Atomic Decomposition of Human EEG Oscillations In Medical Research And Pharmaceutical Trials

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[3] Comenius University, Bratislava, Slovakia

IPEG, 21 - 25 November, 2018, Zurich

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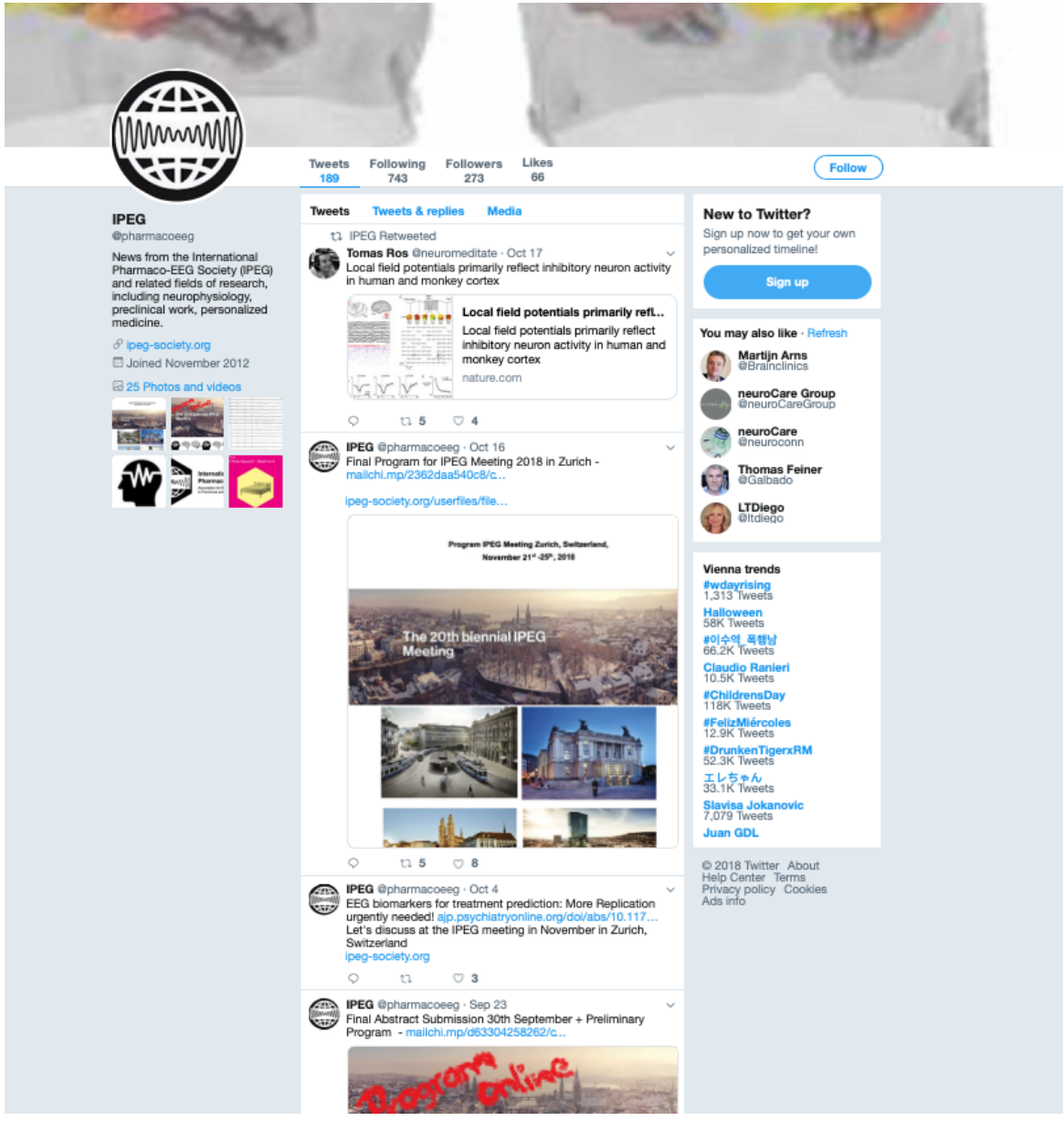

Articles

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Electroencephalographic Biomarkers for Treatment Response Prediction in Major Depressive Illness: A Meta-Analysis

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Published Online: 3 Oct 2018 | https://doi.org/10.1176/appi.ajp.2018.17121358

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Objective:

Reducing unsuccessful treatment trials could improve depression treatment. Quantitative EEG (QEEG) may predict treatment response and is being commercially marketed for this purpose. The authors sought to quantify the reliability of QEEG for response prediction in depressive illness and to identify methodological limitations of the available evidence.

Method:

The authors conducted a meta-analysis of diagnostic accuracy for QEEG in depressive illness, based on articles published between January 2000 and November 2017. The review included all articles that used QEEG to predict response during a major depressive episode, regardless of patient population, treatment, or QEEG marker. The primary meta-analytic outcome was the accuracy for predicting response to depression treatment, expressed as sensitivity, specificity, and the logarithm of the diagnostic odds ratio. Raters also judged each article on indicators of good research practice.

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Results:

In 76 articles reporting 81 biomarkers, the meta-analytic estimates showed a sensitivity of 0.72 (95% CI=0.67–0.76) and a specificity of 0.68 (95% CI=0.63–0.73). The logarithm of the diagnostic odds ratio was 1.89 (95% CI=1.56–2.21), and the area under the receiver operator curve was 0.76 (95% CI=0.71–0.80). No specific QEEG biomarker or specific treatment showed greater predictive power than the all-studies estimate in a meta-regression. Funnel plot analysis suggested substantial publication bias. Most studies did not use ideal practices.

Conclusions:

QEEG does not appear to be clinically reliable for predicting depression treatment response, as the literature is limited by underreporting of negative results, a lack of out-of-sample validation, and insufficient direct replication of previous findings. Until these limitations are remedied, QEEG is not recommended for guiding selection of psychiatric treatment.

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IPEG @pharmacoeeg · Oct 4

EEG biomarkers for treatment prediction: More Replication urgently needed!
ajp.psychiatryonline.org/doi/abs/10.117…
Let's discuss at the IPEG meeting in November in Zurich, Switzerland
ipeg-society.org

3

Why this QEEG controversy? A few points ... and our perspective

- standardization of EEG recording, pre-processing steps, etc.
- sample size
- diurnal effects
- task conditions (beyond EC/EO ?)
- effects of long-stay at clinic
- etc.

- wider frequency bands vs. individual narrow-oscillatory rhythms
- inter-individual variability
- electrodes space

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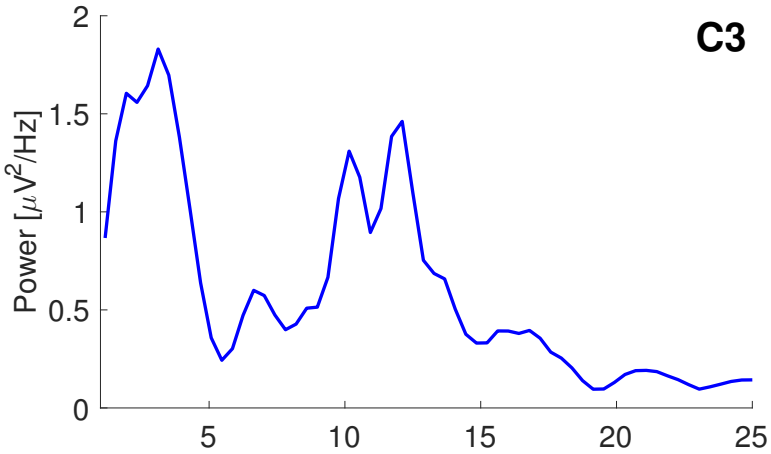
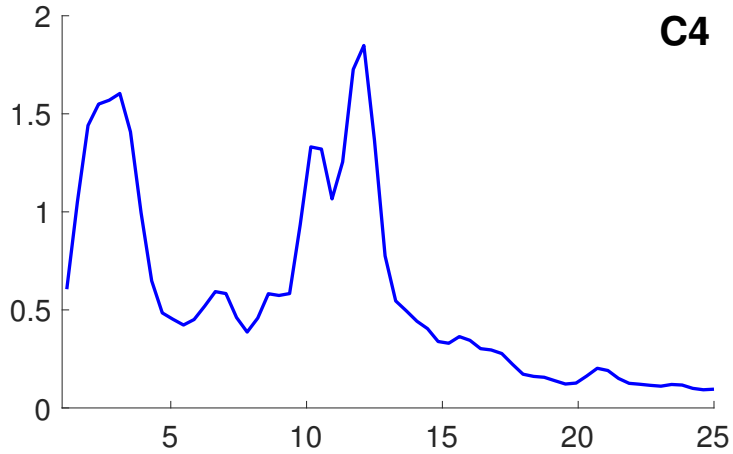
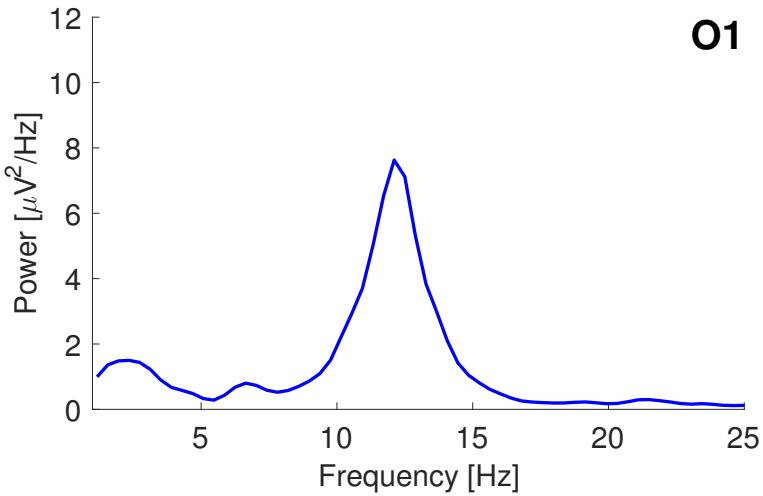
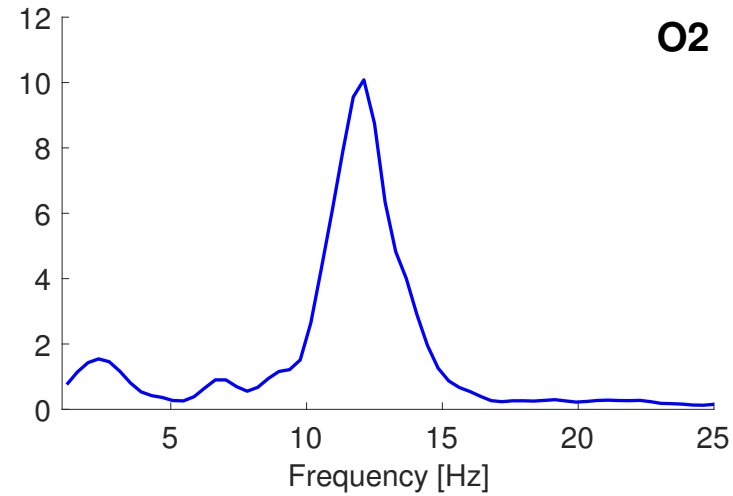
Motivational Examples (frequency)









