PETPARTI: TRADE-OFF ANALYSIS OF HUMAN BRAIN NEUROCHEMISTRY

19/09/2025 I ELIANA NICOLAISEN-SOBESKY & DR. KAUSTUBH R. PATIL

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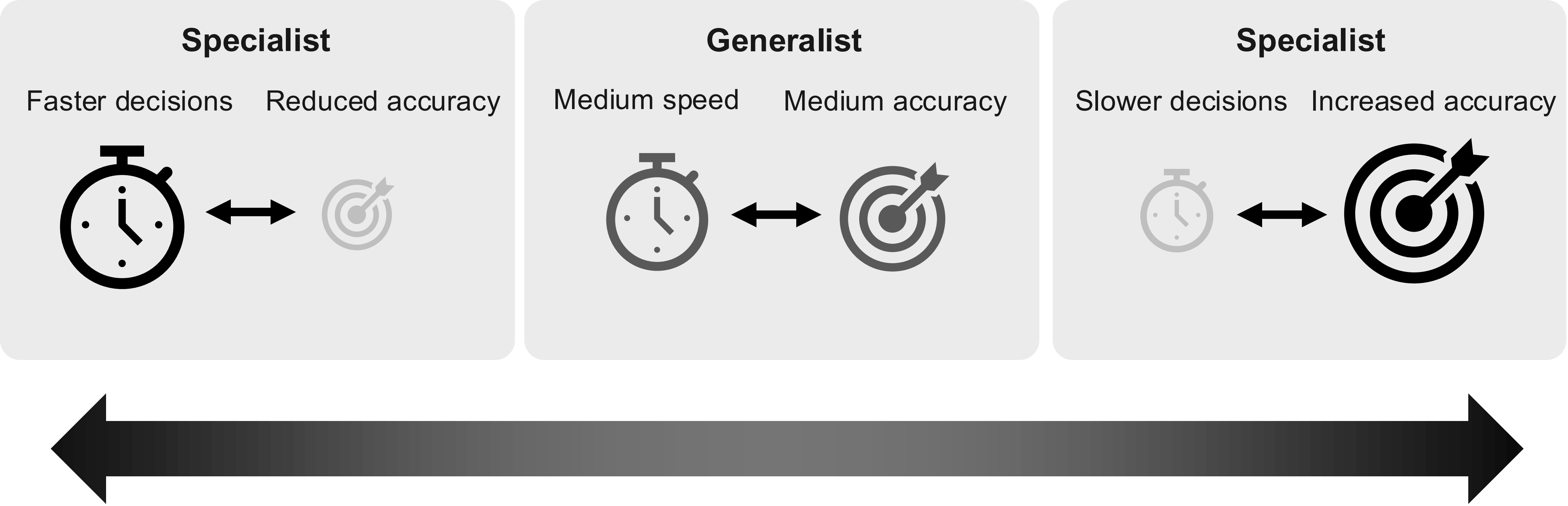
Shaping Change

BIOLOGICAL SYSTEMS FACE TRADE-OFFS

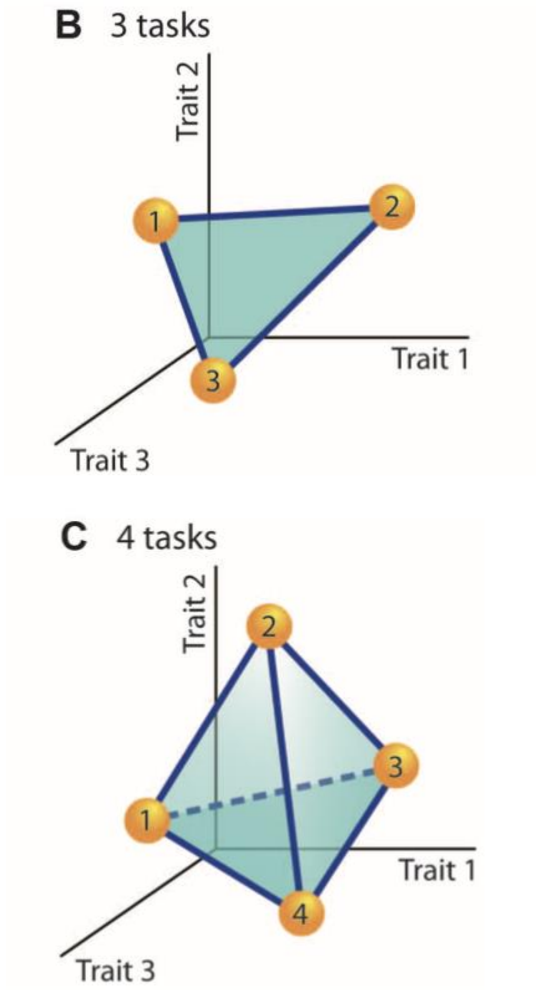
- Biological systems that need to perform multiple tasks face a trade-off: no system can be optimal for all tasks
- Trade-offs affect the range of phenotypes found in nature

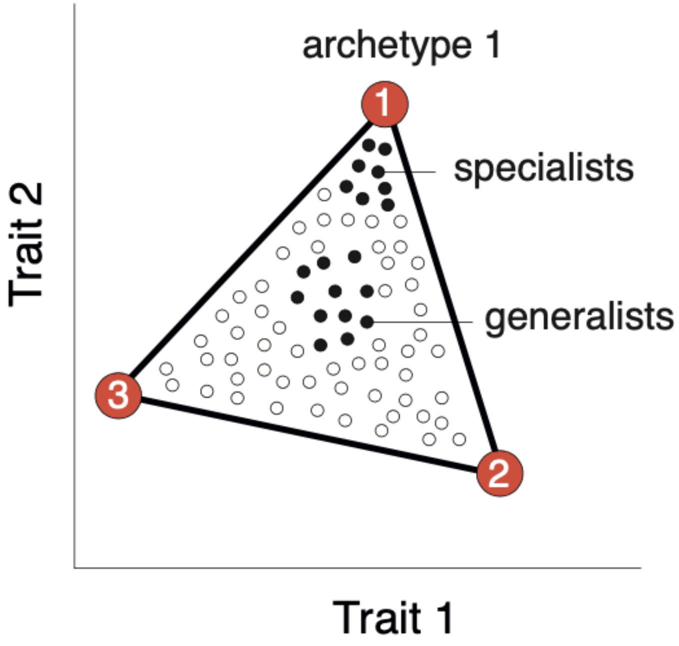


Hart et al., 2015, *Nature Methods*; Shoval et al., 2012, *Science*

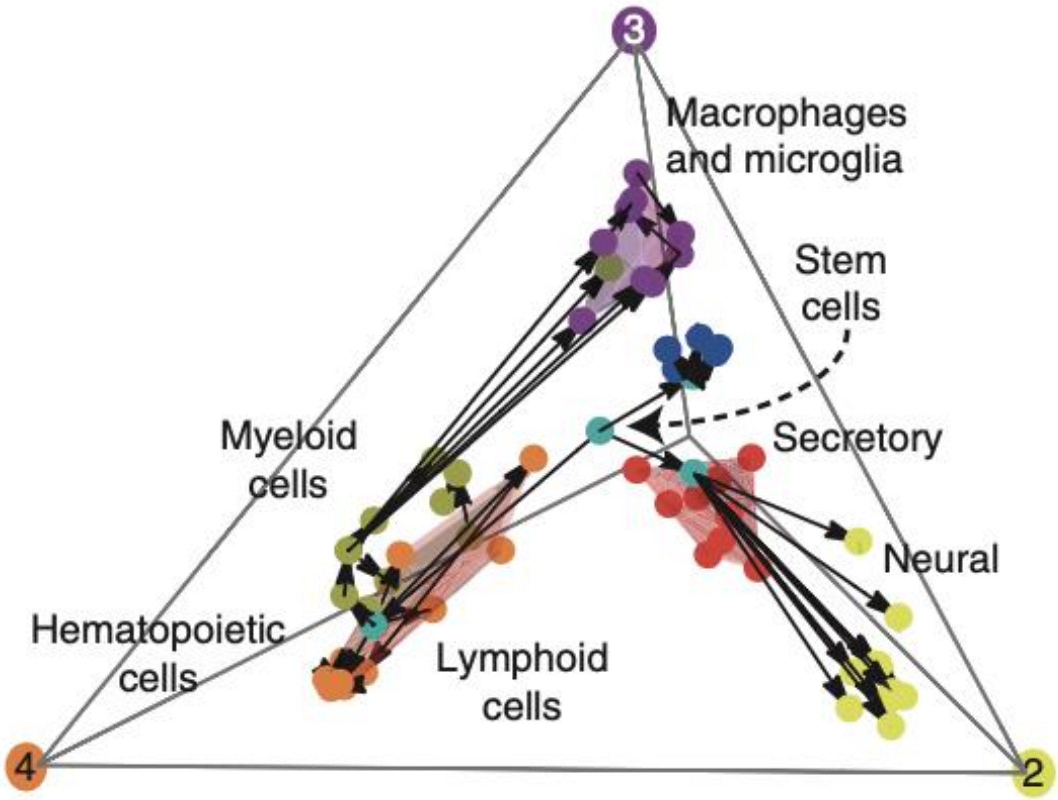
HOW TO STUDY TRADE-OFFS

Pareto Task Inference (ParTI)





