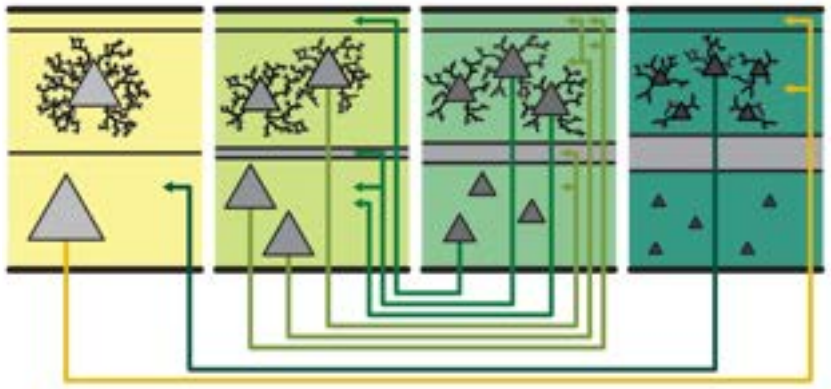
Variation in the laminar origins of connections aligns with variation in laminar structure & cytoarchitecture



Felleman and Van Essen, 1991; Markov et al., 2013



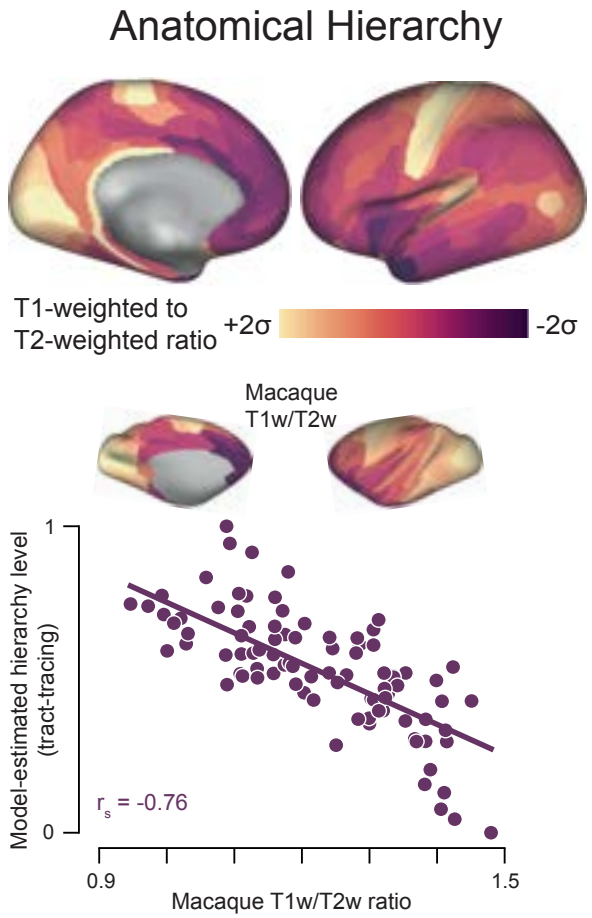
Garcia-Cabezas, Zikopoulos, Barbas, 2019



Hilgetag et al., 2019

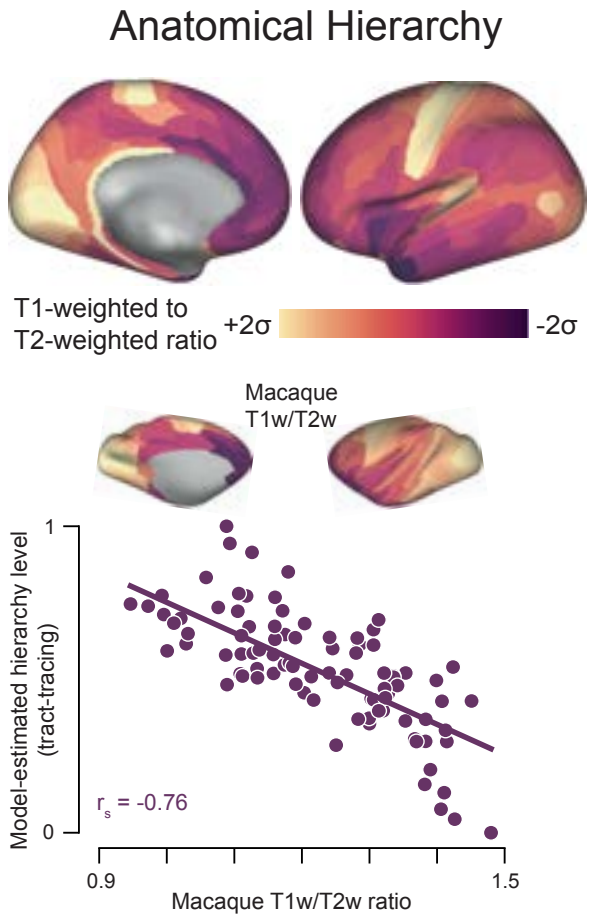
Links Sanides's graded variation, Mesulam's sensory-fugal hierarchy, Barbas's structural model, and Hilgetag's architectonic type principle