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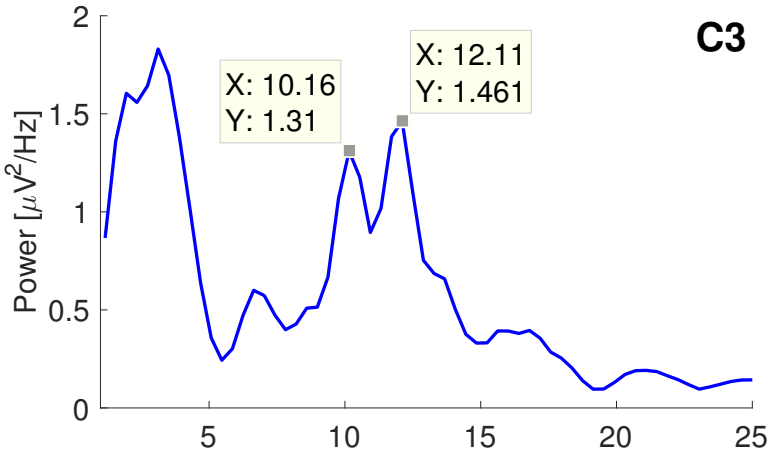

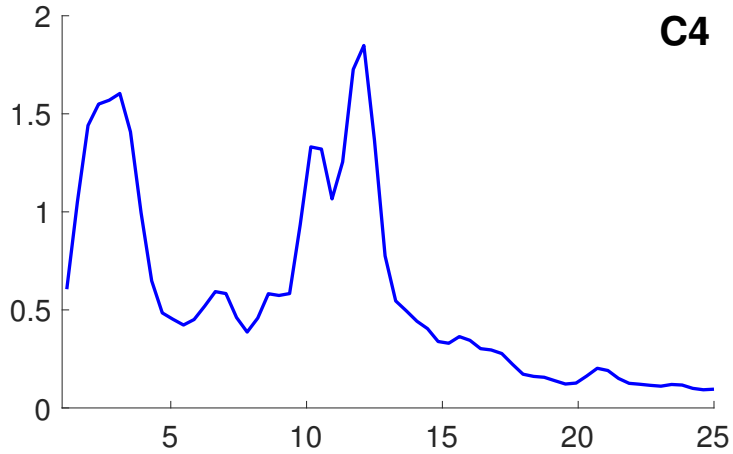

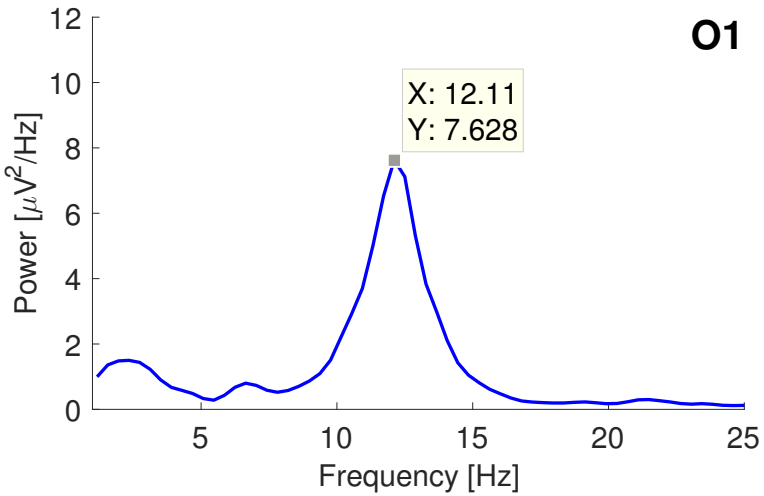

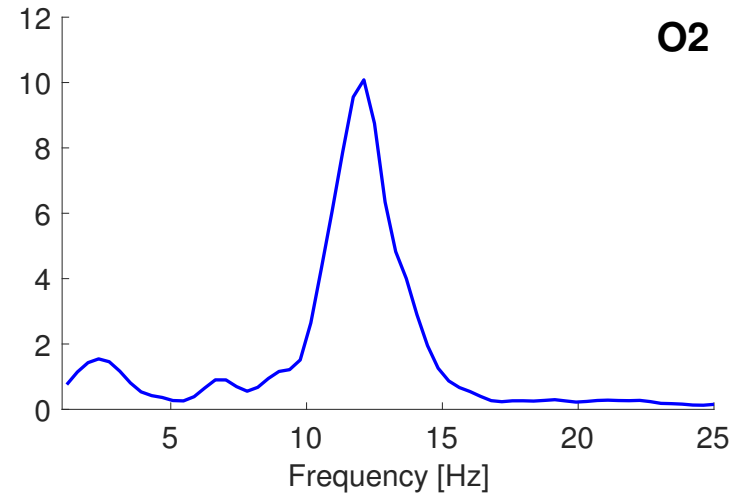

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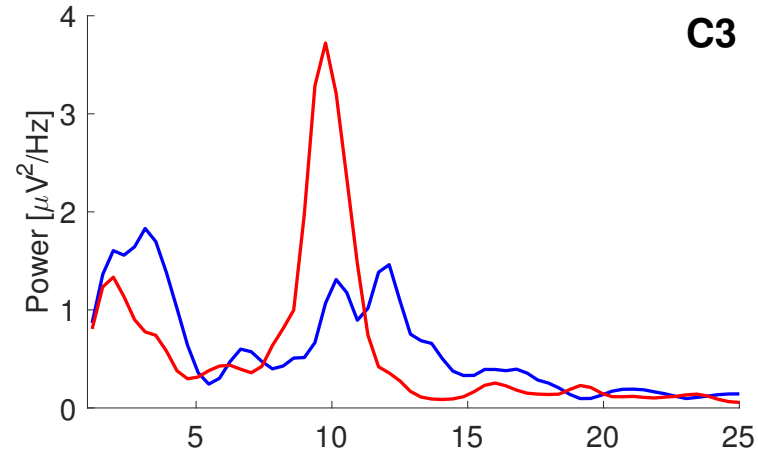

