**Methods**

**Dataset**

*Aperiodic Exponent (Slope)*

EEG data were collected from FXS patients and age- and sex-matched controls (TDC) and processed to extract aperiodic exponent (1/f slope) using the FOOOF algorithm of the power spectrum across multiple brain regions. Source-localized EEG timeseries were mapped to DK atlas, assigning nodes to lobes (e.g., frontal, temporal, cingulate, occipital). To account for subject-level variability, we averaged aperiodic exponents across nodes within each lobe per participant, yielding a dataset of subject-specific lobe slopes (n = 9,588 observations across groups). Group (FXS vs. TDC) and sex (M vs. F) were encoded as categorical factors, and mixed-effects models were employed to assess differences in aperiodic slopes while modeling within-subject correlations across lobes and regions.

**Statistical Analysis**

*Aperiodic Exponent (Slope)*

All analyses were conducted in R (v4.4.3), with significance set at α = 0.05. To assess differences in aperiodic slopes across groups (FXS vs. TDC), sexes (M vs. F), and lobes, we fitted a linear mixed-effects model (LMM) using the R package nlme. The final model included *Yij* is the slope for *subjecti* in *lobej*. The fixed effects included an overall intercept β0, main effects representing differences between *group*, *sex*, and *lobe*, and terms representing all two-way interactions. The β terms conceptually represent the coefficients associated with each fixed effect (note that categorical factors are expanded into appropriate contrasts internally). The random effect μ represent the deviation of each subject average slope from the population average and ε is the residual error.

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Models were fitted using restricted maximum likelihood (REML), and fixed effects were tested with Type III F-tests. Model selection was based on Akaike Information Criterion (AIC), favoring the reduced model (AIC = 796.7) without the three-way interaction (see Supplementary Materials for details). Significance was set at α = 0.05.

**Results**

We examined differences in aperiodic slopes (1/f exponent) across brain lobes between FXS patients and TDC, accounting for sex and within-subject correlations. A linear mixed-effects model revealed significant main effects of group (F(1, 137) = 8.65, p = 0.0038) and lobe (F(6, 828) = 195.99, p < 0.0001), as well as a significant group-by-sex interaction (F(1, 137) = 6.08, p = 0.0149; **see Table 1**).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Effect** | **numDF** | **denDF** | **F-value** | **p-value** |
| (Intercept) | 1 | 828 | 942.44 | <0.0001 |
| Group | 1 | 137 | 8.65 | 0.0038 |
| Sex | 1 | 137 | 0.58 | 0.4481 |
| Lobe | 6 | 828 | 195.99 | <0.0001 |
| Group × Sex | 1 | 137 | 6.08 | 0.0149 |
| Group × Lobe | 6 | 828 | 1.65 | 0.1304 |
| Sex × Lobe | 6 | 828 | 1.23 | 0.2879 |

*Table 1: ANOVA Results for the Reduced Model*

*Regional variations in aperiodic slopes*

Aperiodic activity showed significant regional variation across brain lobes (F(6,828)=195.99, p<0.0001), with greatest differences between prefrontal and parietal regions (Δ=0.87±0.03, p<0.0001). Figure 1a illustrates this regional heterogeneity, with parietal regions exhibiting the shallowest slopes (1.76±0.05), followed by central (1.67±0.05) and cingulate regions (1.53±0.05), while prefrontal (0.89±0.05) and temporal (1.13±0.05) regions showed the steepest slopes.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Lobe | Estimated Mean | SE | 95% CI Lower | 95% CI Upper |
| Parietal | 1.755 | 0.050 | 1.656 | 1.853 |
| Central | 1.668 | 0.050 | 1.569 | 1.767 |
| Cingulate | 1.533 | 0.050 | 1.434 | 1.632 |
| Occipital | 1.476 | 0.050 | 1.378 | 1.575 |
| Frontal | 1.184 | 0.050 | 1.085 | 1.282 |
| Temporal | 1.130 | 0.050 | 1.031 | 1.229 |
| Prefrontal | 0.886 | 0.050 | 0.787 | 0.984 |

*Table 2: Estimated Marginal Means of Aperiodic Slopes by Brain Lobe*

*Group and sex effects*

Analysis revealed a significant main effect of group (F(1,137)=8.65, p=0.0038) and a significant group×sex interaction (F(1,137)=6.08, p=0.0149), while the main effect of sex was not significant (F(1,137)=0.58, p=0.4481). The three-way interaction (group×sex×lobe) was also not significant (p=0.5428). The group×sex interaction was driven by sex-dependent differences between FXS and TDC groups. Sex-matched comparisons showed that males with FXS had significantly steeper aperiodic slopes compared to TDC males (Δ=0.47±0.12, p=0.0002), while FXS and TDC females showed virtually identical slopes (Δ=0.02±0.14, p=0.8769) (Figure 1b).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Sex | Contrast | Estimate | SE | t-ratio | p-value |
| Male | TDC - FXS | 0.467 | 0.121 | 3.86 | 0.0002 |
| Female | TDC - FXS | 0.021 | 0.135 | 0.16 | 0.8769 |

*Table 3: Sex-Matched Group Comparisons of Aperiodic Slopes*

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**Figure 1: Aperiodic Slopes Across Brain Regions in FXS and TDC Groups:** Key findings from our analysis of aperiodic brain activity in FXS and TDC. Panel A demonstrates the significant regional variation in aperiodic slopes across brain lobes (F(6,828)=195.99, p<0.0001), revealing a clear anatomical gradient with steepest slopes in prefrontal regions and shallowest slopes in parietal regions. Panel B highlights the significant group×sex interaction (F(1,137)=6.08, p=0.0149), showing that males with FXS have significantly steeper aperiodic slopes compared to TDC males (p=0.0002), while no significant differences exist between FXS and TDC females (p=0.8769). These findings suggest sex-specific neurophysiological alterations in FXS that may reflect underlying differences in excitation-inhibition balance across brain networks.

**Supplementary Materials: Detailed Model Fitting for Aperiodic Slope Analysis**

We evaluated multiple linear mixed-effects models (LMMs) to identify the optimal structure for analyzing aperiodic slopes across groups (FXS vs. TDC), sexes (M vs. F), and lobes. The initial model included fixed effects for group, sex, lobe, and their two- and three-way interactions (subject\_lobe\_slope ~ group \* sex \* lobe), with random intercepts for subjects (eegid) to account for within-subject correlations (n = 987 observations, 141 subjects). Models were fitted using restricted maximum likelihood (REML) via the R package nlme. To assess the impact of correlation structures, we compared the base model (random intercepts only) to alternatives with an autoregressive AR(1) structure (corAR1) and a compound symmetry structure (corCompSymm). We also tested a different optimization method using lmeControl(opt = "optim"). Model comparisons were conducted using Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). The full model yielded an AIC of 819.4 and BIC of 965.4, while the AR(1) model had an AIC of 815.3 and BIC of 966.2, and the compound symmetry model had an AIC of 821.4 and BIC of 972.3. A reduced model omitting the three-way interaction (subject\_lobe\_slope ~ group + sex + lobe + group:sex + group:lobe + sex:lobe) was preferred (AIC = 796.7, BIC = 913.6), as the three-way interaction was non-significant (LRT: χ²(6) = 10.73, p = 0.097). Residual diagnostics confirmed model adequacy, with standardized residuals ranging from -3.53 to 3.86, indicating no severe violations of normality or homoscedasticity. Fixed effects were tested using Type III F-tests, and post hoc pairwise comparisons were planned using estimated marginal means (package emmeans) with Tukey adjustment for multiple comparisons.