HIERARCHICAL CORTICAL TOPOGRAPHY

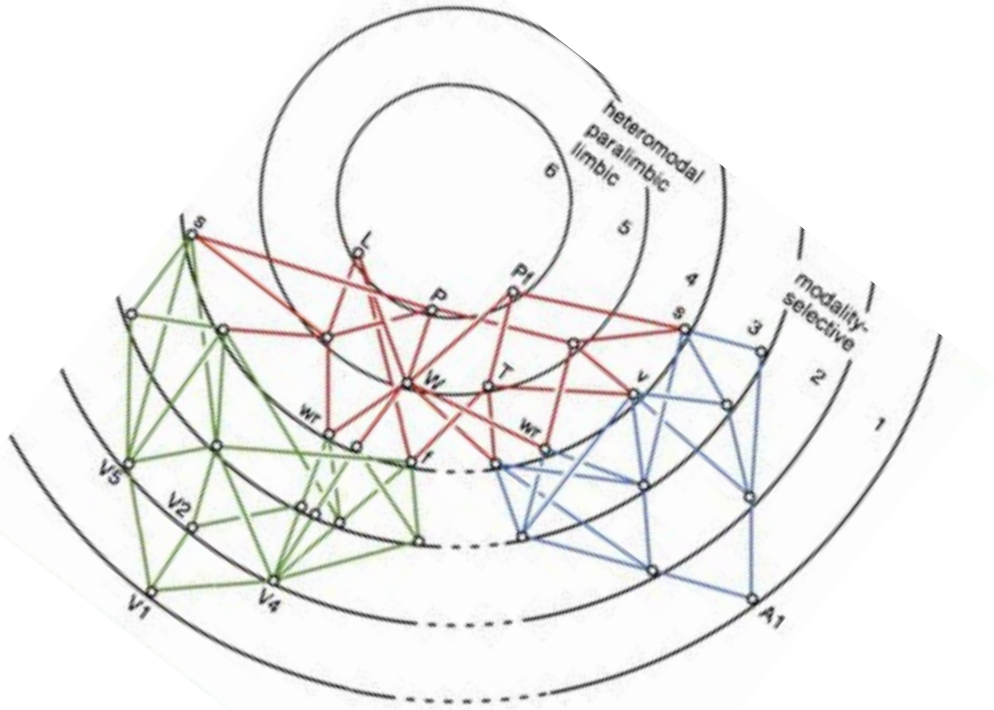


Burt et al., 2018

HIERARCHICAL CORTICAL TOPOGRAPHY

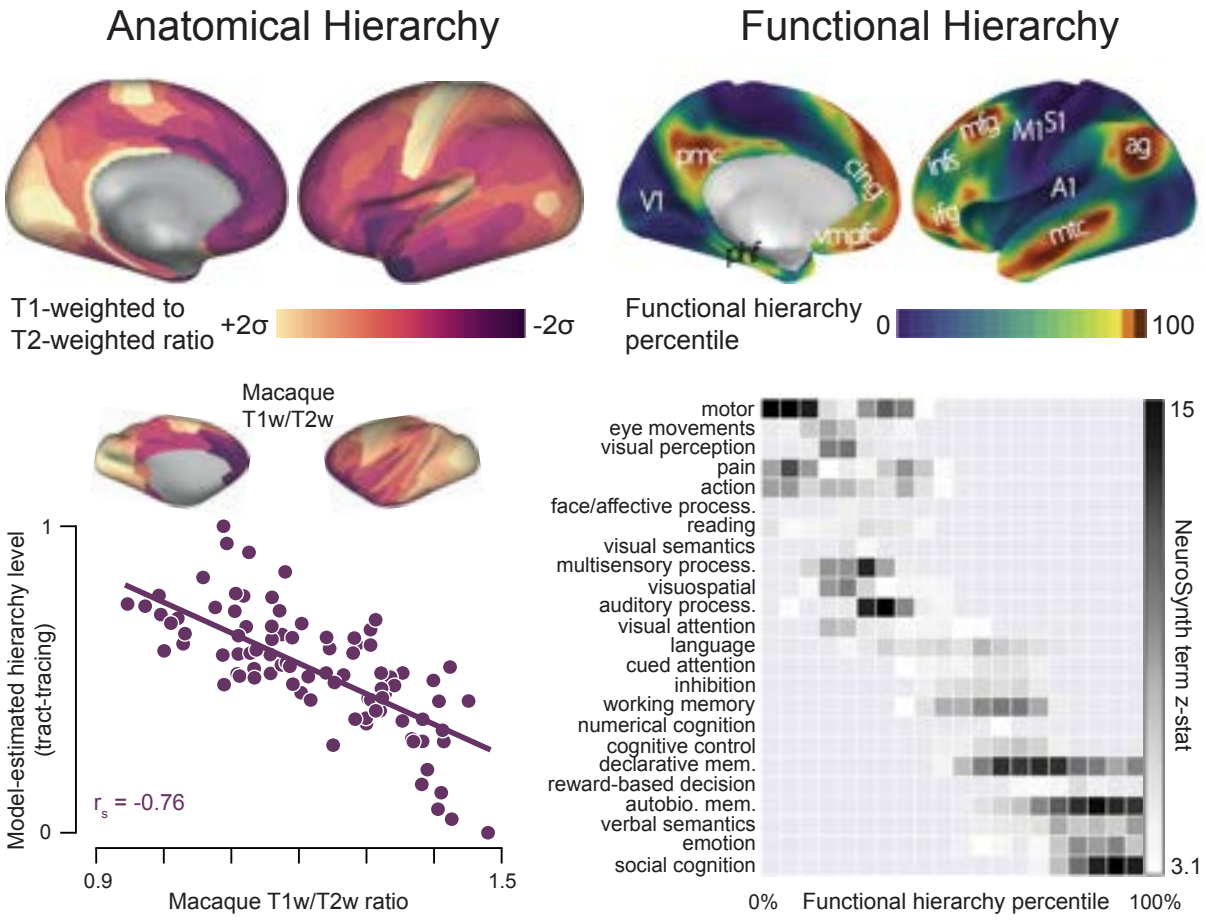


Burt et al., 2018



Mesulam, 1998

HIERARCHICAL CORTICAL TOPOGRAPHY

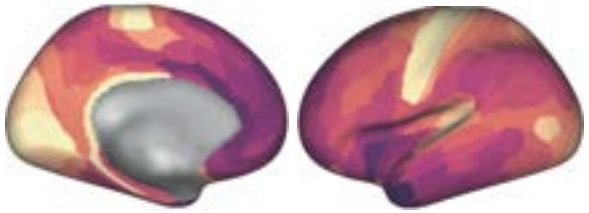


Burt et al., 2018

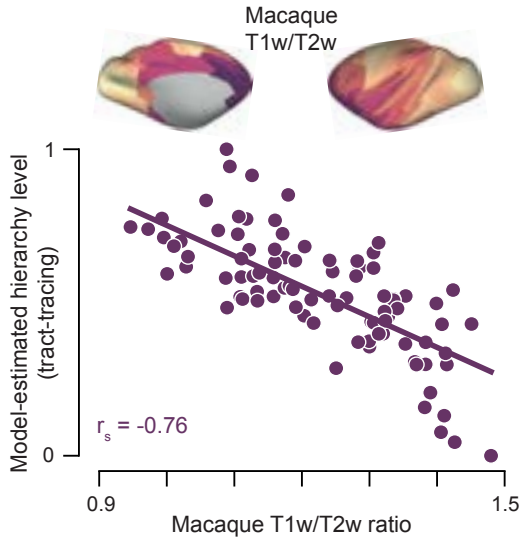
Margulies et al., 2016

HIERARCHICAL CORTICAL TOPOGRAPHY

Anatomical Hierarchy

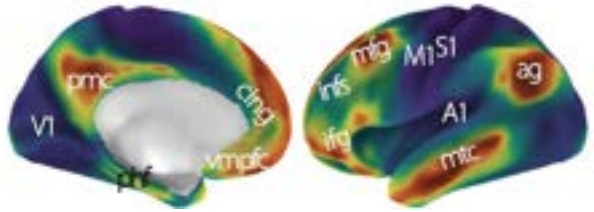


T1-weighted to T2-weighted ratio +2σ -2σ

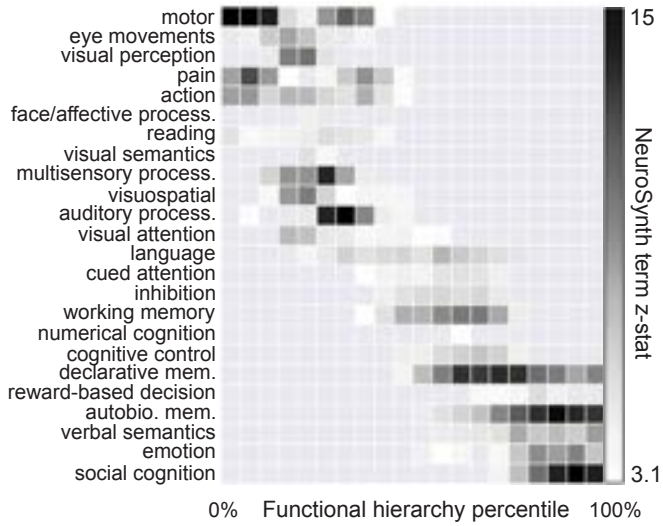


Burt et al., 2018

Functional Hierarchy

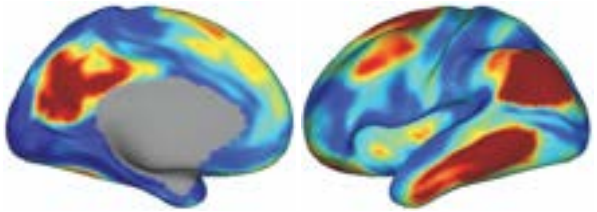


Functional hierarchy percentile 0 100

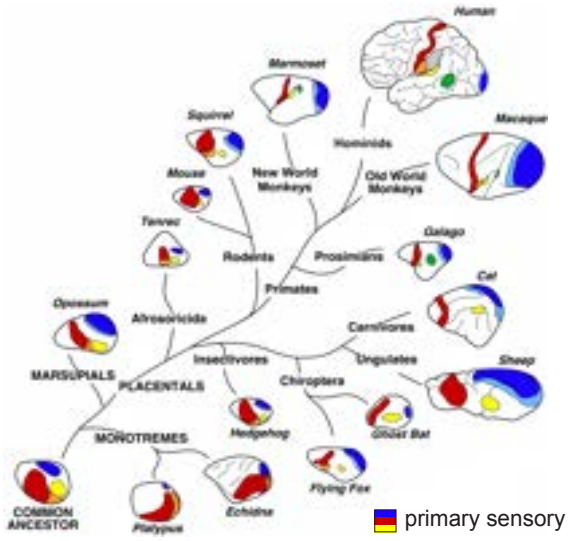


Margulies et al., 2016

Evolutionary Hierarchy



Macaque to human areal expansion 1X 36X

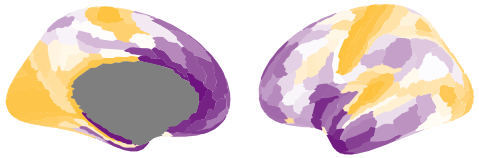


Krubitzer 2007, Xu et al., 2020

B

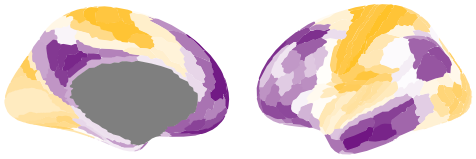
Anatomical Hierarchy

higher T1w/T2w ⟷ lower T1w/T2w



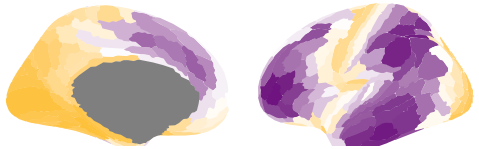
Functional Hierarchy

unimodal ⟷ transmodal



Evolutionary Hierarchy

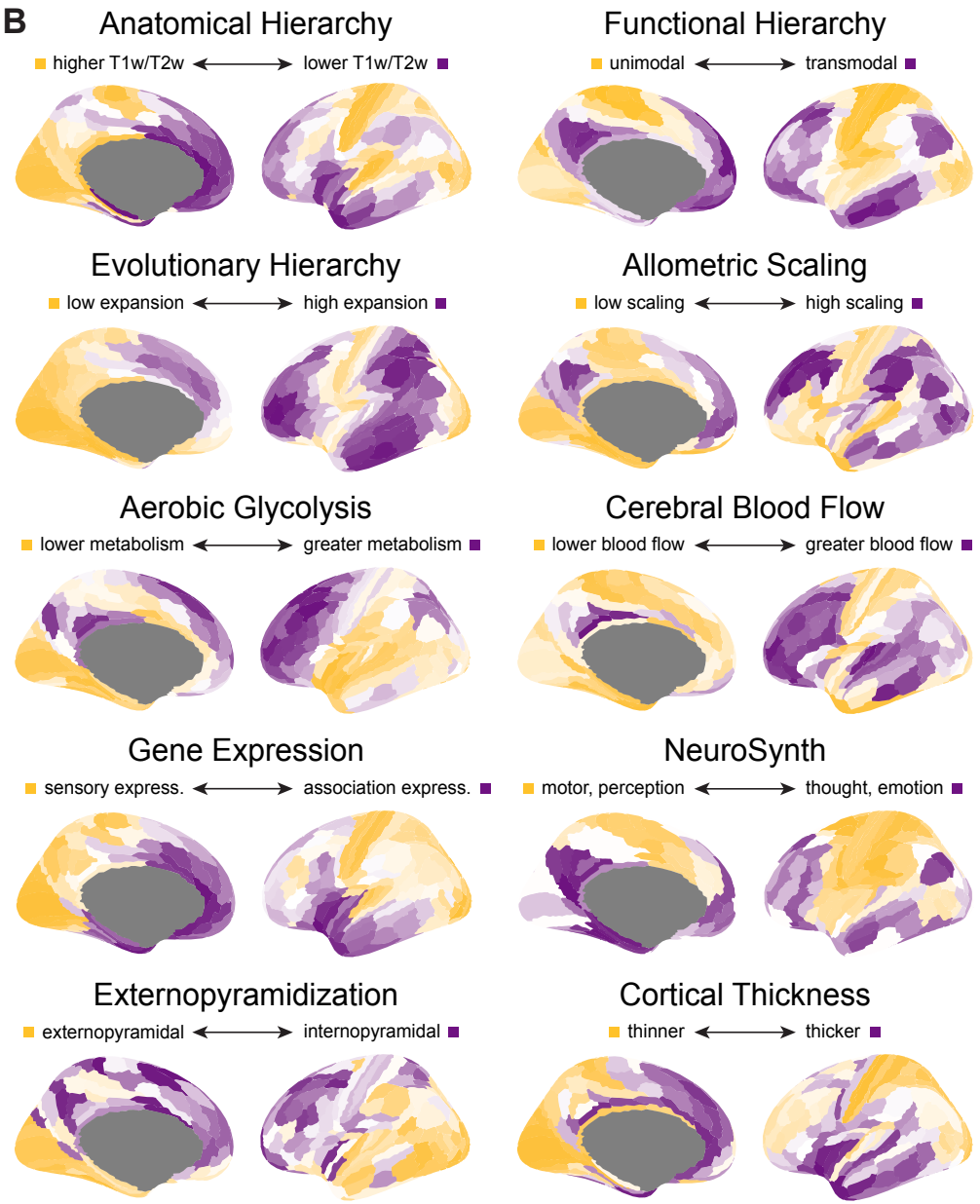
low expansion ⟷ high expansion



Sensorimotor Pole — Association Pole

low rank — *high rank*

B



Sensorimotor Pole — Association Pole

low rank — *high rank*

Intracortical myelination

Cortico-cortical connectivity distance

Timescale length

Structure-function coupling

Neuron density

Pyramidal cell spine count

Temporal receptive windows

Ex/In neurotransmitter receptor densities

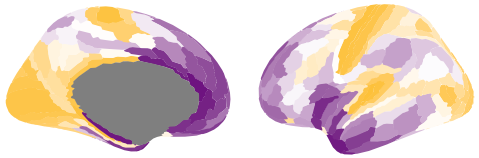
SST/PV interneuron expression