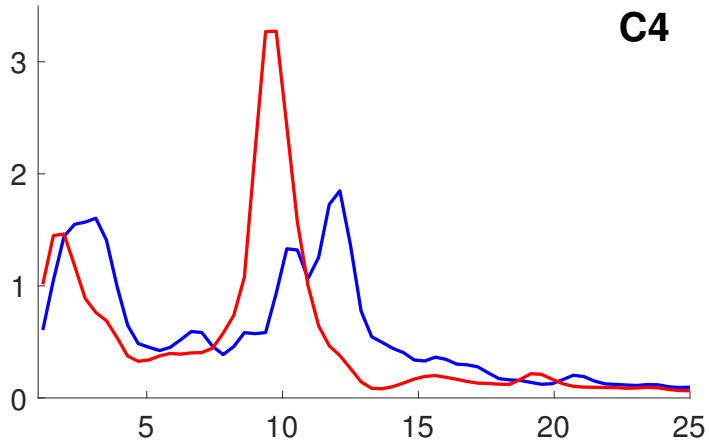

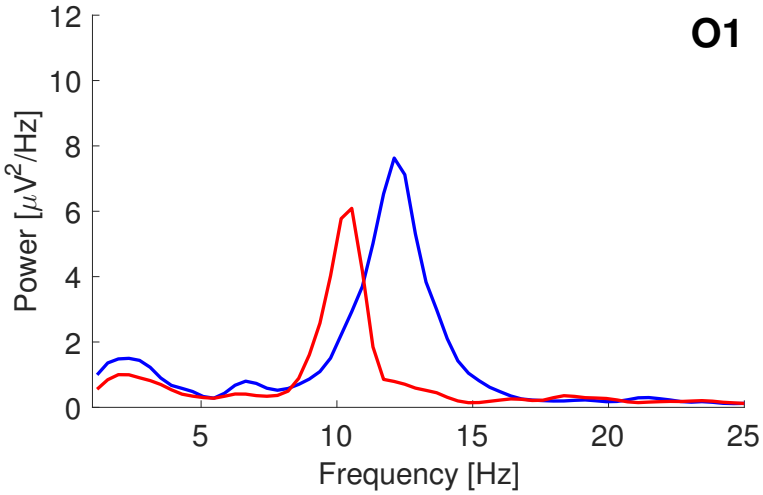

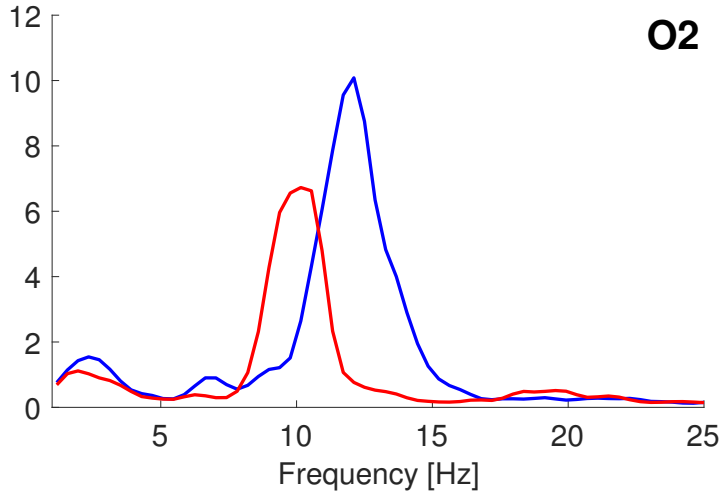

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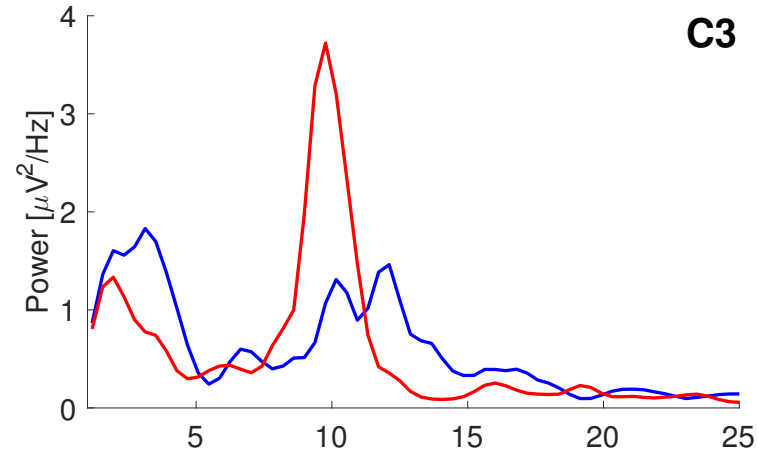
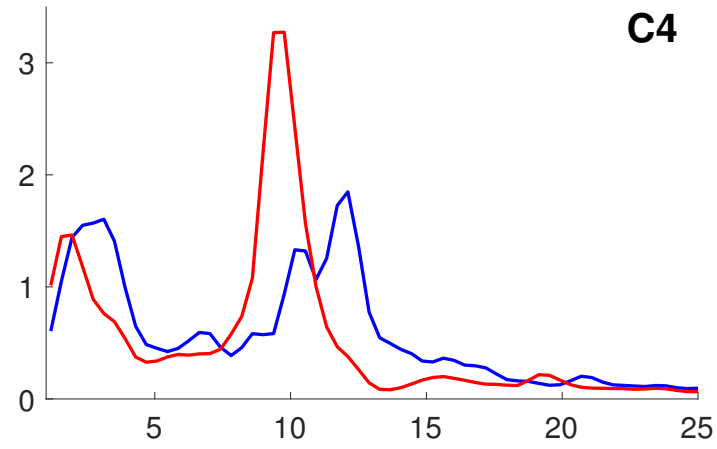
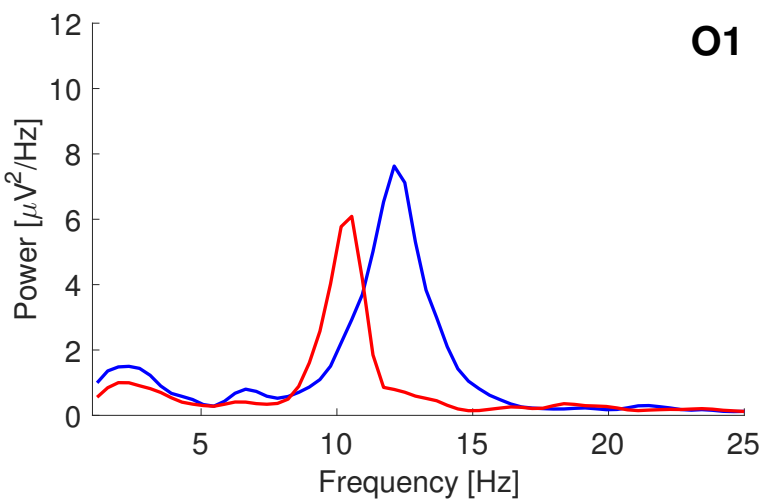
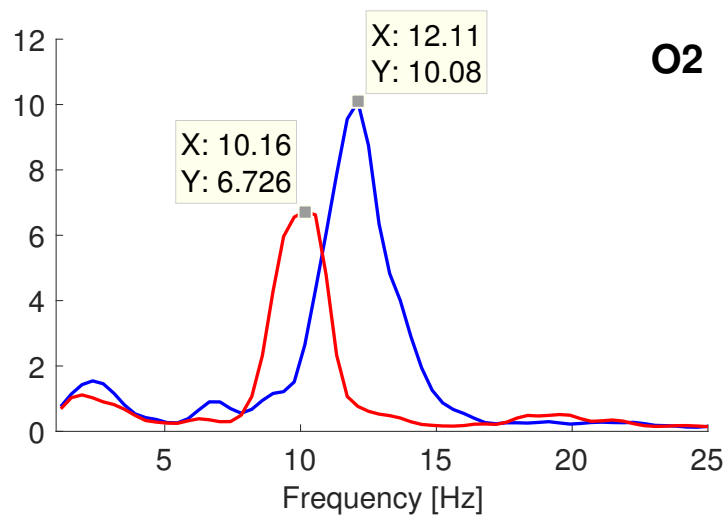
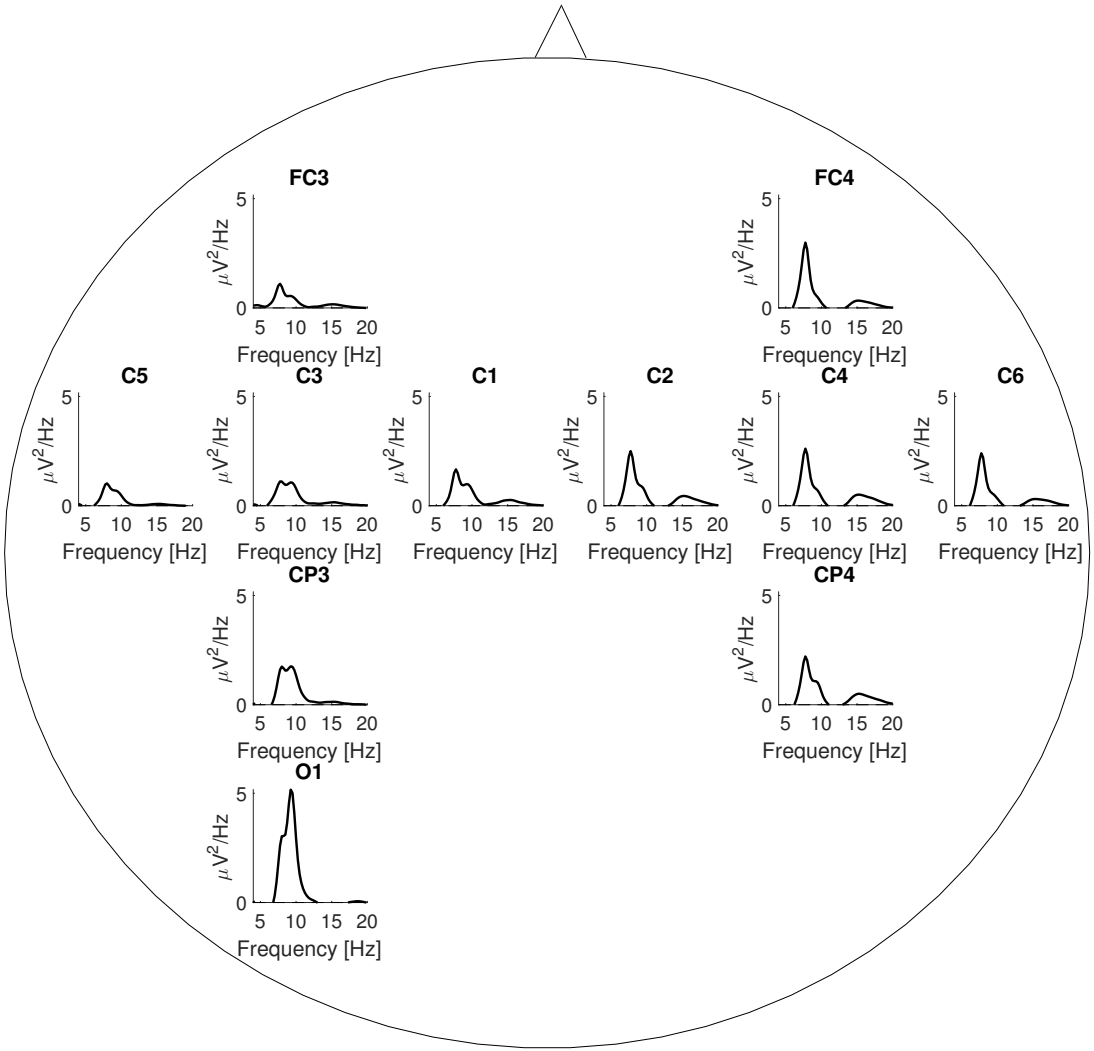