Each dot is a cell



Alon, 2019, An introduction to systems biology; Hart et al., 2015, *Nature Methods;* Shoval et al., 2012, *Science;*

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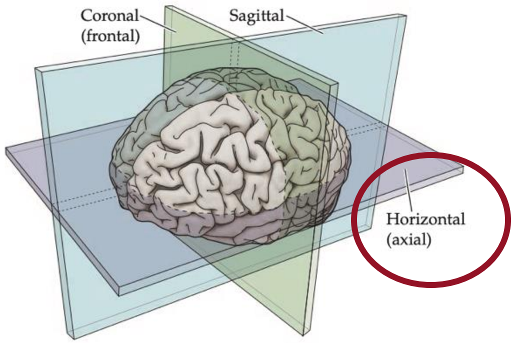
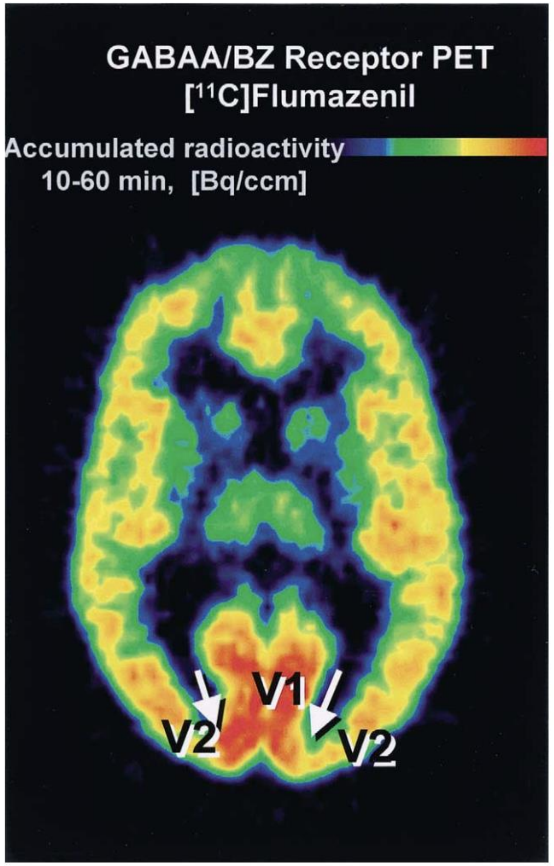
NEUROTRANSMITTER SYSTEMS IN THE BRAIN

Positron emission tomography (PET)





Zilles et al., 2002, *European Neuropsychopharmacology;* Purves et al., 2001, Neuroscience; Wikipedia

NEUROTRANSMITTER SYSTEMS IN THE BRAIN

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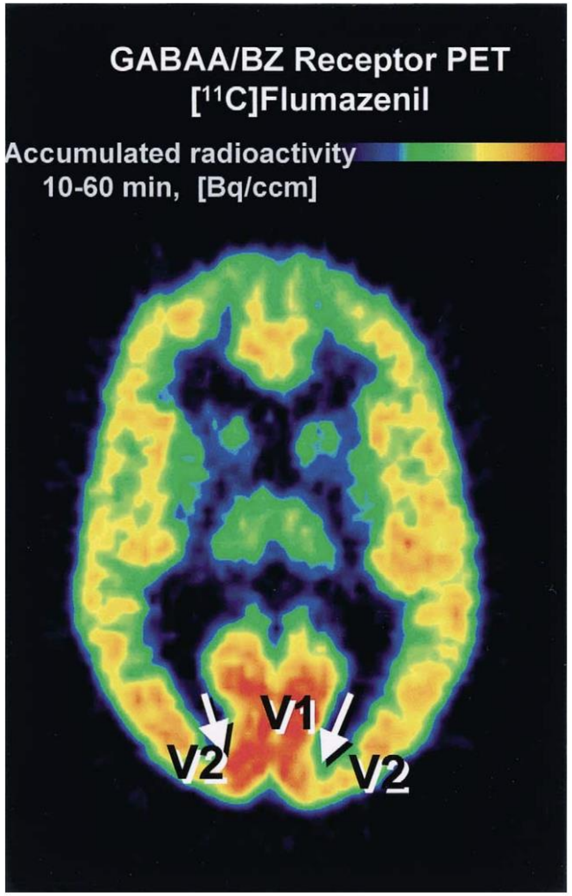

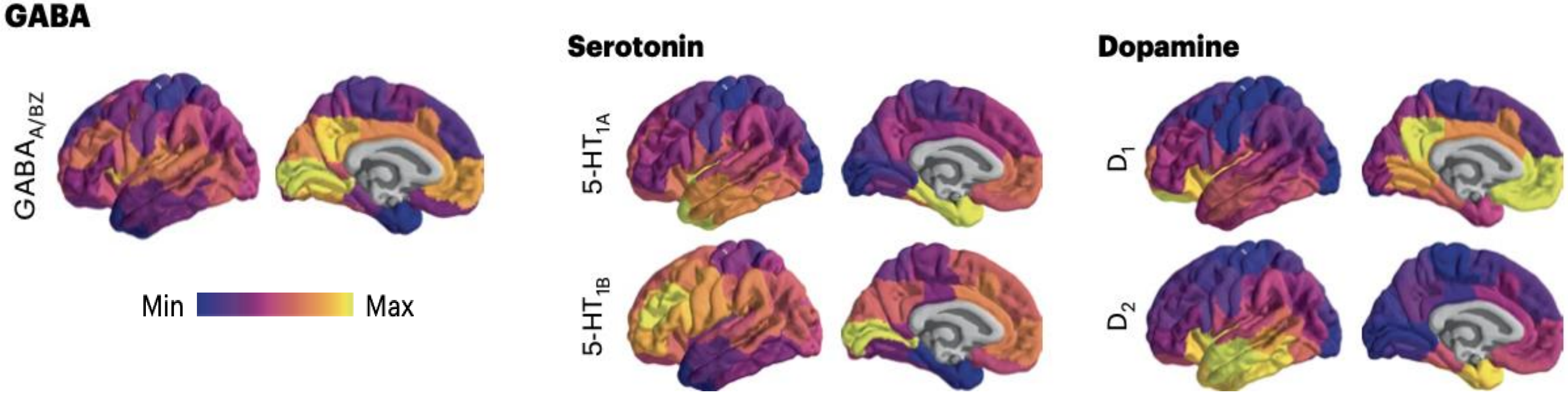

- Physiological functions (heart rate, respiration)
- Cognition and emotion

- Imbalances:
  - Epilepsy (glutamate)
  - Depression (GABA, glutamate, serotonin, dopamine and norepinephrine)

Zilles et al., 2002, *European Neuropsychopharmacology;* Hansen, et al., 2022 *Nature Neuroscience*

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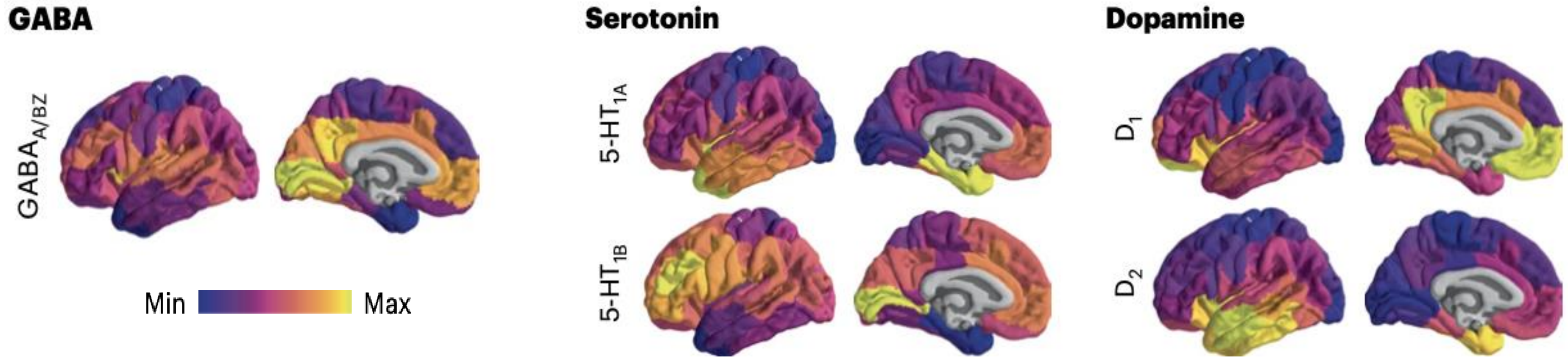
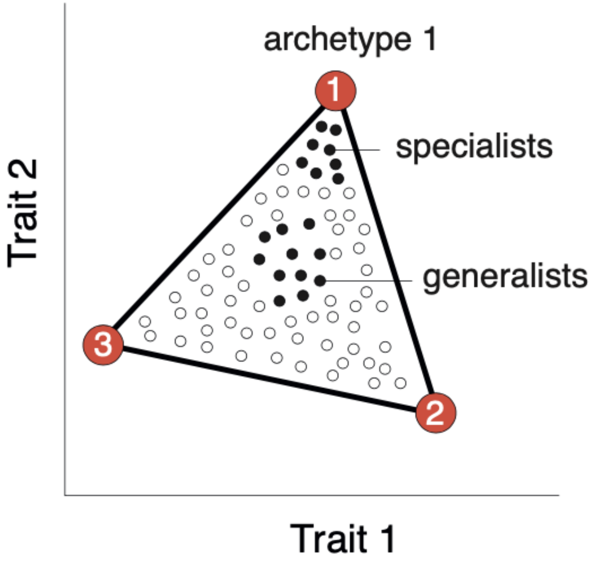
AIM

