UNIVERSITY OF OKLAHOMA

GRADUATE COLLEGE

DEVELOPMENTAL TRAJECTORIES OF NEURAL OSCILLATORY ACTIVITY AND THEIR RELATIONSHIP TO LANGUAGE OUTCOMES IN YOUNG CHILDREN WITH FRAGILE X SYNDROME

A THESIS

SUBMITTED TO THE GRADUATE FACULTY

in partial fulfillment of the requirements for the

Degree of

MASTER OF SCIENCE

By

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Norman, Oklahoma

2026

DEVELOPMENTAL TRAJECTORIES OF NEURAL OSCILLATORY ACTIVITY AND THEIR RELATIONSHIP TO LANGUAGE OUTCOMES IN YOUNG CHILDREN WITH FRAGILE X SYNDROME

A THESIS APPROVED FOR THE

DEPARTMENT OF PSYCHOLOGY

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Abstract

Fragile X Syndrome (FXS) is the most common inherited cause of intellectual disability, yet the developmental emergence of neural abnormalities observed in affected individuals remains poorly understood. This study characterized the developmental trajectory of neural oscillatory activity in young children with FXS (ages 3-9 years) using longitudinal EEG data from the FXLEARN clinical trial. The study used the FOOOF (Fitting Oscillations & One Over F) algorithm to separate periodic oscillatory components from aperiodic background activity, quantifying the theta-to-alpha frequency transition. Logistic regression estimated the age of this transition, and mixed effects models tested whether peak frequency and other FOOOF-derived features predicted language outcomes on the Weighted Communication Scale (WCS). The estimated transition occurred later than the benchmark reported for typical development, but a sensitivity analysis showed that the transition was unstable. Peak frequency did not significantly predict language outcomes beyond age, though its association with language was positive. These findings characterize early oscillatory development in FXS during a period when intervention may be most effective, while indicating that a single peak-frequency estimate has limited value as an individual-level marker.

Introduction and Background

Fragile X Syndrome

Fragile X Syndrome (FXS) is a monogenic neurodevelopmental disorder caused by a CGG trinucleotide repeat expansion (>200 repeats) in the FMR1 gene on the X chromosome, resulting in silencing of the gene and absence of the fragile X messenger ribonucleoprotein (FMRP). FXS is the most common inherited cause of intellectual disability and the leading known single-gene cause of autism spectrum disorder, affecting approximately 1 in 4,000 males and 1 in 8,000 females (Salcedo-Arellano et al., 2020). The condition is associated with a range of cognitive, behavioral, and language challenges, including moderate to severe intellectual disability, attention deficits, anxiety, and significant language delays (Salcedo-Arellano et al., 2020). Early childhood represents a critical period for cognitive and language development in FXS, with detectable differences from other neurodevelopmental conditions emerging as early as 6 months of age (Mullin et al., 2024).

Research in adolescents and adults with FXS has consistently identified distinctive patterns of brain oscillatory activity, including elevated theta power (4-8 Hz) and reduced alpha power (8-12 Hz) compared to typical development (Ethridge et al., 2019; Pedapati et al., 2022). These oscillatory patterns have been linked to excitation-inhibition (E/I) imbalance and altered receptor signaling, particularly involving metabotropic glutamate receptor 5 (mGluR5), which are key neurobiological features of FXS (Scharf et al., 2015). Studies employing FMR1 knockout (KO) mice have demonstrated that the possibility of correcting therapeutically relevant phenotypes in their sample is possible with treatment after disease onset (Scharf et al., 2015). However, despite these promising preclinical results, clinical trials with mGluR5 inhibitors such as mavoglurant

have not shown therapeutic benefit in human studies, highlighting the need for better biomarkers and understanding of developmental timing (Berry-Kravis et al., 2024; R. Hagerman et al., 2018).

Neural Oscillatory Development in Typical Development

In typically developing children, the power spectrum of resting-state EEG undergoes characteristic changes that reflect underlying neural maturations. EEG maturation is commonly used as a marker for structural brain changes, including the development of gray and white matter that occurs across childhood and adolescence (Segalowitz et al., 2010). Theta power, which dominates in early childhood, gradually decreases with age, while alpha power increases, reflecting the progressive maturation of thalamocortical networks (Cellier et al., 2021; Segalowitz et al., 2010). Importantly, this developmental shift does not occur uniformly across the brain. Posterior regions mature earlier than anterior regions, with slower theta activity being replaced by faster alpha activity first in occipital regions and progressing later to frontal regions (Segalowitz et al., 2010). This progress of neural maturation is thought to reflect increased myelination, which wraps neuronal axons in lipid sheaths and greatly increases the speed of neural communication. Faster neural processing is associated with higher oscillation frequencies and improved cognitive abilities, including reading and memory skills (Segalowitz et al., 2010).

Cellier et al. (2021) provided a detailed characterization of this transition using the FOOOF algorithm (Donoghue et al., 2020), which separates periodic oscillatory activity (narrowband peaks reflecting true neural oscillations) from aperiodic background signals (broadband 1/f noise unrelated to oscillations). Analyzing eyes-open resting-state EEG from 96 typically developing participants ages 3 to 24 years across two independent samples (the cross-sectional Sleepy Brain Study and the Child Mind Institute, Multimodal Resource for Studying Information Processing in

the Developing Brain project dataset), they found that both the aperiodic slope and offset decreased with age. Critically, they observed that young children (ages 3-7) showed theta-dominant oscillations in posterior electrodes, whereas alpha-band oscillations emerged as dominant around age 7 and continued to increase peak frequency through age 24. Using logistic regression to model the probability of alpha dominance as a function of age, they estimated the inflection point, the age at which the probability of alpha versus theta dominance reached 50%, at approximately 7.2 years. Notably, peak frequency increased with age only in alpha-dominant older participants but not in theta-dominant younger participants, suggesting that the transition represents a qualitative shift in dominant oscillatory mode rather than a gradual frequency increase.

This developmental transition is thought to have functional significance for cognitive development. Alpha and theta oscillations are developmentally significant because they are closely related to attention and working memory, cognitive functions that exhibit significant developmental improvement from childhood through adolescence (Segalowitz et al., 2010). According to the inhibition-timing hypothesis, alpha oscillations are widely considered to play a functional role in inhibiting task-irrelevant processes, thus supporting focused attention (Klimesch et al., 2007), while theta oscillations have been linked to top-down cognitive control and memory encoding (Buzsáki, 2002; Cavanagh & Frank, 2014). The emergence of alpha-dominant activity during childhood may therefore reflect the maturation of neural circuits that support selective attention and cognitive control. These findings provide a quantitative benchmark for typical neural oscillatory development against which FXS can be compared.

Excitation-Inhibition Imbalance and the Theta-to-Alpha Transition

A core neurobiological feature of FXS is an imbalance between excitatory and inhibitory neural signaling, often referred to as E/I imbalance. This imbalance arises because the loss of FMRP leads to two related problems: enhanced neuronal excitability through activation of glutamatergic signaling pathways, and diminished function of inhibitory signaling mechanisms due to decreased abundance and activity of GABAergic receptors (P. J. Hagerman & Hagerman, 2021). Evidence for this circuit-level dysfunction comes from animal models. In the Fmr1 knockout mouse, Gibson et al. (2008) found that inhibitory interneurons in the neocortex receive weaker excitatory input, which reduces their ability to regulate neural activity. This GABAergic dysfunction is not limited to one brain area; it has been observed across multiple regions relevant to behavior and cognition including the cortex, amygdala, and hippocampus (Paluszkiewicz et al., 2011).

This disruption of inhibitory function has direct implications for neural oscillations. Inhibitory interneurons are essential for generating the precise, synchronized neural activity that produces oscillations (Paluszkiewicz et al., 2011). Consistent with this, Pedapati et al. (2022) found EEG patterns in individuals with FXS that suggest disrupted coordination between the thalamus and cortex. Specifically, reduced alpha power across the brain, elevated theta power, and localized increases in gamma activity. These patterns have been consistently observed across multiple studies over the past decade (Van Der Molen et al., 2014; Wang et al., 2017). Moreover, recent research comparing FXS with autism spectrum disorder suggests that these EEG abnormalities may be more severe or even unique to FXS (Proteau-Lemieux et al., 2024). Mature alpha oscillations depend on precisely coordinated inhibitory signaling. In the context of theta-to-alpha transition, we hypothesize that impaired inhibitory function in FXS may delay the emergence

of alpha-dominant activity, resulting in prolonged theta dominance beyond the typical developmental window.