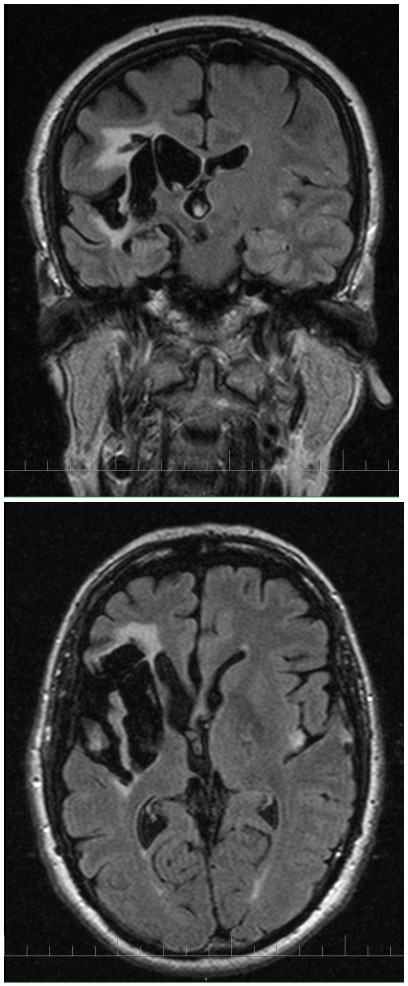






Motivational Examples (space)



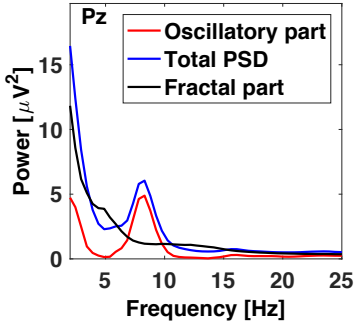


Averaged oscillatory part of the EEG power spectrum recorded during resting eyes-closed. A chronic stroke patient with ischemia in the fronto-temporo-parietal area on the left side

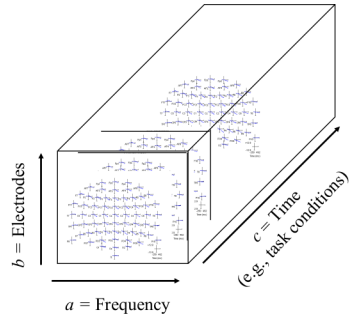
Applied Procedure

Clinical Study (EEG, PK, etc.)
EEG recording & preprocessing

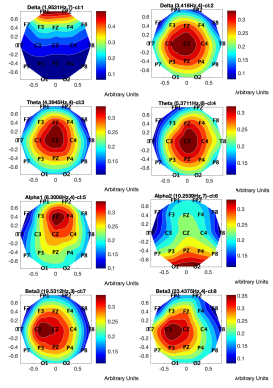
IRASA Spectrum Decomposition



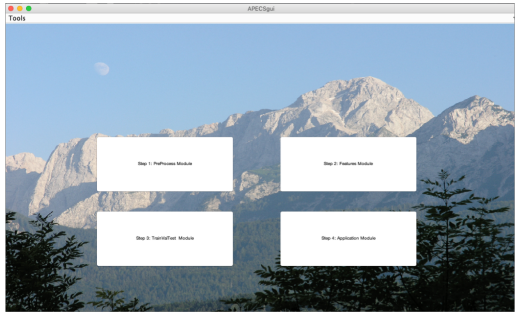
Multi-way Data Structure



PARAFAC



Clustering (e.g. DBSCAN)



Endpoints (e.g. time-scores)

Formal Statistical Testing
ANCOVA, ER, etc.

```
PROC MIXED  DATA=Data_modelB EMPIRICAL;
   CLASS    Subject Treatment Time;
   BY Band;
   MODEL Pre_Pre_Diff = Predose Treatment Time Treatment*Time / SOLUTION CL;
   REPEATED  Time / SUBJECT = subject TYPE = ARH(1);
   LSMEANS   Treatment Time  / CL;
RUN;
```

Brain Oscillations vs. Scale-free Brain Activity

Trends Cogn Sci. 2014 September ; 18(9): 480–487. doi:10.1016/j.tics.2014.04.003.

Scale-free brain activity: past, present and future

Biyu J. He

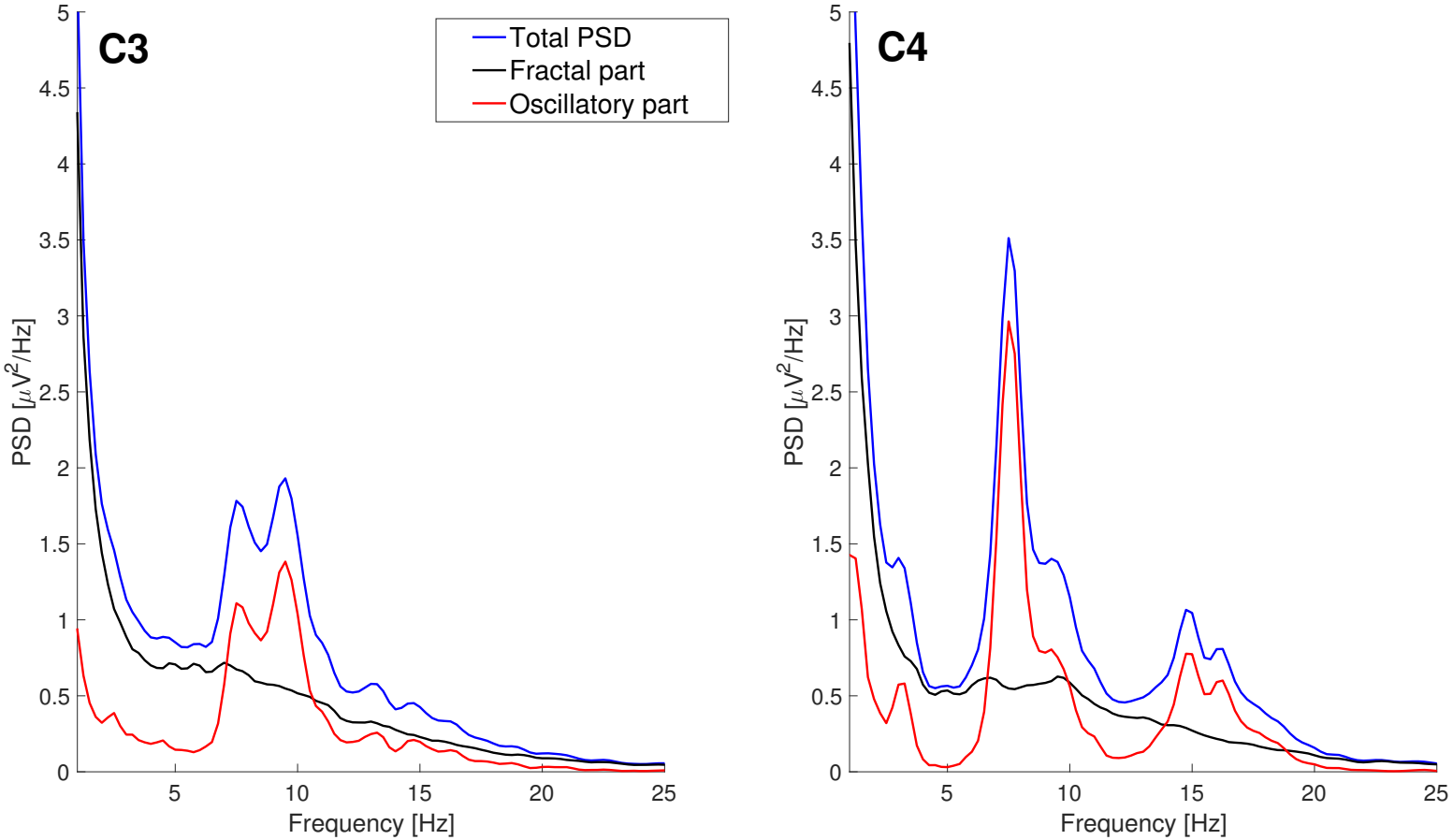
Neuron. 2010 May 13; 66(3): 353–369. doi:10.1016/j.neuron.2010.04.020.

The temporal structures and functional significance of scale-free brain activity

Biyu J. He[1,*], **John M. Zempel**[2], **Abraham Z. Snyder**[1,2], and **Marcus E. Raichle**[1,2,3,4]

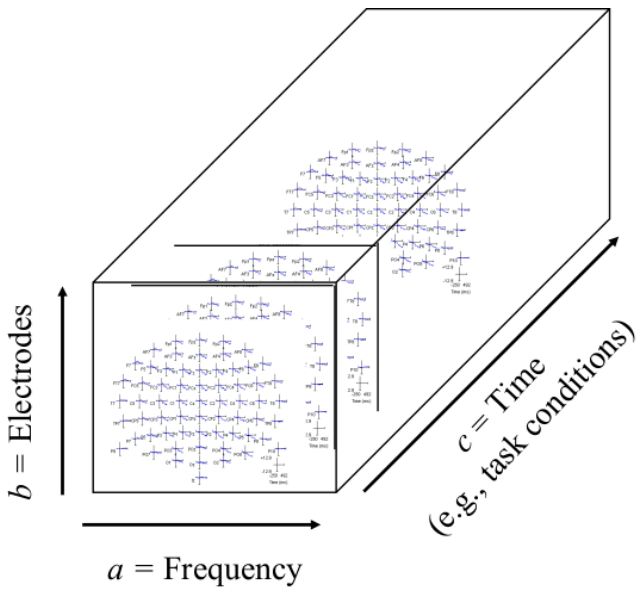
- *"..... there are two types of brain activity that coexist: the broadband, arrhythmic activity and the narrow-band, rhythmic oscillations".* [He, 2014]
- EEG recorded from the scalp originates from electrical currents generated by a mixture of a large number of quasi-random neural sources across the entire cortex (broadband background EEG) and a small number of more localized cortical sources whose power spectra are narrow-band (oscillatory).
[Nunez, 2006; He, 2014]

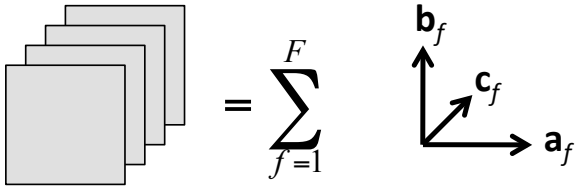
Irregular-Resampling Auto-Spectral Analysis (IRASA) [Wen & Liu, 2016]



Decomposition of the power spectrum density (PSD) into the fractal (scale-free) and oscillatory components underlying the eyes-closed awake state recorded after mirror-box training. Plots represent means of the IRASA decomposition computed separately for 4-s-long overlapping segments of approximately two minutes long resting block at two central EEG electrodes C3 and C4. Frequencies were restricted to the range 1-25 Hz for the visualization purposes..