Brain neurochemistry



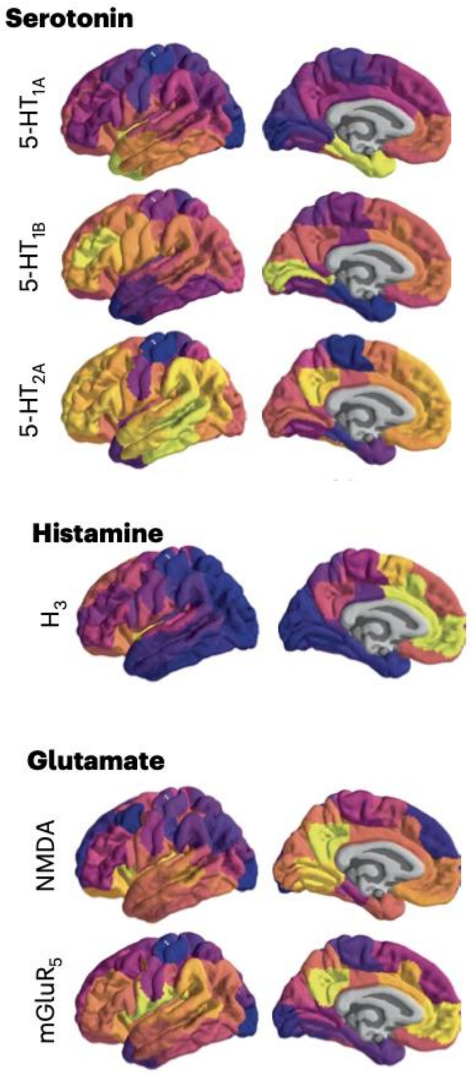


- Study principles of brain organization based on neurochemistry
- Are there trade-offs in the distribution of neurotransmitter systems?
- Examine those trade-offs.
- Analyse several neurotransmitter systems with ParTI.

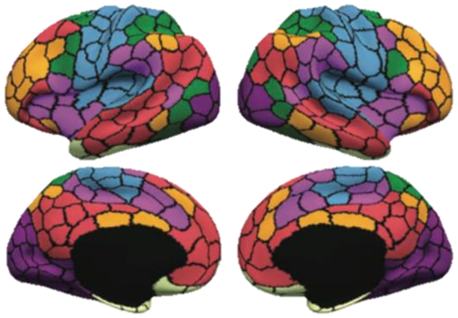
DATA: PET (HUMAN)

neuromaps

Subcategory	**source**
5-HT1a	savli2012
5-HT1b	gallezot2010
5-HT2a	savli2012
5-HT6	radnakrishnan2018
5-HTT	savli2012
a4b2	hillmer2016
CB1	normandin2015
D1	kaller2017
D2	malen2022
DAT	dukart2018
FDOPA	garciagomez2018
GABAa	kaulen2022
GABAa5	lukow2022
H3	gallezot2017
KOR	vijay2018
M1	naganawa2020
mGluR5	smart2019
MOR	kantonen2020
NET	ding2010
NMDA	galovic2021
VAChT	aghourian2017



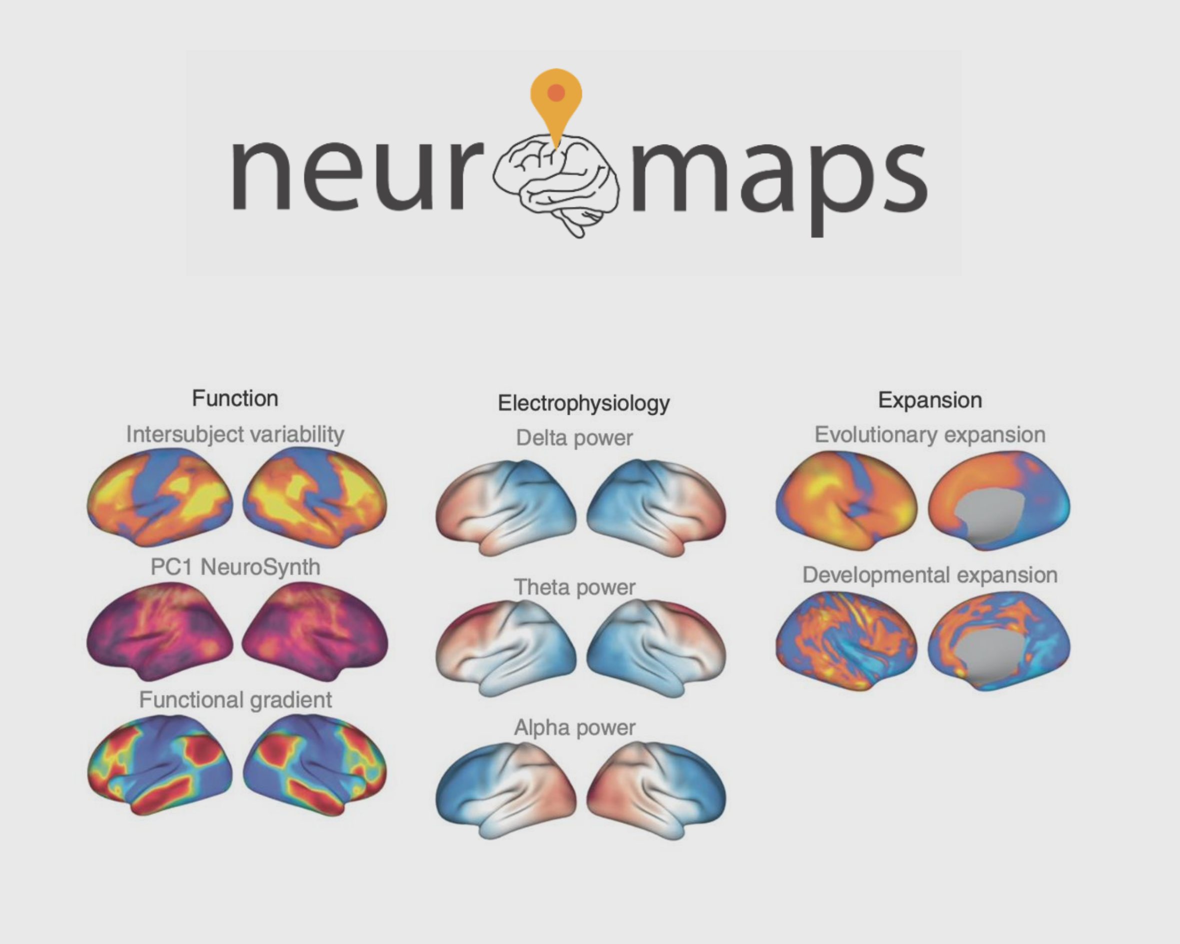
- Average over subjects in each study
- Parcellation with Schaefer atlas (1000)