Intrinsic dynamics

B

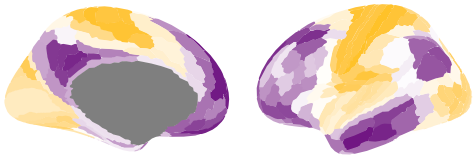
Anatomical Hierarchy

higher T1w/T2w ⟷ lower T1w/T2w



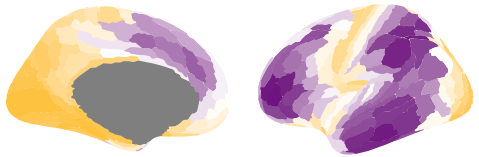
Functional Hierarchy

unimodal ⟷ transmodal



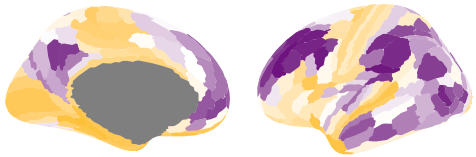
Evolutionary Hierarchy

low expansion ⟷ high expansion



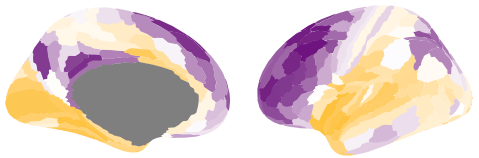
Allometric Scaling

low scaling ⟷ high scaling



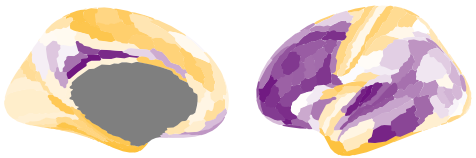
Aerobic Glycolysis

lower metabolism ⟷ greater metabolism



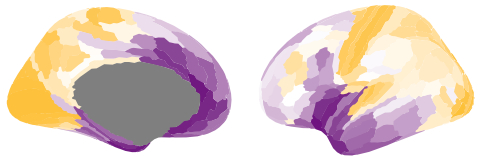
Cerebral Blood Flow

lower blood flow ⟷ greater blood flow



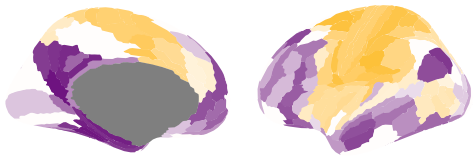
Gene Expression

sensory express. ⟷ association express.



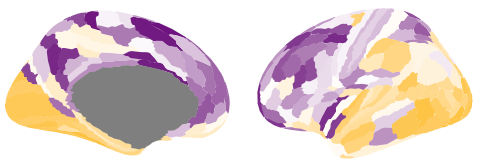
NeuroSynth

motor, perception ⟷ thought, emotion



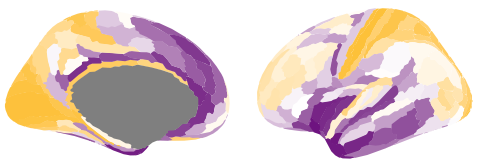
Externopyramidization

externopyramidal ⟷ internopyramidal



Cortical Thickness

thinner ⟷ thicker

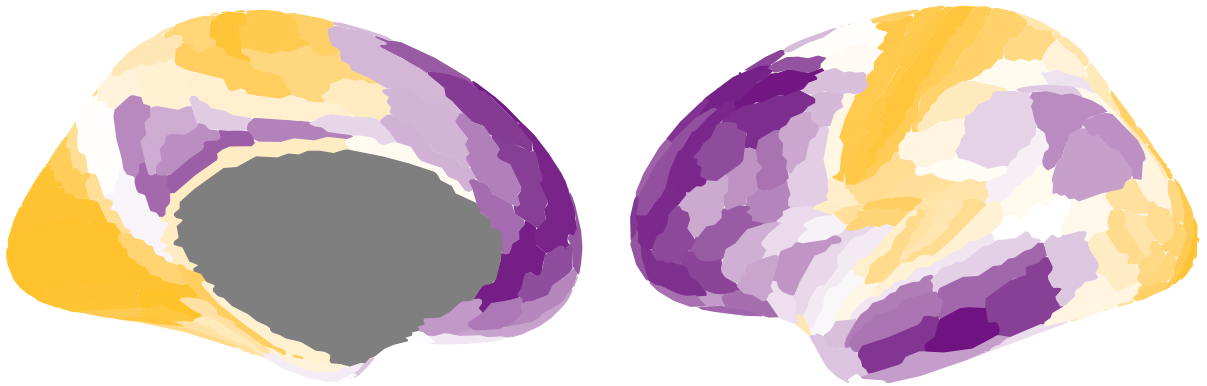


Sensorimotor Pole — Association Pole

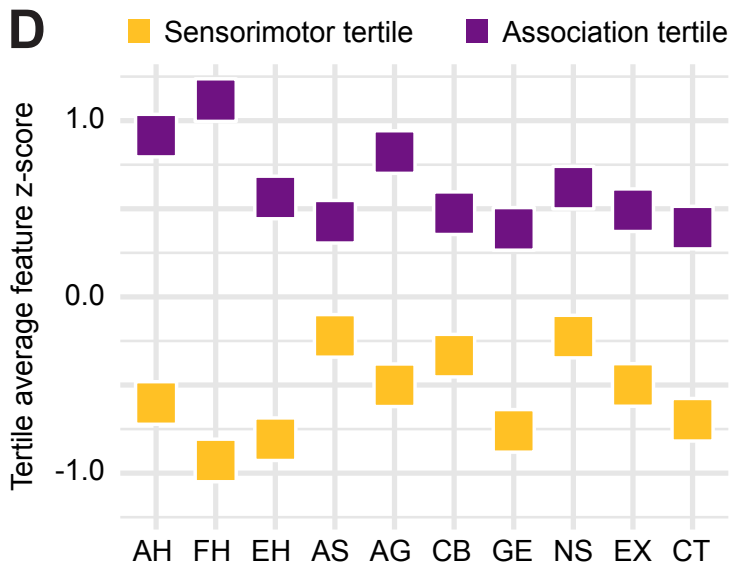
low rank — *high rank*

A

Sensorimotor-Association Axis



D



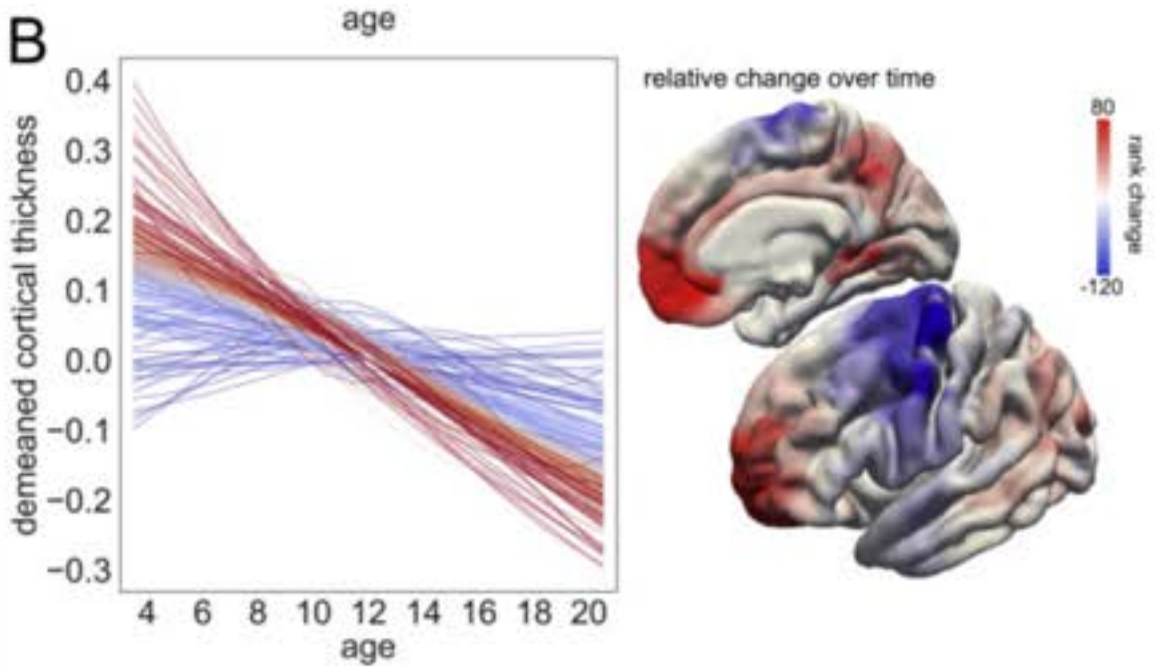
S-A NEURODEVELOPMENTAL HIERARCHY

In addition to the three canonical hierarchies of anatomy, function, and evolution, there is a fourth hierarchy—*a neurodevelopmental hierarchy*—that describes the spatiotemporal sequence of brain development and aligns with the principal S-A axis

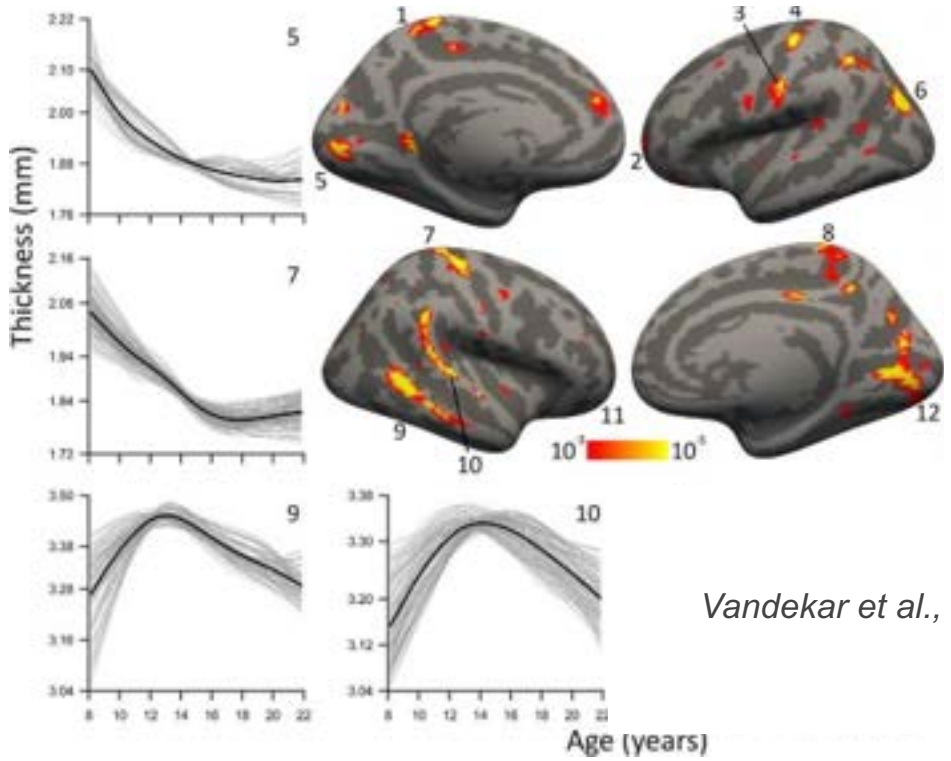
The S-A neurodevelopmental hierarchy provides insight into the progression and the biobehavioral outcomes of cortical maturation

