Altered Frontal Connectivity as a Mechanism for Executive Function Deficits in Fragile X Syndrome

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Abstract

Background

Fragile X Syndrome (FXS) is the leading inherited monogenetic cause of intellectual disability and autism spectrum disorder. Executive function (EF), necessary for adaptive goal-oriented behavior and dependent on frontal lobe function, is impaired in individuals with FXS. Yet, little is known how alterations in frontal lobe neural activity is related to EF deficits in FXS.

Methods

Sixty-one participants with FXS (54% males) and 71 age- and sex-matched TDC (58% males) completed a five-minute resting state electroencephalography (EEG) protocol and a computerized battery of tests of EF, the Test of Attentional Performance for Children (KiTAP). Following source localization (minimum-norm estimate), we computed debiased-weighted phase lag index (dWPLI), a phase connectivity value, for pairings between 18 nodes in frontal regions for gamma (30–55 Hz) and alpha (10.5–12.5 Hz) bands. Linear models were generated with fixed factors of group, sex, frequency, and connection. Relationships between frontal connectivity and EF variables also were examined.

Results

Individuals with FXS demonstrated increased gamma band and reduced alpha band connectivity across all frontal regions and across hemispheres compared to TDC. After controlling for nonverbal IQ, increased error rates on EF tasks were associated with increased gamma band and reduced alpha band connectivity.

Limitations:

Frontal connectivity findings are limited to intrinsic brain activity during rest and may not generalize to frontal connectivity during EF tasks or everyday function.

Conclusions

We report gamma hyper-connectivity and alpha hypo-connectivity within source-localized frontal brain regions in FXS compared to TDC during resting-state EEG. For the first time, we report significant associations between EF and altered frontal connectivity, with increased error rate relating to increased gamma band connectivity and reduced alpha band connectivity. These findings suggest increased phase connectivity within gamma band may impair EF performance, whereas greater alpha band connectivity may provide compensatory support for EF. Together, these findings provide important insight into

neurophysiological mechanisms of EF deficits in FXS, and provide novel targets for treatment development.

Background

Fragile X Syndrome (FXS) is the leading monogenic inherited form of intellectual disability (ID) and autism spectrum disorder (ASD) and is caused by a cysteine-guanine-guanine (CGG) trinucleotide repeat expansion in the fragile X messenger ribonucleoprotein 1 (*FMR1*) gene (> 200 repeats) located on the X chromosome (1, 2). The repeat trinucleotide expansion in the *FMR1* gene leads to a decrease or absence of fragile X messenger ribonucleoprotein (FMRP) expression, which is essential for brain development and cognitive function (2).

It is well-documented that individuals with FXS exhibit impairments in executive functions (EF), an important set of cognitive functions involved in adaptive goal-oriented behavior, including subdomains of cognitive flexibility, working memory, response inhibition, and processing speed (3). EF impairments are present to a lesser degree in females with FXS compared to males with FXS, as expected based on obligate mosaicism (4, 5). However, even in the absence of general cognitive impairment in females with FXS, EF impairments are still observed (3). EF impairments can cause significant distress to both the individual with FXS and their families, and is a common reason for clinic visits (6–8). Yet, our lack of understanding of its underlying physiology has stalled treatment development targeting EF for individuals with FXS despite its critical clinical significance.

EF historically has been associated with frontal lobe function with distinct domains of EF demonstrate a degree of regional specificity within the frontal lobe (9). Although few structural or functional magnetic resonance imaging (MRI and fMRI, respectively) studies have been conducted in individuals with FXS (for review see 3), differences in frontal lobe structure and function are present and related to impaired EF in this patient population. For example, individuals with FXS have shown reduced frontal lobe grey (10, 11) and white matter volume (10) as well as reduced activation of frontal regions during EF tasks of working memory and inhibitory control (12, 13).

MRI and fMRI studies in this population are inherently challenging since cardinal features of the disorder (e.g., anxiety, hyperactivity) prevent many full mutation males with FXS from participating, thus limiting the ability to generalize findings. Electroencephalography (EEG) offers a minimally invasive neuroimaging technique that can be more broadly applied in this population while still providing novel insights into the neurophysiological features of frontal lobe dysfunction (14–16). It also can be more readily synchronously leveraged in preclinical studies using the mouse model of the disorder (for example see (17). Our previous EEG research demonstrated that individuals with FXS at rest have reduced alpha power, but increased gamma power, which together suggest cortical hyperexcitability (16, 18), a finding that has been replicated in in-vivo slice physiology and mouse studies (17, 19–21).

