



PETPARTI: TRADE-OFF ANALYSIS OF HUMAN BRAIN NEUROCHEMISTRY

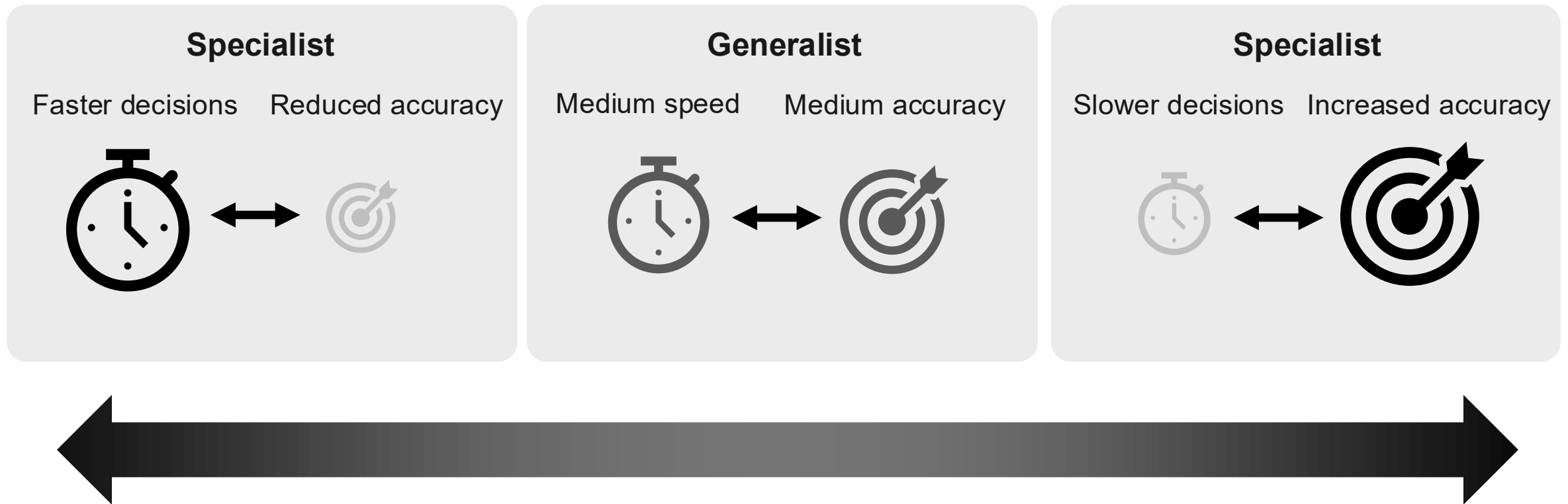
19/09/2025 | ELIANA NICOLAISEN-SOBESKY & DR. KAUSTUBH R. PATIL

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BIOLOGICAL SYSTEMS FACE TRADE-OFFS

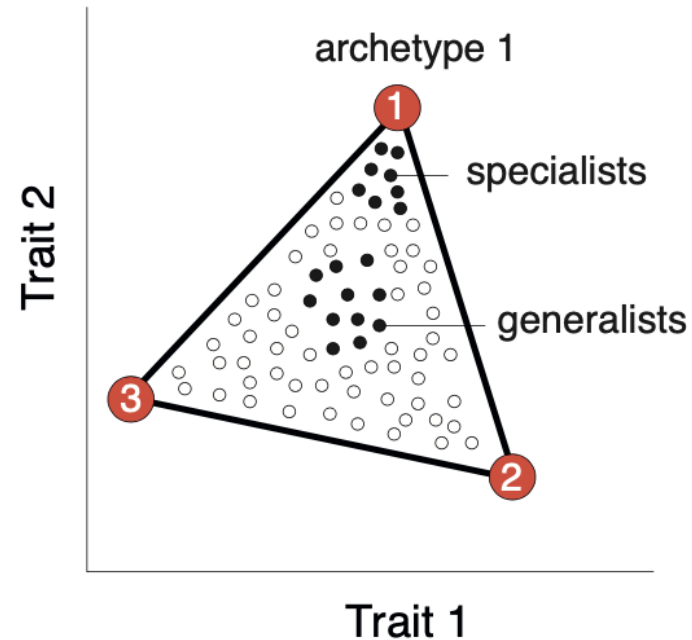
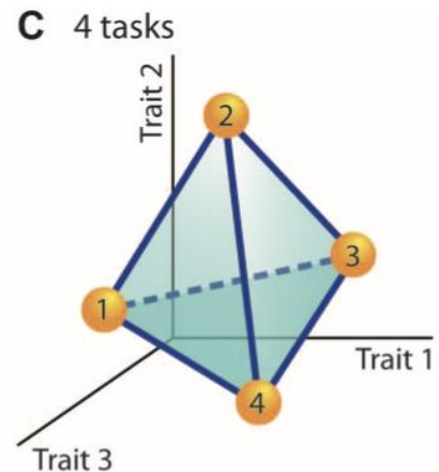
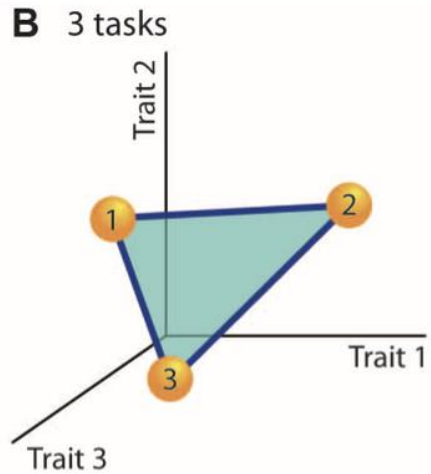
- Biological systems that need to perform multiple tasks face a trade-off: no system can be optimal for all tasks
- Trade-offs affect the range of phenotypes found in nature



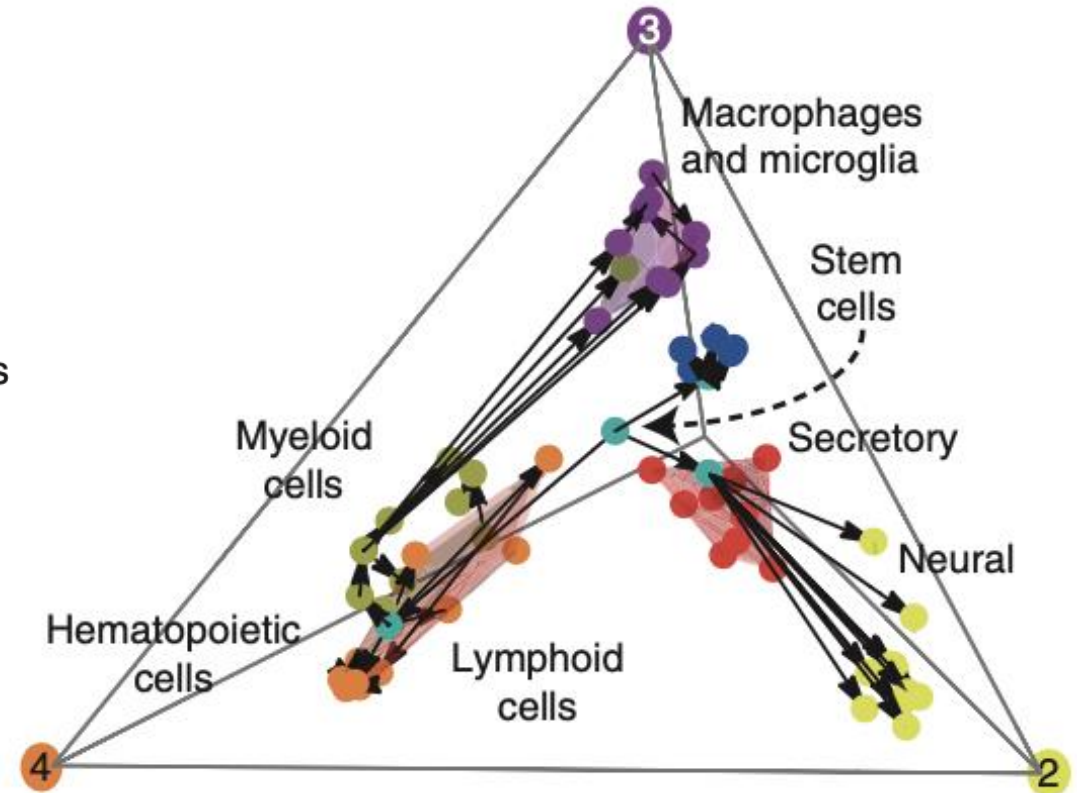
Hart et al., 2015, *Nature Methods*; Shoval et al., 2012, *Science*