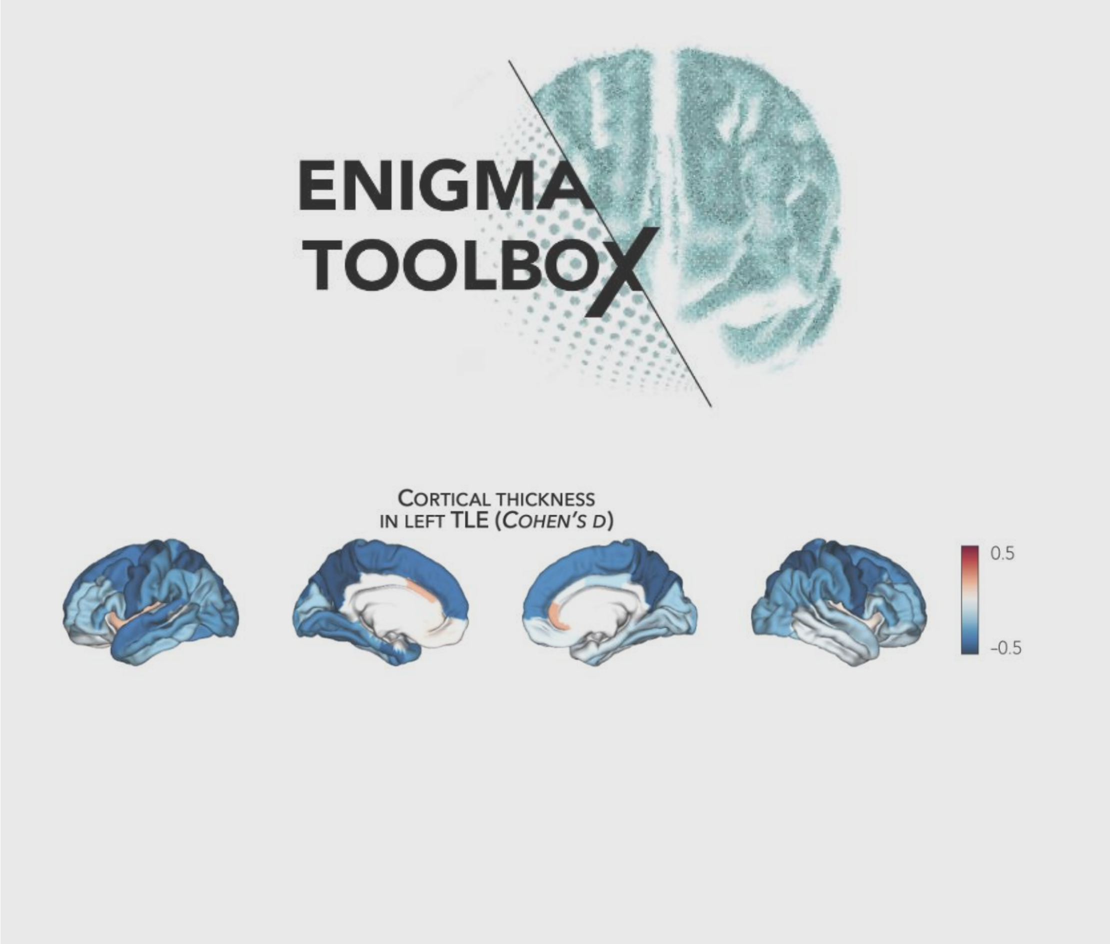


	5-HT1a	**5-HT1b**	**H3**	**NMDA**	**mGluR5 …**
Region 1					
…					
Region 1000					

Hansen, et al., 2022, *Nature Neuroscience*; Schaefer, et al., 2018, *Cereb. Cortex*

DATA: BRAIN PHENOTYPES

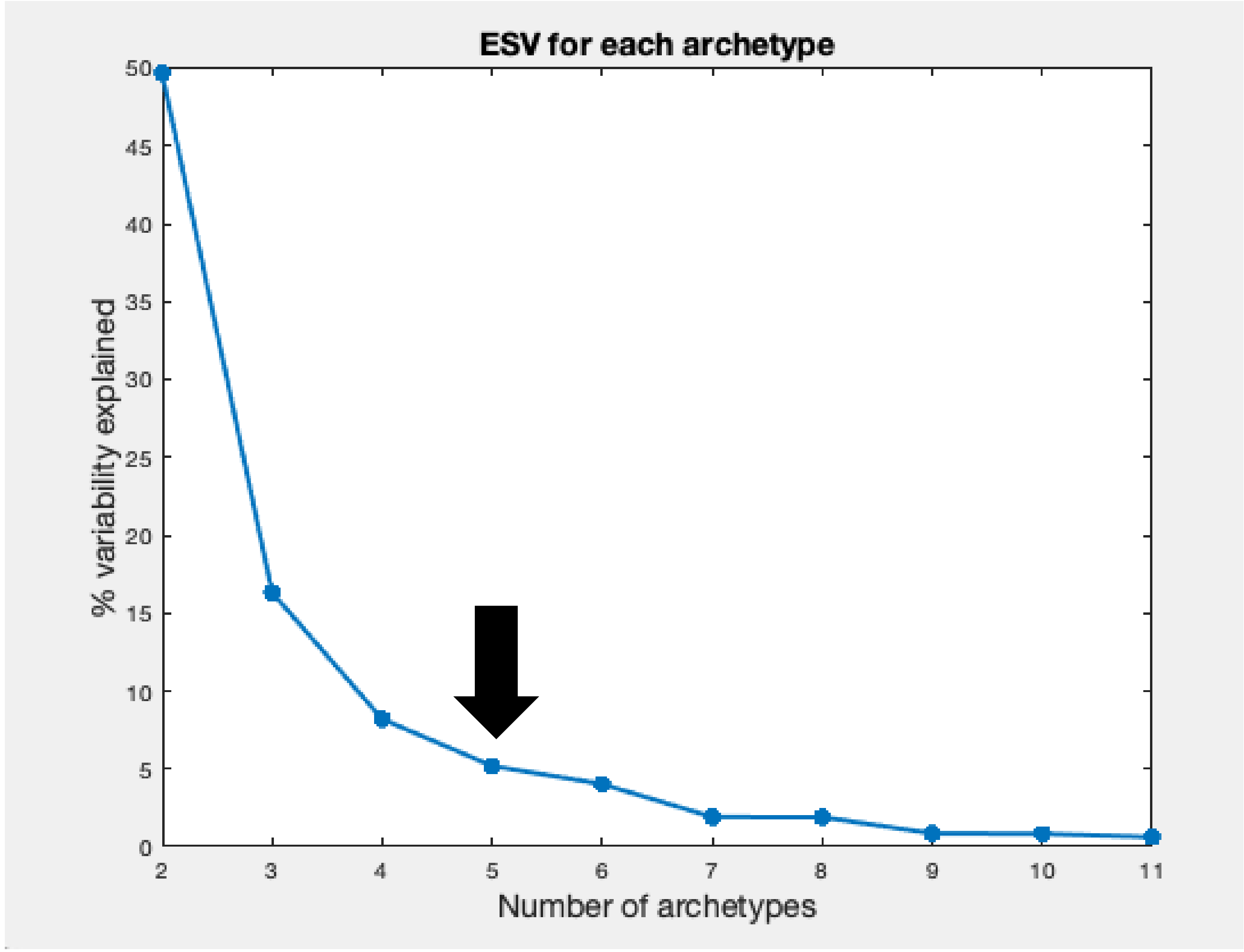




Hansen, et al., 2022, *Nature Neuroscience*; Markello, et al., 2022 *Nature Methods;* Lariviere; et al., 2021 *Nature Methods*

