

S1 Text for "Neural complexity in preterm infants is predicted by developmental variables"

Lorenzo Semeia^{*1,2}, Amer Zaylaa^{1,4}, Dimitrios Metaxas⁹, Mina Nourhashemi³, Mahdi Mahmoudzadeh³, Andreas L. Birkenfeld^{1,4}, Katrin Sippel¹, Pedro A. M. Mediano⁷, Hubert Preissl^{1,2,4,5,6}, Fabrice Wallois³, and Joel Frohlich^{1,8}**

¹IDM/fMEG Center of the Helmholtz Center Munich at the University of Tübingen, Eberhard Karls University of Tübingen, German Center for Diabetes Research (DZD), Tübingen, Germany; ²Graduate Training Centre of Neuroscience, International Max Planck Research School, Eberhard Karls University of Tübingen, Tübingen, Germany; ³INSERM U1105, GRAMFC, Université de Picardie Jules Verne, Amiens, France; ⁴Department of Internal Medicine IV, University Hospital of Tübingen, Tübingen, Germany; ⁵Department of Pharmacy and Biochemistry, Interfaculty Centre for Pharmacogenomics and Pharma Research, Eberhard Karls University of Tübingen, Tübingen, Germany; ⁶German Center for Mental Health (DZPG), Partner Site Tübingen, Tübingen, Germany; ⁷Department of Computing, Imperial College London, London, UK; ⁸Institute for Advanced Consciousness Studies, Santa Monica, California, USA; ⁹Graduate Training Centre of Neuroscience, Eberhard Karls University of Tübingen, Tübingen, Germany

Please address correspondence to: **Lorenzo Semeia (Lorenzo.Semeia@med.uni-tuebingen.de)** and **Joel Frohlich (jfneuro@pm.me)**.

Supplemental Figures

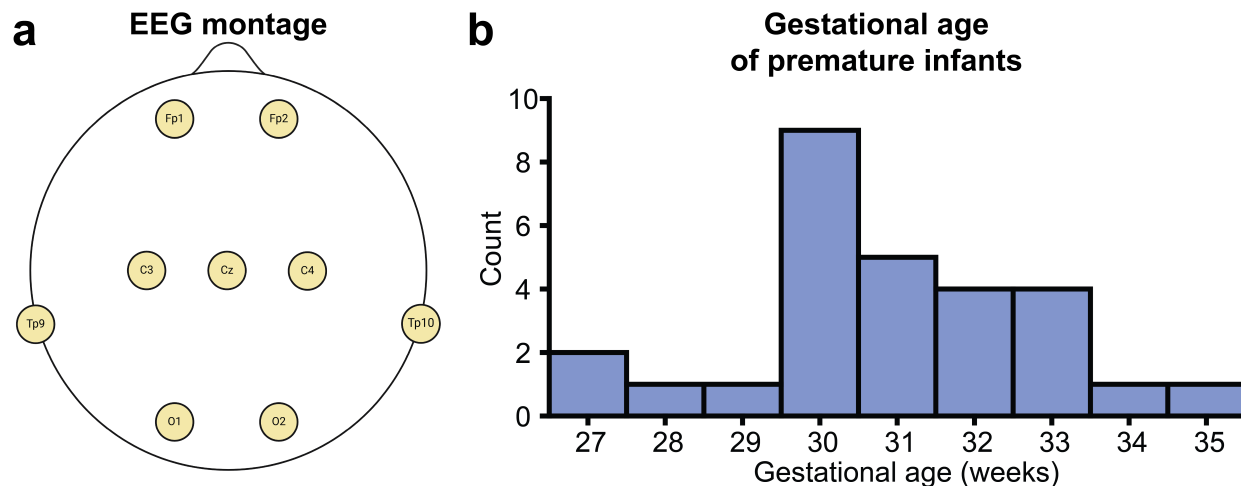


Figure A a) Layout of the EEG recording setup in the 10-20 system (created with BioRender). b) Age distribution of our sample.

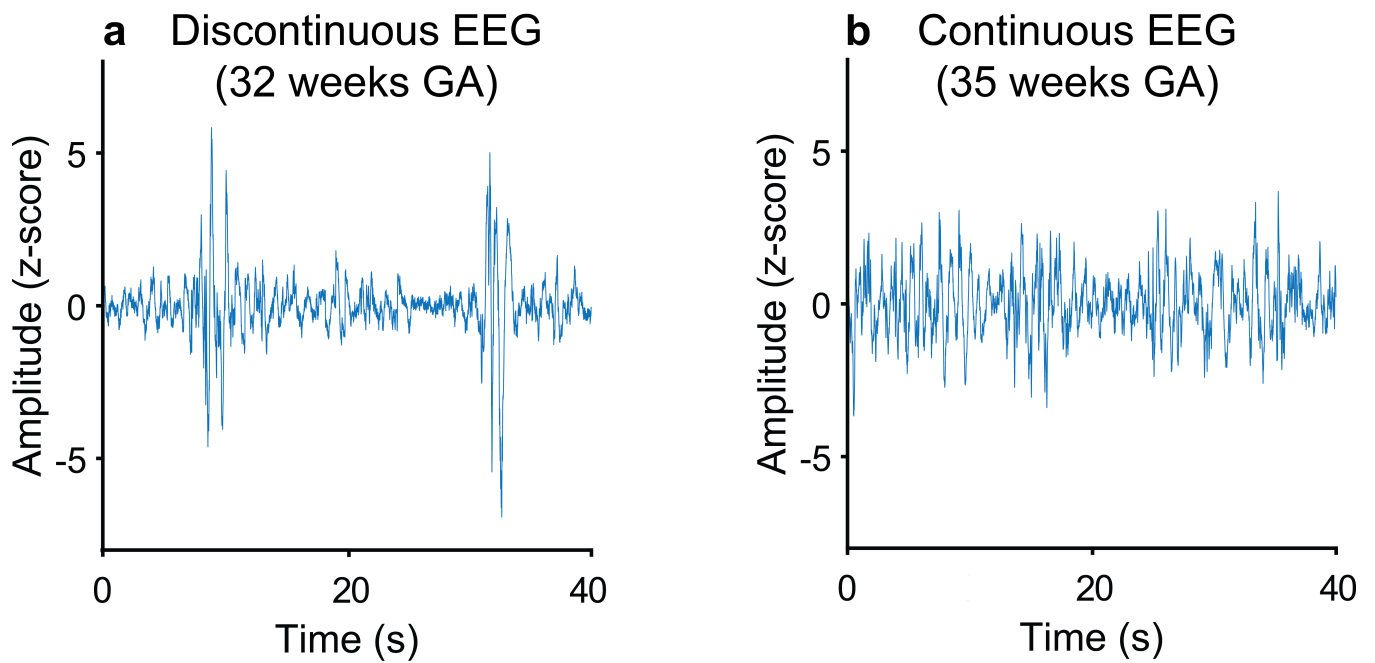


Figure B a) Representative example displaying 40 seconds of EEG activity from a 32 week gestational age infant with a visible spontaneous activity transient. b) Representative example displaying 40 seconds of EEG activity from a 35 week gestational age infant. Compared to (b), the EEG in (a) is characterized by high amplitude bursts of activity followed by low intensity interburst intervals.