- Data matrix construction:
  $\mathbf{X}_{(I \times J \times K)}$
  I - time segments
  J - electrodes
  K - power or amplitude (or log+)





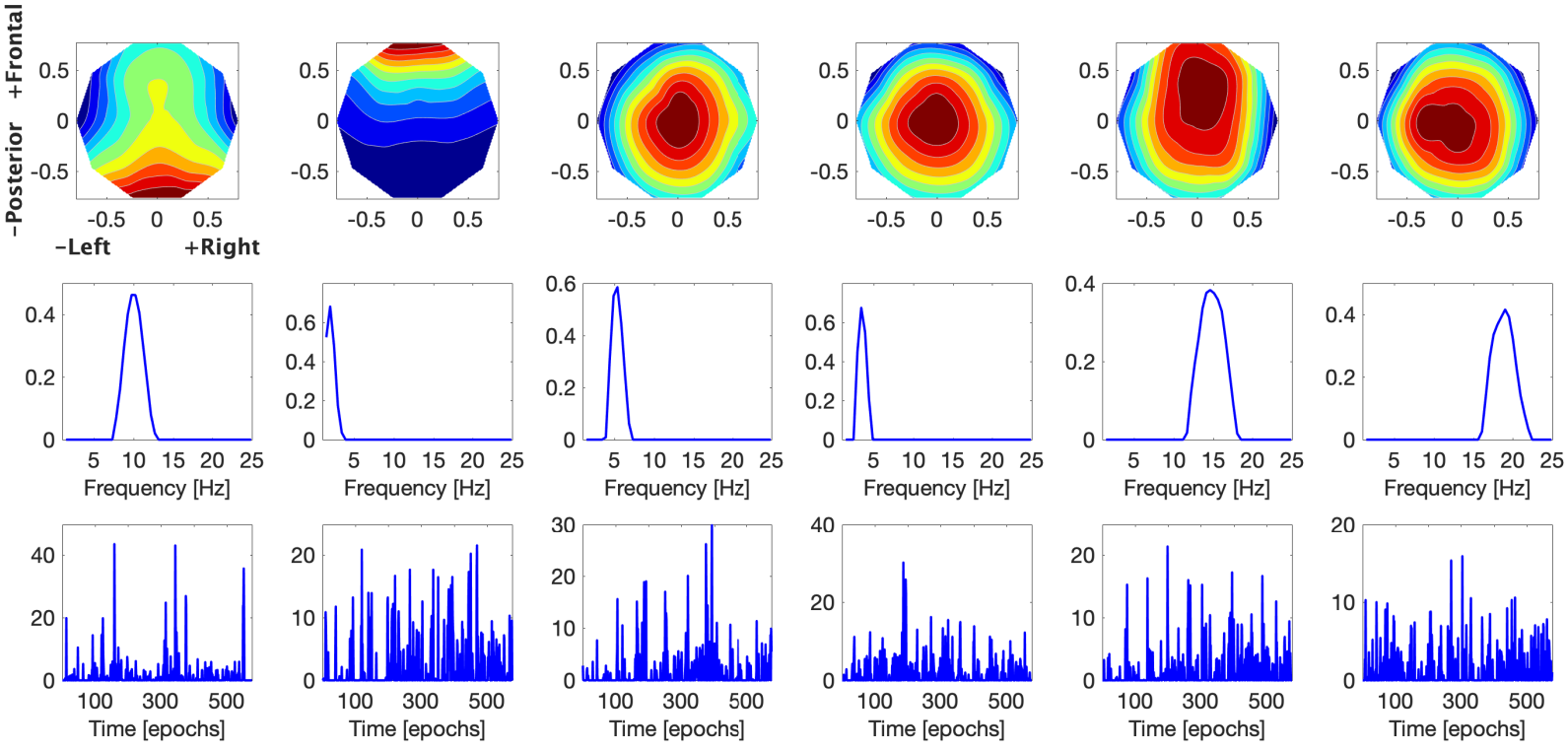
- The PARAFAC model with F factors:

$$x_{ijk} = \sum_{f=1}^{F} a_{if} b_{jf} c_{kf} + \epsilon_{ijk}$$

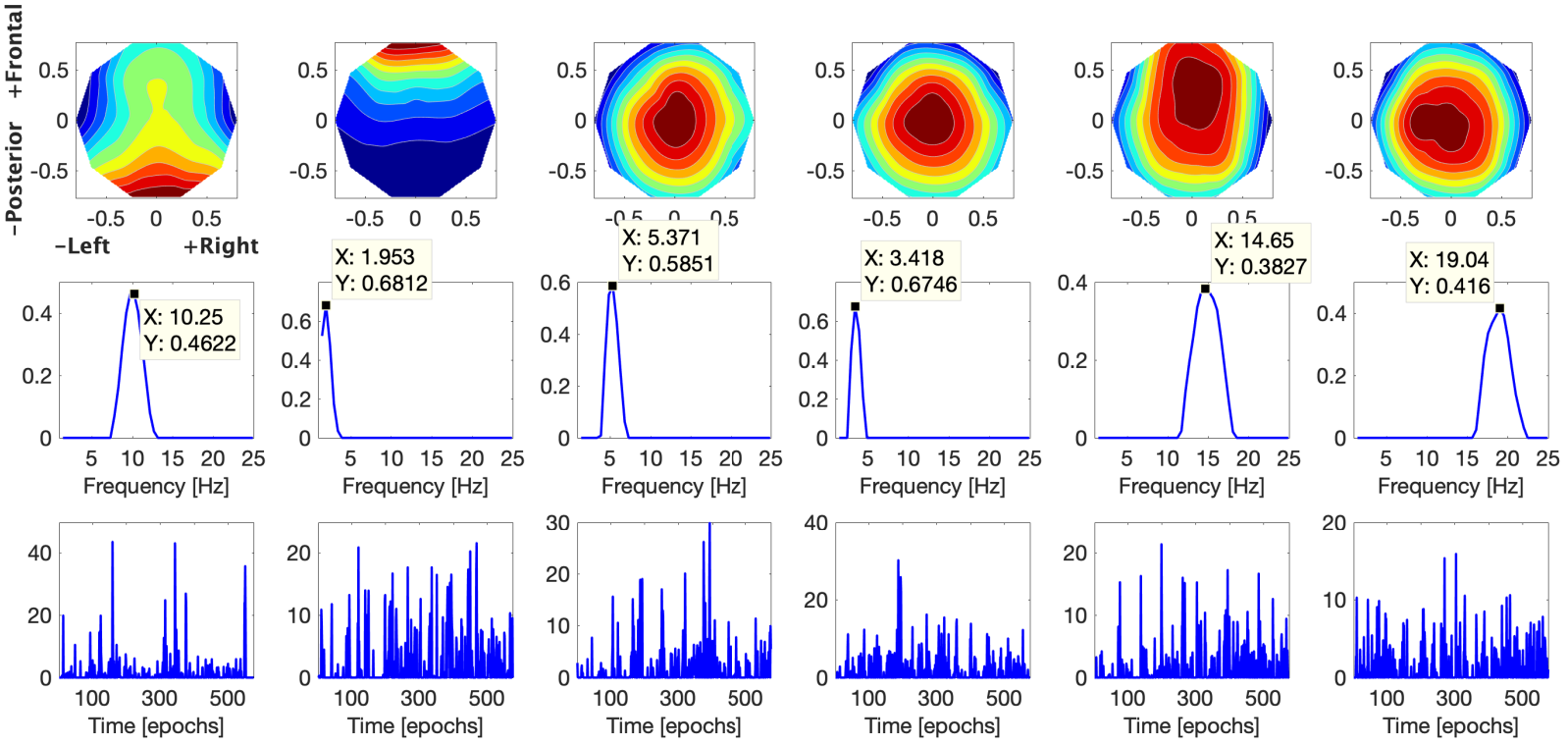
- The criterion:

$$\min_{a_{if}, b_{jf}, c_{kf}} = \| x_{ijk} - \sum_{f=1}^{F} a_{if} b_{jf} c_{kf} \|^2$$