Knowledge Gap

Despite the well-documented oscillatory abnormalities in adolescents and adults with FXS, little is known about how these patterns emerge during early childhood. Wilkinson and Nelson (2021) provided the first published characterization of baseline EEG activity in young children with FXS, examining resting-state EEG in boys ages 2.5 to 7 years. They found increased power in the beta-gamma range (25-50 Hz) compared to both age-matched and cognitive-matched typically developing controls, with both reduced aperiodic slope and increased periodic beta/gamma activity contributing to this elevation. Notably, after separating periodic oscillations from aperiodic background activity, increased gamma power was associated with better language ability. The authors suggested this may reflect compensatory mechanisms, though the underlying neural basis of this relationship remains to be determined. However, the theta-to-alpha transition has not been directly examined in young children with FXS, and longitudinal data tracking developmental trajectories within individuals remain limited.

This knowledge gap is significant because early childhood is a critical period for cognitive and language development in FXS, with detectable differences from other neurodevelopmental conditions emerging early in childhood (Mullin et al., 2024). Understanding when developmental divergence occurs could identify optimal timing windows for therapeutic intervention. Additionally, neural oscillatory measures may serve as objective biomarkers, addressing a major challenge in FXS therapeutic development (Ethridge et al., 2019). However, the lack of

longitudinal EEG data in young children with FXS has precluded studies of developmental trajectories in this population.

Traditional analysis of EEG power within fixed frequency bands conflates two distinct signal components: narrowband oscillatory (periodic) activity and a broadband aperiodic background signal that follows a 1/f power distribution. This conflation can obscure meaningful oscillatory changes, as what appears to be an aged-related shift in oscillatory power may instead reflect changes in the aperiodic signal. The FOOOF (Fitting Oscillations & One Over F) algorithm addresses this limitation by parameterizing the power spectrum into separate periodic and aperiodic components (Donoghue et al., 2020).

The aperiodic component is characterized by two parameters: the offset (intercept), which reflects overall signal power, and the exponent (slope), which reflects the rate of power decrease across frequencies. Developmental research has shown that both offset and exponent decrease with age, reflecting a shift toward relatively more power at higher frequencies (Cellier et al., 2021). Physiologically, the aperiodic exponent has been linked to the balance of excitatory and inhibitory neural activity, with flatter slopes associated with greater excitation (Gao et al., 2017).

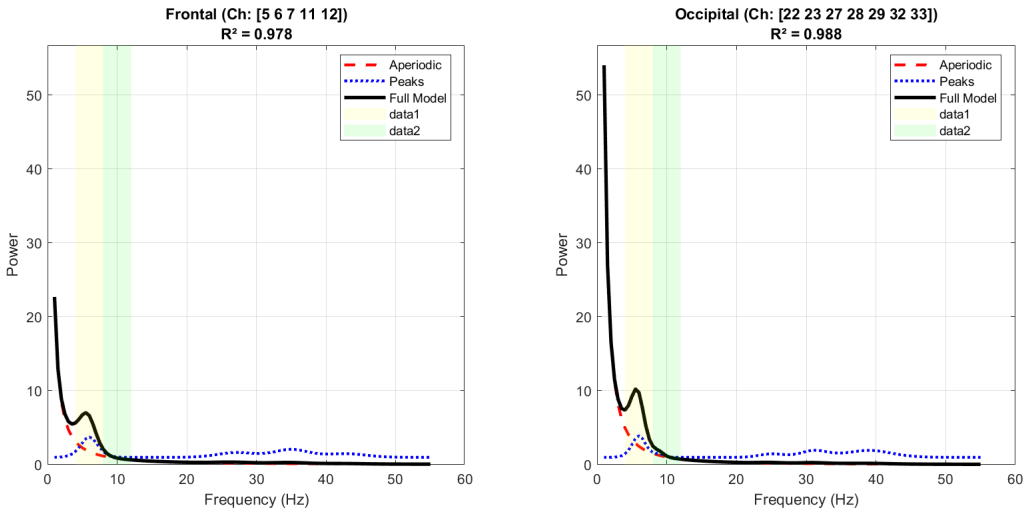

Figure 1. Example FOOOF decomposition of frontal and occipital EEG power spectra from a participant in the present sample. The original power spectrum is shown in black, the aperiodic component is shown as a red dashed line, and the periodic peak component is shown as a blue dotted line. Model fit was high for both regions, with $R^2 = 0.978$ for the frontal region and $R^2 = 0.988$ for the occipital region.

The periodic component consists of narrowband oscillatory peaks characterized by their center frequency (in Hz), amplitude (power above the aperiodic background), and bandwidth. By isolating these peaks from the aperiodic signal, FOOOF enables more precise identification of genuine oscillations and their developmental changes. This approach has been successfully applied to characterize neural development in typical populations (Cellier et al., 2021) and to identify EEG alterations in neurodevelopmental disorders including autism spectrum disorder (Arutiunian et al., 2025).

The FXLEARN Dataset

The FXLEARN study was a multi-site, randomized, double-blind, placebo-controlled clinical trial examining the effects of the mGluR5 negative allosteric modulator AFQ056 (mavoglurant) on language learning outcomes in children with FXS (Berry-Kravis et al., 2024). The trial enrolled 110 participants across 13 sites in the United States, with 99 randomized following a 4-month single-blind placebo lead-in period. Following randomization, participants received either AFQ056 or placebo for 8 months (2 months dose escalation plus 6 months stable dosing), during which both groups received a parent-implemented language intervention (PILI). The total trial duration was approximately 20 months, including the placebo lead-in, placebo-controlled period, and an optional open-label extension phase.

The trial found no significant treatment effects on the primary outcome (Weighted Communication Scale; WCS) or any secondary measures, with both groups showing language progress over time. Given the absence of drug effects, this dataset effectively provides a developmental cohort that can be leveraged to characterize natural neural developmental trajectories in young children with FXS. Resting-state EEG was collected as an exploratory biomarker measure at multiple timepoints throughout the trial, providing a unique opportunity to examine longitudinal neural development in this population.

Preliminary Findings

Prior to the confirmatory analyses, exploratory analyses were conducted to determine which neural features were suitable for formal hypothesis testing.

Relative Power Analysis

Initial analyses examined age-related changes in whole-brain relative theta (4-8 Hz) and alpha (8-12 Hz) power. Relative power refers to the proportion of power in a given frequency band relative to total power across all bands and is commonly used in developmental EEG research because it controls for individual differences in overall signal amplitude (Segalowitz et al., 2010). To properly model individual developmental trajectories, these analyses focused on a subset of 18 participants who had data across 4 timepoints (with minimal imputation for missing values). The developmental pattern suggested a significant decrease in theta power with age ($p<.05$) while alpha power remained relatively flat with no statistical significance. This pattern diverges from what is expected in typical development, where both theta decrease and alpha increase are observed (Cellier et al., 2021). The unexpected flatness of alpha power across the age range might be due to relative power estimates obscuring meaningful oscillatory changes caused by the conflation of periodic and aperiodic signal components, motivating the use of the FOOOF algorithm to separate these components.

The Current Study

Aim 1: Characterize Developmental Trajectory of Peak Frequency

The first aim was to characterize the developmental trajectory of dominant oscillatory frequency in young children with FXS. To address the limitation of raw power analysis, which conflates periodic and aperiodic components, the FOOOF algorithm was applied to parameterize the power spectrum and extract the dominant frequency, defined as the frequency at which the highest amplitude oscillatory peak occurs within the 3-15 Hz range, for frontal and occipital regions of interest.

Frontal and occipital regions were analyzed separately rather than combined because alpha oscillations in posterior and anterior regions appear to be generated by distinct neural mechanisms. In lower visual cortices (V2, V4), alpha rhythms originate in deep cortical layers and propagate to superficial layers, whereas in higher visual cortex (IT), alpha activity originates in superficial layers (Bollimunta et al., 2008). This suggests that combining frontal and occipital regions may obscure region-specific developmental patterns. Recent work has further demonstrated that alpha oscillations participate in distinct information flows along anterior-posterior routes, with feedforward and feedback communication occurring at different frequencies (Suzuki et al., 2025), suggesting distinct functional roles for frontal and occipital alpha.

The correlation between peak frequency and age was examined to establish whether developmental change is detectable. Logistic regression then modeled the probability of alpha dominance (peak frequency ≥ 8 Hz) as a function of age, with the transition age estimated as the point of 50% probability. This estimated transition age was compared to the 7-8 years old transition point found in typical development (Cellier et al., 2021). It was hypothesized that children with FXS would show a delayed theta-to-alpha transition, consistent with the reduced alpha power observed in adults with FXS (Ethridge et al., 2019; Pedapati et al., 2022).