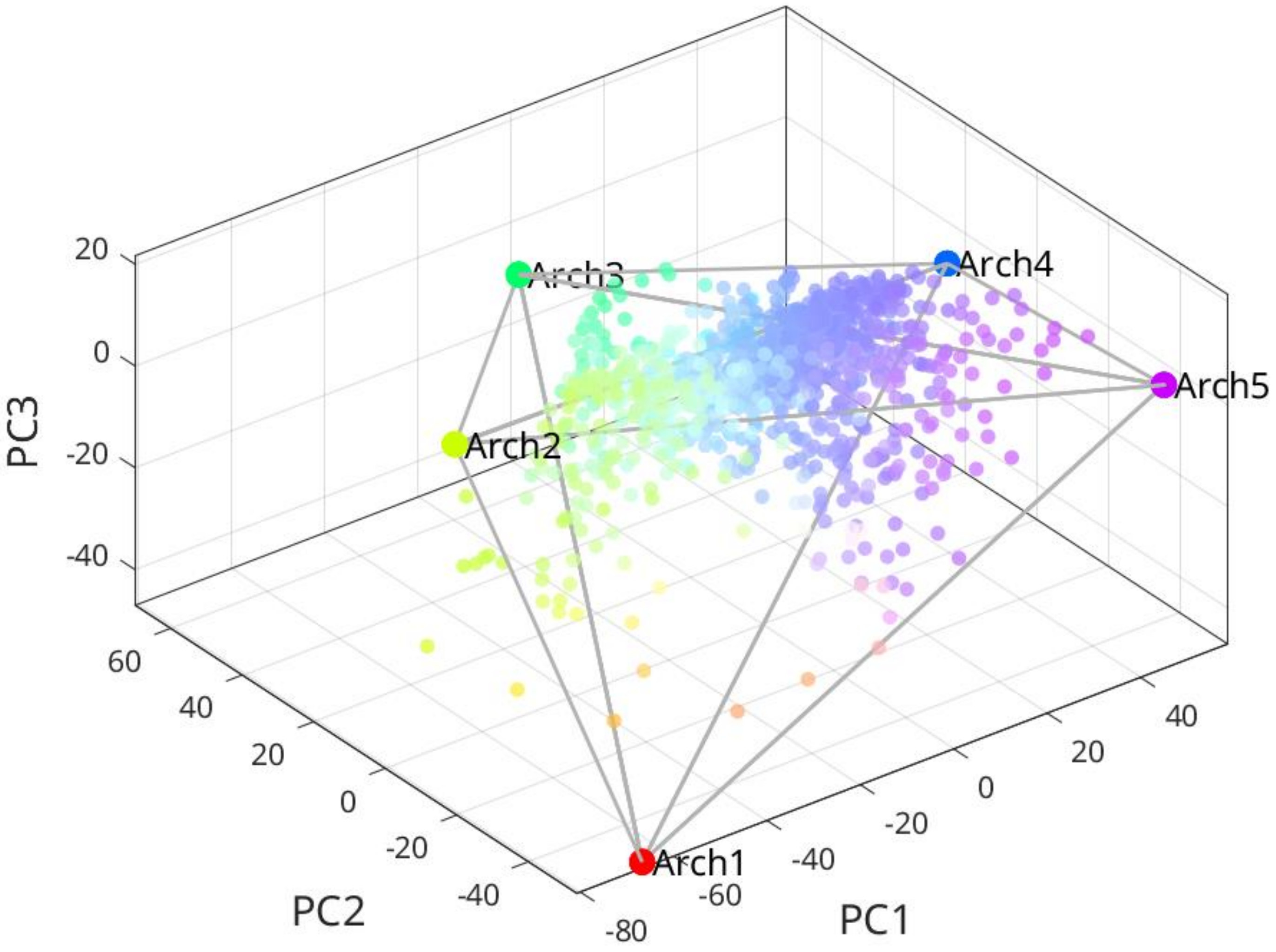
RESULTS

POLYTOPE WITH 5 VERTICES (ARCHETYPES)



- The elbow test suggests the polytope with 5 vertices has the best fit to the data.
- The model with 5 archetypes is significant (p-value = 0.012).

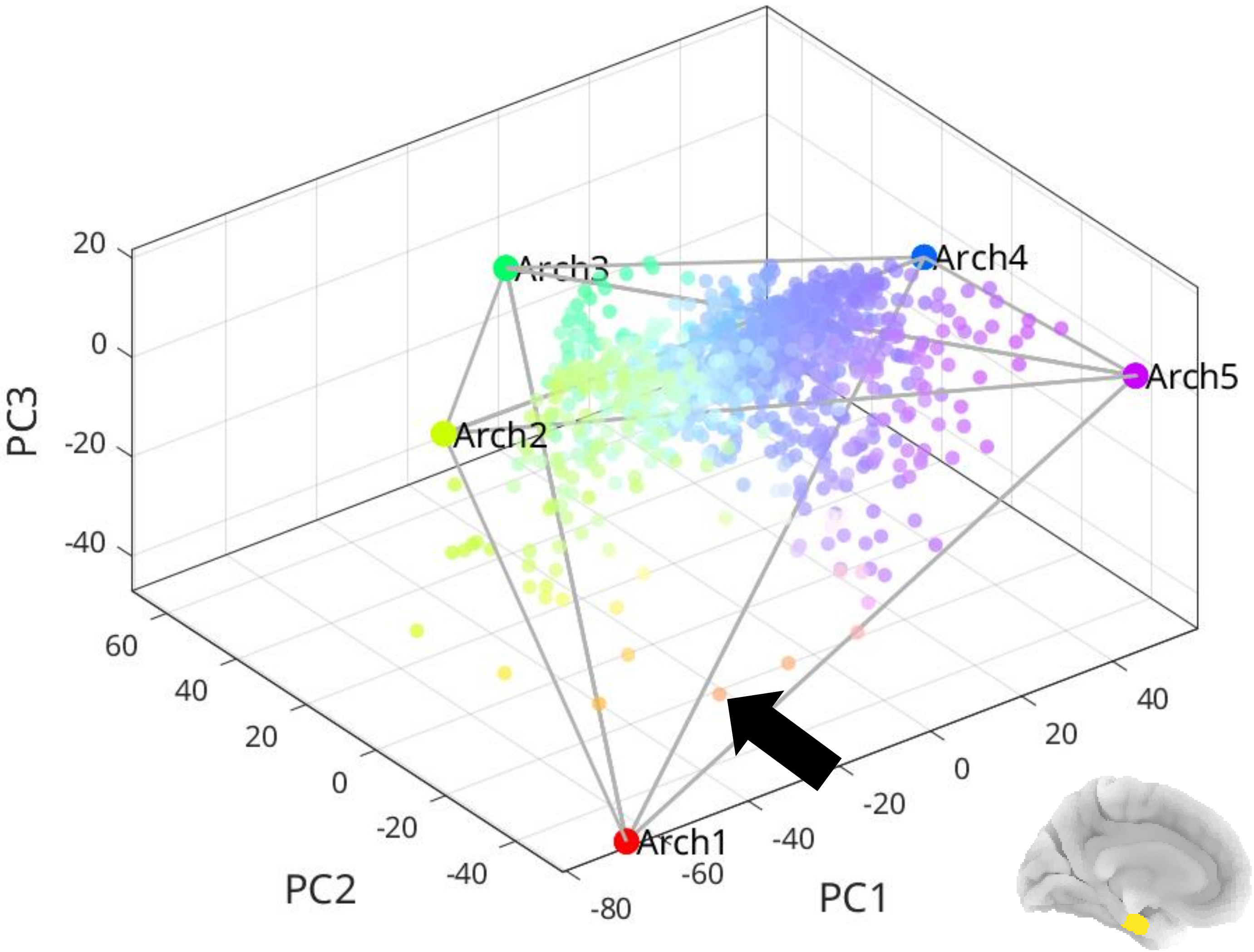
POLYTOPE WITH 5 VERTICES (ARCHETYPES)



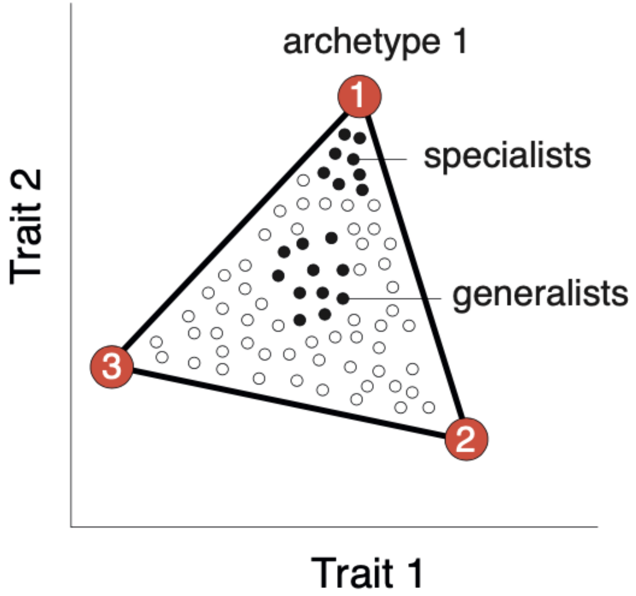
	5-HT1a	5-HT1b	H3	NMDA	mGluR5 …
Region 1					
…					
Region 1000					

	PC1	PC2	PC3	…	…
Region 1					
…					
Region 1000					

POLYTOPE WITH 5 VERTICES (ARCHETYPES)



- Each axis is a principal component reflecting neurochemical profiles.
- Each dot is one brain region.