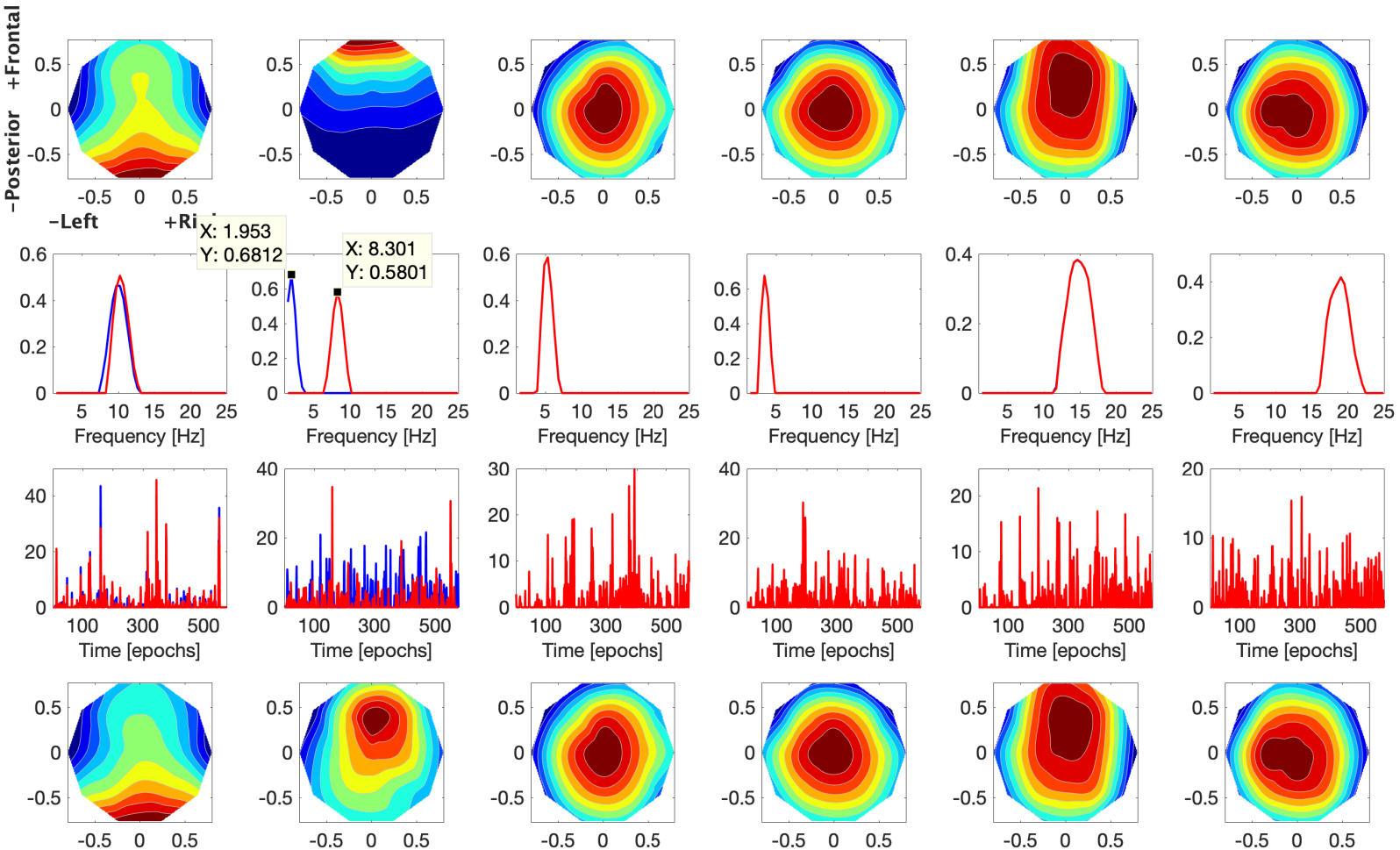
PARAFAC - single subject



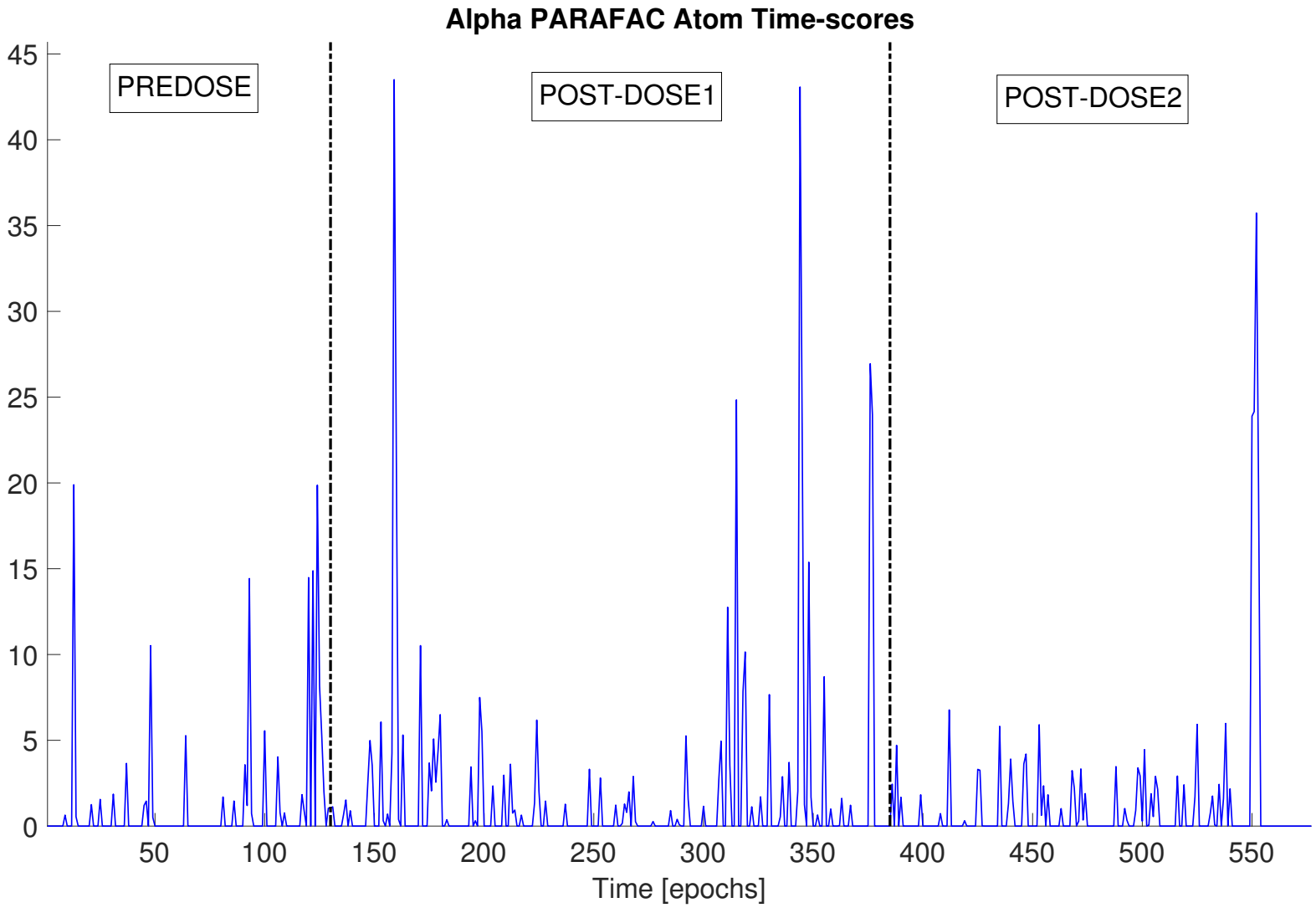
PARAFAC - single subject



PARAFAC - single subject (remove eye-blink atom and re-run)