Aim 2: Test Whether Peak Frequency Predicts Language Outcomes

The second aim was to examine whether peak frequency predicts language outcomes, operationalized as scores on the Weighted Communication Scale (WCS). If the theta-to-alpha transition reflects functionally meaningful neural maturation, then children who are further along in this developmental trajectory are expected to show better language outcomes. It was hypothesized that higher peak frequency would predict better WCS scores after controlling for age

in young children with FXS. Linear mixed effects models tested this relationship, with random effects to account for repeated measures within participants.

In addition to peak frequency, two other FOOOF-derived features were examined as potential predictors of language outcomes. First, aperiodic parameters (offset and exponent) were tested, as prior research has linked the aperiodic exponent to E/I balance (Gao et al., 2017) and Wilkinson and Nelson (2021) found associations between aperiodic-adjusted gamma power and language ability in young boys with FXS. Second, following Arutiunian et al. (2025), who reported associations between the number of detected alpha peaks and language skills in youth with autism spectrum disorder, peak count in the theta/alpha range was examined as a predictor. These secondary analyses helped determine whether features beyond peak frequency contribute to explaining language variability in this population.

Methods

Participants

Participants were children with confirmed FMR1 full mutation who participated in the FXLEARN clinical trial (Berry-Kravis et al., 2024). Inclusion criteria for the original trial required age 32 months to 6 years at screening, developmental quotient below 75, evidence of intentional communication, stable behavioral therapy and medication regimens, and English as the primary language. For the current analyses, 41 participants had usable EEG data. FOOOF analysis produced usable spectral output for 40 of these participants across 116 sessions, yielding 232 region observations (frontal and occipital across all sessions). Participant ages ranged from 2.67-8.75 years at the time of data collection (M = 5.96), and participants contributed varying numbers of sessions depending on attendance and data quality (median = 3 sessions per participant; range

1-6), with EEG and language assessments collected at each attended visit. The primary source for missing data was a temporary shift to virtual visits during the first months of the COVID-19 pandemic, which precluded EEG data collection, however due to staggered enrollment this shift occurred at different visit numbers for different participants and should be considered missing at random relative to developmental trajectory.

Analytic sample sizes differed across analysis because each model required complete data on a different set of variables drawn from this same source dataset. A dominant 3-15 Hz peak was detected in 214 of the 232 region-observations (frontal: 108; occipital: 106); the 18 region-observations without a detectable peak were excluded from peak-based analyses but retained for peak-count analyses. The Aim 1 correlations and logistic regression therefore used 108 frontal and 106 occipital observations. The primary Aim 2 model, which additionally required concurrent WCS data and was fit on region-stacked data with region as a fixed effect, included 190 region-observations from 33 participants. Secondary Aim 2 models (aperiodic parameters, peak count), which did not require a detectable peak and were fit separately by region, included 103 observations from 35 participants. The survival sensitivity analysis was run at the participant level, with 18 participants contributing to the frontal risk set and 21 to the occipital risk set.

The analytic sample was predominantly male, with 37 male participants (92.5%) and 3 female participants (7.5%). This sex distribution reflects the X-linked inheritance pattern of FXS and the inclusion requirement of significant intellectual disability (DQ below 75). In the full FXLEARN trial, 92% of participants were male (Berry-Kravis et al., 2024). Due to the FMR1 gene's location on the X chromosome, males typically exhibit the full clinical phenotype when carrying the full mutation. In contrast, females with the full mutation have a second, unaffected X chromosome, and random X-inactivation results in a mixture of cells expressing either the affected

or healthy FMR1 allele. This mosaicism leads to a generally milder and more variable phenotype in females (Scharf et al., 2015). Consequently, FXS is diagnosed about twice as often in males compared to females and females are more likely to have mild to no intellectual disability.

Measures

EEG Recording and Processing. In the FXLEARN study, approximately 3 minutes of eyes-open resting-state EEG was collected while participants sat and watched a silent cartoon video. Six sites participated in the EEG portion of the study, using four different EEG systems: a Biosemi 32-channel system (1 site), an EGI 32-channel system (1 site), an EGI 64-channel system (1 site), and an EGI 128-channel system (3 sites). Site standardization for EEG collection parameters, including phantom testing, was conducted prior to trial initiation, to minimize equipment effects. Data from all sites were re-referenced to a standard 33-channel montage to enable cross-site aggregation. EEG was collected at each visit throughout the trial. The trial included up to 15 visits per participant.

Data from all sites were processed using an identical procedure. Data were filtered using a low-pass filter of 100 Hz, a high-pass filter of 0.5 Hz, and a notch filter at 60 Hz to remove line noise. Bad channels were identified and interpolated, with no more than 5% of channels interpolated per participant. Sections containing extreme artifacts were identified by visual inspection and removed. Independent component analysis (ICA) was performed using EEGLAB (Delorme & Makeig, 2004), and components containing large amounts of high-amplitude noise, ocular-motor artifact, muscle tension artifact, or cardiovascular artifact were removed. Following ICA, data were segmented into 2-second epochs and subjected to a 120 μV amplitude threshold to remove epochs with remaining artifacts.

Power spectral density was computed using Welch's method. Regional averages were computed prior to FOOOF analysis by averaging power spectra across channels within each region of interest. The frontal region included channels 5, 6, 7, 11, and 12. The occipital region included channels 22, 23, 27, 28, 29, 32, and 33 (see Figure 2). The FOOOF algorithm was applied with the following parameters: frequency range 1-55 Hz, fixed aperiodic mode, maximum 5 peaks, peak threshold of 1, and Gaussian peak type. For each session and region, the highest amplitude peak in the 3-15 Hz range was extracted, providing peak frequency and peak amplitude values. Aperiodic offset and exponent were also extracted for secondary analyses. Sessions with no detectable peaks in this range were excluded from peak-based analyses except for peak count analyses.

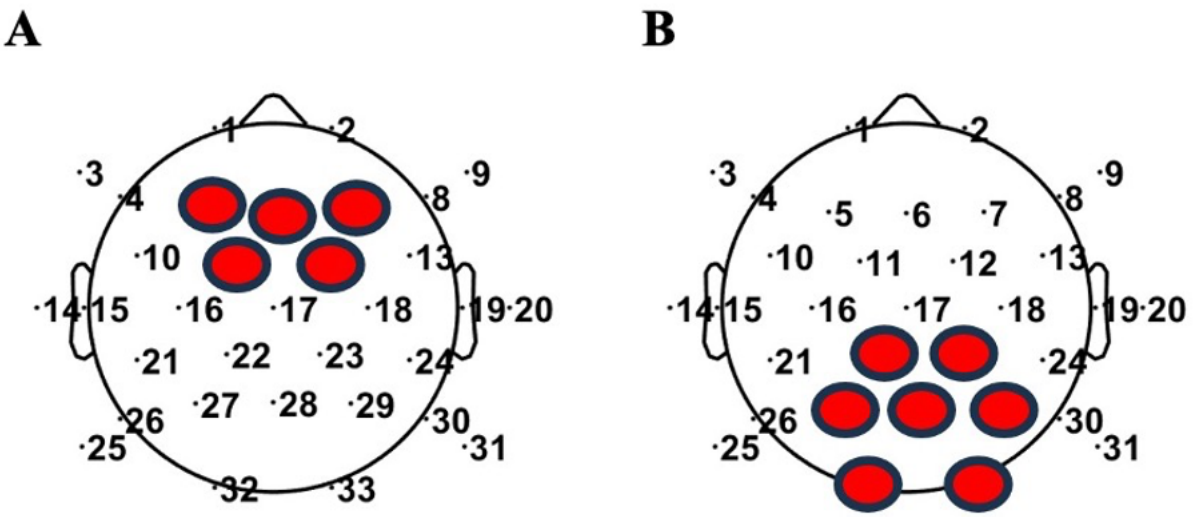

Figure 2. Frontal and occipital regions of interest used for EEG spectral analyses. Panel A shows the frontal region, which included channels 5, 6, 7, 11, and 12. Panel B shows the occipital region, which included channels 22, 23, 27, 28, 29, 32, and 33.

Language Assessment. Language ability was assessed using the Weighted Communication Scale (WCS), which was the primary outcome measure in the FXLEARN trial. During assessment sessions, participants engaged in both structured and unstructured communication tasks while their intentional communicative acts were recorded. The WCS captures the frequency of child-initiated intentional communication and the sophistication of communication methods, with acts weighted by complexity (nonverbal = 1, single symbol = 2, multiple symbols =3). Prior research indicates that this weighted scoring approach is sensitive to developmental change, shows linear growth patterns, and has excellent inter-rater reliability (Berry-Kravis et al., 2024).

