Neurotransmitter systems explain lifespan changes of human resting-state brain activity

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Poster PDF

Introduction & Source Data

- **Human brain activity**, as measured using **resting-state functional (rsf)MRI**, undergoes **changes during neurodevelopment and aging** [1–3].
- Despite solid evidence for age-related alterations, their **interpretation often remains unspecific** as non-invasive methods often cannot provide insights into underlying neurobiological processes.
- In **related studies** [4,5], we developed and validated a framework to identify potential neurobiological mechanisms contributing to **structural brain development**. Here, we explore this approach on the brain-functional level.

I. We establish **regional developmental trajectories** of two rsfMRI measures mapping **brain activity and connectivity – fALFF** (*fractional Amplitude of Low Frequency Fluctuations* [6]) and **GC** (*Global Correlation* between one and all other regions) – by normative modeling [7] of **Lifespan Human Connectome Project** data from 2445 individuals (5 – 90 years).

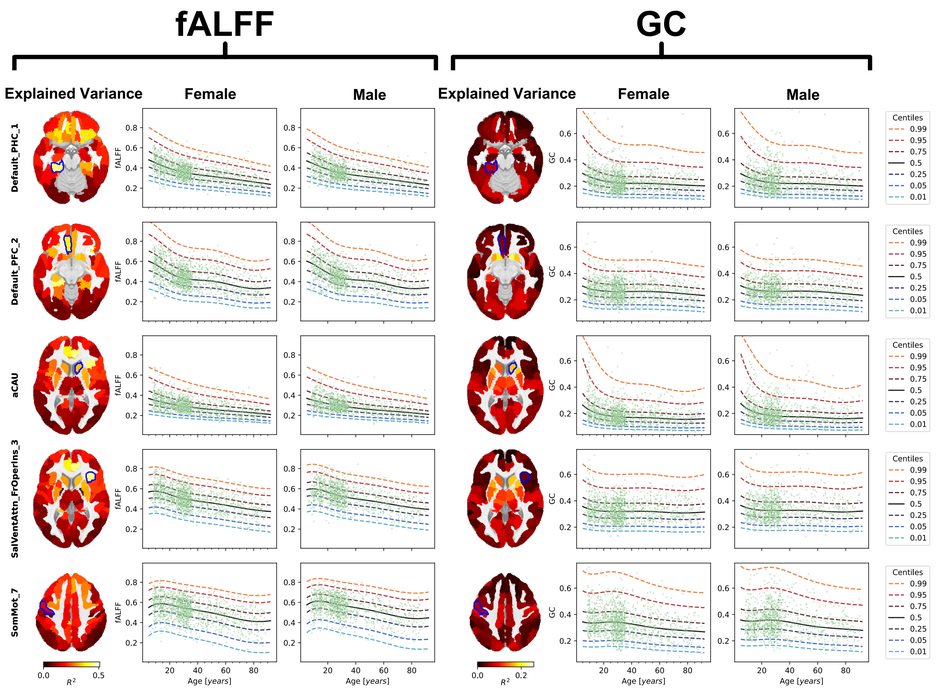
II. Using these trajectories, we construct **"modeled" brain maps** across the **lifespan**: (i) "**cross-sectional**" for a given year and (ii) "**longitudinal**" for the relative change between the cross-sectional maps of two given years in a sliding window approach.

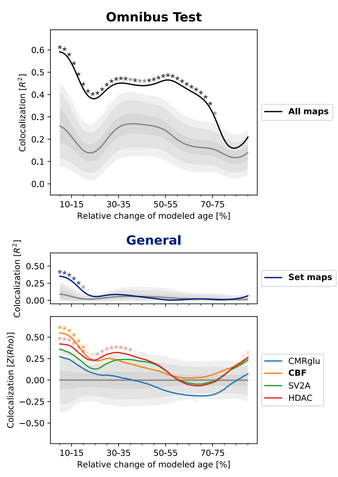
III. We hypothesize that these modeled **spatial rsfMRI change patterns** (i.e., stronger vs. weaker change in one vs. another brain region during a given age span) **reflect developmental changes in specific neurobiological systems** [4,8].