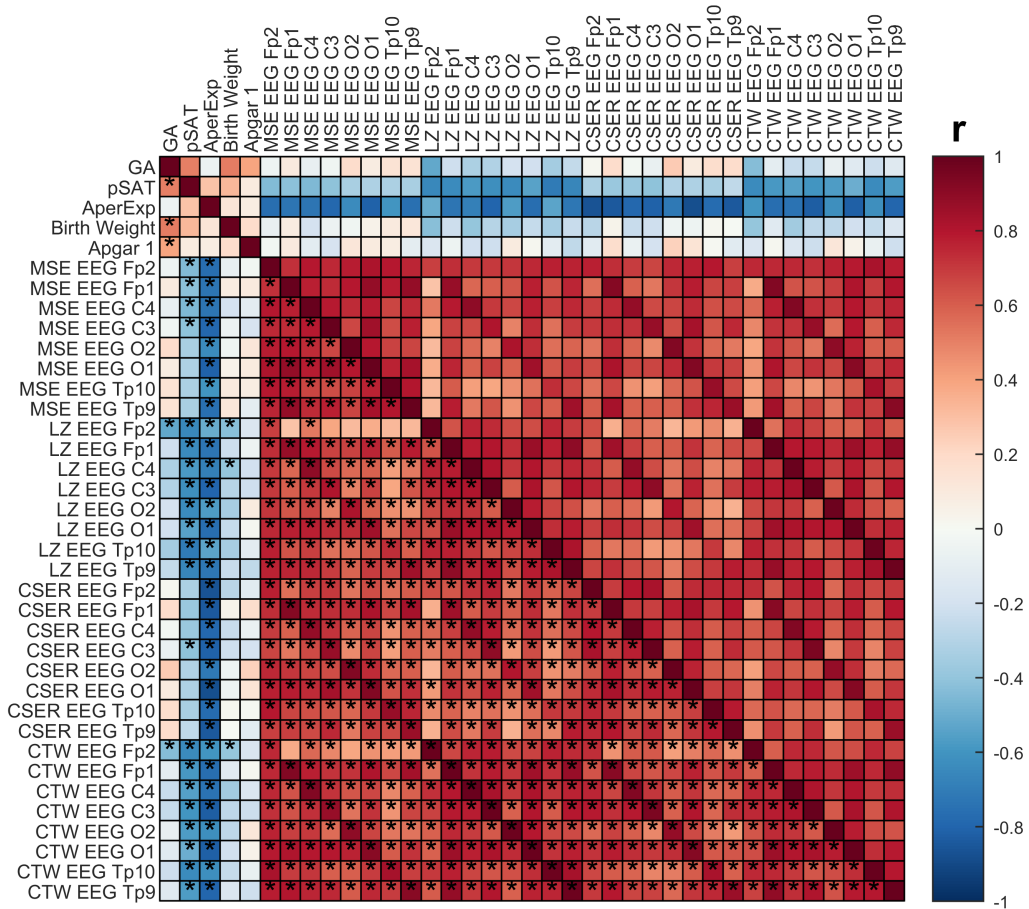


Figure C Correlation matrix for channel-averaged neural entropy measures in relation to gestational age (GA), spontaneous activity transients (pSAT), the aperiodic exponent (AperExp), birth weight, and Apgar 1. *indicates pFDR<0.05.