The total imputed WCS score was used for this study. Imputation was applied when only one session (structured or unstructured) was missing; participants were excluded from analysis if both sessions were missing at a given timepoint (Berry-Kravis et al., 2024). The distribution of total imputed WCS score was examined and found to be approximately normal (skewness = 0.65), so no transformation was applied.

Statistical Analysis

For Aim 1, Pearson correlations assessed the relationship between peak frequency and age. Logistic regression modeled the probability of alpha dominance (peak frequency ≥ 8 Hz) as a function of age to estimate the transition age, with the transition defined as the age at 50% predicted probability. Because participants contributed multiple observations but the primary interest was in estimating a population-level transition point, standard logistic regression was used rather than mixed effects logistic regression. This approach treats observations cross-sectionally, which may underestimate standard errors due to within-participant correlation. However, because the goal was

to estimate the inflection point rather than to make precise inferences about individual coefficients, the reported confidence intervals should be interpreted with this limitation in mind.

For aim 2, linear mixed effects models were fitted using the lme4 package in R, with significance testing via the lmerTest package. The primary model was: WCS ~ peak_frequency + age_years + region + (1 + age_years | participant_id). The model included peak frequency, age (in years), and region (frontal vs. occipital) as fixed effects, with random intercepts and random slopes for age by participant to account for individual differences in both baseline language ability and developmental trajectories. Age was included as a fixed effect to control for age-related differences, allowing the model to test whether peak frequency predicts language ability above and beyond the effect of age alone. Secondary analyses substituted aperiodic parameters (offset, exponent) or peak count as predictors. Model assumptions (normality and homoscedasticity of residuals) were verified. The significance threshold was set at $\alpha = .05$. Because the study used previously collected data, a priori power analysis was not possible; instead, a post-hoc sensitivity analysis was performed to estimate the smallest detectable effect size. With 41 participants contributing 253 observations (effective $N \approx 100$ after adjusting for within-participant clustering, ICC = 0.30), the study was powered (80%, $\alpha = .05$) to detect correlations of $r \geq .28$, corresponding to a small-to-medium effect size.

Results

Aim 1: Developmental Trajectory of Peak Frequency

Peak Frequency Across Age. Across the observed age range, Pearson correlations suggested significant positive association between dominant peak frequency and age in both

regions (frontal: $r = .261$, $p = .006$; occipital: $r = .256$, $p = .008$), indicating measurable developmental change in dominant oscillatory frequency in this sample.

Logistic Regression: Estimated Transition Age. To estimate the age at which dominant peak frequency transitions from theta to alpha, logistic regression modeled the probability of alpha dominance (peak frequency ≥ 8 Hz) as a function of age, with the transition defined as the age at 50% predicted probability. The estimated transition age was 9.26 years in the frontal region (95% CI [6.86, 11.66]; $\beta = 0.45$, $z = 2.54$, $p = .011$, McFadden's pseudo $R^2 = .066$) and 9.36 years in the occipital region (95% CI [7.44, 11.27]; $\beta = 0.68$, $z = 2.80$, $p = .005$, McFadden's pseudo $R^2 = .126$). Both estimates exceed the approximately 7.2-year transition reported in typical development (Cellier et al., 2021), suggesting delayed neural oscillatory maturation in FXS. Notably, both transition ages fall at or beyond the upper limit of the observed age range (~3-8.7 years), so these estimates rely on extrapolation and should be interpreted with caution. When inflection points fall outside of the observed data range, confidence intervals for logistic regression may become very wide, as is the case with our results. However it should be noted that for the occipital peak, the normative transition age of 7.2 years still falls outside of the 95% confidence interval derived for the FXS sample.

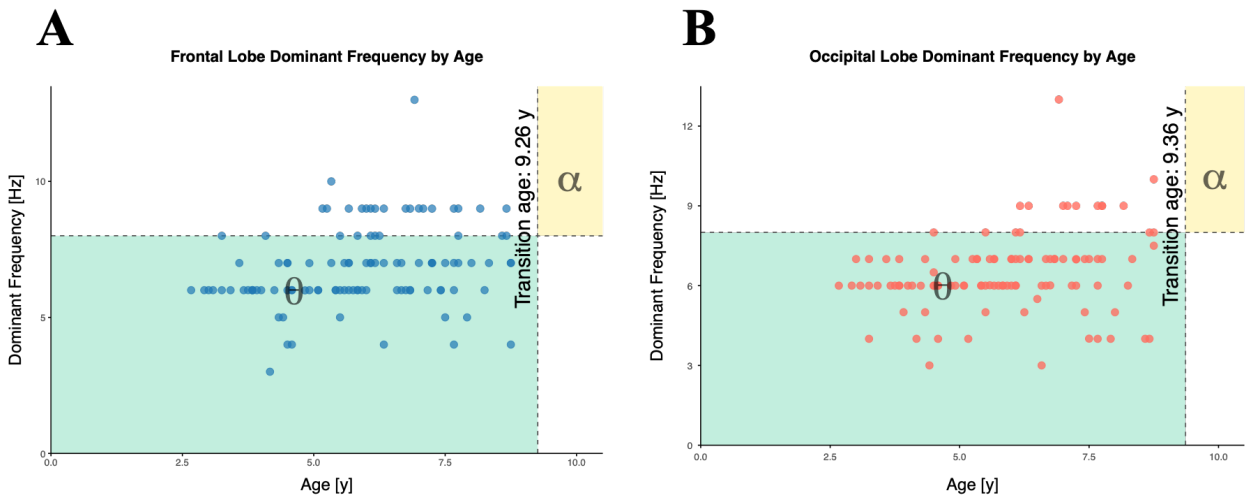

Figure 3. Dominant peak frequency as a function of age in the frontal and occipital regions. Each point represents one session-level observation. The horizontal dashed line marks the 8 Hz threshold used to classify theta versus alpha dominant activity, and the vertical dashed line indicates the estimated theta-to-alpha transition age from the logistic regression model. Panel A shows the frontal region, and Panel B shows the occipital region.

Whether the age-peak frequency association differed by region was also tested, which revealed no significant region x age interaction (p = .44), indicating that the developmental pattern did not differ reliably between the frontal and occipital regions.

Survival Analysis as a Sensitivity Check. To complement the logistic regression approach, the estimated transition was examined as a time-to-event outcome using survival analysis. The event was defined as the first session at which peak frequency reached or exceeded 8 Hz, with each participant entering the risk set at their age at first observation. Participants whose entry and exit ages were identical, including those contributing only a single session, were excluded, leaving 18 participants in the frontal analysis and 21 in the occipital analysis. The estimated median time-to-event was approximately 7 years in the frontal region, with wide

confidence intervals reflecting the small risk sets at each time point. The median in the occipital region was not estimable within the observed age range.

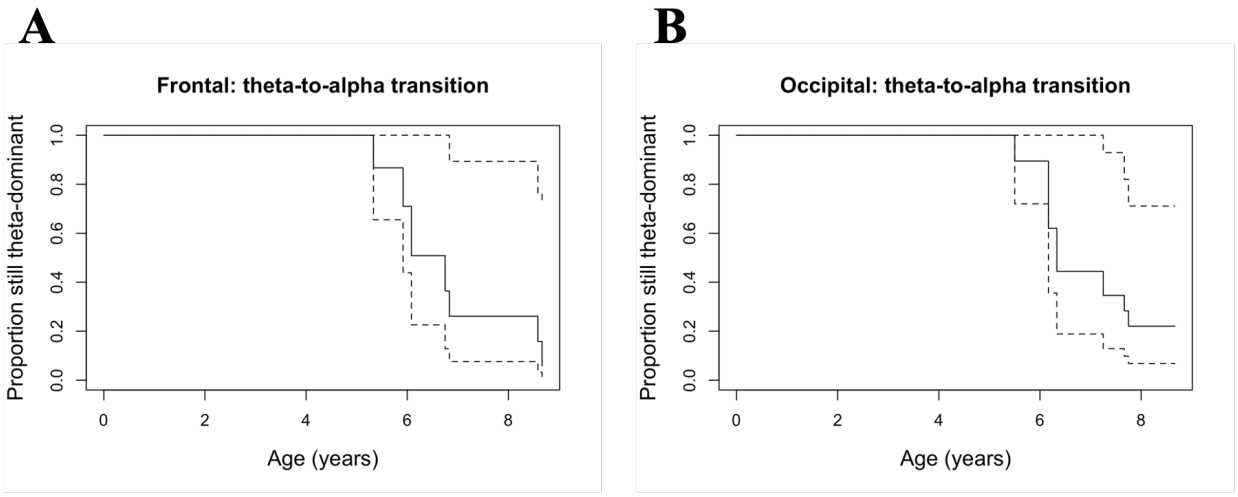

Figure 4. Survival curves showing the estimated proportion of participants who remained theta-dominant across age before first reaching alpha dominance. The event was defined as the first session in which dominant peak frequency reached or exceeded 8 Hz. Panel A shows the frontal region, and Panel B shows the occipital region. Dashed lines indicate confidence intervals.