S-A NEURODEVELOPMENT: CORTICAL THINNING

Cortex thins from age 3 years onwards; thinning rate increases in adolescence
Sensorimotor regions thin early, association regions show protracted thinning



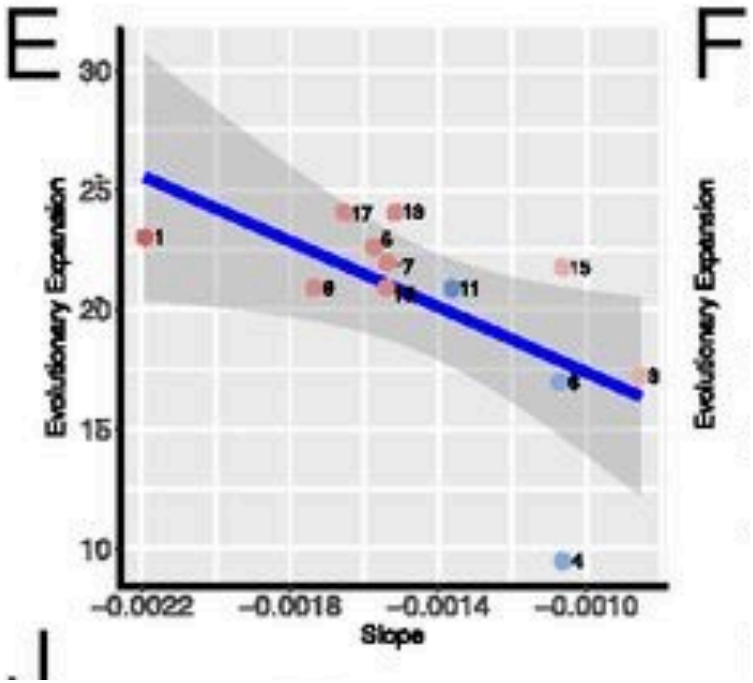
Ball et al., 2020

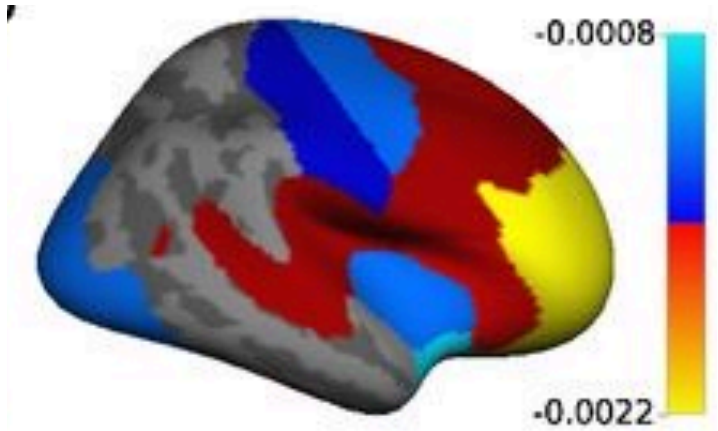


Vandekar et al., 2015

S-A NEURODEVELOPMENT: CORTICAL THINNING

Regions that thin the most in adolescence have expanded the most in evolution

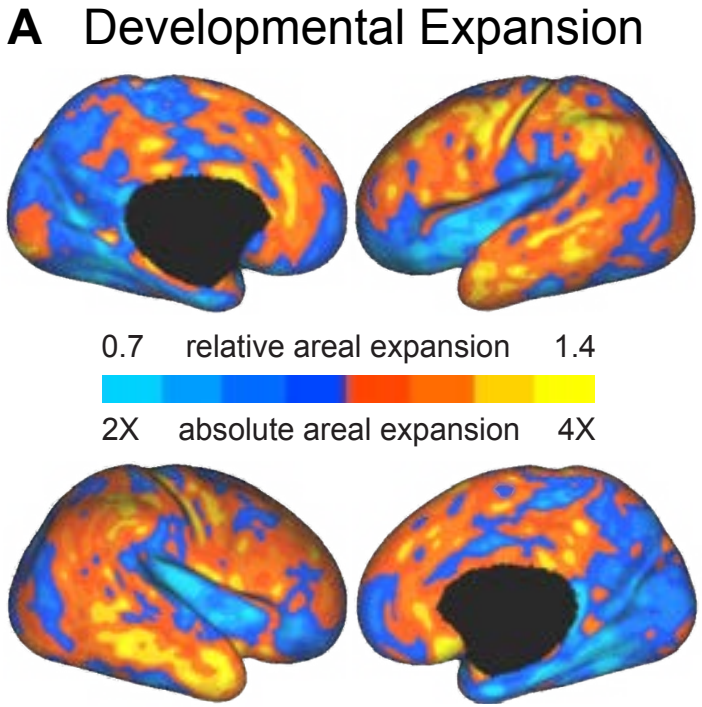




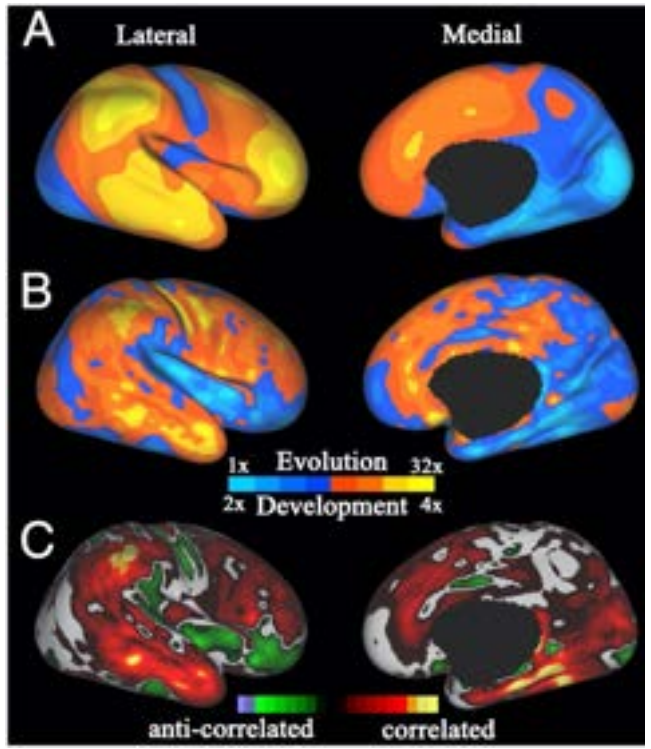
Sotiras et al., 2017

S-A NEURODEVELOPMENT: AREA EXPANSION

Surface area increases through fetal development until 9-12 years of age
Brain expands 3X; heteromodal association cortices expand 4X

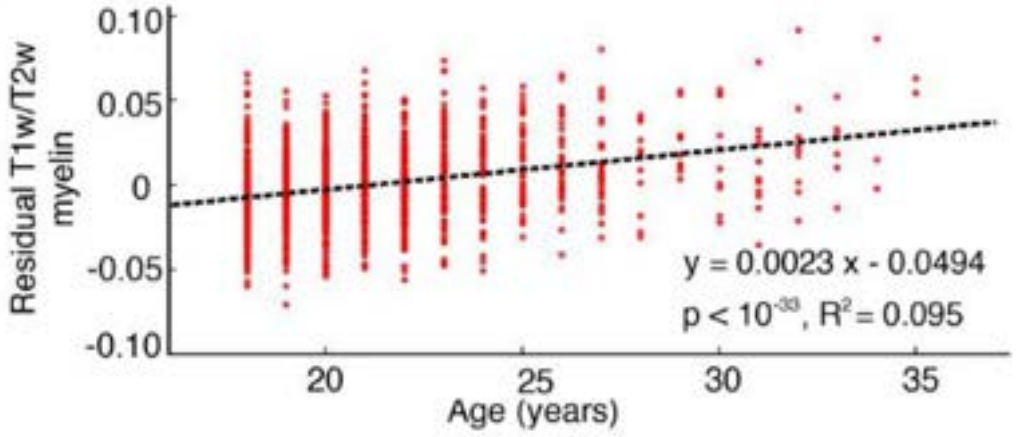


Hill et al. 2010

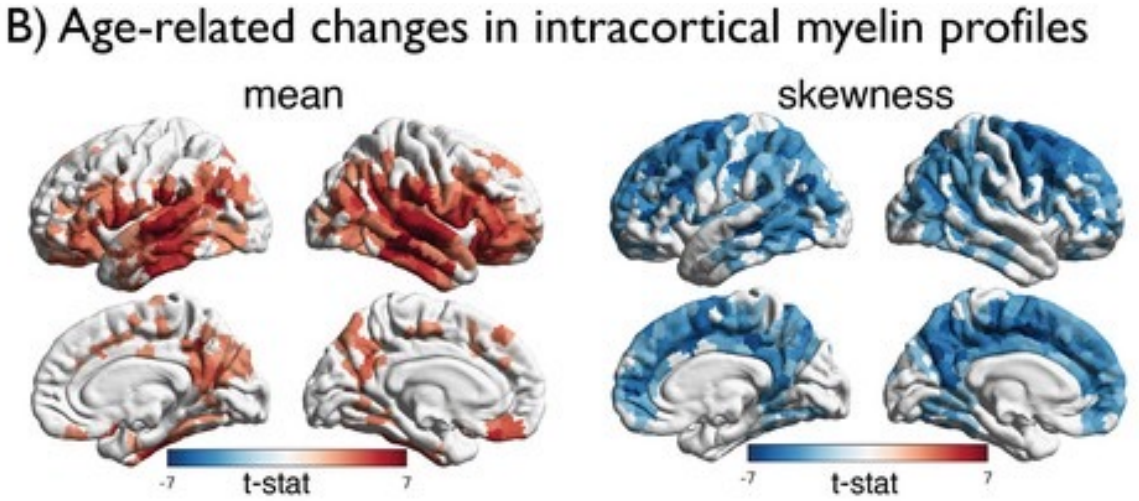


S-A NEURODEVELOPMENT: CORTICAL MYELIN

Intracortical myelination increases until the middle of the third decade
Adolescent increases in intracortical myelination occur in association cortices