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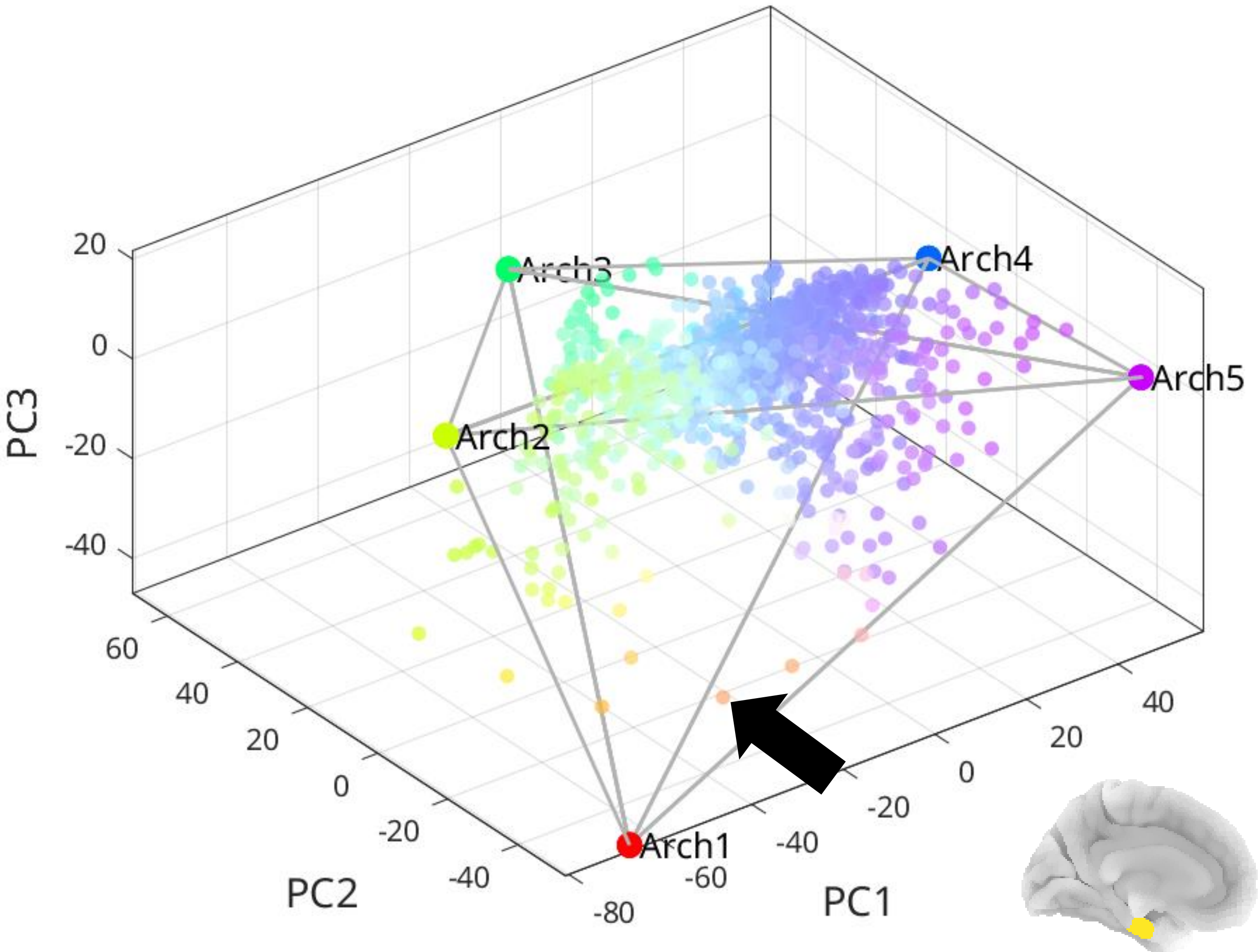
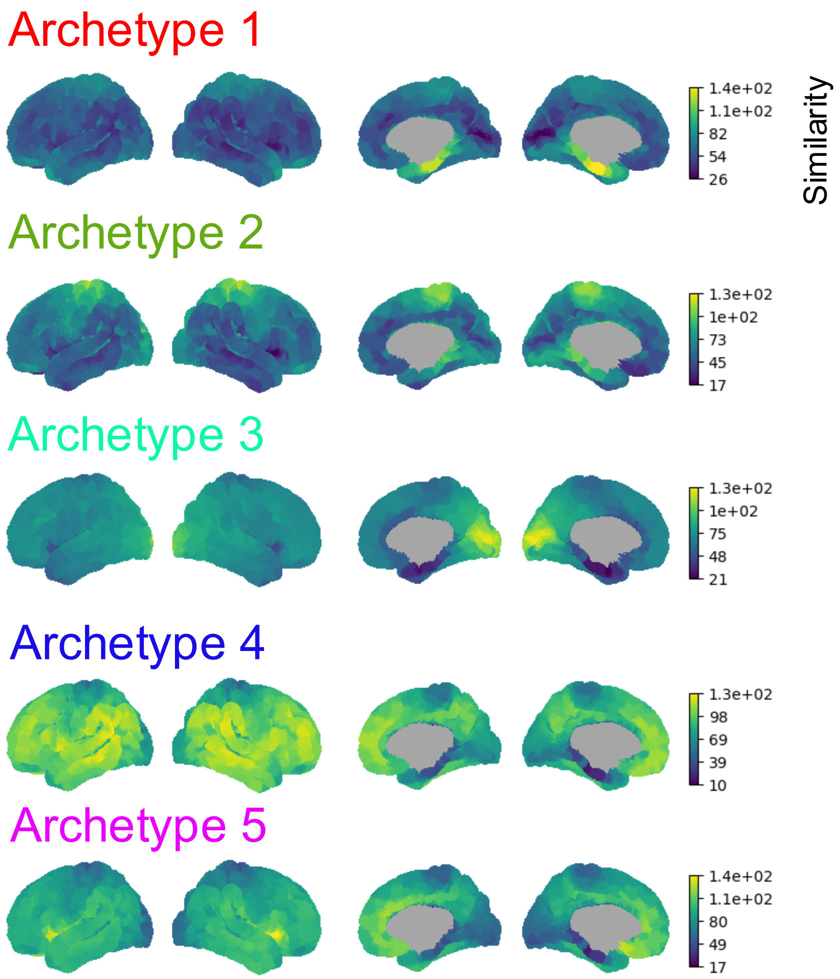
POLYTOPE WITH 5 VERTICES (ARCHETYPES)