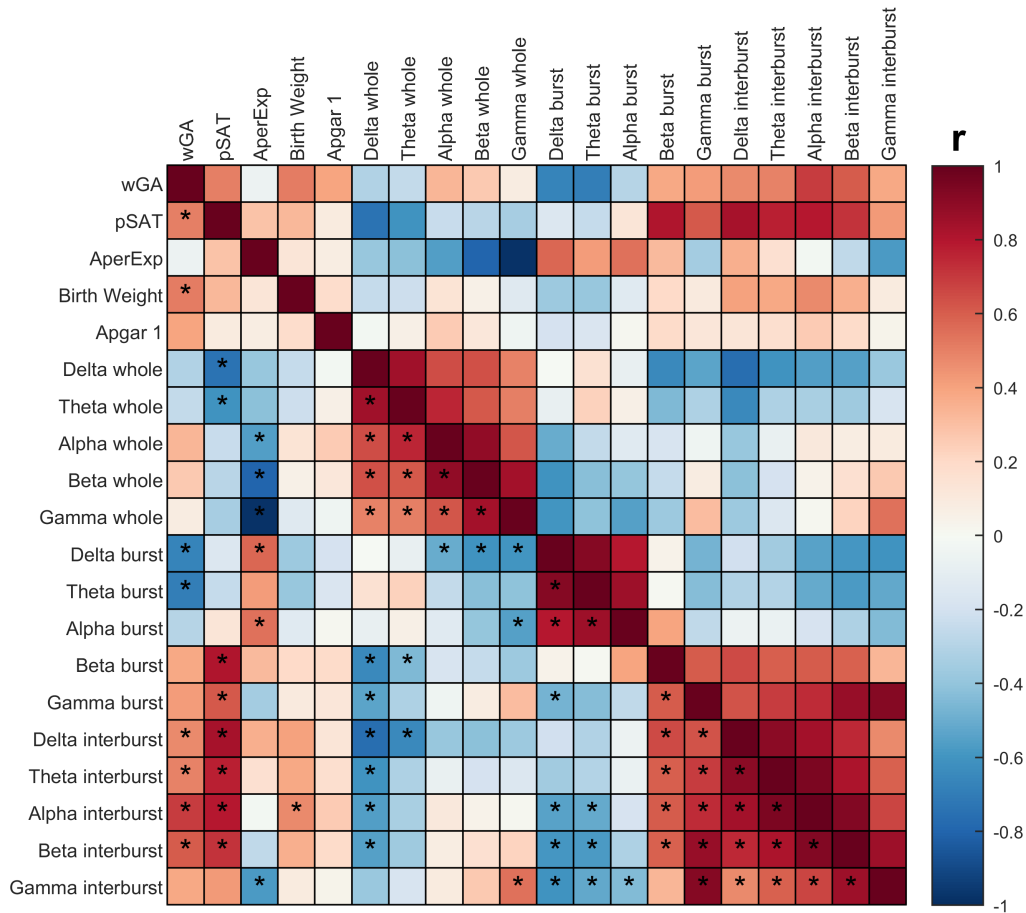


Figure D Correlation matrix for channel-averaged CSER decomposed into separate frequency bands (Delta 1-4Hz, Theta 4-8Hz, Alpha 8-12Hz, Beta 12-30Hz, and Gamma 30-45Hz) in relation to gestational age (GA), spontaneous activity transients (pSAT), the aperiodic exponent (AperExp), birth weight, and Apgar 1. *indicates pFDR<0.05.

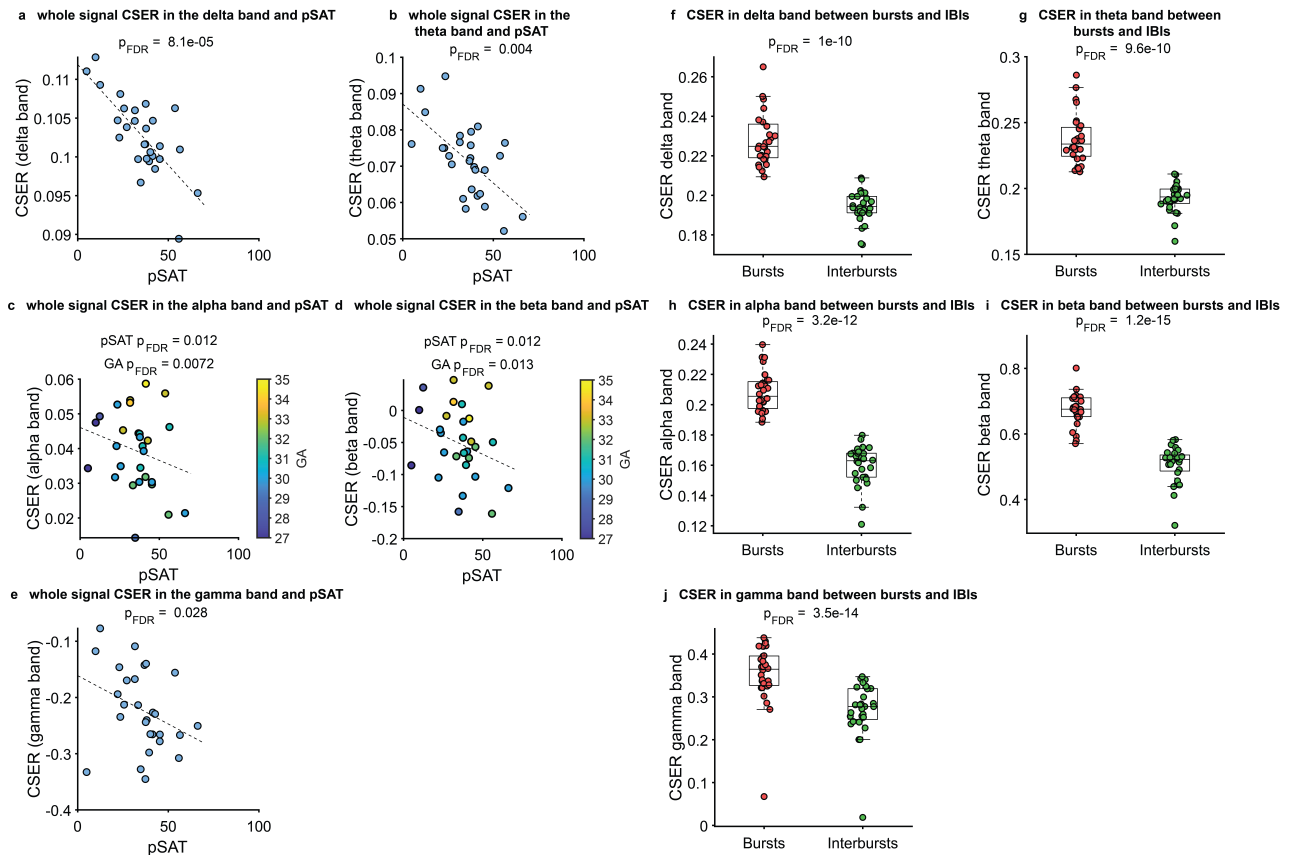


Figure E Predictive variables (a - e) for spectrally decomposed and channel-averaged complexity via state-space entropy rate (CSER) obtained from the whole EEG signal, and (f - j) comparisons of CSER between bursts and interburst periods.

