Spatiotemporal Fractal-based Analysis of fMRI Time Series of ADHD Patients

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Young students reading
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INTRODUCTION

Motivation

- Functional Magnetic Resonance Imaging (fMRI) provides a non-invasive proxy for brain activity by measuring the hemodynamic response, thereby enhancing our understanding of neurodevelopmental disorders like Attention Deficit/Hyperactivity Disorder (ADHD) and informing more effective treatment strategies [1].
- The presence of long-range dependence, also known as the long-memory property, in fMRI signals has motivated us to model the temporal correlation observed in resting-state fMRI time series utilizing long-memory processes [2].

Objective

- We analyze the long-memory properties of brain activity in ADHD patients.
- A long-memory process is defined by its slow decay in spectral density at low frequencies and exhibits a linear trend on a log-spectrum versus log-frequency plot, as illustrated in Figure 1.
- The Discrete Wavelet Transform (DWT) effectively captures the complex signal structure by characterizing long-memory behavior in neurological signal processing [3].

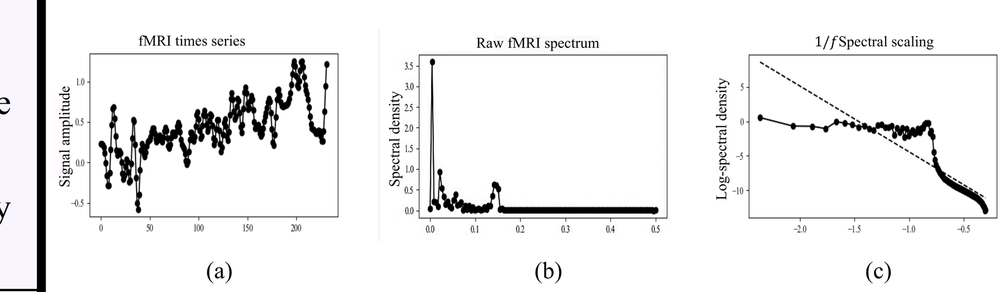


Figure 1: Long-memory behavior of fMRI time series; (a) fMRI time series of a brain voxel; (b) spectral density of fMRI time series at a voxel; (c) log-log plot displays a piecewise slope with a linear section indicative of long-memory behavior in fMRI time series.

METHODS

Single Subject Analysis

Let y_m^v be the fMRI signal for subject m at voxel v. We model this signal with long-memory errors as, shown below.

$$y_m^v = X\beta_m^v + E_m^v \qquad E_m^v \sim N\left(0, \Sigma_m^v\right)$$

Where X is a $T\times p$ design matrix and β_m^v is a p× 1 covariate estimation for subject m at voxel v. We characterize the errors' covariance $\Sigma_v(i,j) = \gamma[|i-j|]$ with $\gamma(h) \propto Ch^{\beta}$, the spectral representation of the long-memory process, where C is a constant, h is the frequency range, and β is the power exponent.

Bayesian Inference for the Long-memory Parameter

Each fMRI signal will be transformed via DWT into the time-frequency domain. For a visual representation of this transformation, refer to Figure 2.

$$W_m y_m^v = W_m X\beta_m^v + W_m E_m^v \qquad E_m^{v\,*} \sim N\left(0, \Sigma_m^{v\,*}\right) \qquad \Sigma_m^{v\,*} = W_m \Sigma_m^v W_m^T$$

Where W is a $T\times T^*$ DWT matrix, and s is the wavelet scaling level, and α_m^v is the long-memory parameter for voxel v. The transformed covariance matrix is defined using the **variance progression formula** $\Sigma_m^{v\,*} = diag\left(\sigma_m^2\left(2^{\alpha_m^v}\right)^{-s}\right)$[3, 4].

The parameters σ_m^2 and α_m^v are estimated via Gibbs and truncated Metropolis-Hasting sampling for each subject. Figure 3 shows the estimated long-memory maps for two subjects.