Diagnostic analyses revealed instability in the operationalized event. Among participants who ever reached 8 Hz, 8 of 11 (73%) in the frontal region had at least one subsequent session below 8 Hz, indicating that the "transition" event was not absorbing. Inspection of these trajectories revealed large oscillations across sessions (e.g., 7 - 9 - 6 - 9 Hz, see Figure 5 for examples), rather than small fluctuations near the threshold. By contrast, only 1 of 7 (14%) occipital participants showed reversion. A small minority of participants (4 of 36 frontal, 0 of 37 occipital) were already alpha-dominant at their first observation, indicating modest left truncation in the frontal model only.

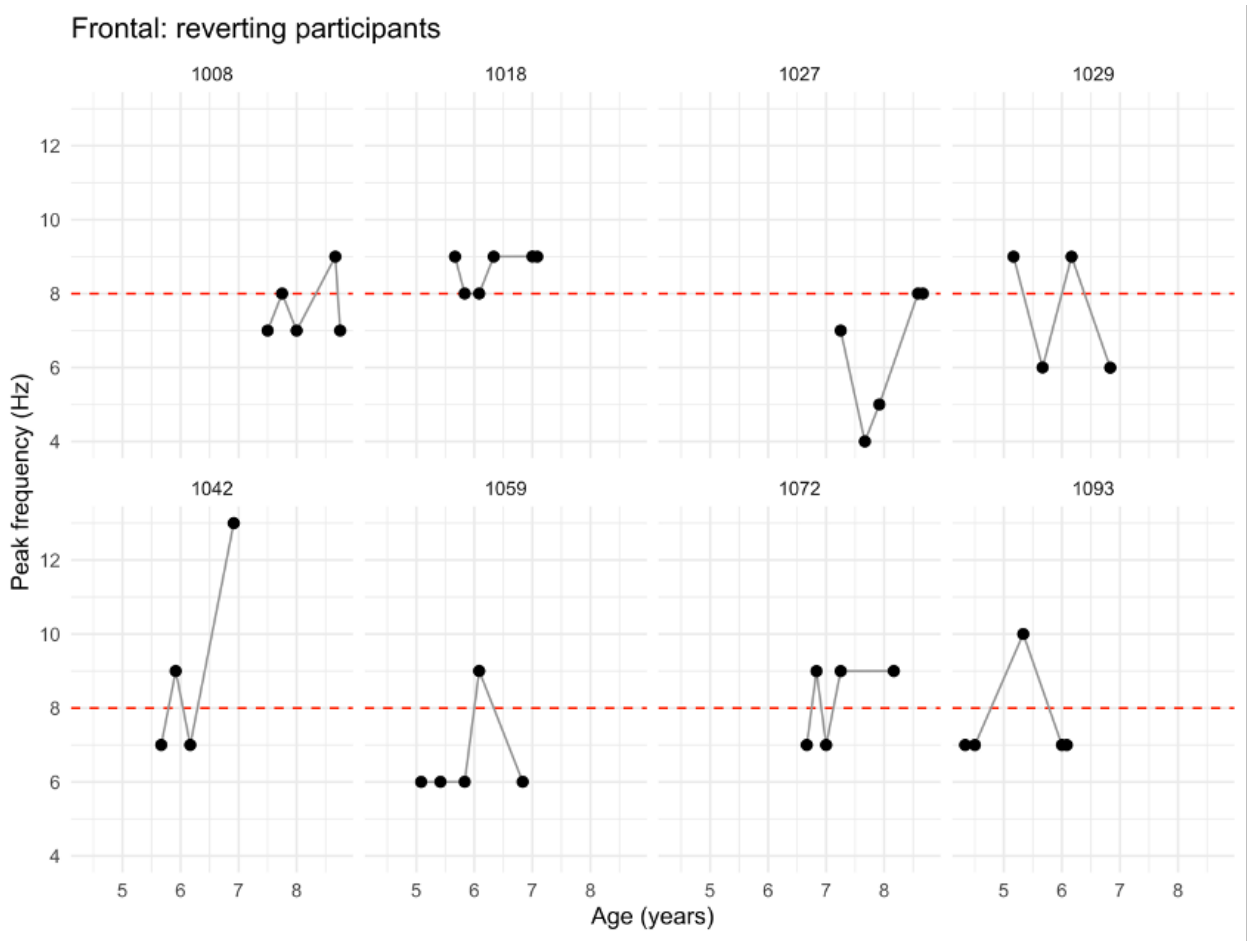

Figure 5. Individual frontal peak-frequency trajectories for participants who showed reversion after reaching alpha dominance. Each panel shows one participant's session-level peak frequency across age. The red dashed line marks the 8 Hz threshold for alpha dominance. These trajectories illustrate that several participants crossed above 8 Hz and later returned below the threshold.

Because the definition of first crossing allowed unstable transitions to count as events, the survival estimates were checked against the actual proportion of alpha-dominant cases near age 7, the typical transition age in typical development. Among sessions occurring between 6.5 and 7.5 years, only 27% of frontal sessions (6 of 22) and 18% of occipital sessions (4 of 22) were alpha-dominant. By contrast, the survival curve implied that about 70% of frontal participants had

already transitioned by this age. This discrepancy indicates that the survival framework substantially overestimated transition in the present sample, particularly in the frontal area. The survival analysis is therefore reported as a sensitivity check rather than as a primary characterization of transition timing.

Session Level Variability in Peak Frequency. The reversion pattern observed in the frontal region motivated qualitative assessment of FOOOF peak parameters across sessions for participants with unstable transitions. Two illustrative cases are described.

For one participant, the dominant frontal peak alternated across sessions between 7 Hz and 9 Hz. At the session in which the participant was classified as alpha-dominant, the FOOOF output contained both a 7 Hz peak (amplitude = 0.43) and a 9 Hz peak (amplitude = 0.49), with the two peaks differing by only 14% in amplitude. The dominance label in the session was therefore sensitive to small differences in peak estimation that could plausibly be driven by measurement noise.

For another participant, several sessions classified as theta-dominant contained a single peak with a frequency of 7.9998 Hz, just below the 8 Hz cutoff. In adjacent sessions, the peak crossed slightly above 8 Hz and was therefore classified as alpha-dominant. The apparent oscillation between theta and alpha here reflected small variation in a single peak's estimated frequency around the cutoff, rather than switching between two competing peaks.

These examples illustrate two distinct sources of transition instability and motivate caution when interpreting categorical dominance classifications in this developmental window.

Aim 2: Peak Frequency and Language Outcomes

A linear mixed effects model with peak frequency, age, and region as fixed effects and random intercepts and slopes for age by participant was used to predict total imputed WCS scores. Fixed effect results for the primary and secondary Aim 2 models are presented in Table 1. Peak frequency showed a positive coefficient that did not reach statistical significance but trended in the hypothesized direction ($\beta = 13.11$, $t = 1.82$, $p = .070$). Age was the only significant fixed effect in the model, and the region was not associated with WCS ($p = .977$). The marginal R^2 for the model was .066 and the conditional R^2 was .864, indicating that the fixed effects accounted for a small portion of total variance and that between-participant differences accounted for the majority. A model including a peak frequency x region interaction did not improve fit over the additive model ($\chi^2(1) = 0.52$, $p = .469$), suggesting that the relationship between peak frequency and WCS did not differ meaningfully between frontal and occipital regions. A model comparison between the full model and an age-only reduced model confirmed that adding peak frequency and region did not significantly improve model fit ($\chi^2(2) = 2.54$, $p = .281$), indicating that peak frequency did not add explanatory value beyond age alone.