Shafee et al., 2015

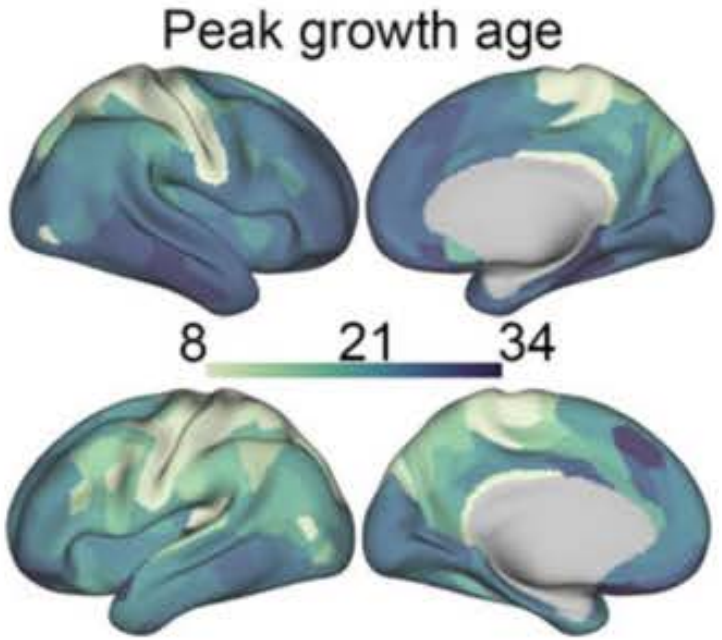


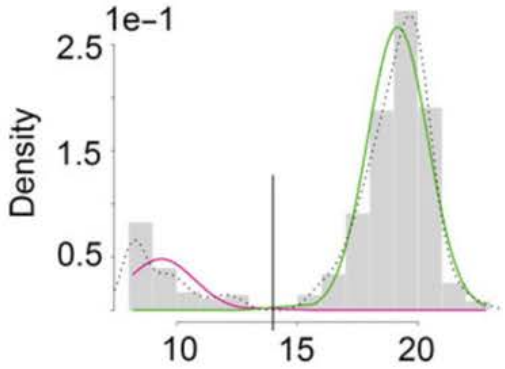
14-27 years

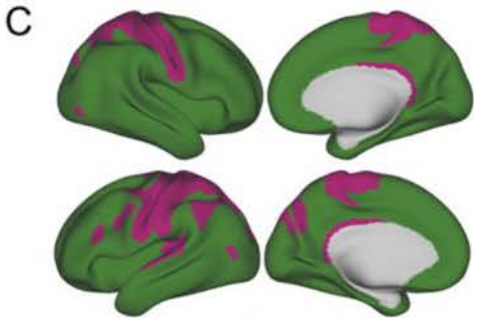
Paquola et al., 2019

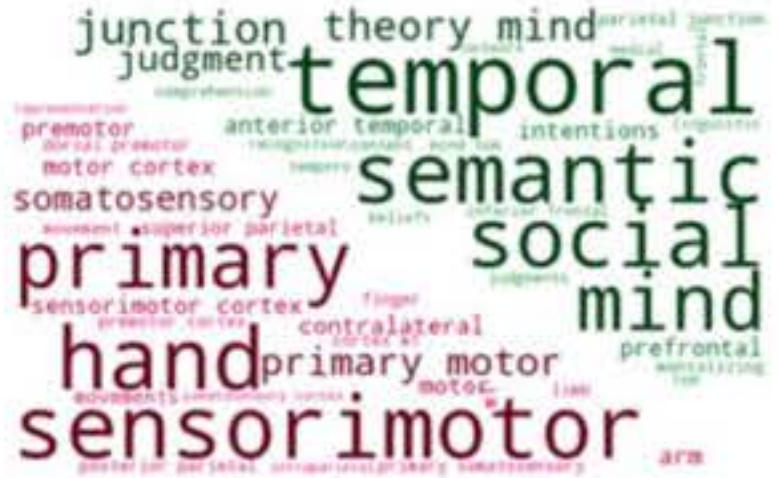
S-A NEURODEVELOPMENT: CORTICAL MYELIN

There are early (somatomotor) and late (association) waves of myelination





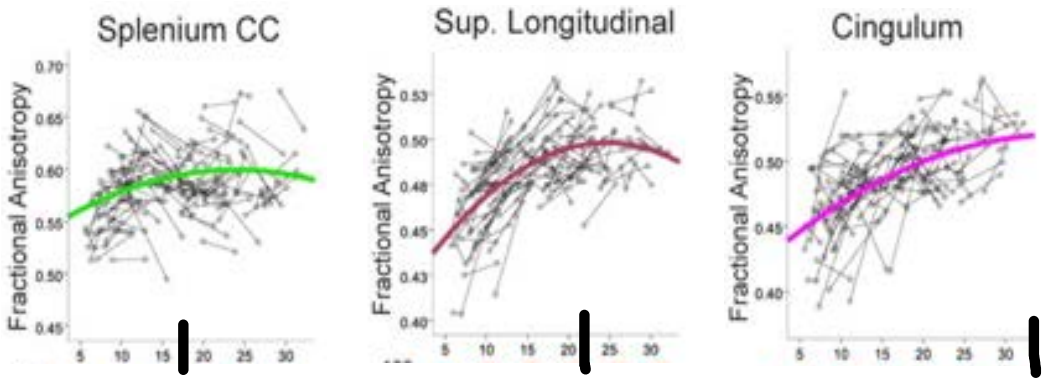




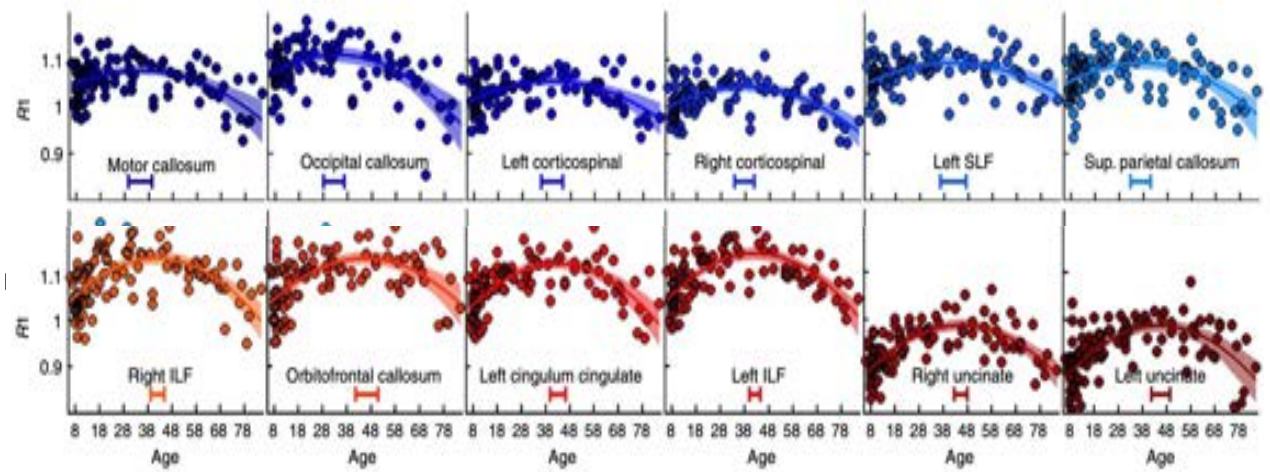
Grydeland et al., 2019

S-A NEURODEVELOPMENT: WHITE MATTER

White matter FA, neurite density (NODDI), fiber density (fixels), R1 and MT increase in a hierarchical fashion from childhood to mid-adulthood