HOW TO STUDY TRADE-OFFS

Pareto Task Inference (ParTI)



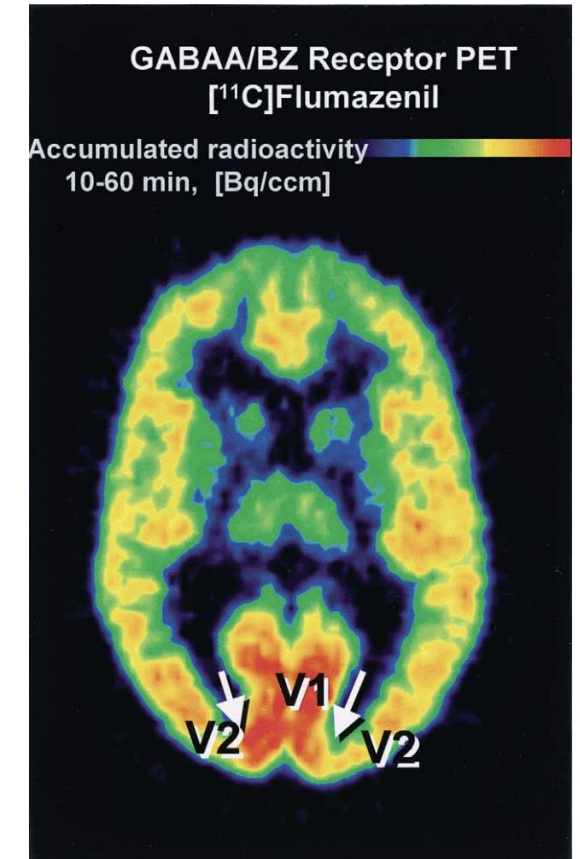
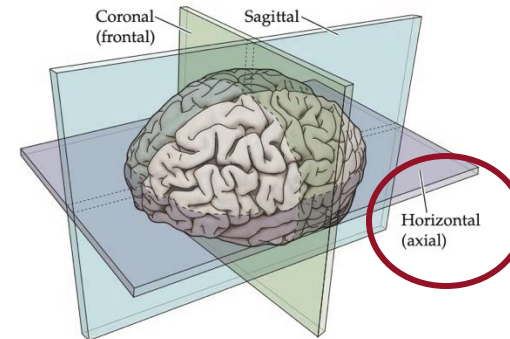
Each dot is a cell



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

NEUROTRANSMITTER SYSTEMS IN THE BRAIN

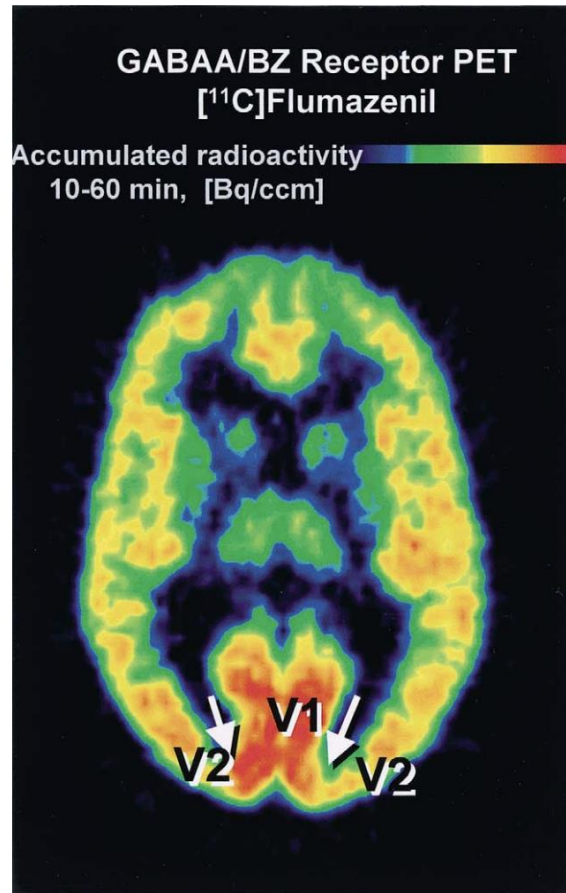
Positron emission tomography (PET)



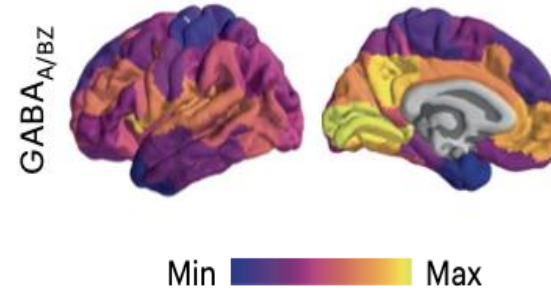
Zilles et al., 2002, *European Neuropsychopharmacology*; Purves et al., 2001, *Neuroscience*; Wikipedia

NEUROTRANSMITTER SYSTEMS IN THE BRAIN

Positron emission tomography (PET)



GABA

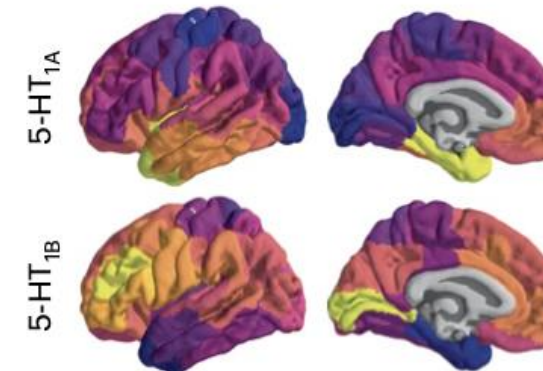


- Physiological functions (heart rate, respiration)

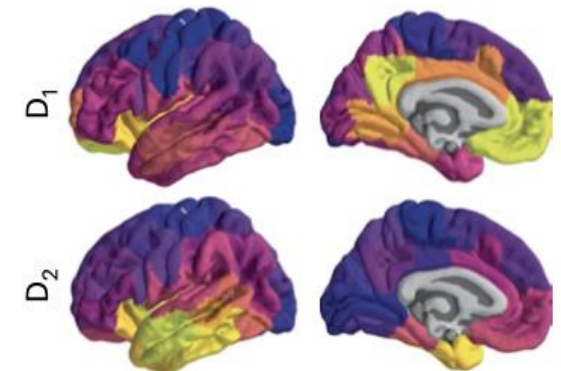


- Cognition and emotion

Serotonin



Dopamine

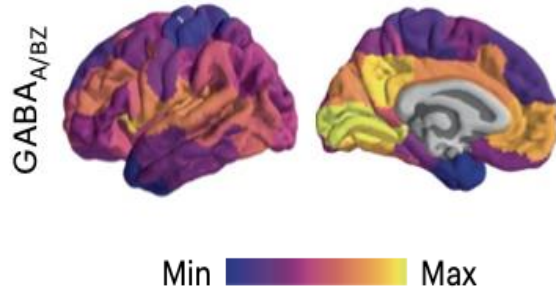


- Imbalances:
 - Epilepsy (glutamate)
 - Depression (GABA, glutamate, serotonin, dopamine and norepinephrine)