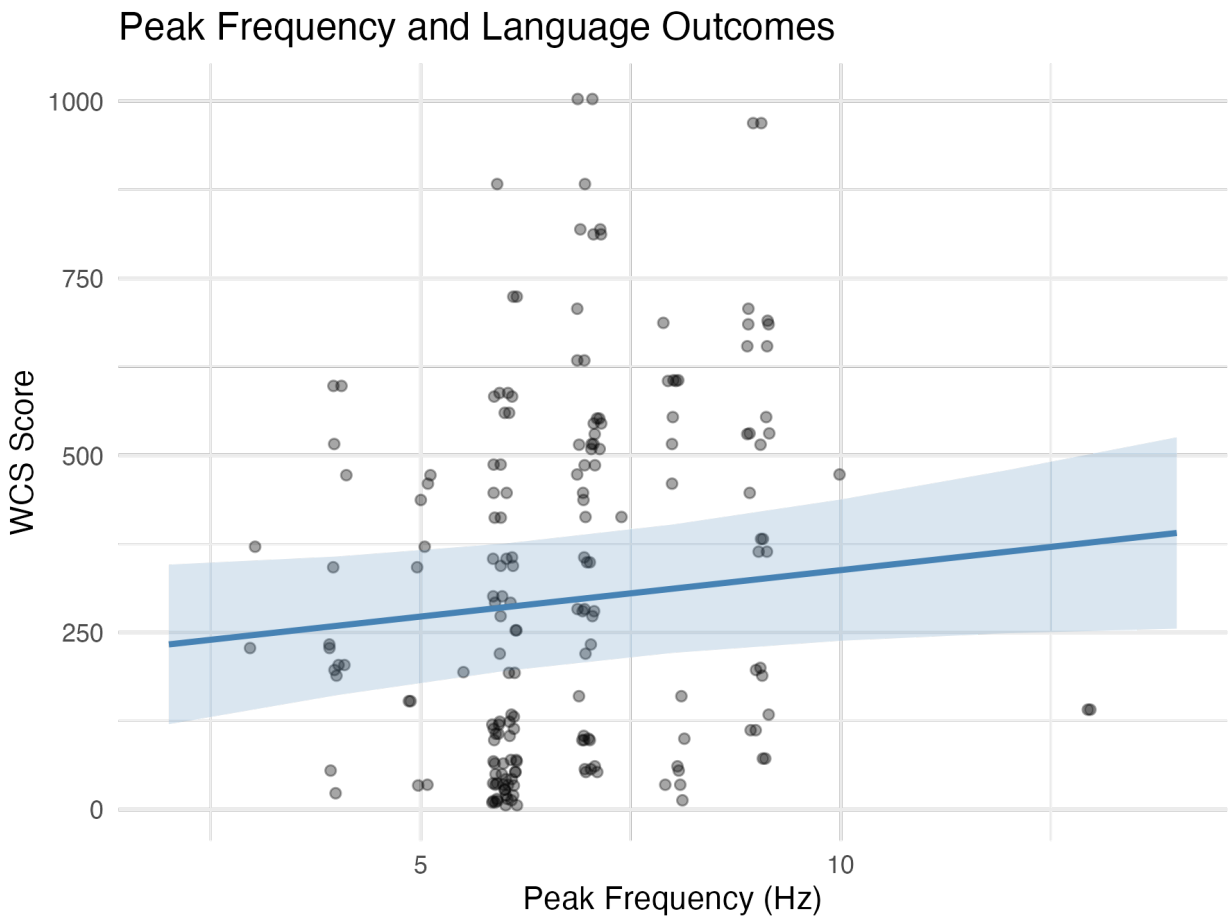

Figure 6. Association between dominant peak frequency and language outcomes. Points represent session-level observations, the solid line shows the fitted linear association, and the shaded band represents the 95% confidence interval.

Secondary Predictors: Aperiodic Parameters and Peak Count. In follow-up models substituting other FOOOF derived features for peak frequency, no predictor reached significance after controlling for age. Aperiodic offset (frontal: p = .388; occipital: p = .376) and aperiodic exponent (frontal: p = .176; occipital: p = .192) were not associated with WCS. The number of detected peaks in the theta/alpha range was also not associated with WCS in either region (frontal: p = .880; occipital: p = .206).

Table 1. Linear Mixed-Effects Model Results Predicting WCS Scores from FOOOF-Derived Features.

Model	Region	Predictor	β	SE	df	t	p
Peak frequency	Frontal + Occipital	Peak frequency	13.11	7.19	162.17	1.82	0.070
Aperiodic offset	Frontal	Offset	-41.16	47.48	86.41	-0.87	0.388
Aperiodic exponent	Frontal	Exponent	-83.36	61.04	75.31	-1.37	0.176
Aperiodic offset	Occipital	Offset	-33.67	37.81	84.52	-0.89	0.376
Aperiodic exponent	Occipital	Exponent	-73.26	55.64	77.56	-1.32	0.192
Peak count	Frontal	Peak count	-3.20	21.07	89.17	-0.15	0.880
Peak count	Occipital	Peak count	-26.93	21.14	83.71	-1.27	0.206

Note. β represents the fixed-effect estimate for each predictor. Secondary models tested aperiodic offset, aperiodic exponent, and peak count separately by region. WCS = Weighted Communication Scale; SE = standard error.

Discussion

The present study characterized the developmental trajectory of dominant oscillatory peak frequency in young children with FXS and tested whether peak frequency and other FOOOF-derived features predicted language outcomes. Three findings emerged. First, dominant peak frequency increased with age in both frontal and occipital regions, and the estimated theta-to-alpha transition occurred later than the benchmark reported for typically developing children. Second, this transition was not stable. Many participants who reached alpha dominance subsequently

returned to theta dominance, and this instability was substantially greater in the frontal region. Third, neither peak frequency nor any registered secondary FOOOF feature significantly predicted language outcomes after accounting for age, although the association between peak frequency and language was positive, marginal, and in the hypothesized direction.

The positive association between peak frequency and age confirms that change in dominant oscillatory frequency is detectable in this FXS sample, and the estimated transition ages (9.26 years frontal, 9.36 years occipital) were later than the approximately 7.2 year transition reported in typical development (Cellier et al., 2021). This is consistent with the hypothesized delay and aligns with the reduced alpha band activity documented in adolescents and adults with FXS (Ethridge et al., 2019; Pedapati et al., 2022), suggesting that the oscillatory abnormalities observed later in life have a developmental basis detectable in early childhood. These estimates should be interpreted cautiously, however, because both fall at or beyond the maximum observed age (8.75 years) and therefore rely on extrapolation; the wide confidence intervals reflect this uncertainty.

An important qualification comes from sensitivity analysis. When the transition was modeled as a time-to-event outcome, the assumption that reaching alpha dominance is an absorbing event was violated. 73% of frontal and 14% of occipital participants who reached alpha dominance later reverted to theta dominance, and the proportion of sessions that were actually alpha-dominant near age 7 was far below what the survival curve implied. Inspection of individual trajectories showed substantial session-to-session frequency change in several cases, though in others the instability reflected small fluctuations around the 8 Hz cutoff as detailed in the results. Both sources indicate that a single categorical classification is fragile in this window. Together, these results indicate that any single transition age estimate describes a population level tendency

rather than a stable developmental milestone achieved by individual children. A definition based on stable alpha dominance is therefore more defensible than one based on first crossing.

The greater instability in the frontal region is notable and is consistent with known differences in the developmental and generative mechanisms of frontal versus posterior oscillations. The frontal cortex matures considerably more slowly than sensory cortices, so a less stable developmental transition within early childhood in the frontal region may be expected. In addition, the two regions differ in how their alpha rhythm is produced. Posterior alpha has two generative drivers, thalamocortical and intracortical, whereas frontal alpha is likely driven primarily by thalamocortical input (Bollimunta et al., 2008). The maturation of local intracortical connections in the occipital region may therefore stabilize the rhythm and override variability in thalamocortical drive, producing the more orderly transition observed occipitally, where reversion was uncommon and no participant was alpha-dominant at study entry. The frontal region, lacking this second stabilizing generator, would be more directly exposed to session-to-session variation in thalamocortical input, consistent with the high frontal reversion rate observed. Thalamocortical driving deficits have been reported in adolescents and adults with FXS (Elmaghraby et al., 2025; Pedapati et al., 2022) and specifically for medial dorsal thalamic nuclei projecting to medial prefrontal cortex in fmr1 knockout mice (Ordemann et al., 2026). On this account, occipital peak frequency is the more reliable index of the maturation, and frontal instability reflects a substantive developmental feature rather than measurement error.

Contrary to the hypothesis, peak frequency did not significantly predict WCS after controlling for age, and no registered secondary feature - aperiodic offset, aperiodic exponent, or peak count - added predictive value beyond age. Although the peak frequency association did not reach significance, its positive direction leaves open the possibility of a small effect that the present

sample was underpowered to detect, particularly given the small number of alpha-dominant observations available.