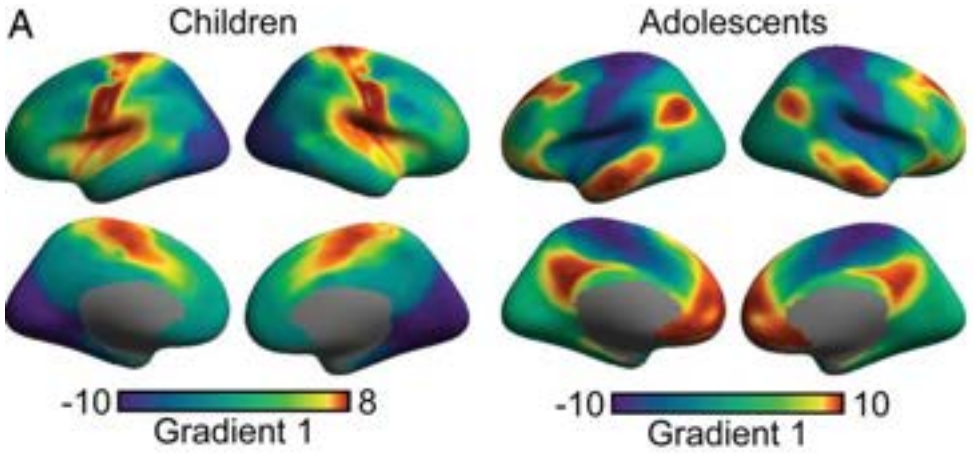
Lebel and Beaulieu, 2011



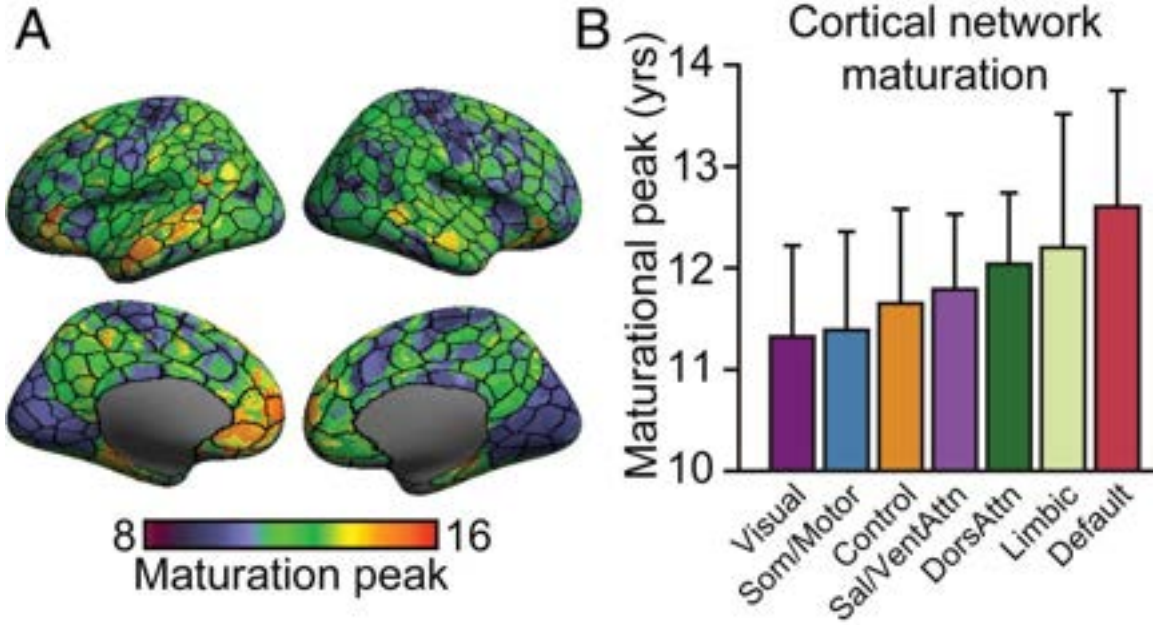
Yeatman et al., 2014

S-A NEURODEVELOPMENT: FUNCTIONAL SYSTEMS

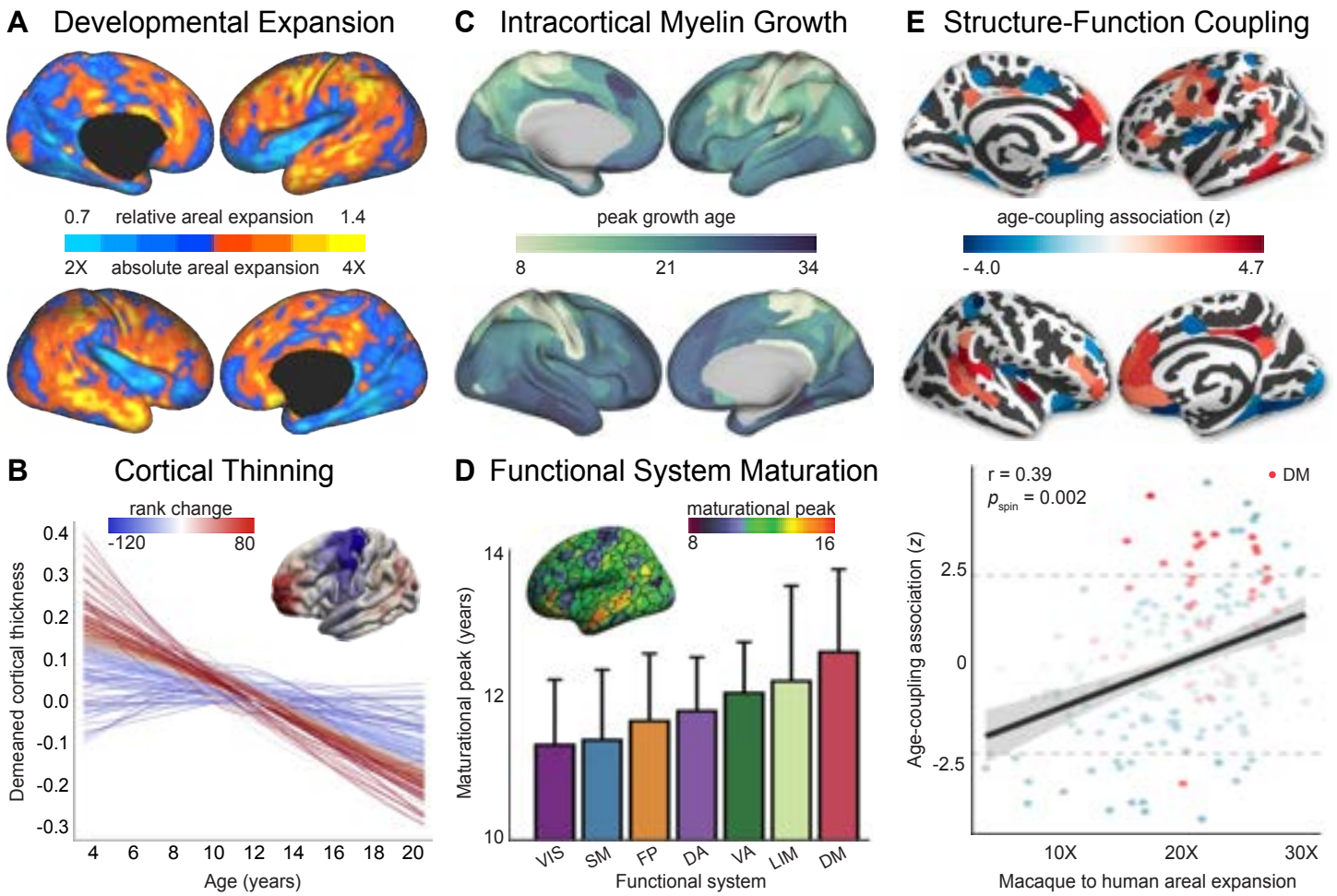
Visual and somatomotor systems display an adult-like topography in infants
FPN, DMN, CO systems refine boundaries/connectivity strength in adolescence



Dong et al., 2021

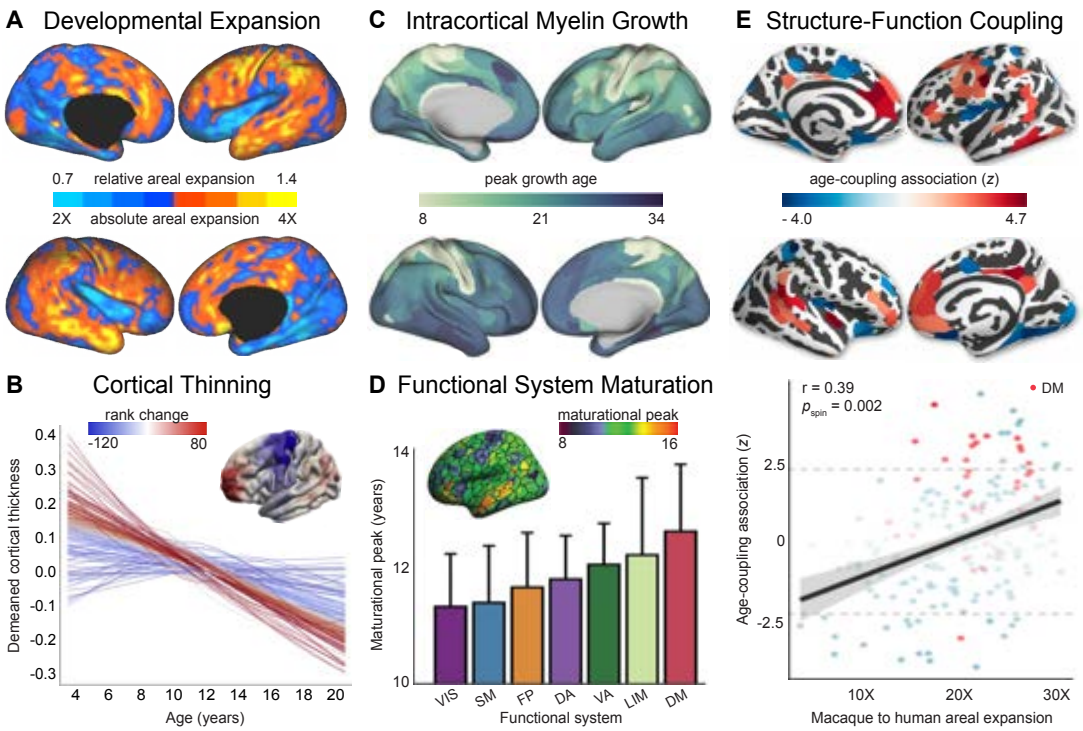


S-A NEURODEVELOPMENTAL HIERARCHY



S-A NEURODEVELOPMENTAL HIERARCHY

This spatiotemporal pattern of maturation is driven by the hierarchical unfolding of neurodevelopmental programs that influence cortical plasticity



PLASTICITY MECHANISMS UNDERLYING HIERARCHICAL DEVELOPMENT

Excitatory Changes

Experience-dependent pyramidal cell pruning
NMDA NR2B-mediated neurotransmission

Inhibitory Changes

Inhibitory synapse increases
Strengthening of PV signaling

Structural Changes

Intracortical myelination increases
Perineuronal net formation

PLASTICITY MECHANISMS UNDERLYING HIERARCHICAL DEVELOPMENT

Excitatory Changes

Experience-dependent pyramidal cell pruning Elston et al., 2009; Glantz et al., 2007; Huttenlocher, 1979; Petanjek et al., 2011

NMDA NR2B-mediated neurotransmission Flores-Barrera et al., 2014; Morales and Spear, 2014 ; Gamrill and Barria, 2011

Inhibitory Changes

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PLASTICITY MECHANISMS UNDERLYING HIERARCHICAL DEVELOPMENT

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NMDA NR2B-mediated neurotransmission

Inhibitory Changes

Inhibitory synapse increases Gonzalez-Burgos et al., 2015b; Piekarski et al., 2017a; Zhang et al., 2011b

Strengthening of PV signaling Caballero et al., 2014; Condé et al., 1996; Fung et al., 2010; Hof et al., 1999; Hoftman et al., 2015; Larsen and Luna, 2018