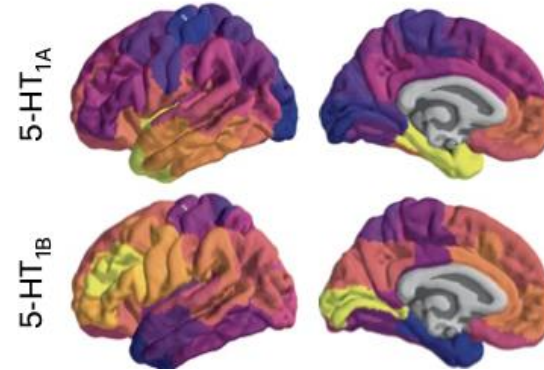
Zilles et al., 2002, *European Neuropsychopharmacology*; Hansen, et al., 2022 *Nature Neuroscience*

Brain neurochemistry

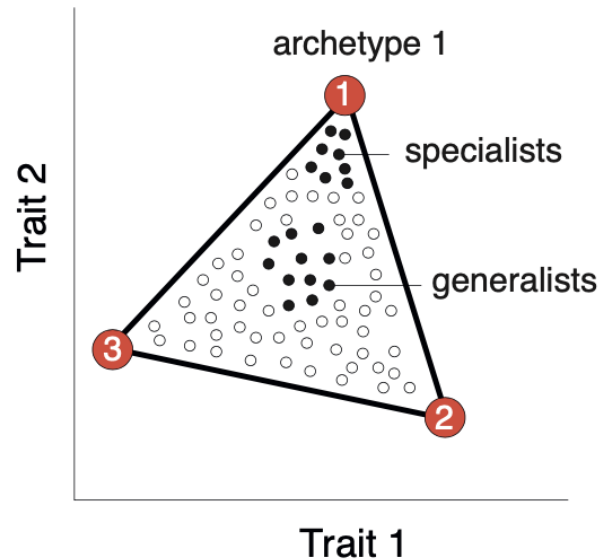
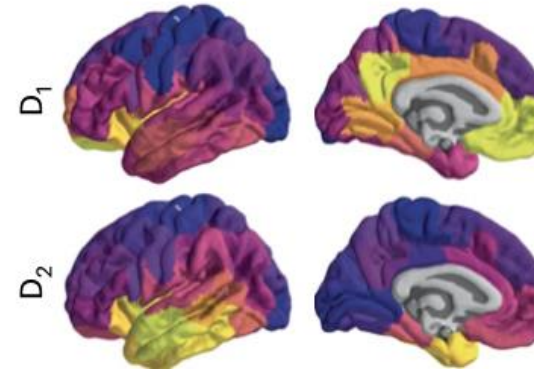
GABA



Serotonin



Dopamine

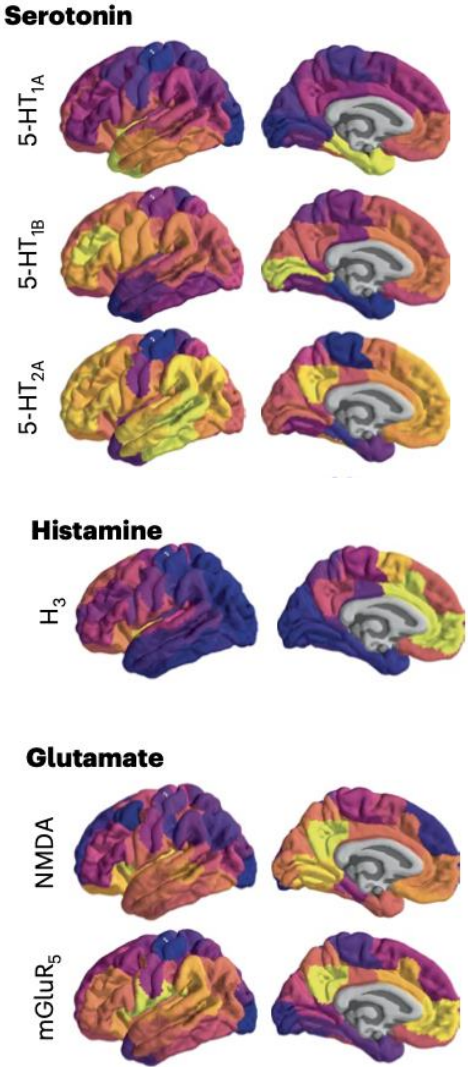


- Study principles of brain organization based on neurochemistry
- Are there trade-offs in the distribution of neurotransmitter systems?
- Examine those trade-offs.
- Analyse several neurotransmitter systems with ParTI.

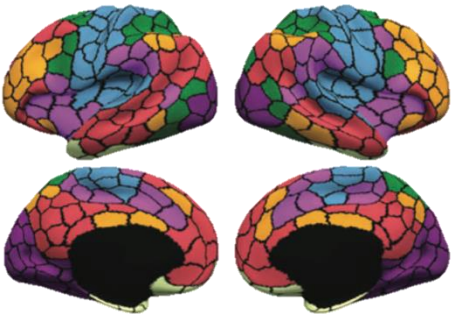
DATA: PET (HUMAN)



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



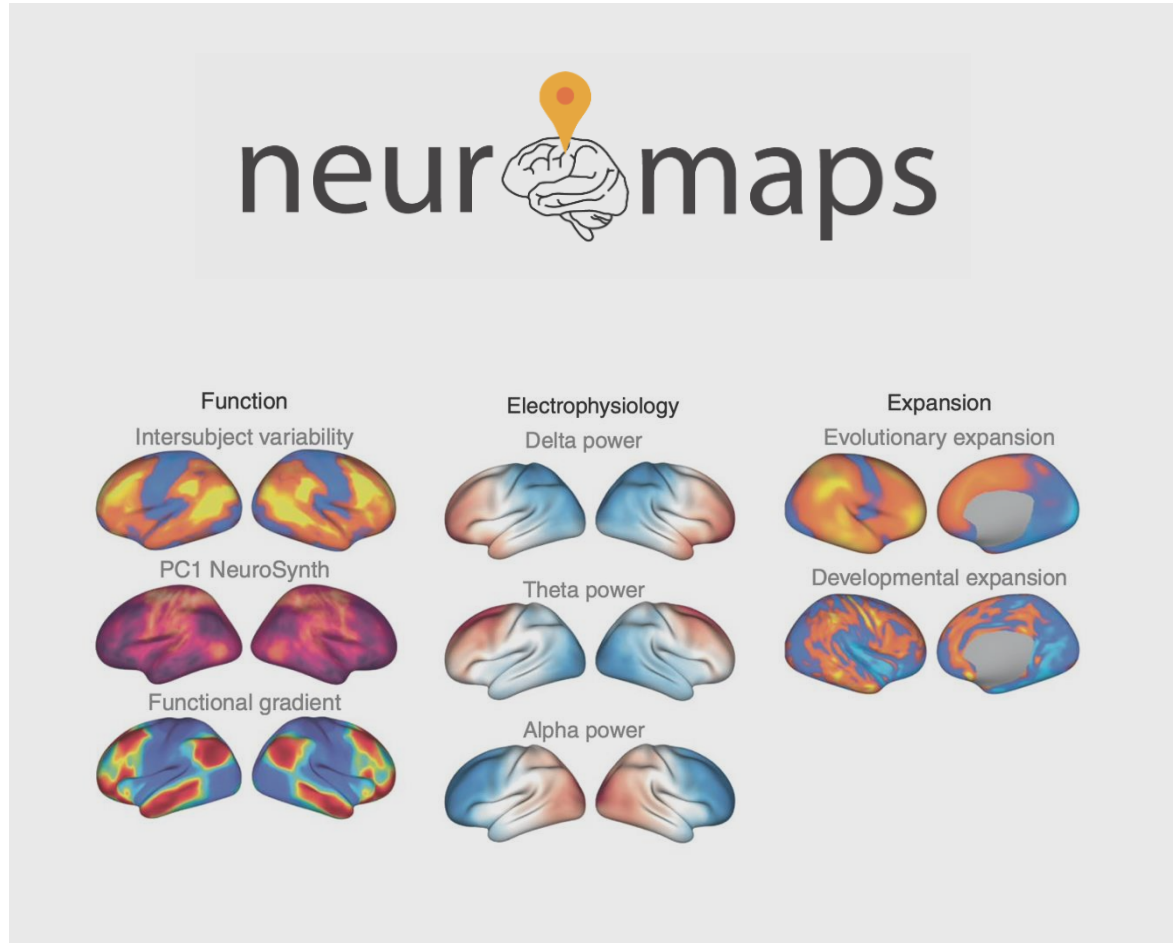
- Average over subjects in each study
- Parcellation with Schaefer atlas (1000)