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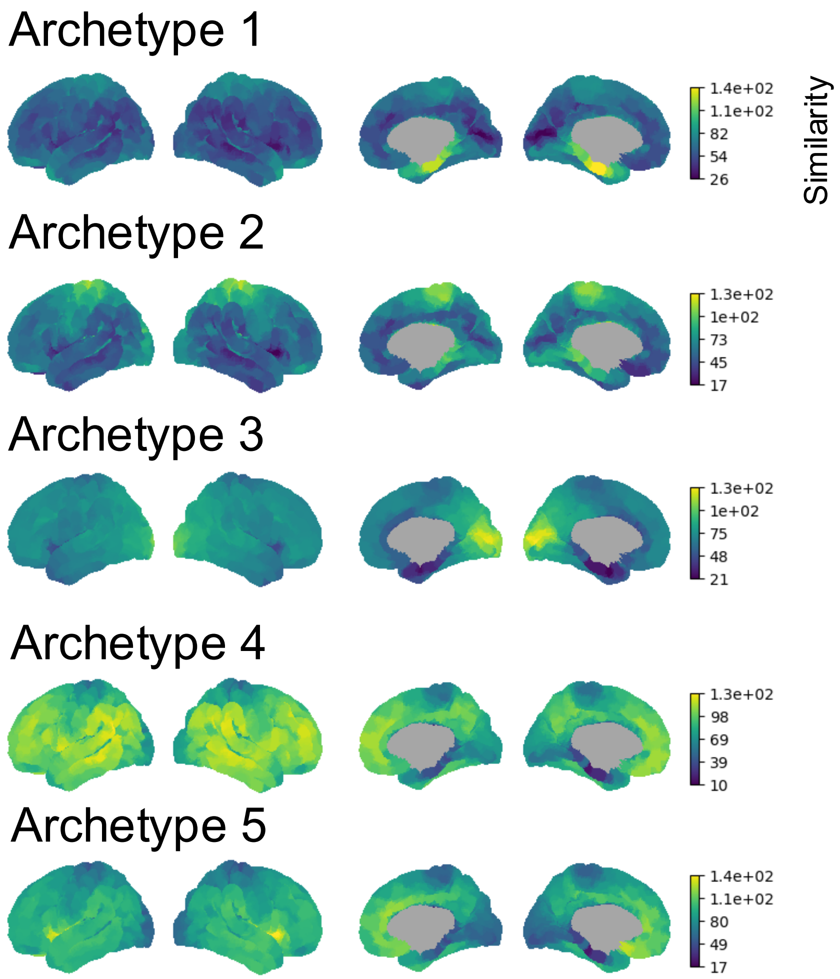
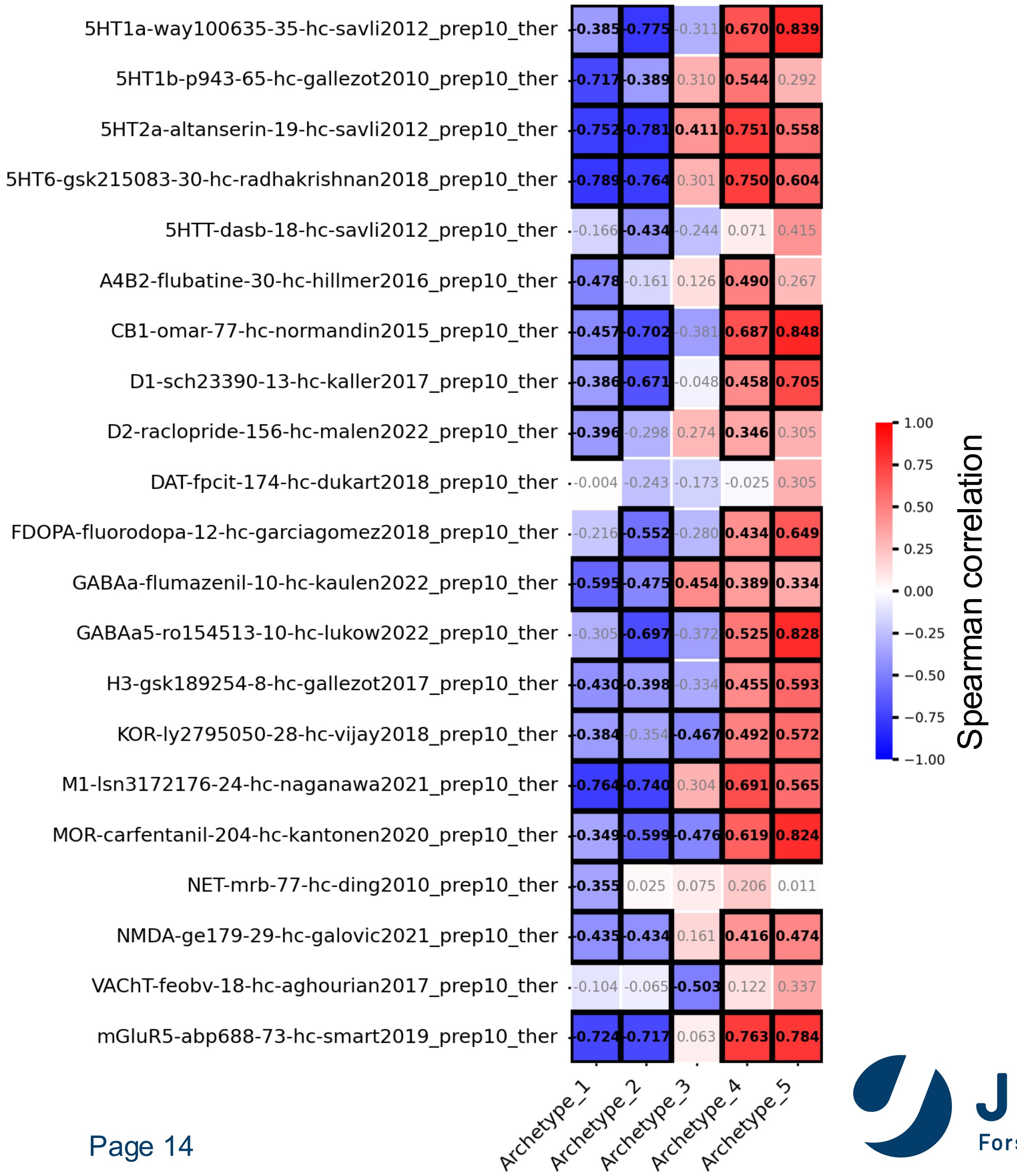
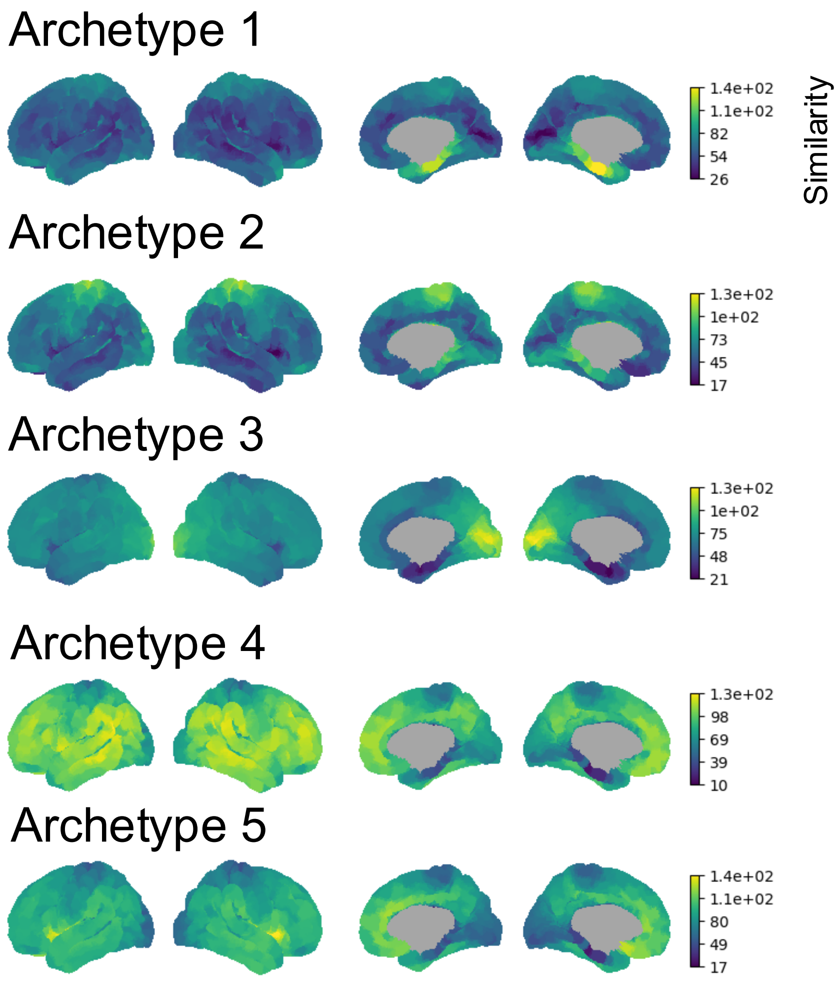
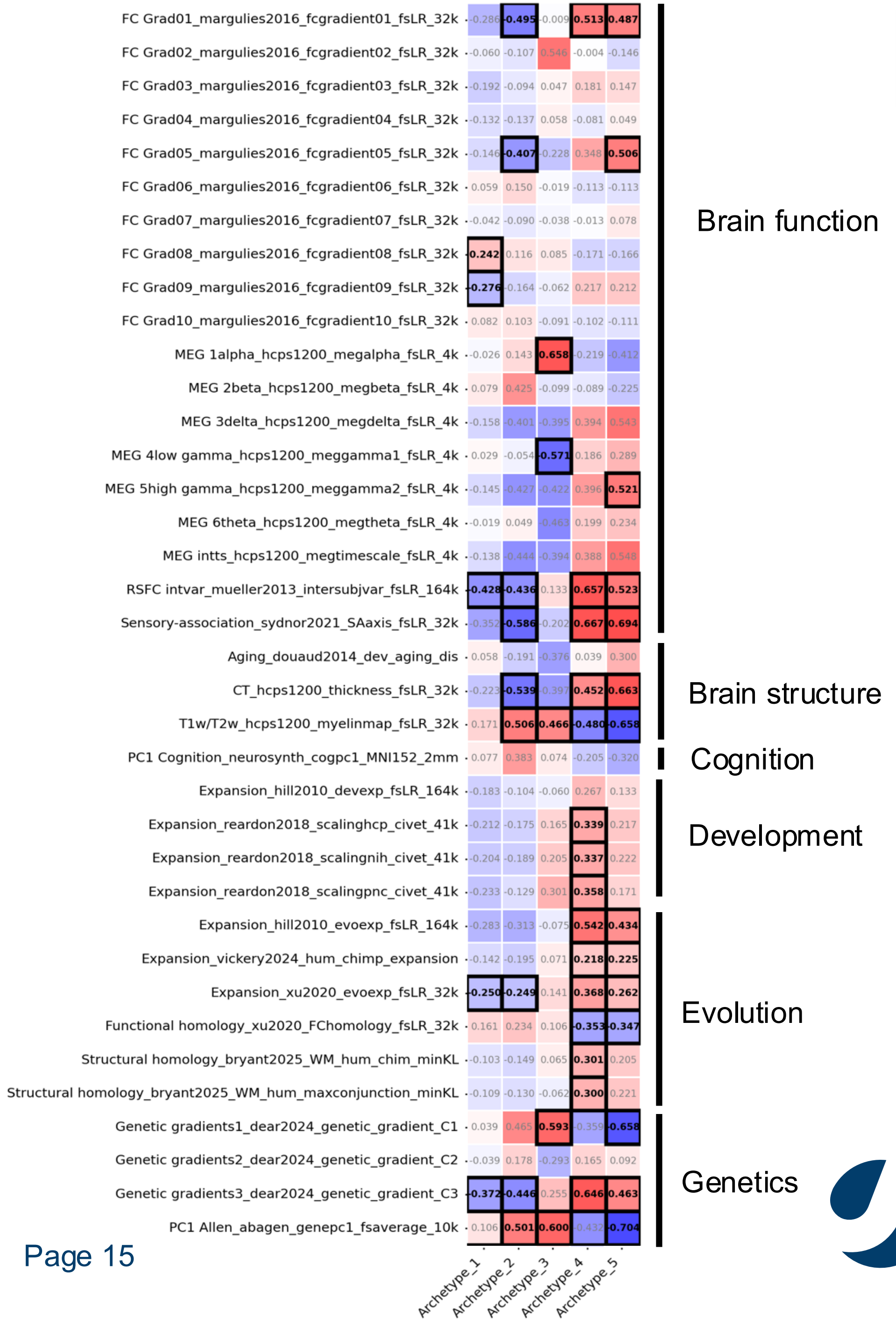
FEATURE ENRICHMENT