Neural complexity whole EEG signal

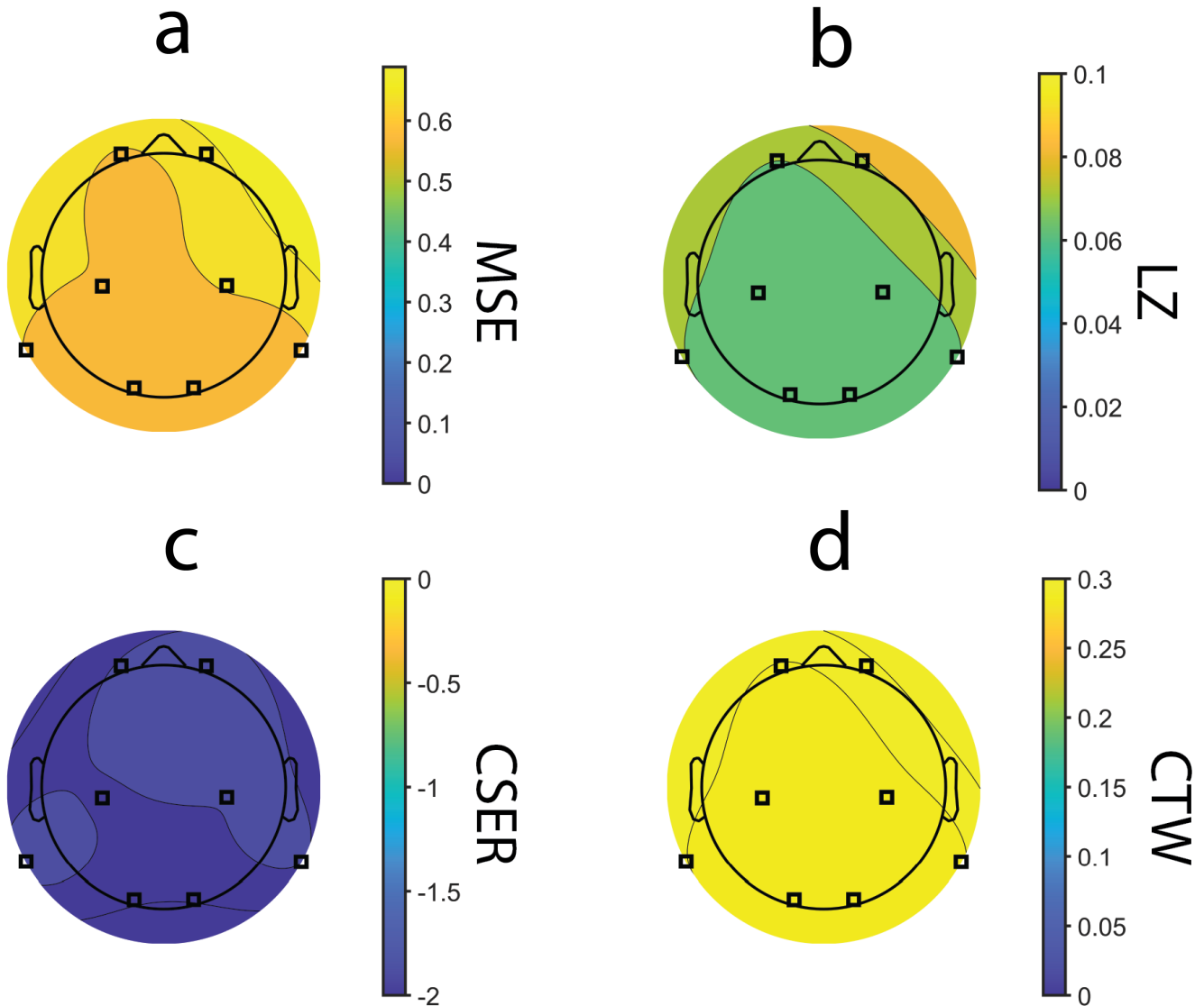


Figure F Topographic scalp plots displaying the spatial distribution of average neural complexity computed from the whole EEG signal according to a) multiscale entropy (MSE), b) Lempel-Ziv (LZ), c) complexity via state-space entropy rate (CSER), and d) context tree weighting (CTW). Because only 8 electrodes were used, we avoided interpolation artifacts by passing 'fill' as the style argument to the EEGLAB topoplot function. The resulting plots suggest that neural complexity computed from the whole EEG signal is spatially homogeneous.

Neural complexity during signal bursts

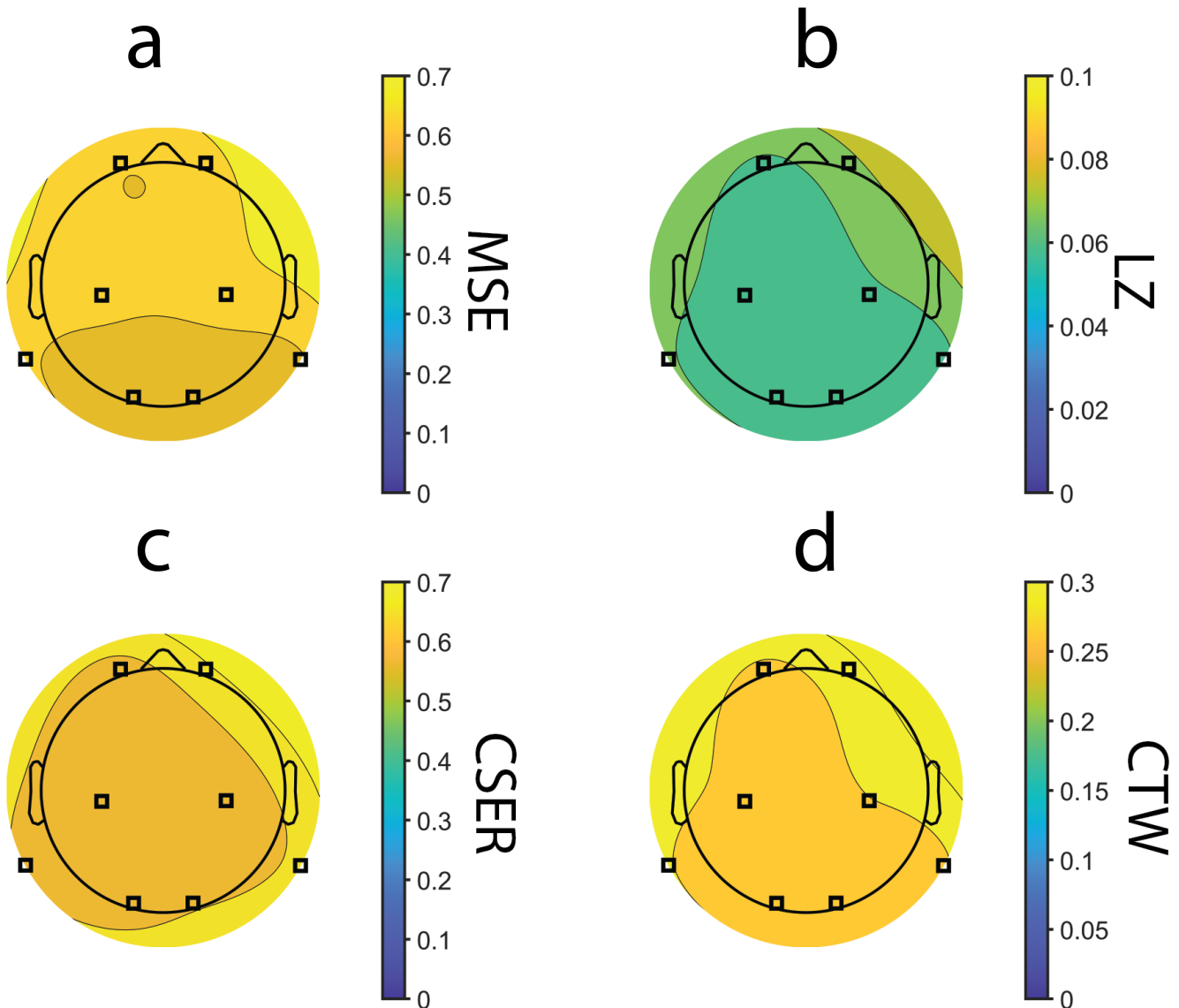


Figure G Topographic scalp plots displaying the spatial distribution of average neural complexity *computed during EEG bursts* according to a) multiscale entropy (MSE), b) Lempel-Ziv (LZ), c) complexity via state-space entropy rate (CSER), and d) context tree weighting (CTW). Because only 8 electrodes were used, we avoided interpolation artifacts by passing 'fill' as the style argument to the EEGLAB topoplot function. The resulting plots suggest that neural complexity computed during bursts is spatially homogeneous.