IV. We test this assumption using **spatial colocalization analyses (Poster 2265)** quantifying the degree to which the **spatial pattern of a modeled rsfMRI map** aligns with spatial patterns found in independent **in-vivo neurotransmitter maps** [4,8,9].

Outlook: Our results clearly require validation in independent longitudinal data. Tests in atypical developing cohorts will explore the approach's clinical potential.

Normative modeling of fALFF and GC development trajectories
Warped bayesian linear regression models fitted for each of 232 brain regions (Schaefer-200/Melbourne-S2) to predict fALFF/GC from age, while accounting for effects of sex, study site, and motion [7]. Data: Cross-sectional preprocessed data from 2445 HCP subjects (5 – 90 years). The 0.5th centile predictions were used as "modeled" cross-sectional MRI data in the following analyses. Relative change maps across 5 years (1-year steps) were used for (pseudo)longitudinal analyses.

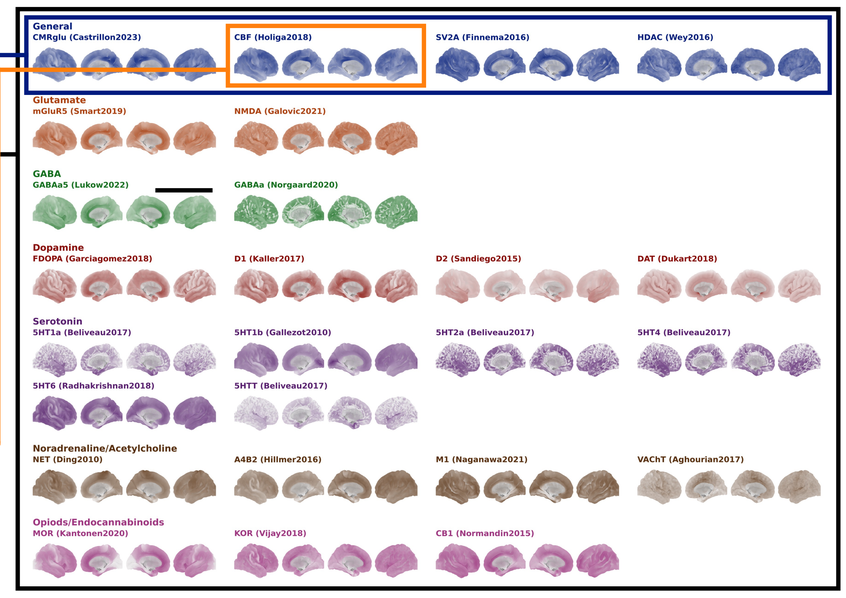




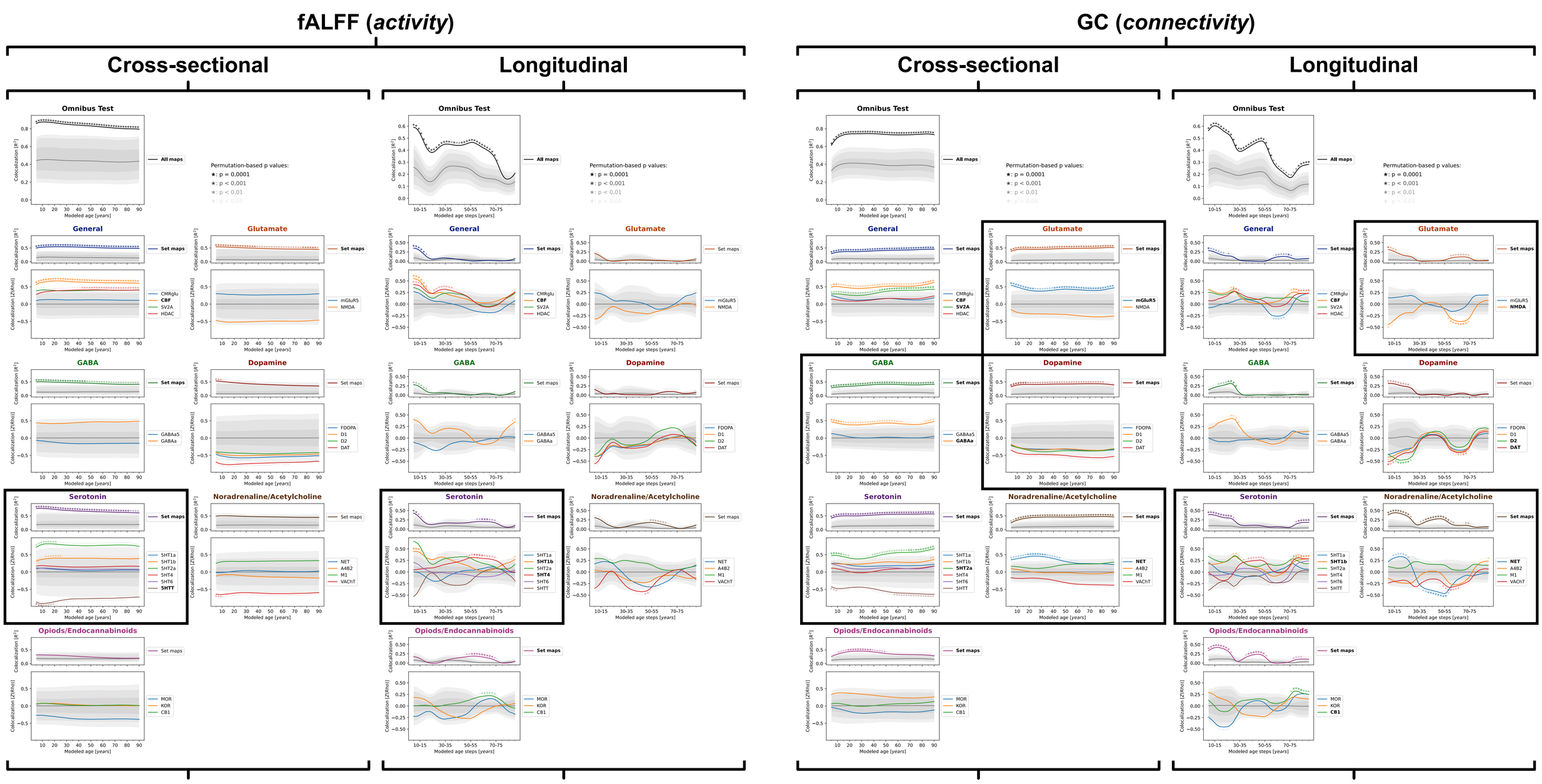
Step 1:
"Omnibus Test"
Multivariate Regression
All transmitter maps ➔ each age map

Step 2:
System-wise
Multivariate Regression
System-wise transmitter maps ➔ each age map

Step 3:
System-wise
Spearman Correlations
Single transmitter maps ➔ each age map



Results