PARAFAC Time-scores



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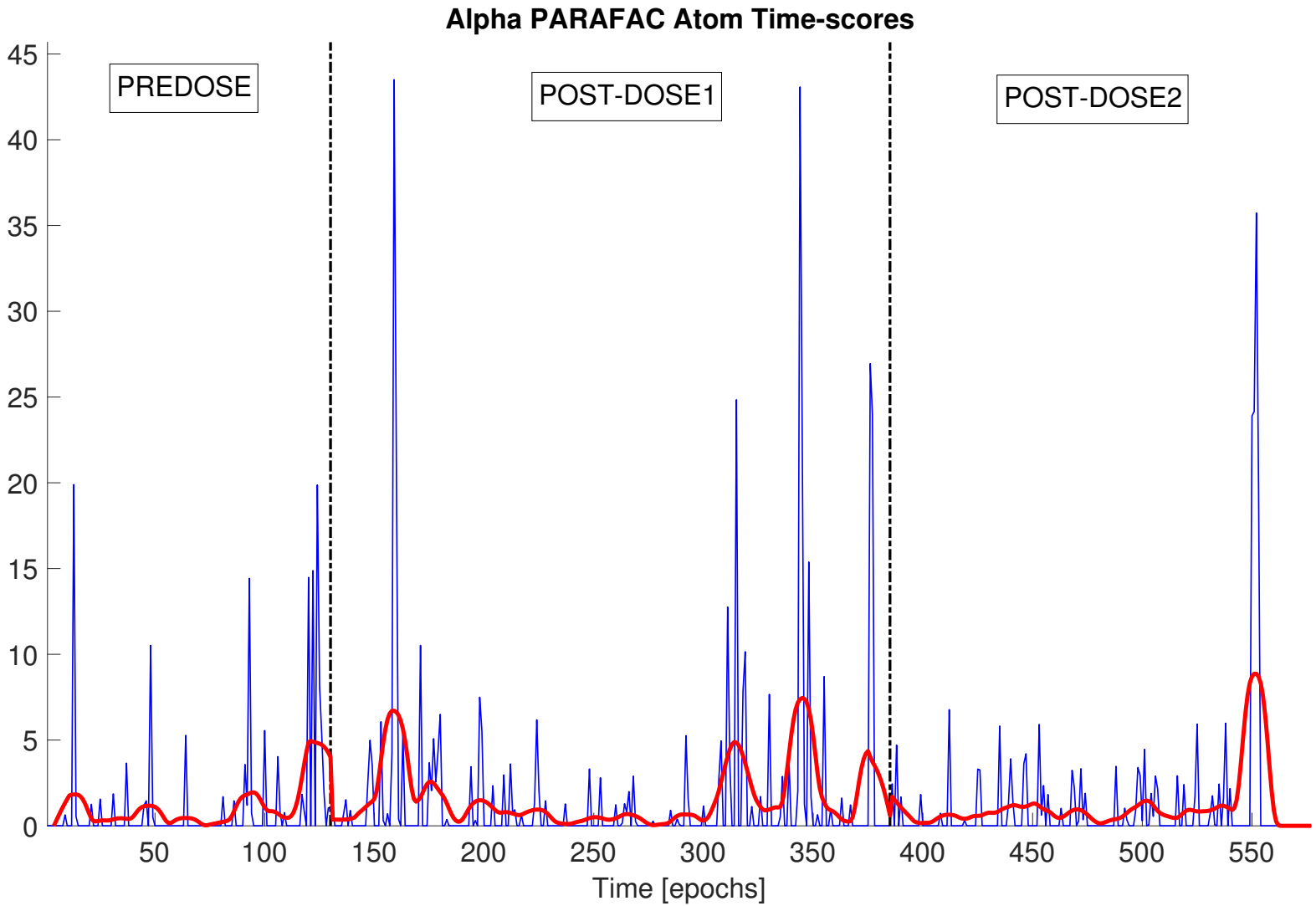
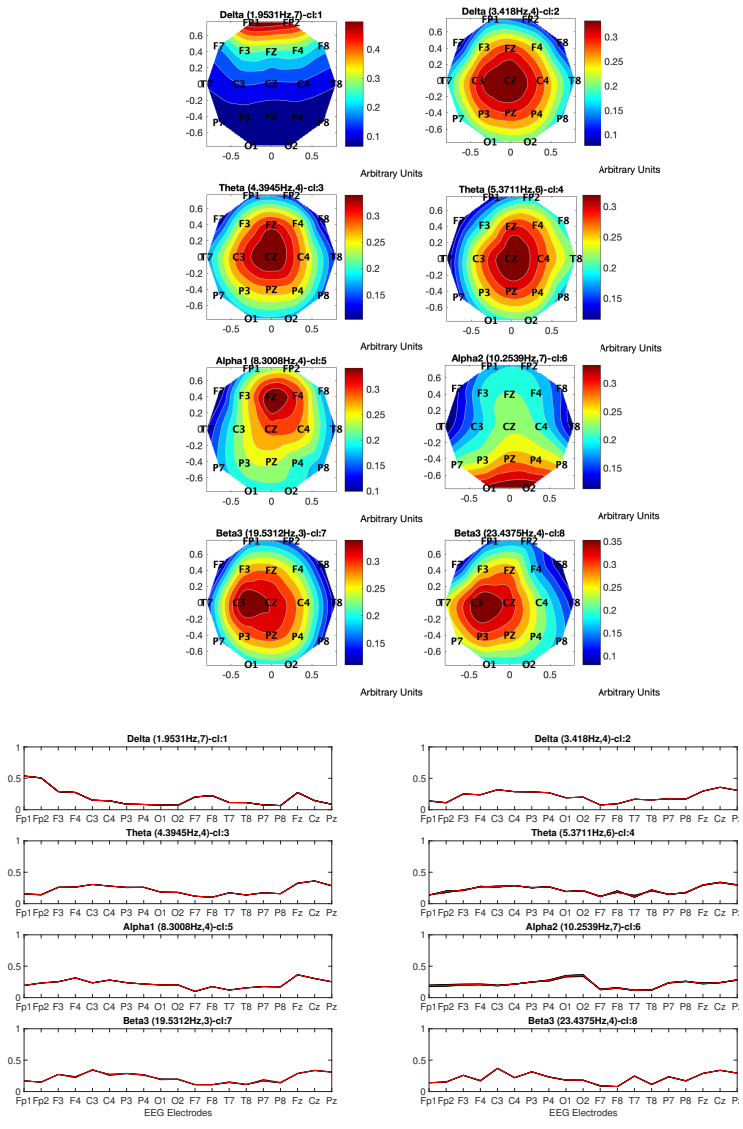
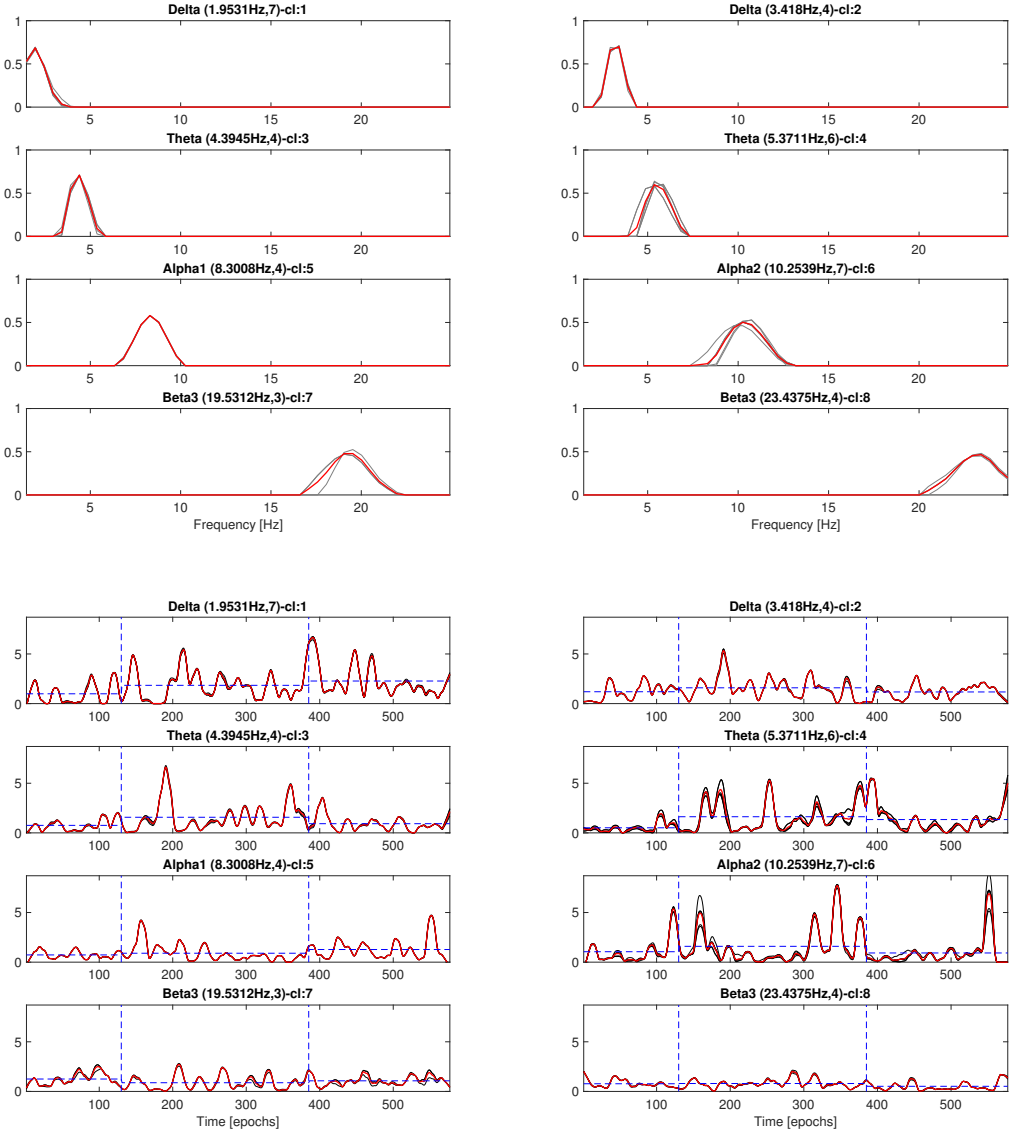


Clustering PARAFAC runs - DBSCAN (by space, frequency and time-scores)