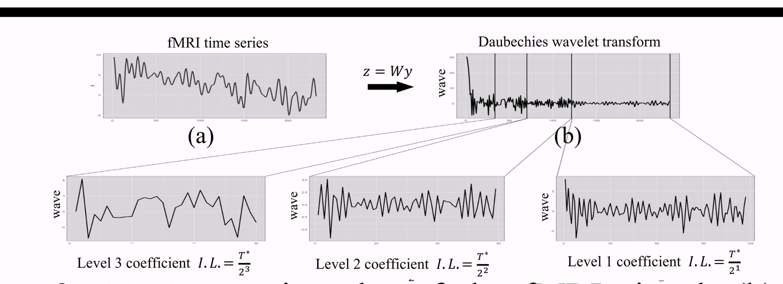
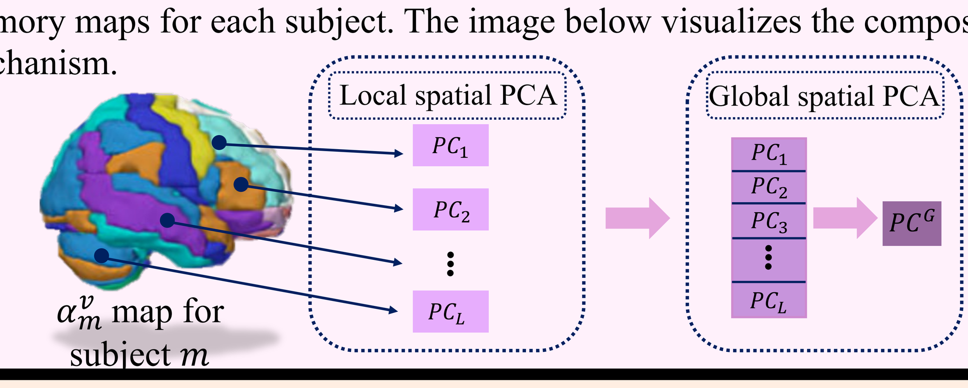


Figure 2: (a) time series plot of the fMRI signal; (b) discrete wavelet transformation of the fMRI signal. The second row shows the decomposed signals with their interval length (I.L.). The I.L. is equal to the transformed signal length (T^*) over the sth scale level $\frac{T^*}{2^s}$.

Dimension Reduction of the Long-memory Maps

We used the composite-hybrid decomposition described in [5] for dimension reduction of the long-memory maps for each subject. The image below visualizes the composite-hybrid decomposition mechanism.



Multi-subject Analysis

We study how **age**, **medication status**, **ADHD index**, and their **interactions** affect long-memory across subjects. We fitted a linear regression model on reduced long-memory maps PC^G :

$$PC^G = x\beta^T + e \quad e \sim N(0, \delta^2 I)$$

β prior

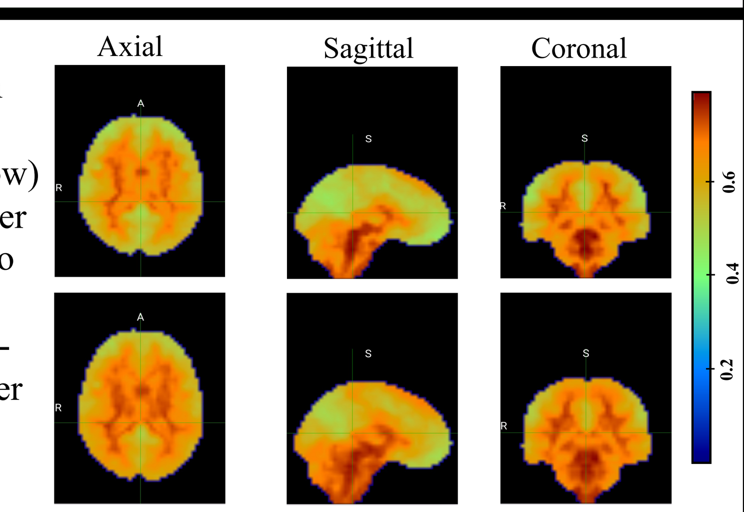
$$\beta_{PC_i^G} | \delta^2_{PC_i^G} \sim MVN(\mu_0, \Lambda_0)$$

δ prior

$$\delta^2_{PC_i^G} \sim Inv\_gamma(a_0, b_0)$$

We use MCMC Gibbs sampling for parameter inferences.

Figure 3: Mean long-memory maps of (top row) 12-years or older subjects with no medication; (bottom row) 9-years or younger subjects with medication.



RESULTS

ADHD Medication and Long-memory

- The inferred β coefficients through MCMC sampling are projected back into their higher-dimensional brain space.
- Bayesian approach
  1. We have adopted an exploratory Bayesian multiple comparison correction based on [6] at a significance level of 0.05.
  2. To ensure robust visualization and avoid sparsity, we display significant voxels in clusters (Figure 4 (a)), with each cluster comprising more than 50 voxels. This approach facilitates a clearer interpretation of the spatial distribution and relevance of the findings.
- Comparison with a frequentist approach
  1. We use a hypothesis t-test at a significance level of 0.05.
  2. To control the false positive rate, we implement False Discovery Rate (FDR) corrections for multiple comparisons by maintaining the same significance threshold.
  3. Figure 4 (b) displays the significant voxels in clusters greater than 50.
- The intersection of Bayesian and frequentist approaches is represented by the white areas in Figure 4(c).