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

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

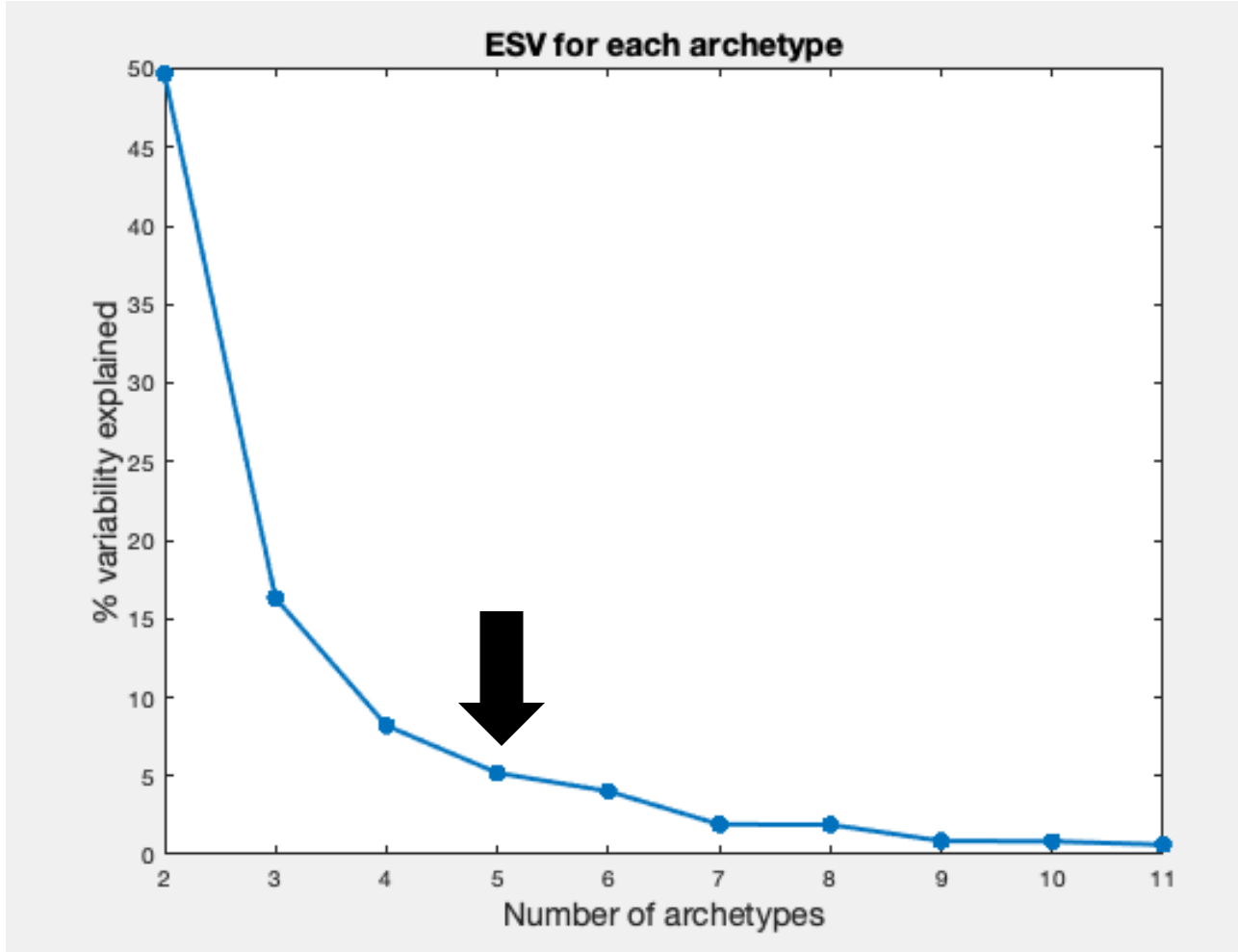
DATA: BRAIN PHENOTYPES



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

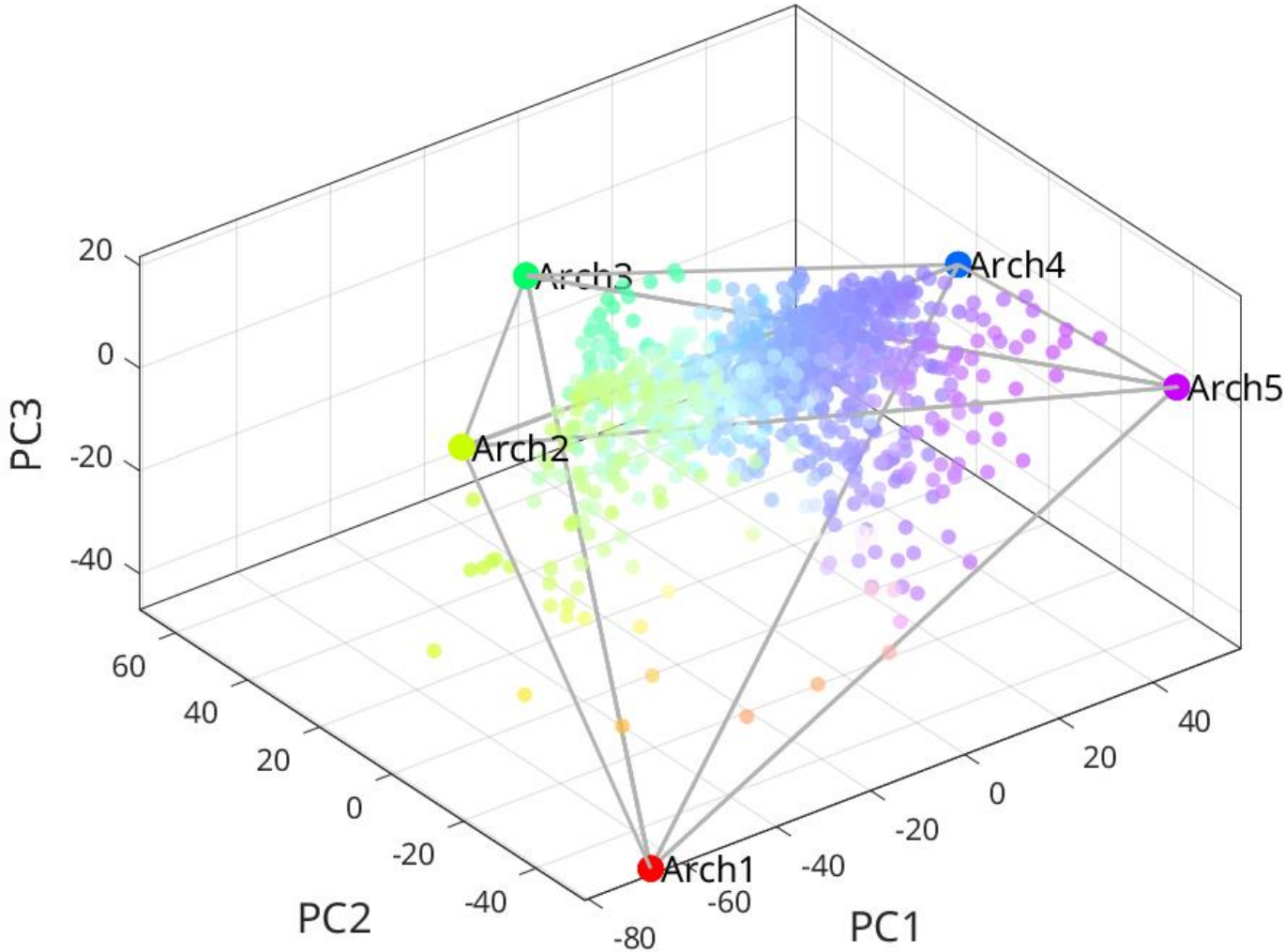