Structural Changes

Intracortical myelination increases

Perineuronal net formation

PLASTICITY MECHANISMS UNDERLYING HIERARCHICAL DEVELOPMENT

Excitatory Changes

Experience-dependent pyramidal cell pruning
NMDA NR2B-mediated neurotransmission

Inhibitory Changes

Inhibitory synapse increases
Strengthening of PV signaling

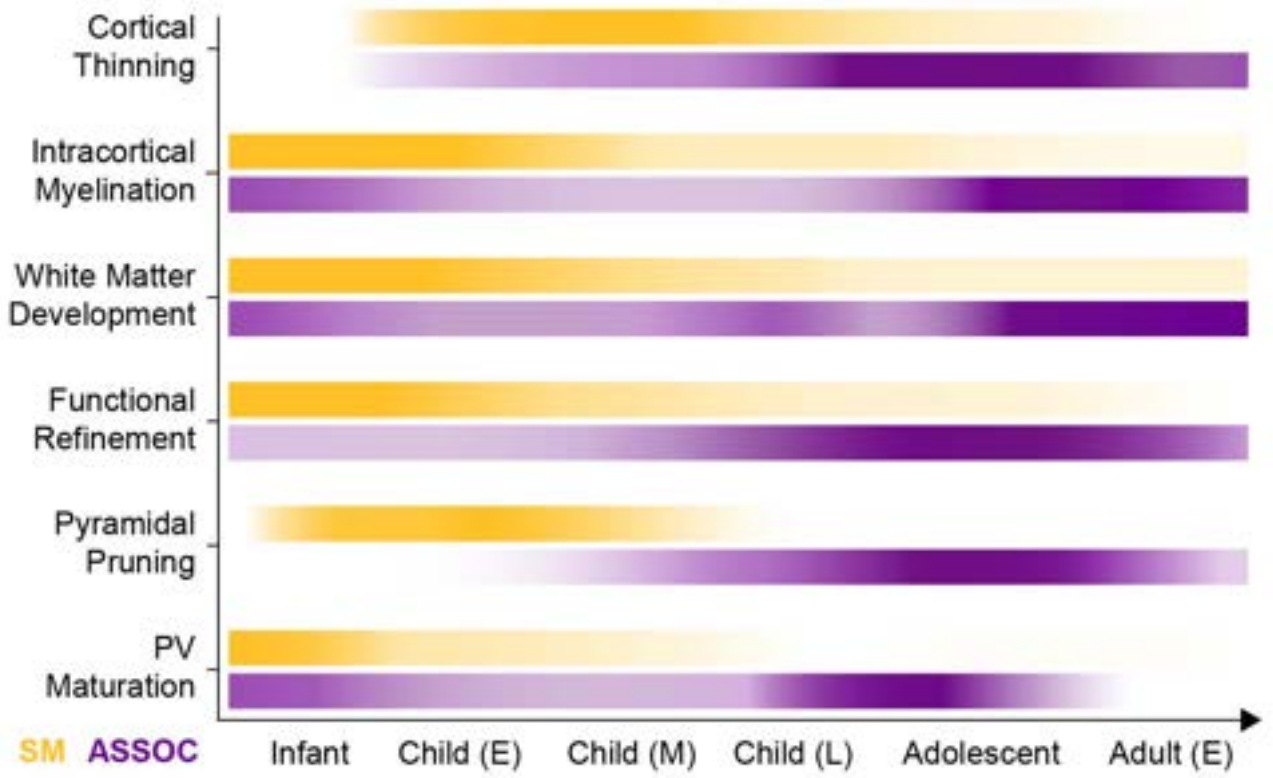
Structural Changes

Intracortical myelination increases Nabel et al., 2013; McGee et al., 2005; Syken et al., 2006; Takesian and Hensch, 2013
Perineuronal net formation Carulli et al., 2010; Hensch, 2005; Mauney et al., 2013; Takesian and Hensch, 2013

PROTRACTED ASSOCIATION CORTEX PLASTICITY

Association cortices display a slower and later increase in plasticity facilitating excitatory mechanisms, plasticity modulating inhibitory signaling, and plasticity stabilizing features

Length of cortical plasticity increases as regions fall higher in the sensorimotor-association axis



BIOBEHAVIORAL CONSEQUENCES OF HIERARCHICAL NEURODEVELOPMENT

- Systematic enhancement of feature divergence across the sensorimotor-association axis
- Heightened inter-individual variability in association cortices
- Association cortex-linked vulnerability to transdiagnostic psychopathology

BIOBEHAVIORAL CONSEQUENCES OF HIERARCHICAL NEURODEVELOPMENT

- **Systematic enhancement of feature divergence across the sensorimotor-association axis**
- Heightened inter-individual variability in association cortices
- Association cortex-linked vulnerability to transdiagnostic psychopathology

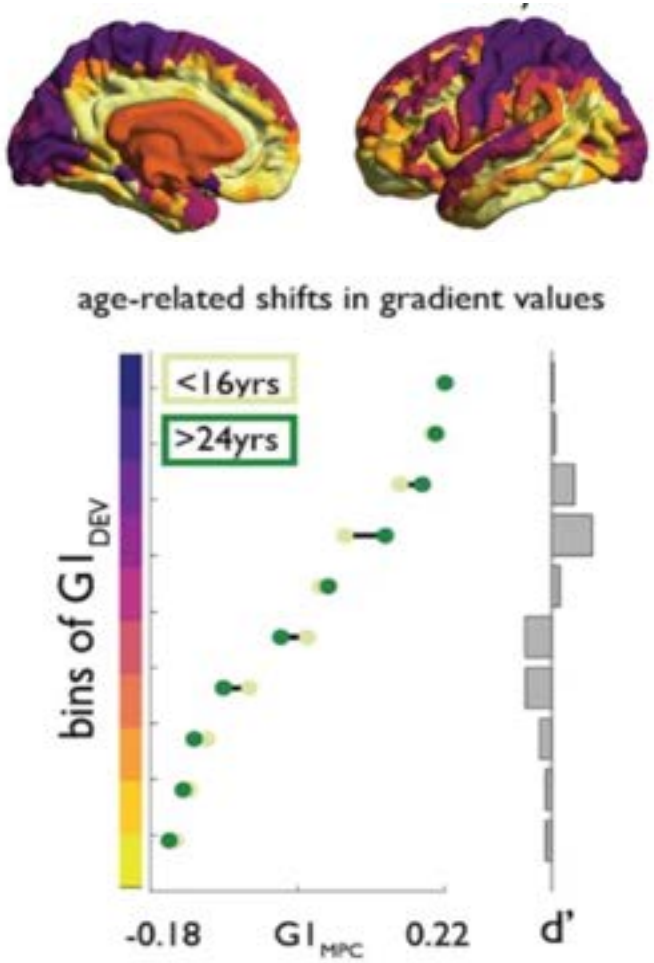
Temporal neurodevelopmental variability engenders spatial feature variability

(Charvet and Finlay, 2014)

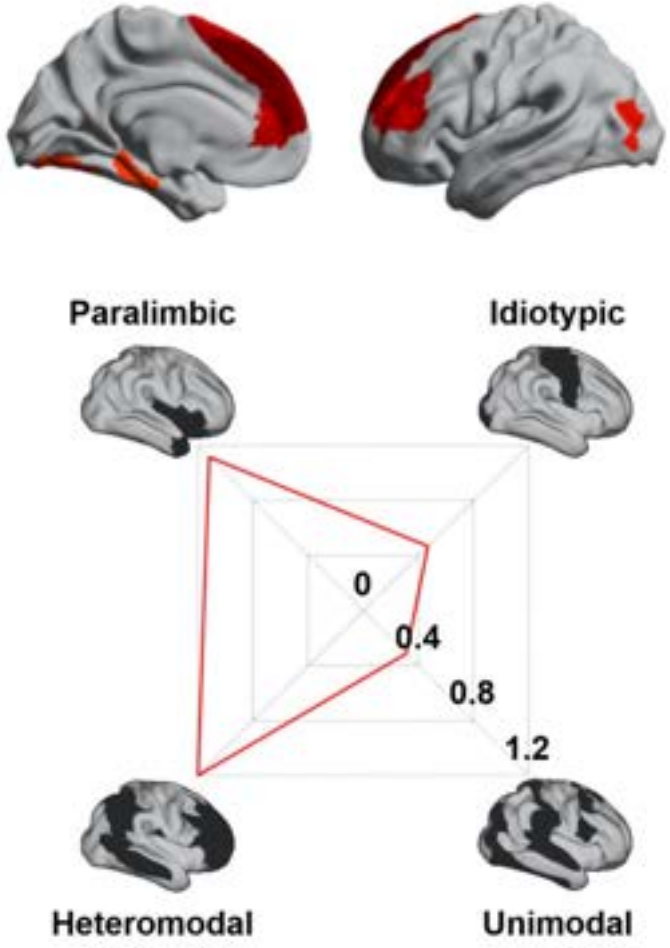
Because human development is asynchronous and hierarchical, it should strengthen and expand the sensorimotor-association feature axis

Temporal neurodevelopmental variability engenders spatial feature variability

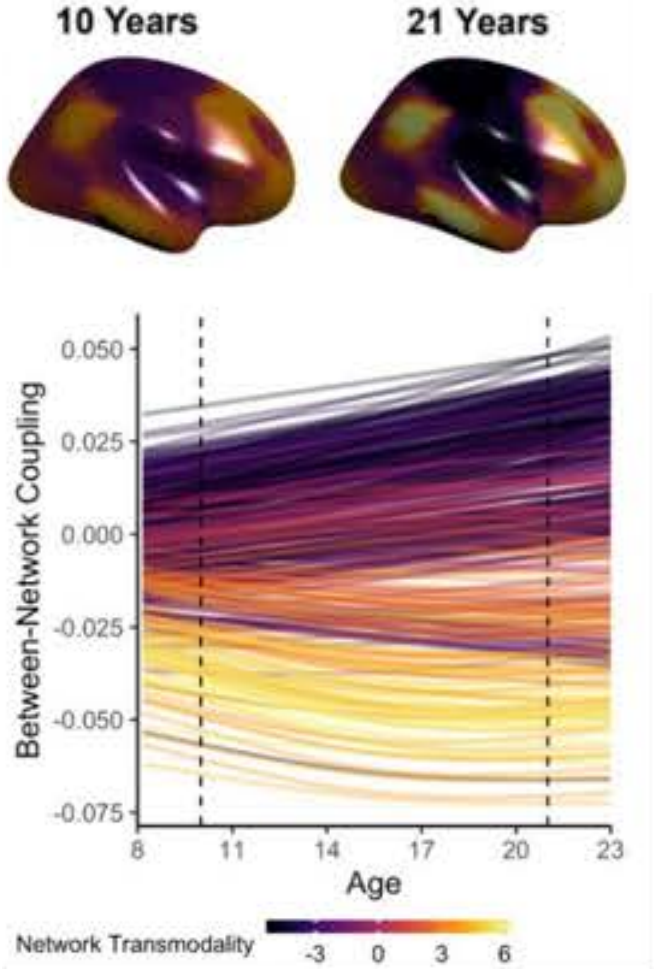
(Charvet and Finlay, 2014)



Paquola et al., 2019



Park et al., 2021



Pines et al., 2021

S-A FEATURE DIVERGENCE

Though variation in areal properties exists to a degree along the S-A axis at birth, the temporal and topographical sequence of neurodevelopment enhances feature divergence between lower-order and higher-order cortices