In addition, our group (16) has previously studied whole-brain connectivity in different frequency bands using EEG. Individuals with FXS demonstrated reduced inhibitory (alpha band) and enhanced excitatory

(gamma band) connections across frontal, parietal, and occipital regions relative to age-matched controls. Similar findings of reduced alpha band connectivity in FXS, including within frontal regions, have been reported by other groups (14, 22). Since frontal oscillatory activity has established importance for optimal EF task performance (23–25), increased neural excitability in frontal cortex may contribute to the cognitive alterations seen clinically in FXS. To date, EEG studies in FXS have reported on small samples ($n < 20$) and have not be source-localized. Further, connectivity features in male and female patients have not been contrasted and have not be examined in relation to EF performance. Thus, examining phase connectivity within the frontal cortex and its relation to performance-based EF measures may provide novel insight into the functional relevance of altered alpha and gamma band oscillatory activity in FXS.

The present study compared intrinsic resting frontal phase connectivity in individuals with FXS and matched typically developing controls (TDC), and examined the relationship between frontal connectivity and performance-based measures of EF in FXS. We predicted that individuals with FXS would display increased connectivity of gamma oscillations but reduced connectivity of alpha oscillations in frontal cortex compared to TDC, and these findings would be particularly pronounced among males with FXS. We also predicted that frontal connectivity alterations would be associated with greater EF dysfunction in FXS, even after controlling for general cognitive functioning.

Methods

Participants

Sixty-one participants with a genetic diagnosis of FXS (Mean age = 21.0, SD = 10.2; age range: 5.9–45.7; 28 females) and 71 age- and sex-matched controls (Mean age = 22.2, SD = 10.7; age range: 5.9–48.2; 30 females) participated in study procedures (Table 1). Full mutation FXS was confirmed via Southern Blot and polymerase chain reaction (PCR) assays performed at Rush University in the laboratory of Dr. Elizabeth Berry-Kravis. FXS participants were excluded from the study if they were being treated for seizures within the past year or taking benzodiazepines, which are known to impact electrophysiological recordings. Several FXS participants were being treated with psychiatric medications at the time of testing, but were on stable dosing for at least six weeks. Twenty-one participants with FXS were receiving stimulants, 14 antipsychotics, and 28 antidepressants. Two controls were receiving stable dosing of SSRIs with no active psychiatric symptoms; removal of these participants from analysis did not result in any substantive changes in results and thus were included in final analyses.

Participants completed the abbreviated Stanford Binet-5th edition (SB-5, (26)) to estimate general cognitive functioning. Standard scores were converted to Deviation IQ scores and scaled scores were converted to z-scores in order reduce floor effects present for individuals with severe cognitive impairments and to better evaluate inter-individual variability (27). All participants or their legal guardian, when appropriate, provided written informed consent and assent before participating. The study was approved by Cincinnati Children's Hospital Medical Center institutional review board.

Table 1
Participant Demographic Information

	FXS (n = 61)	TDC (n = 71)
Age in years	21.0 (10.2)	22.2 (10.7)
Sex (n, % male)	33 (54)	41 (58)
IQ Deviation Score	50.6 (30.9) ***	103.2 (9.2)
Nonverbal Z-Score	-3.96 (2.5) ***	0.23 (0.7)
Verbal Z-Score	-2.62 (1.9) ***	0.21 (0.9)
Mean (Standard Deviation) unless otherwise noted, *** p < .001		

Data Acquisition

In order to facilitate cooperation during EEG data collection, participants were seated comfortably while watching a silent video as done in previous studies (15, 16, 18, 28). Five minutes of continuous resting EEG was collected by 128-channel EGI HydroCel Geodesic Sensor Net with a sampling rate at 1000Hz. As previously described, data was preprocessed by filtering, visual inspection on 2 second epochs and channels, and ICA artifact removal (EEGLAB)(15, 18). After preprocessing, an average of 125 epochs (SD: 20.8, Range: 44–187) for FXS and 131 (SD: 18.1, Range: 43–161) epochs for TDC of artifact-free data remained with no group differences (p = 0.10).

Neural Connectivity

Source-localized time series for each subject were constructed by the minimum norm estimate method in Brainstorm (29). The reconstructed cortical model consisted of 15,002 vertices which were parcellated into 68 nodes via the Desikan-Killiany atlas (30). Subsequent analysis steps were focused on eighteen nodes which were designated as frontal regions known contributions to EF (31–33)(Additional File 1).