RESULTS

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).

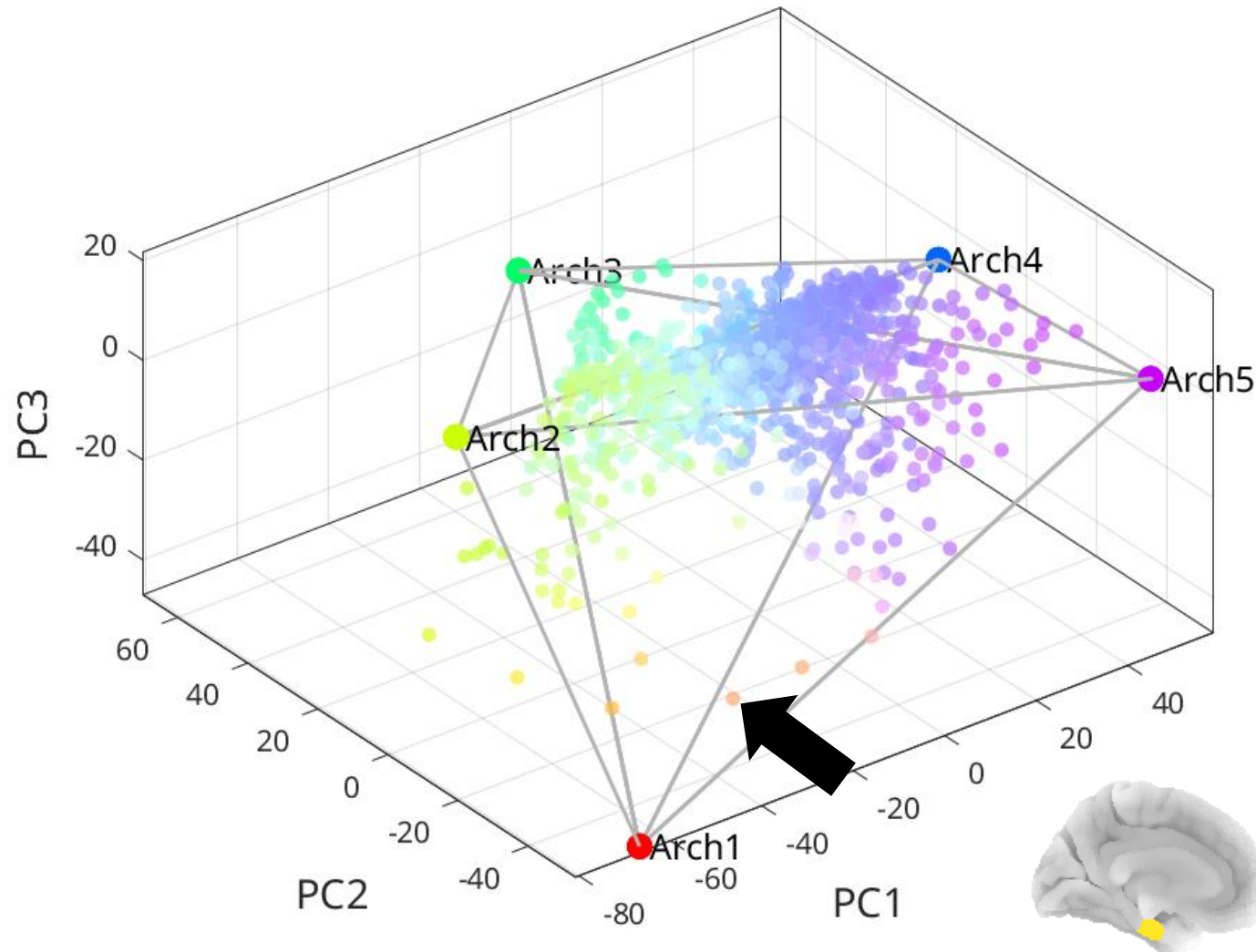
POLYTOPE WITH 5 VERTICES (ARCHETYPES)



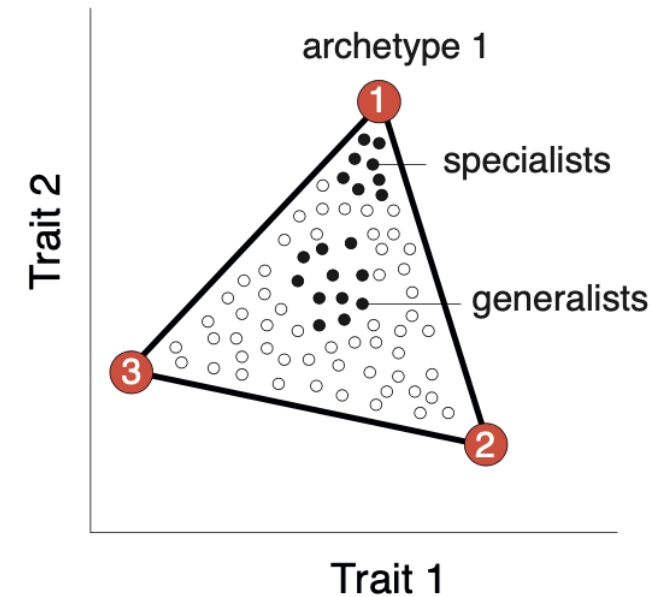
	5-HT1a	5-HT1b	H3	NMDA	mGluR5 ...
Region 1					
...					
Region 1000					