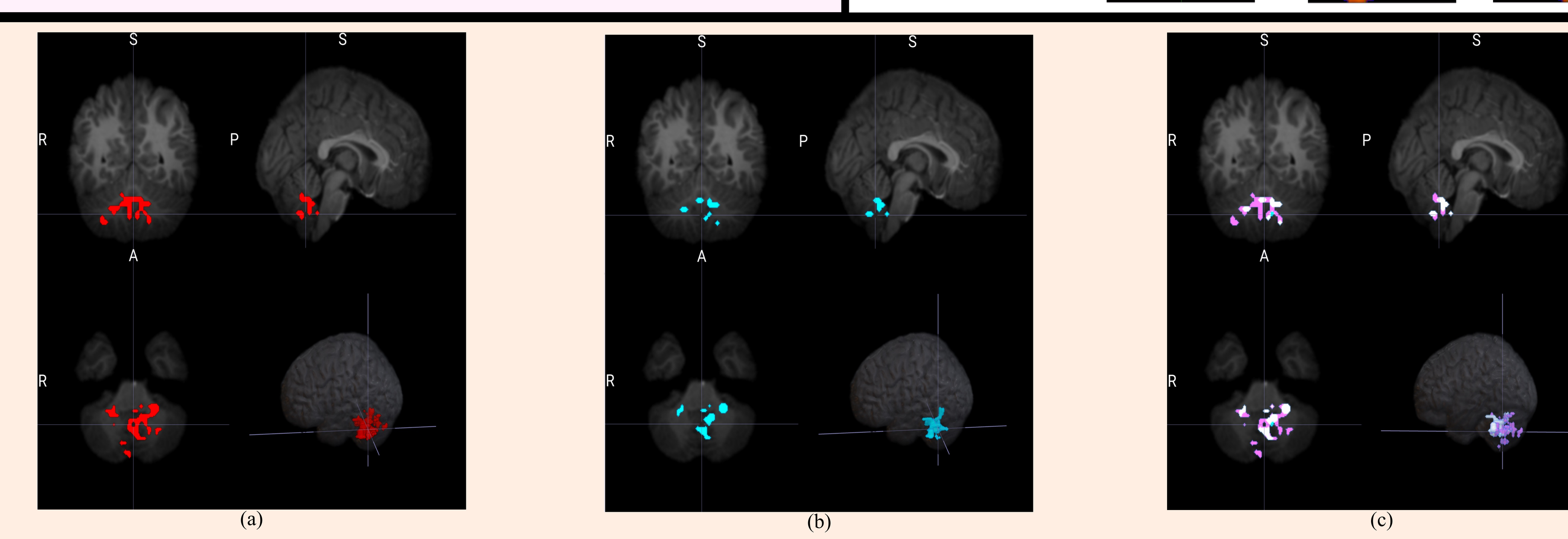
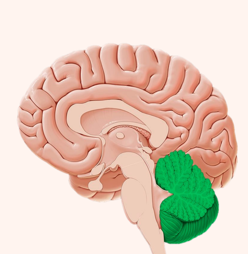


Figure 4: Binary maps of estimated β coefficients of **Medication status** via both (a) Bayesian and (b) frequentists methods, both corrected for multiple comparison errors. in (c), the highlighted yellow areas represent intersection between two methods.

CONCLUSION

The Results Suggest that Long-memory Structure of rs-fMRI is Associated with ADHD Medication in the Cerebellum



Decrease of Long-memory in Cerebellum

Medication is associated with a smaller long-memory parameter, or, in other words, less persistent dependence in the cerebellum.

α negatively relates to brain complexity[4]

Brain Complexity

A change in long-memory implies a change in fractal dimension of resting state brain activity[8]. This may suggest that medication fundamentally alters brain complexity in the cerebellum[9].

Cerebellum

Our findings align well with previous findings [9] where stimulant medication is associated with larger regional volumes over the left cerebellar surface for ADHD patients. Thus, the relationship between ADHD medication and the cerebellum appears relevant to both brain structure and function.

References

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Future Work

- It might be helpful to consider implementing a more sophisticated Bayesian model, such as image-on-scalar regression, or incorporating informative selective priors like the Dirichlet process or spike-and-slab priors, to potentially enhance model precision and reliability.
- Continuation this line of research, analysing long-memory properties of fMRI time series and investigate their correlations with fractal properties and brain morphology.
- While the cerebellum's significance is intriguing, further exploration regarding the medication dosage effect, medication type, and control of comorbid conditions is needed to solidify the connection to ADHD medication.

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