BRAIN PHENOTYPES





neuromaps

ENIGMA TOOLBOX

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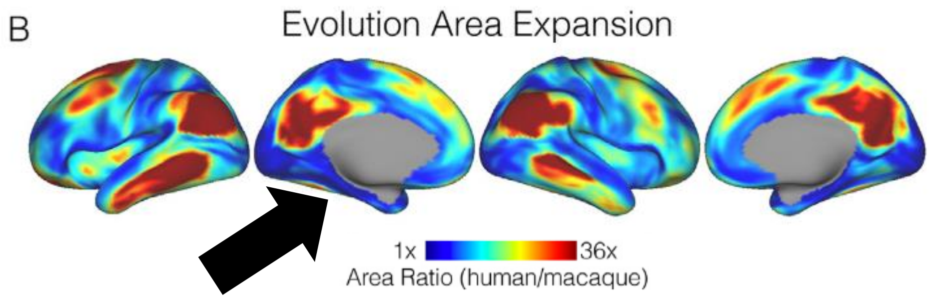
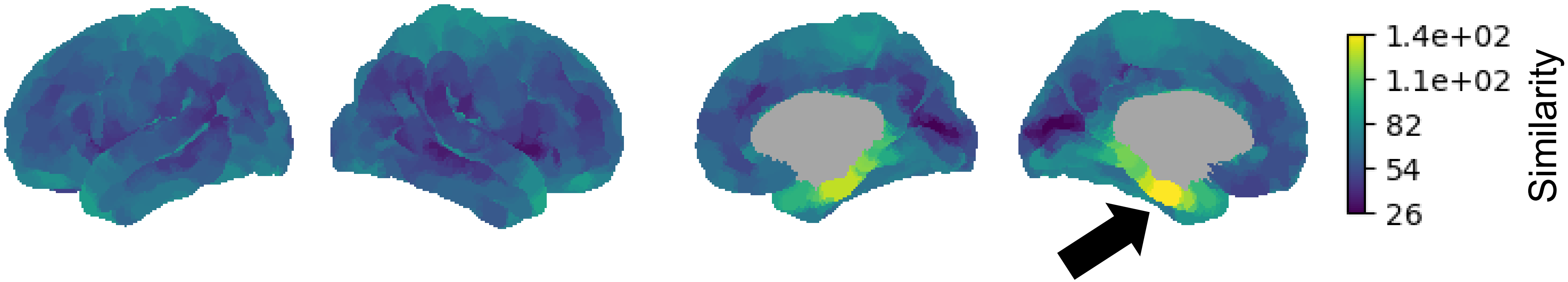
ARCHETYPE 1

Parahippocampal gyrus and allocortex

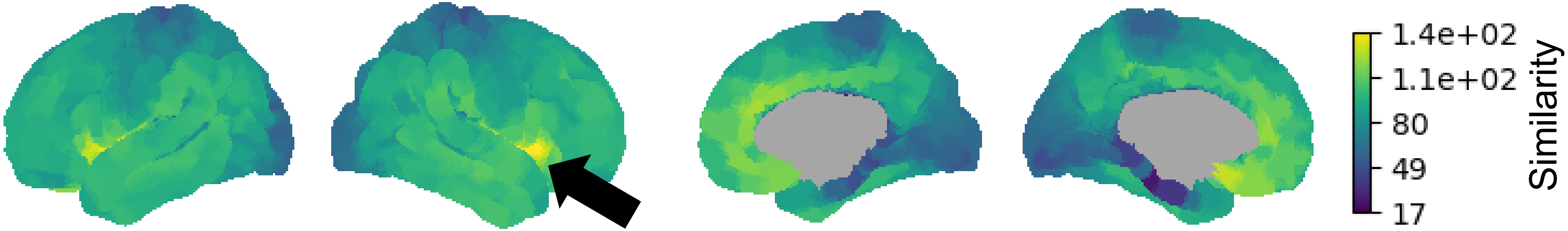




- Evolutionarily very old cortex.
- Not particularly enriched for any of the studied molecules.
- Neuromaps: Evolutionarily less expanded cortex (r = -0.25, p = 0.008).

ARCHETYPE 5

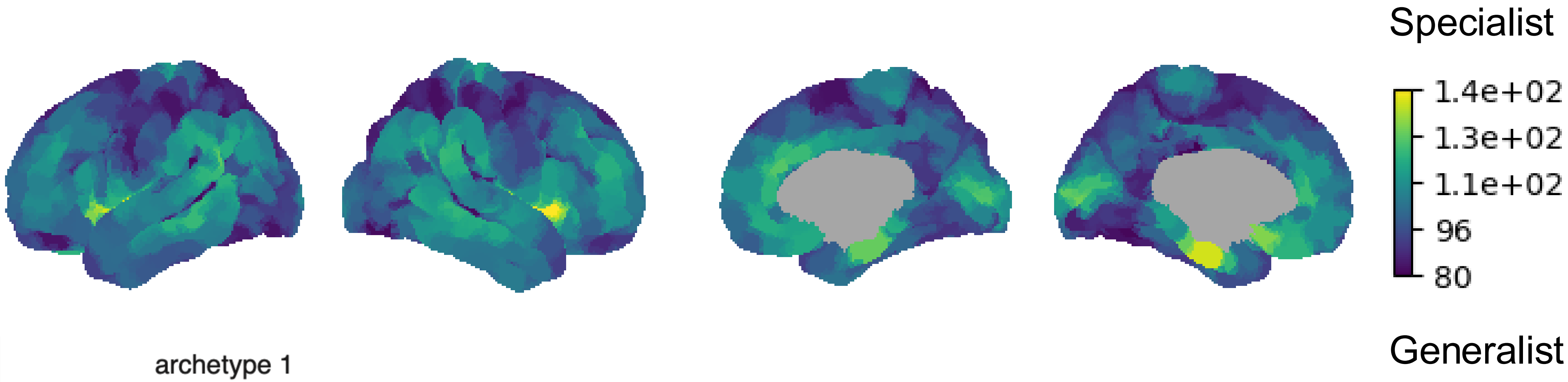
Insula

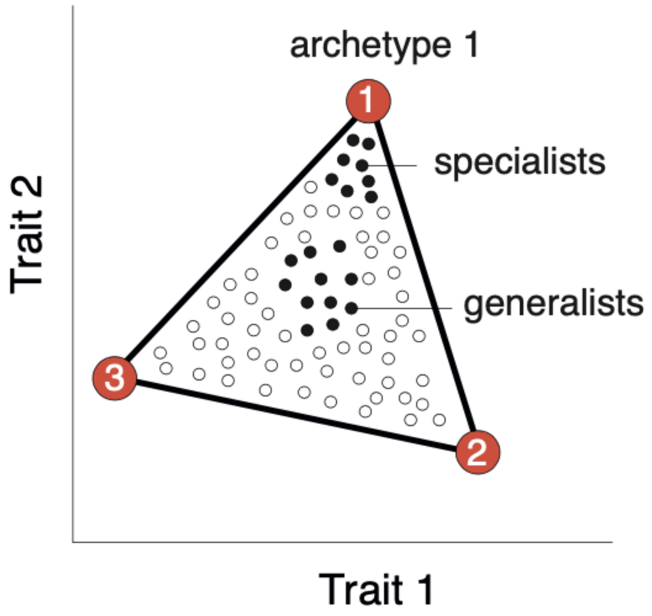


Feature enrichment:
Positive:
- Serotonin (5-HT1a, 5-HT2a, 5-HT6)
- CB1
- Dopamine (D1, FDOPA)
- GABA (GABAa, GABAa5)
- H3
- Opioid (KOR, MOR)
- Acetylcholine (M1)
- Glutamate (NMDA, mGluR5)

- Neuromaps and ENIGMA:
  - Most evolutionarily expansion (Hill2010: $r = 0.43$, $p = 0.29$; vickery2024: $r = 0.22$, $p = 0.02$; Xu2020: $r = 0.26$, $p = 0.01$).
  - Less functional homology (Xu2020: $r = -0.35$, $p = 0.006$).
  - High gamma (MEG) ($r = 0.52$, $p = 0.04$)
  - Depression ($r = -0.49$, $p = 0.04$)

GENERALIST VS SPECIALIST





- Neuromaps:
  - PC1 cognition (r = -0.25; p = 0.046)

ONGOING AND FUTURE ANALYSES

- Interpretation of results

- Cross-species comparison (macaques)

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CONCLUSION

- Neurotransmitter systems in the human brain reflect trade-offs that have influenced brain organisation

- These trade-offs appear to be linked with different:
  - receptors and transporters.
  - patterns of brain structure and function.
  - neuropsychiatric disorders.

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THANK YOU!

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Evolutionary optimization
of neuronal processing

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