	PC1	PC2	PC3	...	...
Region 1					
...					
Region 1000					

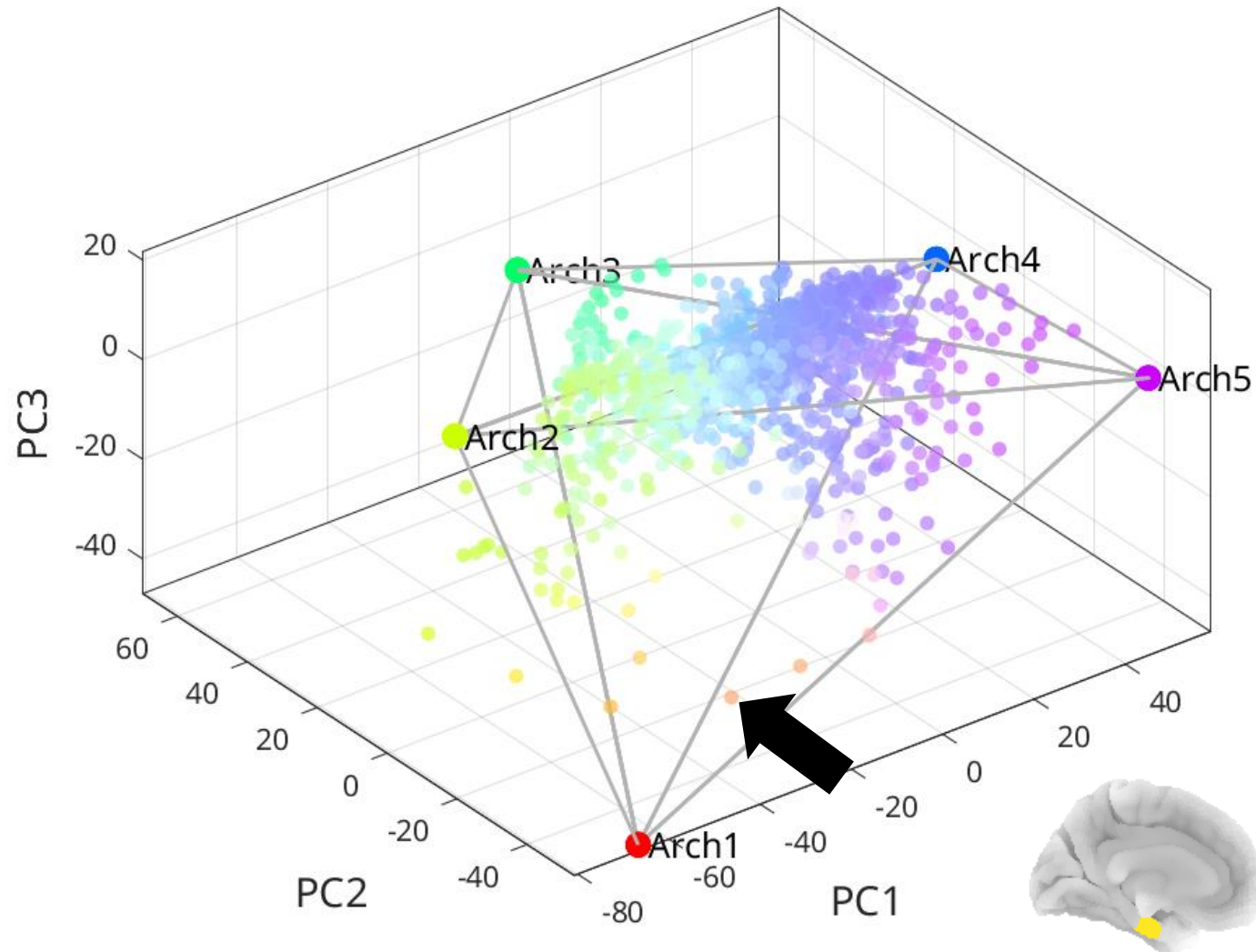
POLYTOPE WITH 5 VERTICES (ARCHETYPES)



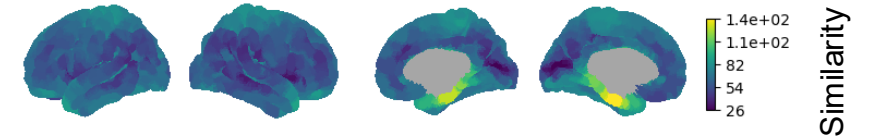
- Each axis is a principal component reflecting neurochemical profiles.
- Each dot is one brain region.



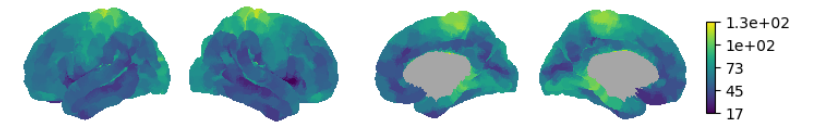
POLYTOPE WITH 5 VERTICES (ARCHETYPES)