This effect may also be hard to detect because it sits alongside a predictor as strong and developmentally expected as age. Age accounts for a large and anticipated share of variance in language ability, and when one predictor is this dominant, model comparison is relatively insensitive to smaller contributions from peak frequency. The marginal peak frequency effect may therefore reflect a real but secondary relationship that is overshadowed by age, rather than a true null. An exploratory follow-up was consistent with this possibility. Among the frontal participants whose peak frequency reverted, language scores were themselves fluctuating across sessions, rising and falling rather than increasing steadily. The fluctuation is consistent with longitudinal evidence that skills in children with FXS do not follow a uniform upward course, with a substantial proportion showing regression or plateau in adaptive behavior, including communication skills during childhood (Hahn et al., 2015). Prior work in younger children with FXS has also reported considerable variability in language and developmental trajectories, although these studies do not directly characterize session-to-session within-participant fluctuations (Kover et al., 2015; Roberts et al., 2009). It is possible that this fluctuation reflects a pattern clinically observed in this population, in which children repeatedly gain and lose a skill before it stabilizes. Session-to-session changes in peak frequency and language tended to move in the same direction more often than not, but the pattern was inconsistent across individuals, and the small number of paired observations per participant precluded formal testing (see Figure 7 for examples). These observations are therefore offered as suggestive rather than confirmatory. These within-participant comparisons used only sessions with observed (non-imputed) language scores, so the fluctuations described do not reflect imputation. Taken together, they raise the possibility that peak frequency

tracks language ability at the level of within-participant fluctuation in a way that a single cross-sectional estimate cannot capture.

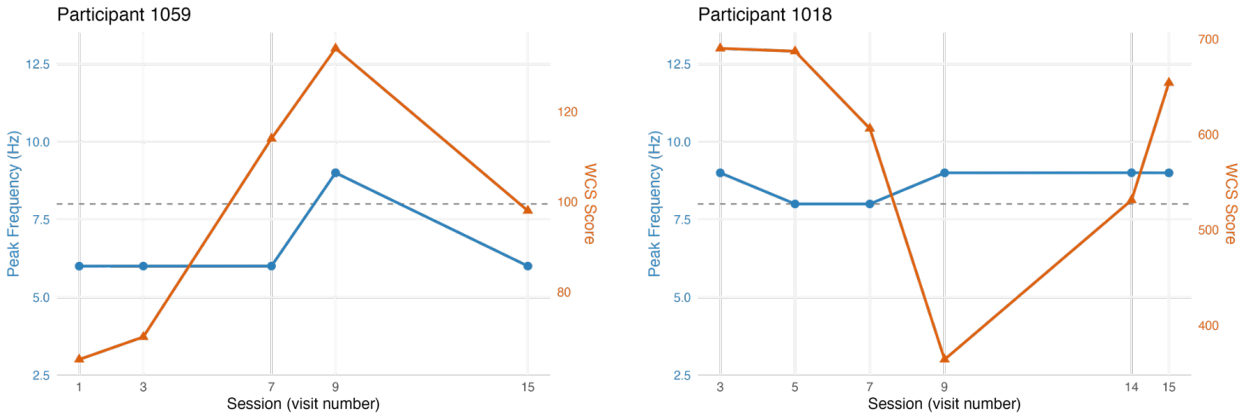

Figure 7. Illustrative within-participant fluctuations in frontal peak frequency and WCS scores. Example participants were selected from those showing reversion in frontal alpha dominance. This figure is intended as an illustrative visualization of session-to-session fluctuation and was not used for formal statistical inference.

Implications

These findings have implications for the use of EEG-derived measures as biomarkers in FXS. The delayed and unstable transition indicates that early childhood oscillatory development in FXS departs from typical patterns in ways that are measurable during a period when intervention may be most effective, supporting the broader effort to characterize neural development in this age window. At the same time, peak frequency was unstable and did not relate to language ability. This suggests caution against treating an individual child's peak frequency, measured at a single session, as a biomarker of language outcome. Characterizing development at the group level, and using the more stable occipital region, may be more informative than predicting outcomes from a single value in one child. However, it remains unclear whether the session-to-session variability

observed here is specific to FXS or reflects broader developmental variability before oscillatory rhythms stabilize. Peak alpha frequency increases rapidly across early childhood and appears to level off later in development (Freschl, 2022), but relatively few studies have examined peak frequency using repeated measurements within the same children during the theta-to-alpha transition window.

Limitations

Several limitations should be acknowledged. First, comparison to typical development relies on published literature (Cellier et al., 2021) rather than a within-study control group, limiting direct inference about delay. Second, this is a correlational study using secondary data; causal claims about neural maturation driving language outcomes cannot be made. Third, the sample size may limit power for detecting smaller effects. Fourth, the observed age range (3-8 years) may not fully capture the theta-to-alpha transition if it occurs later in FXS; transition age estimates necessarily involve extrapolation beyond the observed data. This is particularly relevant given that the transition may not reflect a linear increase in frequency over time, but a qualitative shift from theta to alpha dominance. However, by employing the same estimation approach as Cellier et al. (2021), the present study uses identical assumptions, allowing for meaningful comparison of transition age estimates between FXS and typically developing populations. Fifth, due to variable missing data patterns across participants and timepoints, some analyses treat the data cross-sectionally rather than modeling full longitudinal trajectories. Finally, due to the secondary nature of the data, a formal prior power analysis was not conducted and very small effects may not be reliably detected.

Future Directions

Future work should prioritize longitudinal designs capable of modeling within-child trajectories and reversion directly, rather than capturing development with a single transition age. Samples spanning older ages would allow the transition to be observed rather than extrapolated, and the inclusion of a within-study typically developing comparison group would strengthen inferences about delay. Given the regional dissociation observed in this study, further work could examine what drives the greater instability of frontal oscillations, including the relative contributions of thalamocortical and intracortical alpha generators across development. Finally, peak frequency and language may fluctuate within participants. Future studies could test whether the stability of the transition, rather than when it happens, relates to a child's outcome.

Conclusion

This study found evidence of a delayed theta-to-alpha transition in young children with FXS, but also showed that the transition is unstable, particularly in the frontal region, and that peak frequency did not predict language outcomes beyond age. By characterizing early oscillatory development in FXS while documenting the instability of the transition, the results clarify both what these EEG-derived measures can offer and their current limits, and they point toward longitudinal, region-specific approaches as the most informative direction for future work.

References

Arutiunian, V., Opdahl, M., Sullivan, C. A. W., Santhosh, M., Neuhaus, E., Borland, H., Bernier, R. A., Bookheimer, S. Y., Dapretto, M., Jack, A., Jeste, S., McPartland, J. C., Naples, A., Van Horn, J. D., Pelphrey, K. A., Webb, S. J., & Gupta, A. R. (2025). Number of Alpha Peaks in the Electroencephalogram Is Associated With Clinical Phenotype and Copy Number Variants in Youths With Autism. *Biological Psychiatry. Cognitive Neuroscience and Neuroimaging*, S2451-9022(25)00302-7. https://doi.org/10.1016/j.bpsc.2025.10.001

Berry-Kravis, E., Abbeduto, L., Hagerman, R., Coffey, C. S., Cudkowicz, M., Erickson, C. A., McDuffie, A., Hessl, D., Ethridge, L., Tassone, F., Kaufmann, W. E., Friedmann, K., Bullard, L., Hoffmann, A., Veenstra-VanderWeele, J., Staley, K., Klements, D., Moshinsky, M., Harkey, B., … Pearson, B. (2024). Effects of AFQ056 on language learning in fragile X syndrome. *Journal of Clinical Investigation*, *134*(5), e171723. https://doi.org/10.1172/JCI171723

Bollimunta, A., Chen, Y., Schroeder, C. E., & Ding, M. (2008). Neuronal Mechanisms of Cortical Alpha Oscillations in Awake-Behaving Macaques. *The Journal of Neuroscience*, *28*(40), 9976–9988. https://doi.org/10.1523/JNEUROSCI.2699-08.2008

Buzsáki, G. (2002). Theta Oscillations in the hippocampus. *Neuron, 33*(3), 325-340.