Neural complexity interburst intervals (IBIs)

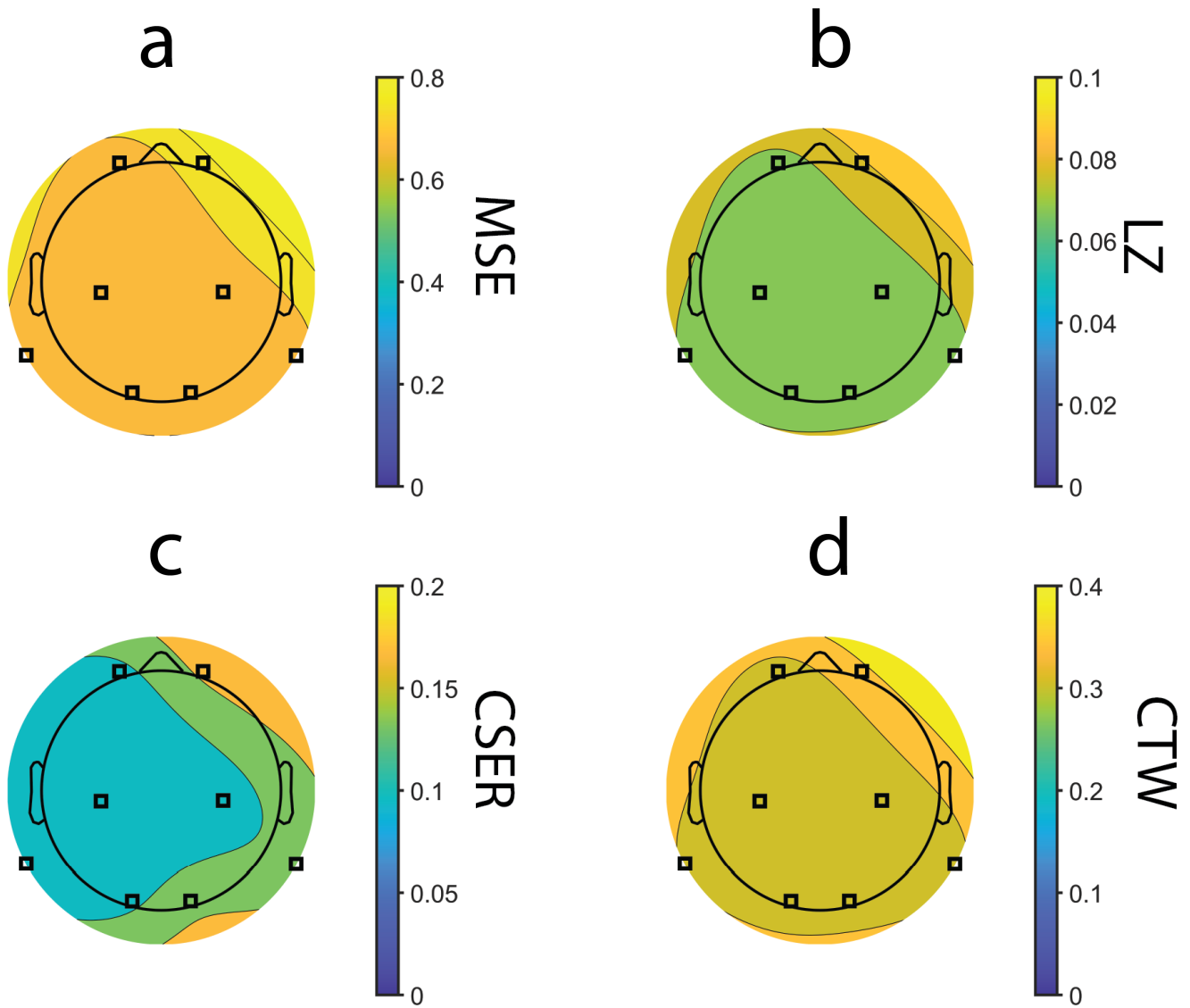


Figure H Topographic scalp plots displaying the spatial distribution of average neural complexity computed during interburst intervals (IBIs) according to a) multiscale entropy (MSE), b) Lempel-Ziv (LZ), c) complexity via state-space entropy rate (CSER), and d) context tree weighting (CTW). Because only 8 electrodes were used, we avoided interpolation artifacts by passing 'fill' as the style argument to the EEGLAB topoplot function. The resulting plots suggest that neural complexity computed during IBIs is largely spatially homogeneous, though CSER shows some right-lateralization.