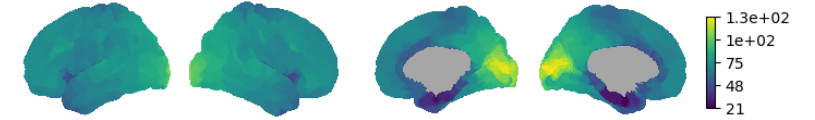
Archetype 1



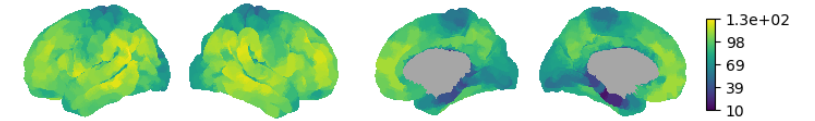
Archetype 2



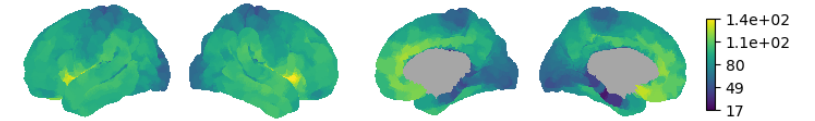
Archetype 3



Archetype 4

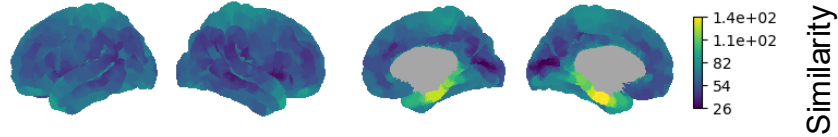


Archetype 5

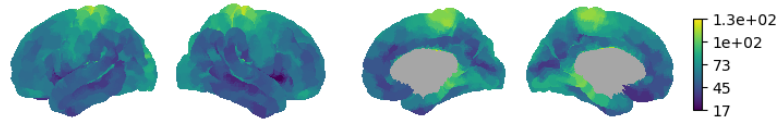


FEATURE ENRICHMENT

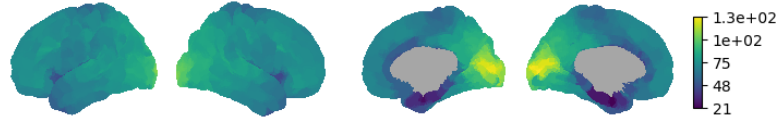
Archetype 1



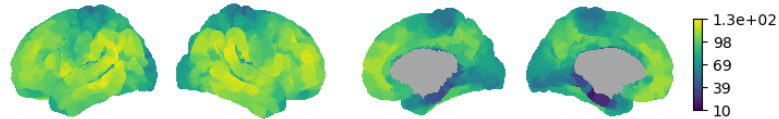
Archetype 2



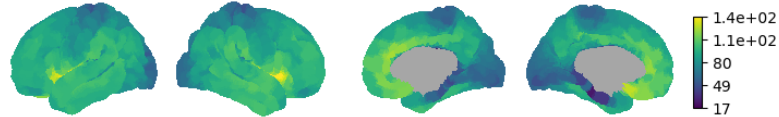
Archetype 3



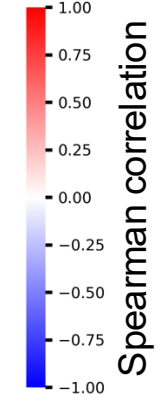
Archetype 4



Archetype 5



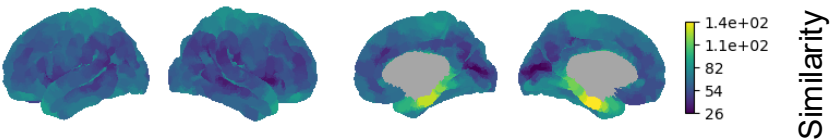
5HT1a-way100635-35-hc-savli2012_prep10_ther	-0.385	-0.775	-0.311	0.670	0.839
5HT1b-p943-65-hc-gallezot2010_prep10_ther	-0.717	-0.389	0.310	0.544	0.292
5HT2a-altanserlin-19-hc-savli2012_prep10_ther	-0.752	-0.781	0.411	0.751	0.558
5HT6-gsk215083-30-hc-radhakrishnan2018_prep10_ther	-0.789	-0.764	0.301	0.750	0.604
5HTT-dasb-18-hc-savli2012_prep10_ther	-0.166	-0.434	-0.244	0.071	0.415
A4B2-flubatine-30-hc-hillmer2016_prep10_ther	-0.478	-0.161	0.126	0.490	0.267
CB1-omar-77-hc-normandin2015_prep10_ther	-0.457	-0.702	-0.381	0.687	0.848
D1-sch23390-13-hc-kaller2017_prep10_ther	-0.386	-0.671	-0.048	0.458	0.705
D2-raclopride-156-hc-malen2022_prep10_ther	-0.396	-0.298	0.274	0.346	0.305
DAT-fpcit-174-hc-dukart2018_prep10_ther	-0.004	-0.243	-0.173	-0.025	0.305
FDOPA-fluorodopa-12-hc-garciagomez2018_prep10_ther	-0.216	-0.552	-0.280	0.434	0.649
GABAA-flumazenil-10-hc-kaulen2022_prep10_ther	-0.595	-0.475	0.454	0.389	0.334
GABAA5-ro154513-10-hc-lukow2022_prep10_ther	-0.305	-0.697	-0.372	0.525	0.828
H3-gsk189254-8-hc-gallezot2017_prep10_ther	-0.430	-0.398	-0.334	0.455	0.593
KOR-ly2795050-28-hc-vijay2018_prep10_ther	-0.384	-0.354	-0.467	0.492	0.572
M1-lsn3172176-24-hc-naganawa2021_prep10_ther	-0.764	-0.740	0.304	0.691	0.565
MOR-carfentanil-204-hc-kantonen2020_prep10_ther	-0.349	-0.599	-0.476	0.619	0.824
NET-mrb-77-hc-ding2010_prep10_ther	-0.355	0.025	0.075	0.206	0.011
NMDA-ge179-29-hc-galovic2021_prep10_ther	-0.435	-0.434	0.161	0.416	0.474
VACHT-feobv-18-hc-aghourian2017_prep10_ther	-0.104	-0.065	-0.503	0.122	0.337
mGluR5-abp688-73-hc-smart2019_prep10_ther	-0.724	-0.717	0.063	0.763	0.784



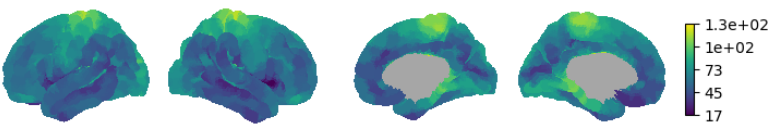
Archetype_1
Archetype_2
Archetype_3
Archetype_4
Archetype_5

BRAIN PHENOTYPES

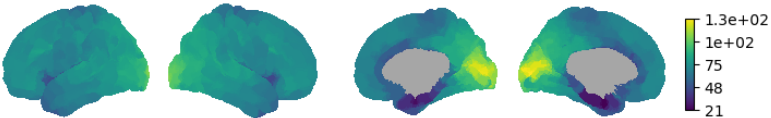
Archetype 1



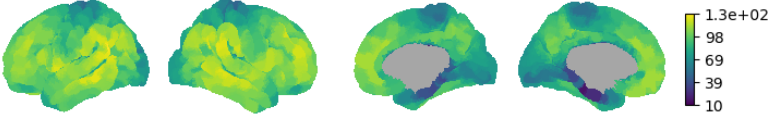
Archetype 2



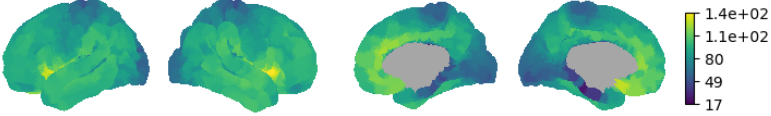
Archetype 3



Archetype 4



Archetype 5



Similarity

FC Grad01_margulies2016_fcgradient01_fsLR_32k	-0.284	-0.495	-0.009	0.513	0.487
FC Grad02_margulies2016_fcgradient02_fsLR_32k	-0.060	-0.107	0.548	-0.004	-0.146
FC Grad03_margulies2016_fcgradient03_fsLR_32k	-0.192	-0.094	0.047	0.181	0.147
FC Grad04_margulies2016_fcgradient04_fsLR_32k	-0.132	-0.137	0.058	-0.081	0.049
FC Grad05_margulies2016_fcgradient05_fsLR_32k	-0.144	-0.407	0.228	0.348	0.506
FC Grad06_margulies2016_fcgradient06_fsLR_32k	-0.059	0.150	-0.019	-0.113	-0.113
FC Grad07_margulies2016_fcgradient07_fsLR_32k	-0.042	-0.090	-0.038	-0.013	0.078
FC Grad08_margulies2016_fcgradient08_fsLR_32k	0.242	0.116	0.085	-0.171	-0.166
FC Grad09_margulies2016_fcgradient09_fsLR_32k	0.276	0.164	-0.062	0.217	0.212
FC Grad10_margulies2016_fcgradient10_fsLR_32k	0.082	0.103	-0.091	-0.102	-0.111
MEG 1alpha_hcps1200_megalpha_fsLR_4k	-0.026	0.143	0.658	0.219	0.412
MEG 2beta_hcps1200_megbeta_fsLR_4k	-0.079	0.425	-0.099	-0.089	-0.225
MEG 3delta_hcps1200_megdelta_fsLR_4k	-0.158	0.401	0.395	0.394	0.543
MEG 4low gamma_hcps1200_meggamma1_fsLR_4k	-0.029	-0.054	0.571	0.186	0.289
MEG 5high gamma_hcps1200_meggamma2_fsLR_4k	-0.145	0.417	0.422	0.396	0.521
MEG 6theta_hcps1200_megtheta_fsLR_4k	-0.019	0.049	0.463	0.199	0.234
MEG intts_hcps1200_megtimescale_fsLR_4k	-0.138	0.444	0.394	0.388	0.548
RSFC intvar_mueller2013_intersubjvar_fsLR_164k	-0.428	-0.436	0.133	0.657	0.523
Sensory-association_sydnor2021_SAaxis_fsLR_32k	-0.357	-0.586	-0.202	0.667	0.694
Aging_douaud2014_dev_aging_dis	-0.058	-0.191	-0.376	0.039	0.300
CT_hcps1200_thickness_fsLR_32k	-0.223	-0.539	0.397	0.452	0.663
T1w/T2w_hcps1200_myelinmap_fsLR_32k	-0.171	0.506	0.466	0.480	0.658
PC1 Cognition_neurosynth_cogpc1_MNI152_2mm	-0.077	0.383	0.074	-0.205	-0.320
Expansion_hill2010_devepx_fsLR_164k	-0.183	-0.104	-0.060	0.267	0.133
Expansion_reardon2018_scalinghcp_civet_41k	-0.212	-0.175	0.165	0.339	0.217
Expansion_reardon2018_scalingnih_civet_41k	-0.204	-0.189	0.205	0.337	0.222
Expansion_reardon2018_scalingpnc_civet_41k	-0.233	-0.129	0.301	0.358	0.171
Expansion_hill2010_evoexp_fsLR_164k	-0.283	-0.313	-0.075	0.542	0.434
Expansion_vickery2024_hum_chimp_expansion	-0.142	-0.195	0.071	0.218	0.225
Expansion_xu2020_evoexp_fsLR_32k	-0.250	-0.249	0.141	0.368	0.262
Functional homology_xu2020_FChomology_fsLR_32k	-0.161	0.234	0.106	-0.353	-0.347
Structural homology_bryant2025_WM_hum_chim_minKL	-0.103	-0.149	0.065	0.301	0.205
Structural homology_bryant2025_WM_hum_maxconjunction_minKL	-0.109	-0.130	-0.062	0.300	0.221
Genetic gradients1_dear2024_genetic_gradient_C1	-0.039	0.465	0.593	0.359	0.658
Genetic gradients2_dear2024_genetic_gradient_C2	-0.039	0.178	0.293	0.165	0.092
Genetic gradients3_dear2024_genetic_gradient_C3	-0.372	-0.446	0.255	0.646	0.463
PC1 Allen_abagen_geneipc1_fsaverage_10k	-0.106	0.501	0.600	0.432	0.704