Time series decomposition was performed via a series of Morlet wavelets where the frequencies included 10.5–12.5 Hz with a step size of 0.5 Hz representing the upper alpha band range and 30 to 55 Hz with a step size of 5 Hz representing the gamma band range. These bands were selected

based on their relevance in previous FXS and EF studies (34–40). Debiased weighted phase lag index (dWPLI), a measure that quantifies phase lead and lag relationship from a pair of signals (41), was chosen to study frequency-dependent spatial phase synchronization.

dWPLI was selected over other phase connectivity measures for its robustness against volume conduction in hypothesis-driven studies (42, 43). The dWPLI estimator is negatively biased and has a theoretical range of [-1, 1], in practice 0 and negative dWPLI values indicate lack of synchrony and 1 denotes consistent synchrony between two signals. Properties of the dWPLI measure are discussed in supplementary materials (Additional File 2). For any hypothetical bi-node connections at a target

frequency, cross frequency spectrum was built from wavelet decompositions; the instantaneous phase differences were represented by the corresponding imaginary part of the complex-valued cross spectrum. dWPLI estimator averaged the magnitude weighted pair products along the time dimension within each epoch (14). dWPLI values were then averaged over epochs within each participant to characterize overall signal coherence, with an outlier criterion such that values greater than three standard deviations outside their individual mean were rejected.

Computerized Testing of EF

Performance-based EF was estimated using the Test of Attentional Performance for Children (KiTAP) (44), a computerized measure of EF that is reproducible and clinically valid in individuals with FXS (45). Participants completed four subtests: Alertness (processing speed), Distractibility (attention), Go/NoGo (response inhibition), and Flexibility (cognitive flexibility). Prior to each subtest, participants received verbal instructions and completed a practice task to ensure comprehension. Due to poor comprehension, five individuals with FXS did not complete Distractibility, five did not complete Go/NoGo, and eleven did not complete Flexibility tests. All controls completed subtasks with the exception of one who did not complete Go/NoGo due to technical issue.

A total of eight KiTAP variables were selected for analysis based on *a priori* hypotheses. Six KiTAP variables have established clinical validity and reproducibility in FXS (45): Median response times for Alertness (1) and Flexibility (2); Standard deviation of response times for Alertness (3); and Number of Errors for Distractibility (4), Go/NoGo (5), and Flexibility (6). An additional two variables, median response times for Distractibility (7) and Go/NoGo (8) were included based on previous studies documenting impaired speed and accuracy trade-off during tasks of cognitive control in neurodevelopmental disorders (3, 46).

Statistics

Linear mixed effect models (from R library lme4) were constructed to test for group differences for each connection. Connection methods included connectivity within frontal regions, both within and across hemispheres. We grouped connectivity measures as: 1) left prefrontal, 2) right prefrontal, 3) left posterior frontal, and 4) right posterior frontal. Cross-hemispheric connections also were evaluated. Single region comparisons analyzed connections within that particular region. Cross hemisphere comparison analyzed connections that linked the same location between left and right hemispheres. In each model, the response variable was dWPLI values transformed (Box-Cox 1-parameter) for residual normality. Each model started with all 4 fixed effects (group, sex, connection, and frequency band), and a random effect of subject as an intercept. For fixed effect frequency band, we used step sizes consistent with time series decomposition for both alpha and gamma frequency bands (alpha: 10.5–12.5 Hz, 0.5 Hz step; gamma: 30—55 Hz, 5 Hz step). The final model was based on a parsimonious principle on the fixed side. Maximum likelihood was used for parameter estimation and the Satterthwaite approximation was used for the degrees of freedom. P-values were adjusted for multiple pair comparisons using the False Discovery Rate (FDR).

Clinical Correlations

To examine the relationship between frontal connectivity and EF, correlations were conducted between connectivity measures and KiTAP variables in participants with FXS. Given the strong association between IQ and EF, and to evaluate EF functions independent from general cognitive ability, partial Spearman correlations adjusted for non-verbal IQ z-scores in order to limit the effect of impaired intellectual functioning on potential relationships between our neurophysiological and EF measures. This would allow us to interpret any significant corrections as a valid estimate of the relationship of phase connectivity with specific EF domain, independent from general cognitive functioning. Correlations were calculated across all FXS participants as well as for males and females separately. Due to the ceiling effect on KiTAP in TDC, correlations of EEG features and cognition were not examined in TDC.

Regression Models

To further characterize the relationship between frontal connectivity and EF, generalized linear models were conducted to determine the best dWPLI predictors, if any, for each of the KiTAP scores adjusting for sex and nonverbal IQ. The backward elimination variable selection technique was used to achieve the most parsimonious model. The criterion used to select the variables was based on the corrected Akaike Information Criterion (AICC), with a variable retained in the model if its p-value < 0.05. If none of the dWPLI variables was selected, then separate models were examined for males and females with IQ forced in the model. Second-order interaction terms were also examined but none survived the variable selection procedure. Lastly, for each model selected, residuals were examined to see whether a different distribution (and its associated link function) was necessary to achieve a better fit. All correlations and regression modeling were conducted using SAS ® software version 9.4 (SAS Institute Inc., Cary, NC).