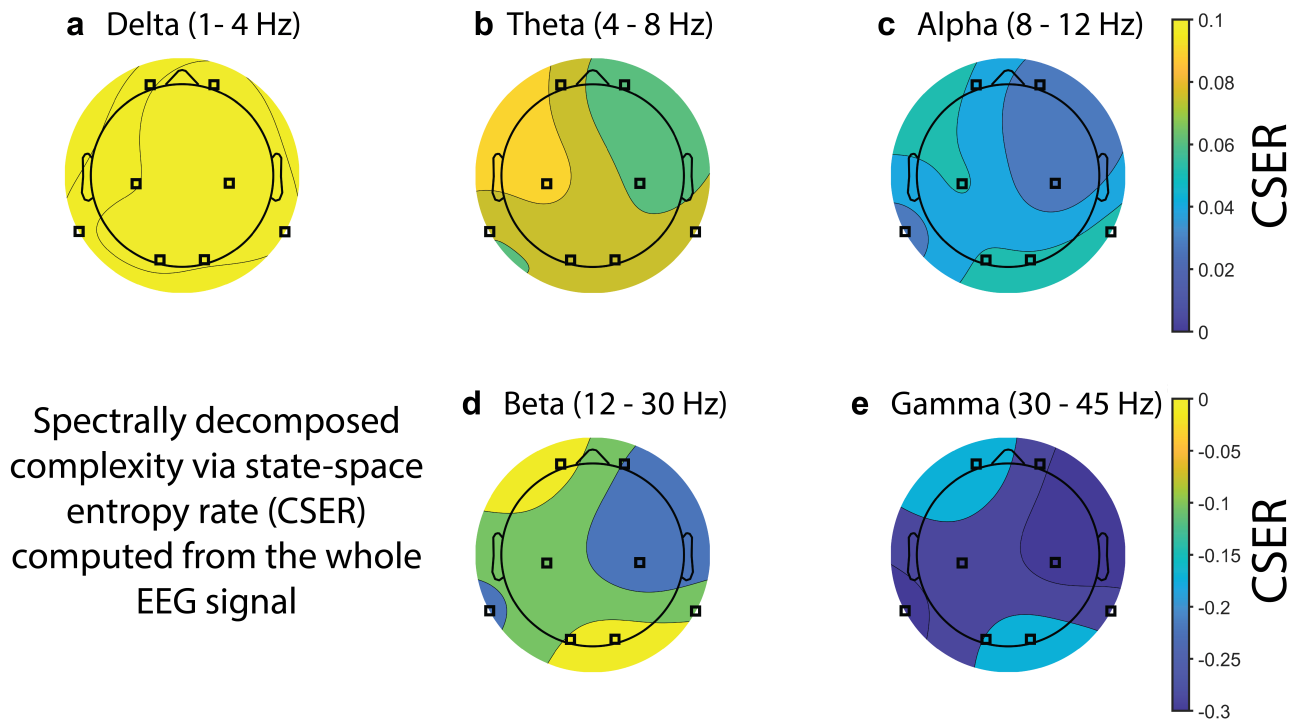


Figure 1 Topographic scalp plots displaying the spatial distribution of complexity via state-space entropy rate (CSER) computed from the whole EEG signal and spectrally decomposed into the conventional EEG frequency bands a) delta, b) theta, c) alpha, d) beta, and e) gamma. Note that a separate color scale is used for beta and gamma, as CSER values were negative in these frequency bands. Because only 8 electrodes were used, we avoided interpolation artifacts by passing 'fill' as the style argument to the EEGLAB topoplot function. The resulting plots suggest that spectrally decomposed neural complexity is greater at lower EEG frequencies. Scalp topographies varied in their degree of spatial variability, ranging from largely homogeneous in the delta band to rather heterogeneous in the beta band.

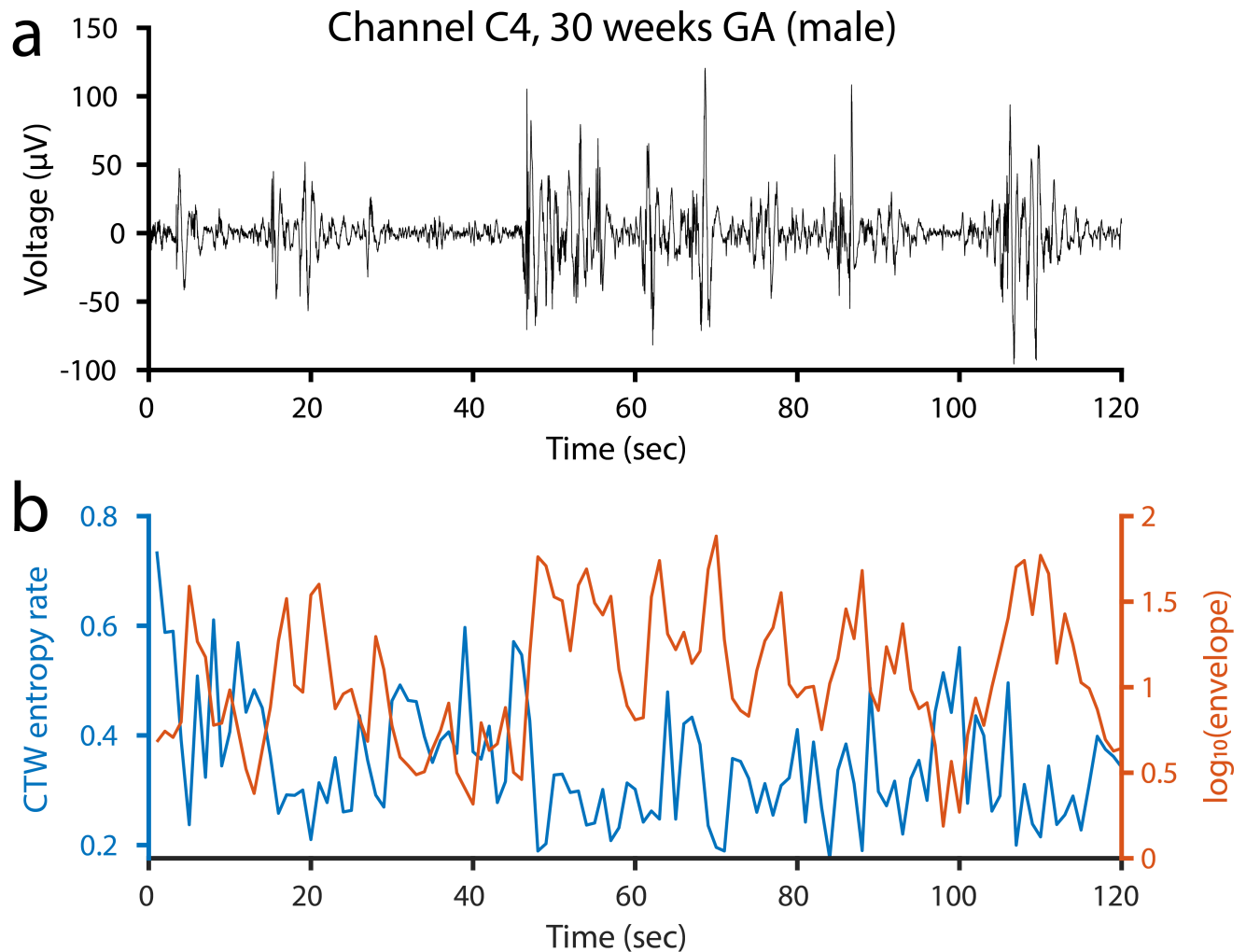


Figure J The CTW entropy rate decreases with the wave envelope of the EEG signal. We used 2 minutes of data recorded from a representative EEG channel from a representative dataset (a) and computed both the CTW entropy rate (b, blue trace) and the wave envelope (b, orange trace), which may serve as a continuous proxy for EEG bursts, within short windows of 1000 ms duration to demonstrate an inverse relationship, which we later quantified in Fig K in S1 Text (see below). The wave envelope was derived from the Hilbert transform with a 2000 ms smoothing and log-scaling. The above suggests that neural complexity decreases during EEG bursts even when a very short window size is used to measure complexity.