Divergence facilitates the refinement of key association cortex properties:

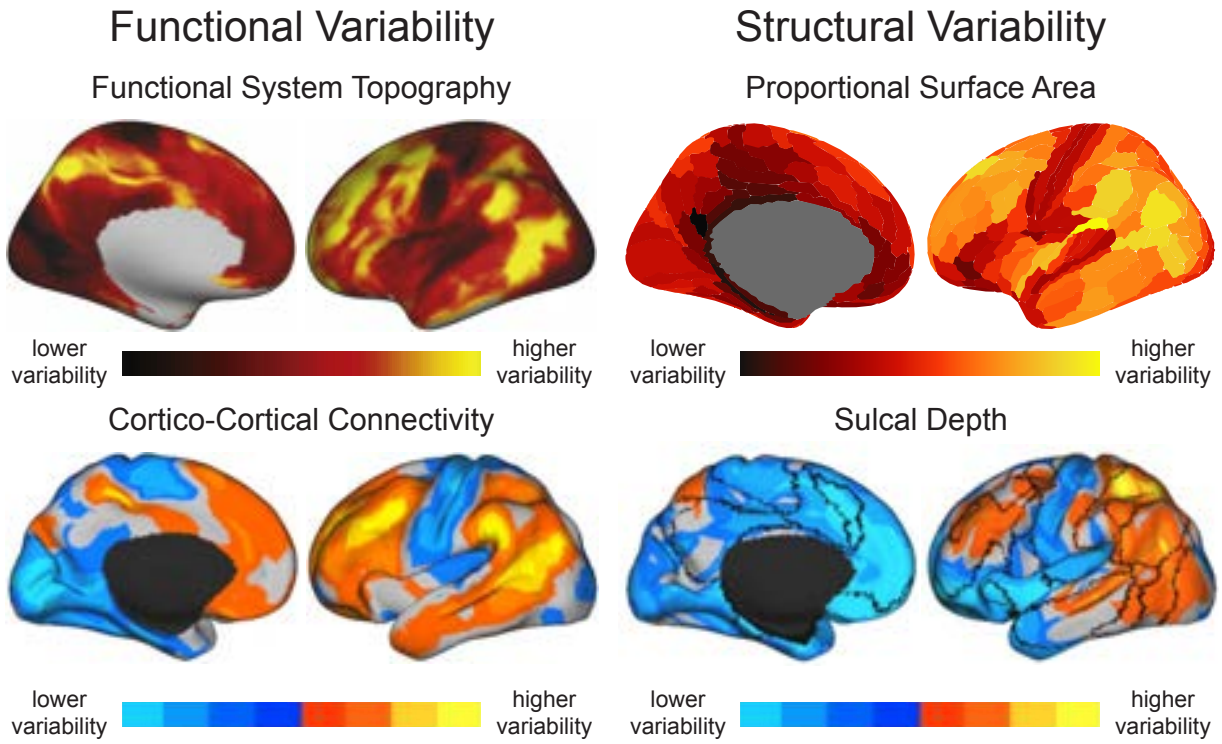
- Higher E:I ratio → *intrinsically-driven signaling, functional dynamics*
- Interconnected connectivity profile → *integration, top-down control*
- Longer intrinsic timescales → *information accumulation, cumulative cognition*
- Mixed selectivity → *adaptable, multifunctional, high-dimensional encoding*

BIOBEHAVIORAL CONSEQUENCES OF HIERARCHICAL NEURODEVELOPMENT

- Systematic enhancement of feature divergence across the sensorimotor-association axis
- **Heightened inter-individual variability in association cortices**
- Association cortex-linked vulnerability to transdiagnostic psychopathology

Plasticity allows brain regions to be sculpted by genetic influences, signaling molecules, and environments and experiences

Cortices that are plastic for longer should exhibit elevated inter-individual developmental variability



Cui et al,, 2020

Reardon et al., 2018

Mueller et al., 2013

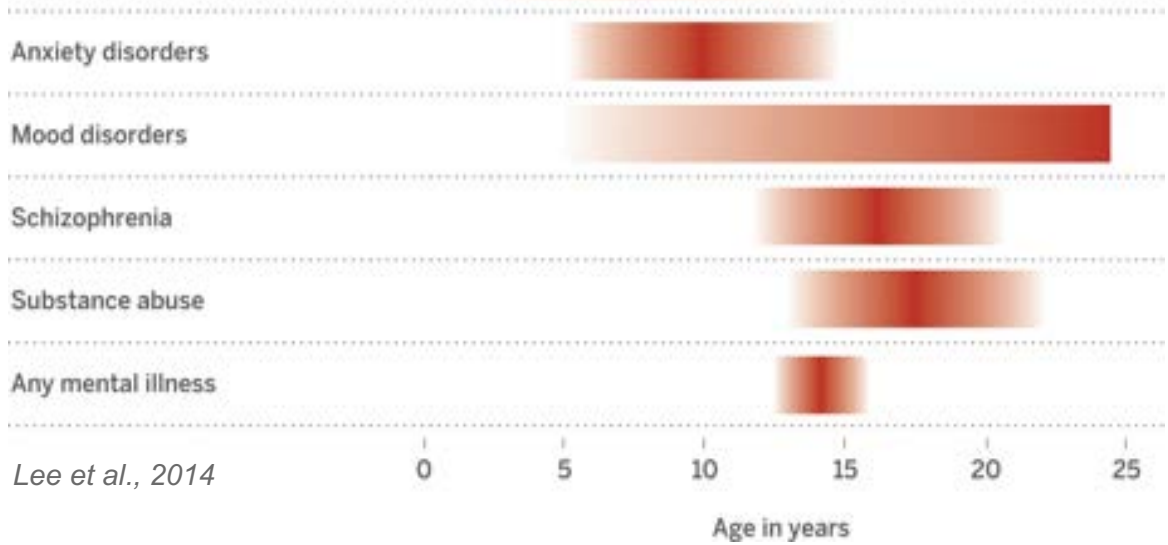
Mueller et al., 2013

BIOBEHAVIORAL CONSEQUENCES OF HIERARCHICAL NEURODEVELOPMENT

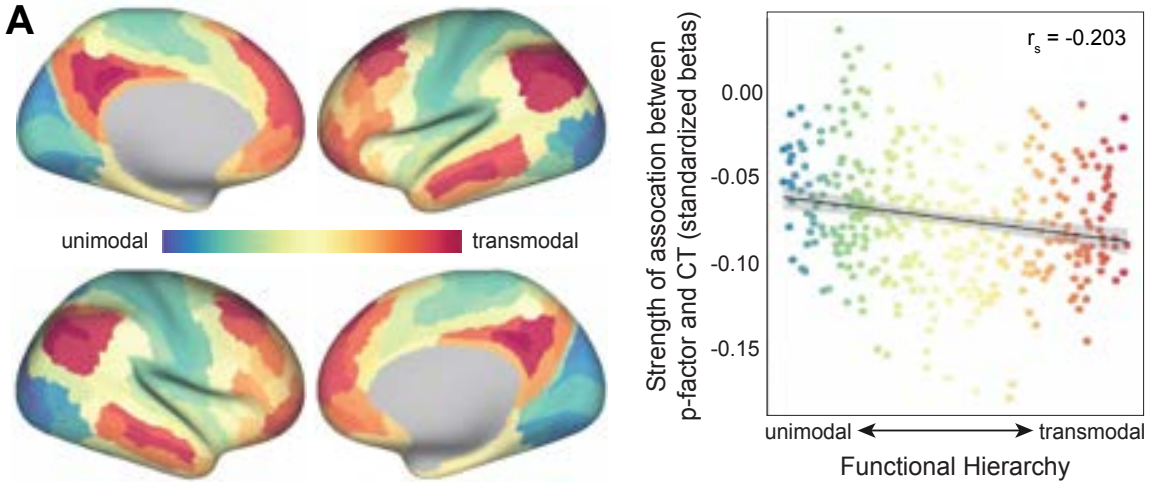
- Systematic enhancement of feature divergence across the sensorimotor-association axis
- Enhanced inter-individual variability in association cortices
- **Association cortex-linked vulnerability to transdiagnostic psychopathology**

Mental illness symptoms emerge relatively later in the brain's hierarchical neurodevelopmental program

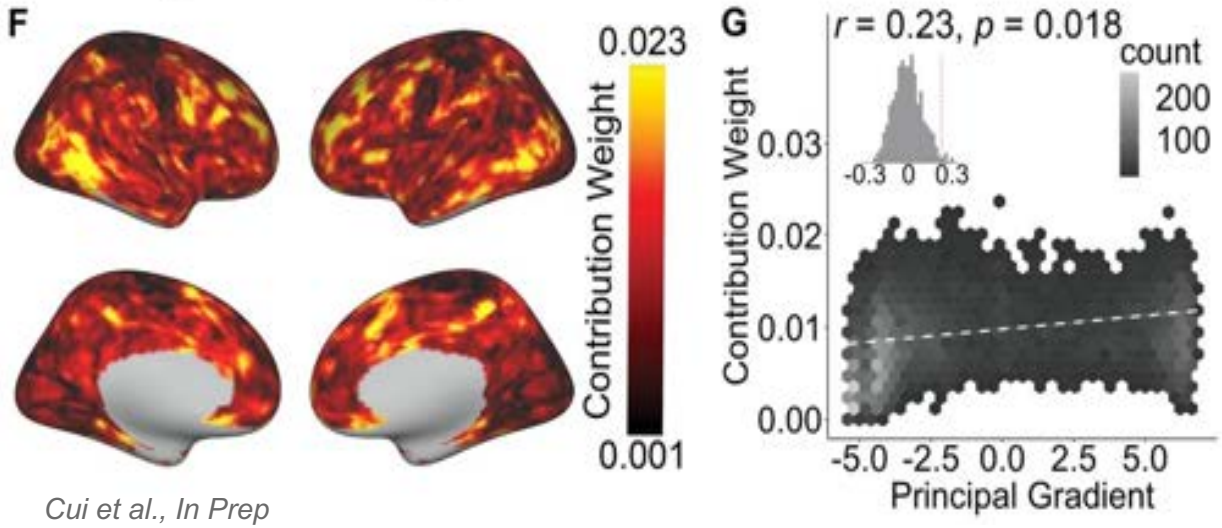
This implicates non-normative maturation of transmodal association cortices in transdiagnostic psychopathology



Lee et al., 2014



Romer et al., 2021



Cui et al., In Prep

Plasticity-related neurodevelopmental mechanisms may play a key role in psychopathology