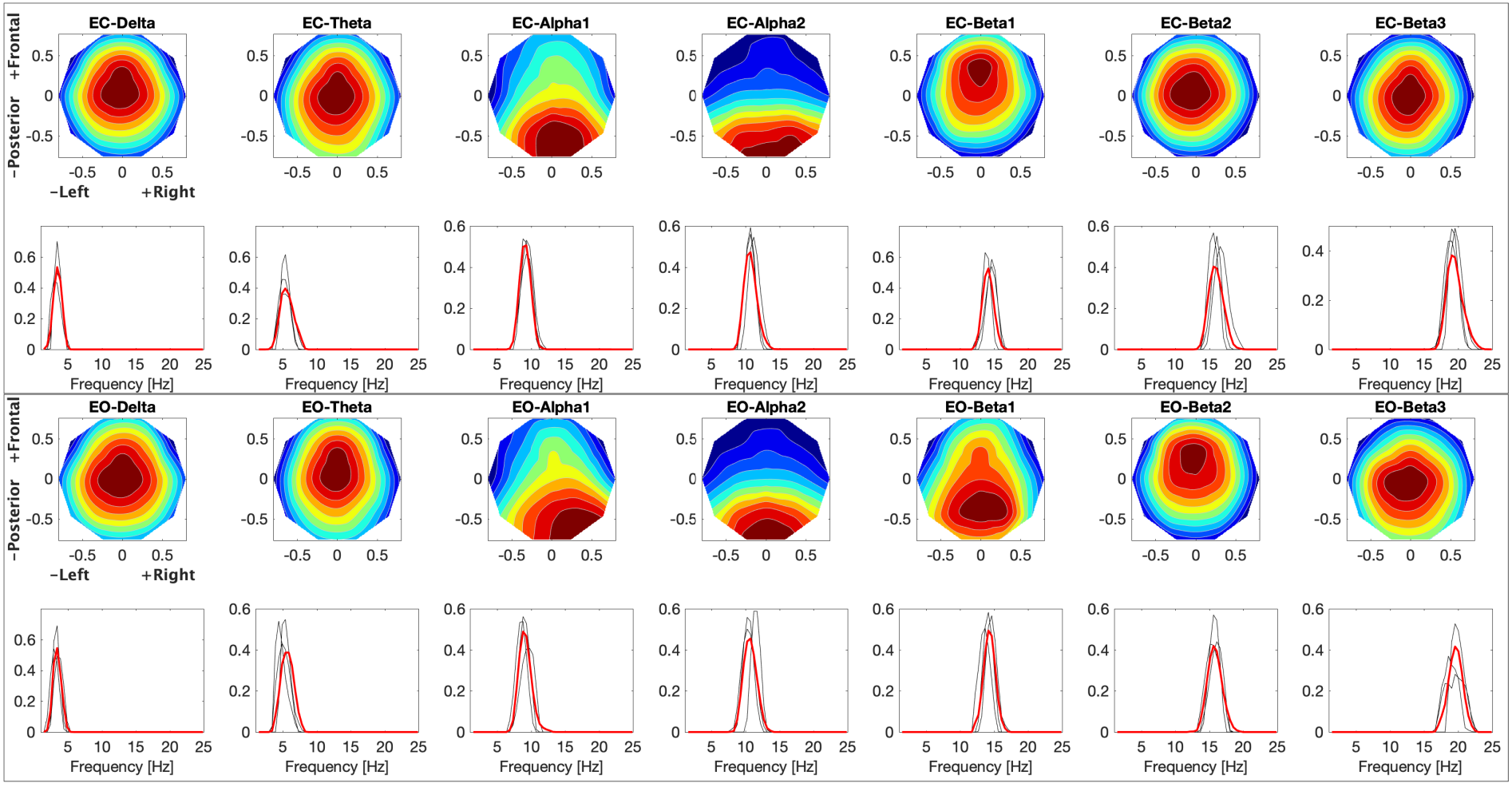


Space PARAFAC weights

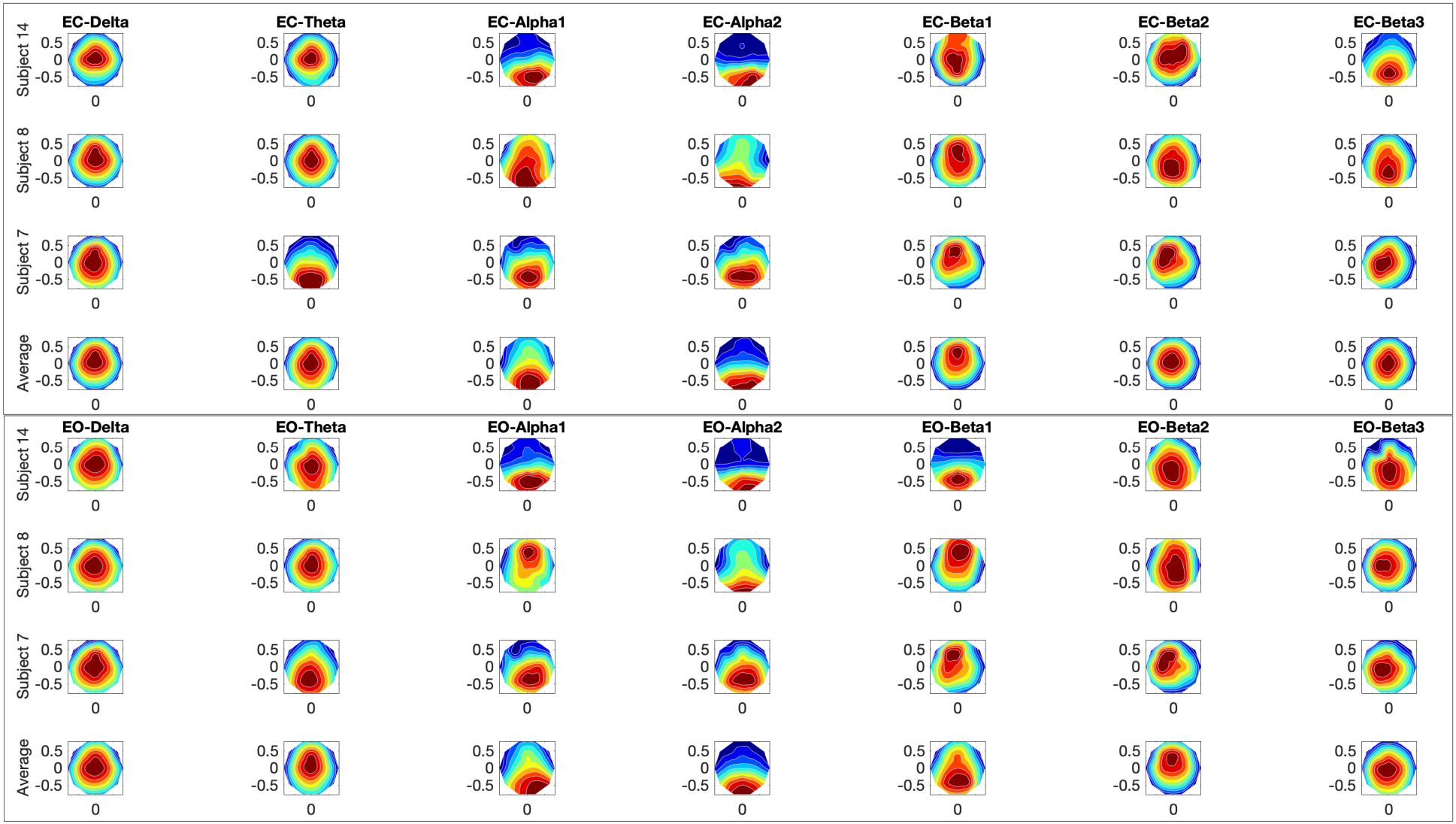


Frequency PARAFAC weights (top) and time scores

Averaged space and frequency PARAFAC weights (8 subjects)



Variability of the PARAFAC spatial weights: individual subjects



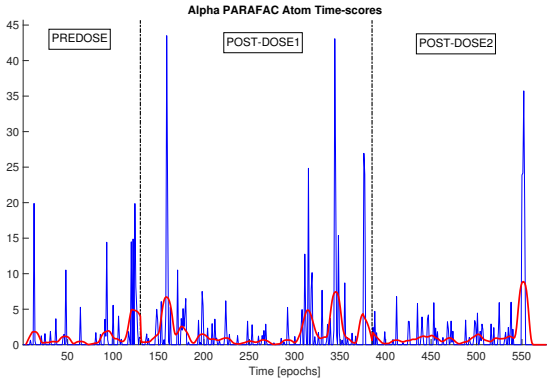
Time-scores to Endpoints and Beyond

A statistic(s) of time-scores can be computed

- mean over time-points
- frequency, duration of activation
- etc.

and used for formal testing

- ANOVA or ANCOVA,
- exposure response
- etc.

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```

Conclusions

- Using the approach we analyzed a collection of data from:
  - two pharmaco-clinical studies
  - longitudinal study focused on motor neurorehabilitation
  - neurobiofeedback studies
- We found that:
  - A discrete set of common PARAFAC atoms can be identified across different task conditions and subjects
  - The atoms show a high day-to-day stability
  - Time-scores allow to build parsimonious EEG representation suitable for formal drug effects testing
  - Pharmaco-clinical studies indicate that effects not assessed by standard QEEG testing can be found

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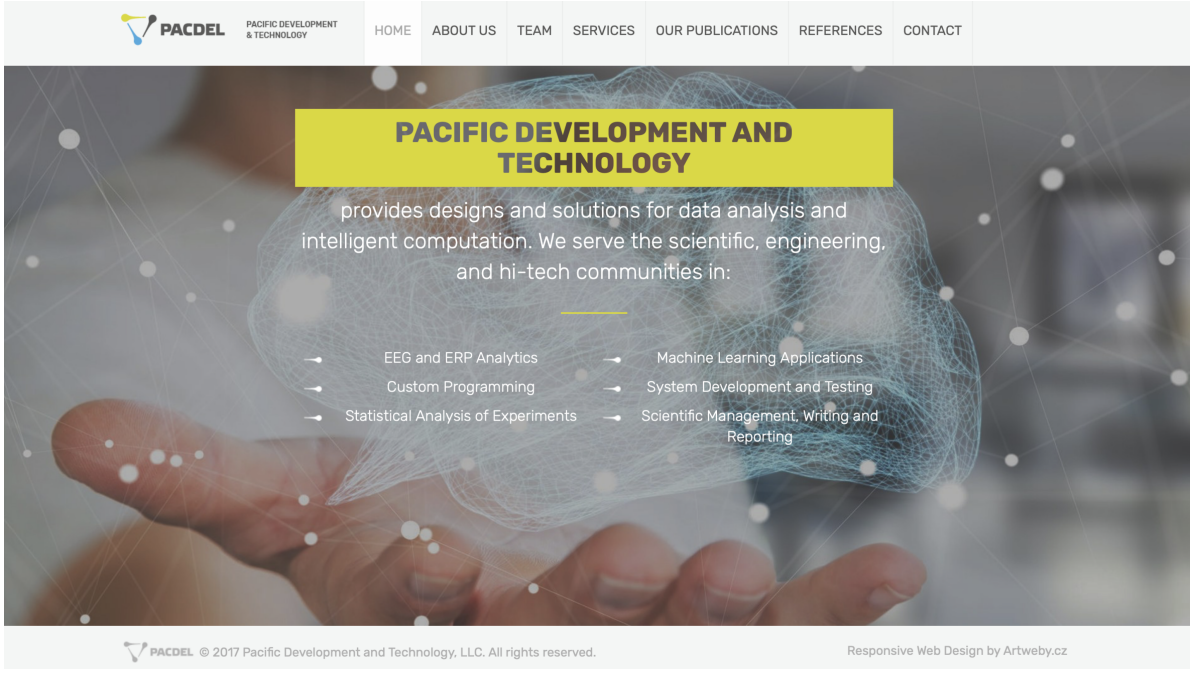

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Acknowledgments

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