Wave envelope vs. short window complexity

● Fp2 ● Fp1 ● C4 ● C3 ● O2 ● O1 ● Tp10 ● Tp9

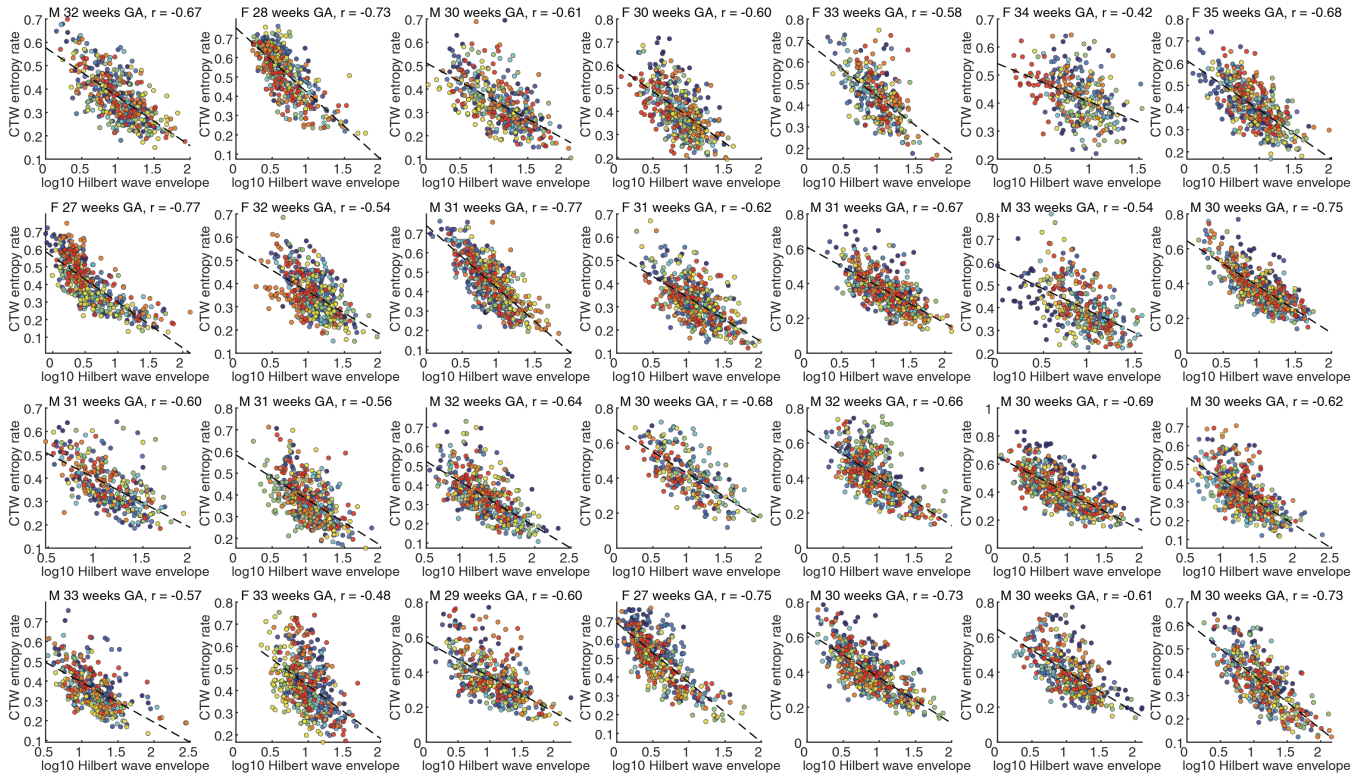


Figure K A consistently negative correlation was measured between the CTW entropy rate, computed from short (1000 ms) windows, and the wave envelope across EEG recordings from all infants (median Pearson coefficient, $r = -0.63$). Because the signal's wave envelope increases during EEG bursts (Fig J in S1 Text, see above), this suggests that neural complexity is inversely related to bursts even within short segments of data.

Note: the correlational analysis was conducted by choosing 60 windows at random for each infant's EEG dataset and computing the CTW entropy rate within each window from all 8 EEG channels, which are color-coded in the figure above. Noisy windows were excluded, and at least 30 valid windows were retained for each dataset. We then correlated CTW with the smoothed, log-scaled EEG signal wave envelope from corresponding 1000 ms windows.