Cavanagh, J. F., & Frank, M. J. (2014). Frontal theta as a mechanism for cognitive control. *Trends in Cognitive Sciences*, *18*(8), 414–421. https://doi.org/10.1016/j.tics.2014.04.012

Cellier, D., Riddle, J., Petersen, I., & Hwang, K. (2021). The development of theta and alpha neural oscillations from ages 3 to 24 years. *Developmental Cognitive Neuroscience*, *50*, 100969. https://doi.org/10.1016/j.dcn.2021.100969

Donoghue, T., Dominguez, J., & Voytek, B. (2020). Electrophysiological Frequency Band Ratio Measures Conflate Periodic and Aperiodic Neural Activity. *Eneuro*, *7*(6), ENEURO.0192-20.2020. https://doi.org/10.1523/ENEURO.0192-20.2020

Donoghue, T., Haller, M., Peterson, E. J., Varma, P., Sebastian, P., Gao, R., Noto, T., Lara, A. H., Wallis, J. D., Knight, R. T., Shestyuk, A., & Voytek, B. (2020). Parameterizing neural power spectra into periodic and aperiodic components. *Nature Neuroscience*, *23*(12), 1655–1665. https://doi.org/10.1038/s41593-020-00744-x

Elmaghraby, R., Liu, Y., Ramesh, P., Westerkamp, G., Nelson, M. A., Larsh, T., Smith, E., Gilbert, D. L., Wu, S. W., Erickson, C. A., & Pedapati, E. V. (2025). Divergent aperiodic slope and alpha dynamics expose cortical excitability gradients in fragile X syndrome. *Molecular Autism*, *16*(1), 49. https://doi.org/10.1186/s13229-025-00682-0

Ethridge, L. E., De Stefano, L. A., Schmitt, L. M., Woodruff, N. E., Brown, K. L., Tran, M., Wang, J., Pedapati, E. V., Erickson, C. A., & Sweeney, J. A. (2019). Auditory EEG Biomarkers in Fragile X Syndrome: Clinical Relevance. *Frontiers in Integrative Neuroscience*, *13*, 60. https://doi.org/10.3389/fnint.2019.00060

Freschl, J. (2022). The development of peak alpha frequency from infancy to adolescence and its role in visual temporal processing: A meta-analysis. *Developmental Cognitive Neuroscience*.

Gao, R., Peterson, E. J., & Voytek, B. (2017). Inferring synaptic excitation/inhibition balance from field potentials. *NeuroImage*, *158*, 70–78. https://doi.org/10.1016/j.neuroimage.2017.06.078

Gibson, J. R., Bartley, A. F., Hays, S. A., & Huber, K. M. (2008). Imbalance of Neocortical Excitation and Inhibition and Altered UP States Reflect Network Hyperexcitability in the

Mouse Model of Fragile X Syndrome. *Journal of Neurophysiology*, *100*(5), 2615–2626. https://doi.org/10.1152/jn.90752.2008

Hagerman, P. J., & Hagerman, R. (2021). Fragile X syndrome. *Current Biology*, *31*(6), R273–R275. https://doi.org/10.1016/j.cub.2021.01.043

Hagerman, R., Jacquemont, S., Berry-Kravis, E., Des Portes, V., Stanfield, A., Koumaras, B., Rosenkranz, G., Murgia, A., Wolf, C., Apostol, G., & von Raison, F. (2018). Mavoglurant in Fragile X Syndrome: Results of two open-label, extension trials in adults and adolescents. *Scientific Reports*, *8*, 16970. https://doi.org/10.1038/s41598-018-34978-4

Hahn, L. J., Brady, N. C., Warren, S. F., & Fleming, K. K. (2015). Do Children With Fragile X Syndrome Show Declines or Plateaus in Adaptive Behavior? *American Journal on Intellectual and Developmental Disabilities*, *120*(5), 412–432. https://doi.org/10.1352/1944-7558-120.5.412

Klimesch, W., Sauseng, P., & Hanslmayr, S. (2007). EEG alpha oscillations: The inhibition–timing hypothesis. *Brain Research Reviews*, *53*(1), 63–88. https://doi.org/10.1016/j.brainresrev.2006.06.003

Kover, S. T., McCary, L. M., Ingram, A. M., Hatton, D. D., & Roberts, J. E. (2015). Early Language Development in Infants and Toddlers with Fragile X Syndrome: Change over Time and the Role of Attention. *American Journal on Intellectual and Developmental Disabilities*, *120*(2), 125–144. https://doi.org/10.1352/1944-7558-120.2.125

Mullin, L. J., Rutsohn, J., Gross, J. L., Caravella, K. E., Grzadzinski, R. L., Weisenfeld, L. A., Flake, L., Botteron, K. N., Dager, S. R., Estes, A. M., Pandey, J., Schultz, R. T., St. John, T., Wolff, J. J., Shen, M. D., Piven, J., Hazlett, H. C., & Girault, J. B. (2024). Differential

cognitive and behavioral development from 6 to 24 months in autism and fragile X syndrome. *Journal of Neurodevelopmental Disorders*, *16*, 12. https://doi.org/10.1186/s11689-024-09519-y

Ordemann, G. J., Lyuboslavsky, P., Kizimenko, A., & Brumback, A. C. (2026). Fmr1 knockout disrupts multiple intrinsic properties via reduced HCN channel activity in mediodorsal thalamocortical neurons. *Experimental Physiology*, *111*(3), 1340–1364. https://doi.org/10.1113/EP092894

Paluszkiewicz, S. M., Martin, B. S., & Huntsman, M. M. (2011). Fragile X Syndrome: The GABAergic System and Circuit Dysfunction. *Developmental Neuroscience*, *33*(5), 349–364. https://doi.org/10.1159/000329420

Pedapati, E. V., Schmitt, L. M., Ethridge, L. E., Miyakoshi, M., Sweeney, J. A., Liu, R., Smith, E., Shaffer, R. C., Dominick, K. C., Gilbert, D. L., Wu, S. W., Horn, P. S., Binder, D. K., Lamy, M., Axford, M., & Erickson, C. A. (2022). Neocortical localization and thalamocortical modulation of neuronal hyperexcitability contribute to Fragile X Syndrome. *Communications Biology*, *5*(1), 1–14. https://doi.org/10.1038/s42003-022-03395-9

Proteau-Lemieux, M., Knoth, I. S., Davoudi, S., Martin, C.-O., Bélanger, A.-M., Fontaine, V., Côté, V., Agbogba, K., Vachon, K., Whitlock, K., Biag, H. M. B., Thurman, A. J., Rosenfelt, C., Tassone, F., Frei, J., Capano, L., Abbeduto, L., Jacquemont, S., Hessl, D., … Lippe, S. (2024). Specific EEG resting state biomarkers in FXS and ASD. *Journal of Neurodevelopmental Disorders*, *16*(1), 53. https://doi.org/10.1186/s11689-024-09570-9

Roberts, J. E., Mankowski, J. B., Sideris, J., Goldman, B. D., Hatton, D. D., Mirrett, P. L., Baranek, G. T., Reznick, J. S., Long, A. C. J., & Bailey, D. B., Jr. (2009). Trajectories

and Predictors of the Development of Very Young Boys with Fragile X Syndrome. *Journal of Pediatric Psychology*, *34*(8), 827–836. https://doi.org/10.1093/jpepsy/jsn129

Salcedo-Arellano, M. J., Dufour, B., McLennan, Y., Martinez-Cerdeno, V., & Hagerman, R. (2020). Fragile X Syndrome and associated disorders: Clinical aspects and pathology. *Neurobiology of Disease*, *136*, 104740. https://doi.org/10.1016/j.nbd.2020.104740

Scharf, S. H., Jaeschke, G., Wettstein, J. G., & Lindemann, L. (2015). Metabotropic glutamate receptor 5 as drug target for Fragile X syndrome. *Current Opinion in Pharmacology*, *20*, 124–134. https://doi.org/10.1016/j.coph.2014.11.004

Segalowitz, S. J., Santesso, D. L., & Jetha, M. K. (2010). Electrophysiological changes during adolescence: A review. *Brain and Cognition*, *72*(1), 86–100. https://doi.org/10.1016/j.bandc.2009.10.003

Suzuki, S., Grabowecky, M., & Menceloglu, M. (2025). Characteristics of Spontaneous Anterior–Posterior Oscillation-Frequency Convergences in the Alpha Band. *Eneuro*, *12*(3), ENEURO.0033-24.2025. https://doi.org/10.1523/ENEURO.0033-24.2025

Van Der Molen, M. J. W., Stam, C. J., & Van Der Molen, M. W. (2014). Resting-State EEG Oscillatory Dynamics in Fragile X Syndrome: Abnormal Functional Connectivity and Brain Network Organization. *PLoS ONE*, *9*(2), e88451. https://doi.org/10.1371/journal.pone.0088451

Wang, J., Ethridge, L. E., Mosconi, M. W., White, S. P., Binder, D. K., Pedapati, E. V., Erickson, C. A., Byerly, M. J., & Sweeney, J. A. (2017). A resting EEG study of neocortical hyperexcitability and altered functional connectivity in fragile X syndrome. *Journal of Neurodevelopmental Disorders*, *9*(1), 11. https://doi.org/10.1186/s11689-017-9191-z

Wilkinson, C. L., & Nelson, C. A. (2021). Increased aperiodic gamma power in young boys with Fragile X Syndrome is associated with better language ability. *Molecular Autism*, *12*, 17. https://doi.org/10.1186/s13229-021-00425-x