Brain function

Brain structure

Cognition

Development

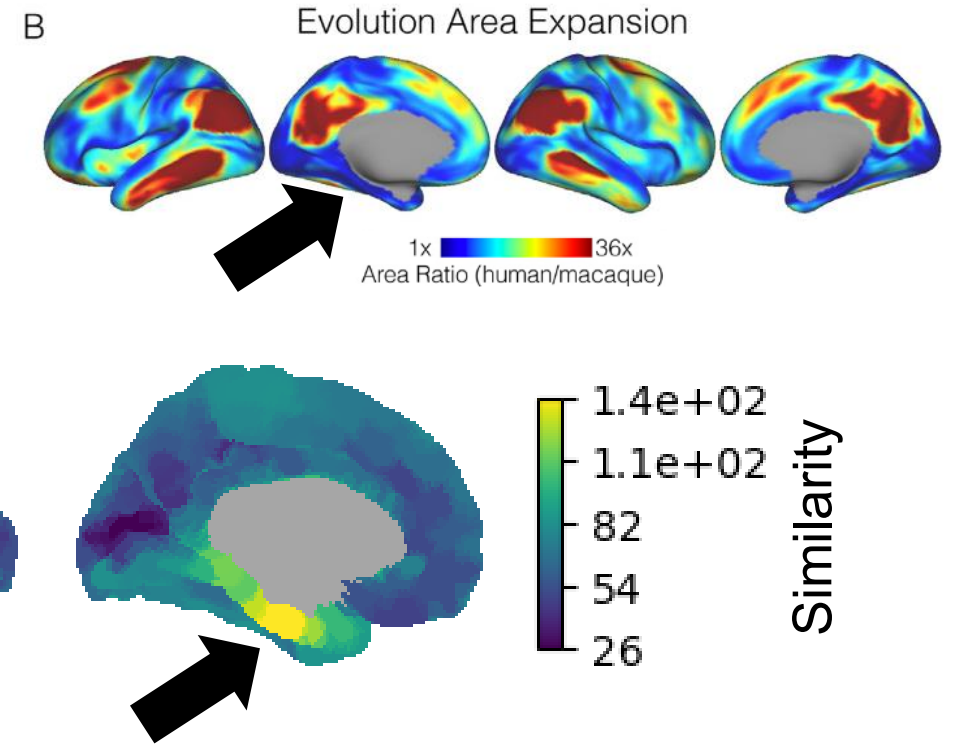
Evolution

Genetics



ARCHETYPE 1

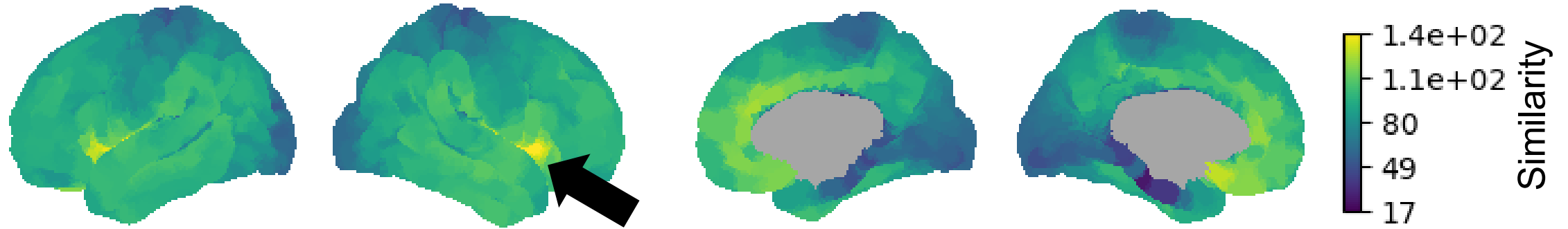
Parahippocampal gyrus and allocortex



- 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:

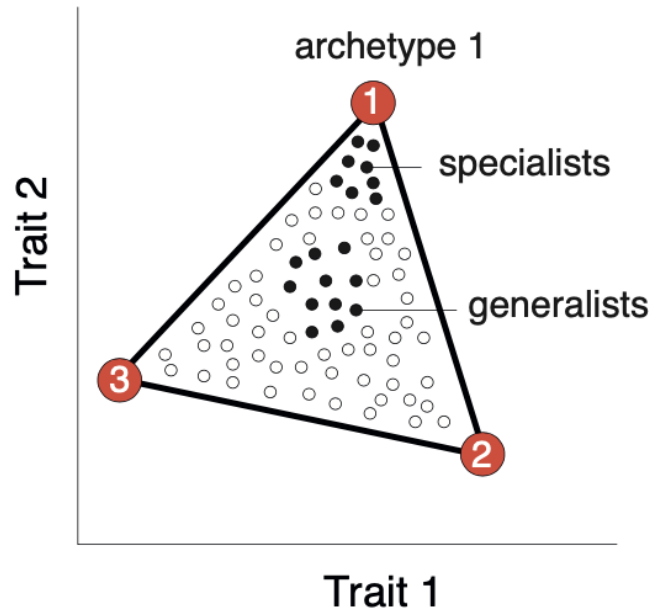
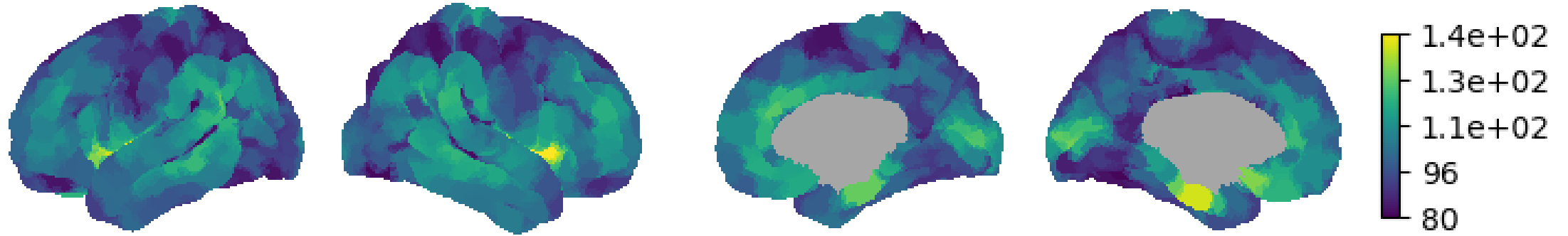
Positive:

- 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)

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.

THANK YOU!



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Prof. Dr. Simon B. Eickhoff

Leonard Sasse

Dr. Dauoia Larabi



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Brain Research,
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Collaborators:

Dr. Camille Giacometti

Dr. Meiqi Niu



SPP 2205

Evolutionary optimization
of neuronal processing