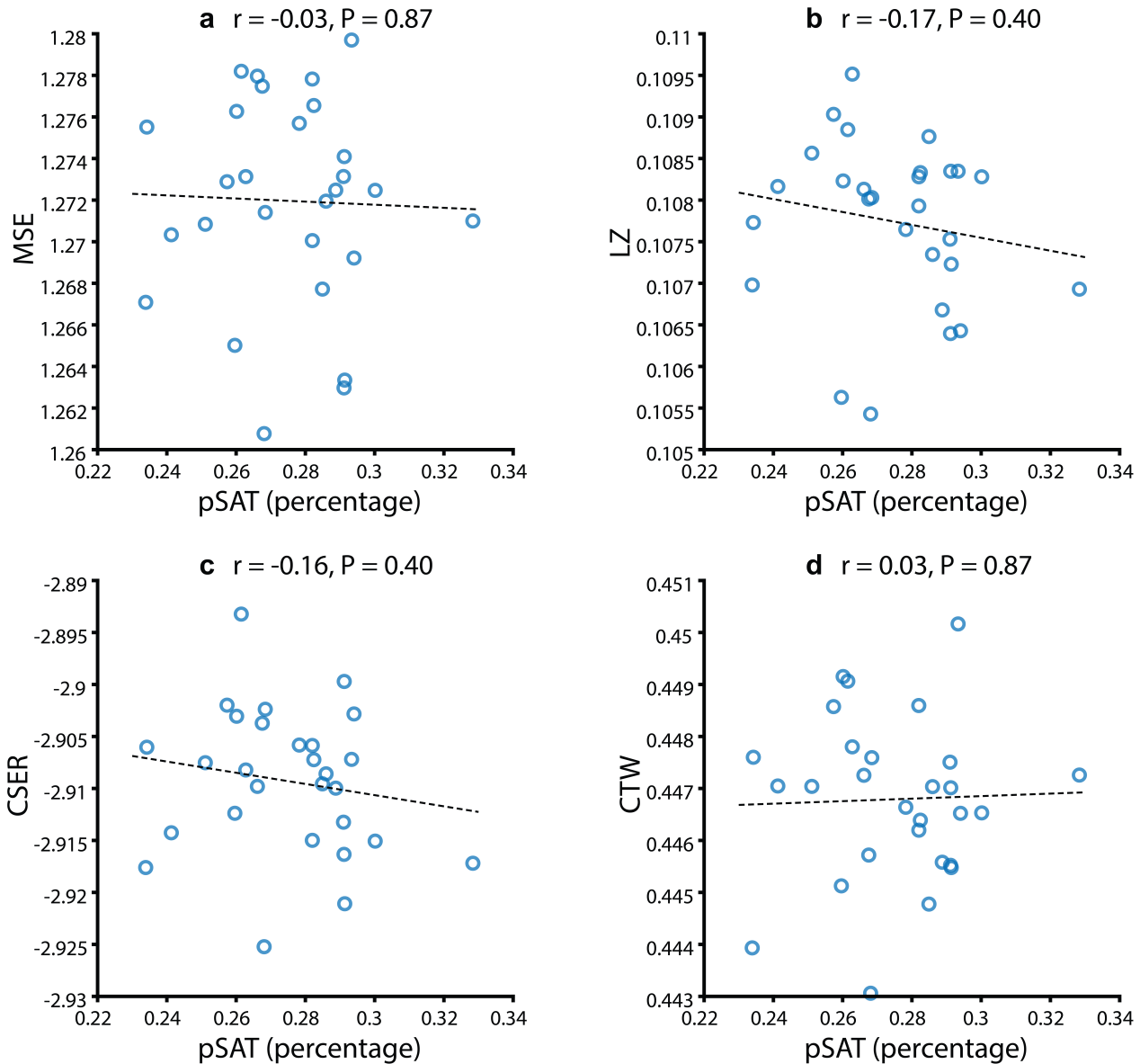


Figure L The proportion of bursts or pSAT (proportion of spontaneous activity transients) does not correlate with complexity measures a) multiscale entropy (MSE), b) Lempel-Ziv (LZ), c) complexity via state-space entropy rate (CSER), or d) context tree weighting (CTW) in simulated signals, i.e., 1/f noise with randomly added bursts.

Table A. Statistical results for spectrally decomposed complexity via state-space entropy rate (CSER)

| Complexity measure | predictor | T stat | P _{FDR} |
|--------------------|--------------|--------|------------------|
| CSER delta | GA | 0.55 | 0.63 |
| CSER delta | pSAT | -5.1 | 8.12e-05 |
| CSER theta | GA | 0.37 | 0.71 |
| CSER theta | pSAT | -3.5 | 0.0040 |
| CSER alpha | GA | 3.2 | 0.0072 |
| CSER alpha | pSAT | -2.9 | 0.012 |
| CSER beta | GA | 2.8 | 0.013 |
| CSER beta | pSAT | -2.9 | 0.012 |
| CSER gamma | GA | 1.6 | 0.13 |
| CSER gamma | pSAT | -2.4 | 0.028 |
| CSER delta | Burst vs IBI | 11 | 1.00e-10 |
| CSER theta | Burst vs IBI | 9.6 | 9.61e-10 |
| CSER alpha | Burst vs IBI | 13 | 3.23e-12 |
| CSER beta | Burst vs IBI | 18 | 1.16e-15 |
| CSER gamma | Burst vs IBI | 16 | 3.54e-14 |

Statistical results for spectrally decomposed CSER. CSER = Complexity via state-space entropy rate; GA = gestational age; pSAT = percent spontaneous activity transients; IBI = interburst interval; P_{FDR} = False Discovery Rate corrected p-values.

Table B. Mediation analysis results

| Signal | Complexity measure | Mediation model | P _{FDR} |
|--------------|--------------------|--------------------|------------------|
| Whole signal | MSE | GA-pSAT-complexity | 0.08 |
| Whole signal | LZ | GA-pSAT-complexity | 0.08 |
| Whole signal | CTW | GA-pSAT-complexity | 0.08 |
| Whole signal | CSER | GA-pSAT-complexity | 0.08 |
| Bursts | MSE | GA-pSAT-complexity | 0.15 |
| Bursts | LZ | GA-pSAT-complexity | 0.15 |
| Bursts | CTW | GA-pSAT-complexity | 0.15 |
| Bursts | CSER | GA-pSAT-complexity | 0.08 |
| Interburst | MSE | GA-pSAT-complexity | 0.08 |
| Interburst | LZ | GA-pSAT-complexity | 0.08 |
| Interburst | CTW | GA-pSAT-complexity | 0.08 |
| Interburst | CSER | GA-pSAT-complexity | 0.08 |
| Whole signal | MSE | pSAT-AE-complexity | 0.15 |
| Whole signal | LZ | pSAT-AE-complexity | 0.15 |
| Whole signal | CTW | pSAT-AE-complexity | 0.15 |
| Whole signal | CSER | pSAT-AE-complexity | 0.15 |
| Bursts | MSE | pSAT-AE-complexity | 0.16 |
| Bursts | LZ | pSAT-AE-complexity | 0.16 |
| Bursts | CTW | pSAT-AE-complexity | 0.16 |
| Bursts | CSER | pSAT-AE-complexity | 0.51 |
| Interburst | MSE | pSAT-AE-complexity | 0.15 |
| Interburst | LZ | pSAT-AE-complexity | 0.15 |
| Interburst | CTW | pSAT-AE-complexity | 0.15 |
| Interburst | CSER | pSAT-AE-complexity | 0.25 |

No mediation effects were statistically significant. MSE = Multiscale Entropy; LZ = Lempel-Ziv complexity; CTW = Context Tree Weighting; CSER = Complexity via State-Space Entropy Rate; GA = Gestational Age; pSAT = proportion of Spontaneous Activity Transients; AE = Aperiodic Exponent. P_{FDR} = False Discovery Rate corrected p-values.