The **fALFF distribution** across brain regions might mirror a **mixture of different neurotransmitter signals**, which may **not change relevantly** during the lifespan. The **serotonergic** system shows the **strongest colocalization**.

Up to ~60% (null: ~27%) of modeled lifespan changes of fALFF are **explained by neurotransmitter systems**. (Pseudo-) longitudinal effects are relatively sparse. The **serotonergic** system shows the **strongest effects at ~5–20 years**.

In line with the fALFF results, the **GC distribution** seems **stable across time**. However, several significant colocalization effects emerge for **glutamatergic**, **GABAergic**, **serotonergic**, and **noradrenergic** systems.

As for fALFF, **up to ~60%** (null: ~25%) of modeled GC changes are **explained**. **Cross-sectional** and **longitudinal** effects largely **converge**. **Noradrenergic** and **serotonergic** systems exhibit the **strongest effects** to up to 30 years.

References: [1] Ferreira, L. K. & Busatto, G. F. (2013). *Neurosci. Biobehav. Rev.* | [2] Hu, S. et al. (2014). *Brain Struct. Funct.* | [3] Uddin, L. Q. et al. (2010). *Front. Syst. Neurosci.* | [4] Lotter, L. D. et al. (2024). In revision at *Nat. Comm.* | [5] Kasper, J. et al. (2024*). Biol. Psychiatry Cogn. Neurosci. Neuroimaging.* | [6] Zou, Q.H. et al. (2008). J. *Neurosci. Methods.* | [7] Rutherford, S. et al. (2021). *Nat. Protocols.* | [8] Dukart, J. et al. (2021). *HBM.* | [9] Hansen, J. Y. et al. (2022). *Nat. Neurosci.*

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