Results

Neural Connectivity

Gamma Band

Gamma band functional connectivity (dWPLI) was significantly increased in all connections in FXS compared to TDC, indicating widespread elevations across all frontal regions in the patients. Linear modeling of gamma band dWPLI detected significant 3-way interactions (group:sex:connection) for left posterior frontal region ($F(9,7584.2) = 3.35$, $p = 0.0004$), right posterior frontal region ($F(9,7563.0) = 2.98$, $p = 0.002$), left prefrontal region ($F(5,4571.1) = 6.63$, $p < .0001$), and cross hemisphere connections ($F(8,6948.6) = 2.24$, $p = 0.0219$). Post-hoc pairwise comparison of group in the left frontal region indicated that connectivity strength was greater in males with FXS compared to their sex matched controls in pars opercularis (adj.p = 0.019) and pars triangularis (adj.p = 0.019). Similar connectivity strength elevations in females with FXS compared to TDC were observed between caudal middle frontal-superior frontal (adj.p = 0.019), pars opercularis-pars triangularis (adj.p = 0.028), pars opercularis-rostral middle frontal gryus

(adj.p = 0.028), and pars triangularis-rostral middle frontal gyrus (adj.p = 0.012) as listed in Additional File 2 (Table S1). The full list of node pairs with significant case-control differences also are presented in Additional File 2 (Tables S2-S5). A descriptive summary of gamma band dWPLI findings are presented in Figs. 1A and 2.

Specifically, in right prefrontal cortex, we detected a 3-way interaction of gamma band activity in group:sex:frequency ($F(5,4559.0) = 3.87$, $p = 0.002$) and a 2-way interaction of group:connection ($F(5,4559.4) = 4.95$, $p < 0.0002$). Post-hoc pairwise comparison of group for group:connection showed increased connectivity strength in the FXS group compared to TDC in frontal pole-lateral orbitofrontal (adj.p = .0185), lateral orbitofrontal-medial orbitofrontal (adj.p < .0003), lateral orbitofrontal-pars orbitalis (adj.p < .0003), and medial orbitofrontal-pars orbitalis (adj.p = .006) as shown in Table S4.2. Interestingly, the 3-way interaction of group:sex:frequency showed increased gamma connectivity strengths in males with FXS compared to sex matched controls in the low gamma band range (30Hz p = 0.04, 35Hz p = 0.0001, 40Hz p = 0.005). Increased connectivity strength also was found in females with FXS compared to their control counterparts in higher gamma band ranges (45Hz p = 0.02, 50Hz p = 0.02, 55Hz p = 0.01).

We further investigated group difference between sexes (i.e. male(FXS-TDC)-female(FXS-TDC)) per EEG frequency, but failed to show significance, indicating the degree of change in males did not differ significantly from those seen in females.

Alpha Band

Upper alpha band functional connectivity was reduced in FXS in right posterior frontal and prefrontal regions relative to controls. In right posterior frontal region, we detected a significant group:sex:connection 3-way interaction in ($F(9,6403.2) = 4.72$, $p < .0001$). In the post hoc group comparison, connectivity strength for the pars triangularis-superior frontal connection was reduced in FXS relative to TDC in both sexes (for details, Additional File 2, Table S6). Alpha band right prefrontal region model also detected a significant 2-way interaction of group:connection ($F(5,3806.2) = 13.43$, $p < .0001$; Additional File 2, Table S7). Post hoc group comparison showed connectivity strength for lateral orbitofrontal-pars orbitalis and medial orbitofrontal-pars orbitalis were reduced in FXS relative to TDC across sexes (Additional File 2, Table S7). A subject-level descriptive summary of upper alpha band dWPLI values by group and region is presented in Figs. 1B and 2.

Band-Specific Lateralization

There were significant group differences among all tested regions in the gamma band in cross hemisphere comparisons. However, group differences in the upper alpha band were lateralized in the right hemisphere only.

We arranged gyri/nodes from each model in a circular order and plotted the conceptual connections that showing statistically significant group difference in the post hoc multiple pair comparisons (FDR-corrected) in Fig. 2. In the right prefrontal region, two connections lateral orbitofrontal-pars orbitalis and medial orbitofrontal-pars orbitalis are not only common cross sex, they also appear in both high and low

alpha bands with opposite directions (gamma band: FXS > TDC and upper alpha band: FXS < TDC). Similarly, in the right frontal region, three connections (pars opercularis-pars triangularis, pars opercularis-rostral middle frontal and pars triangularis-superior frontal) are shared by males and females for significant group difference in the gamma band (FXS > TDC). Among them, one connection (pars triangularis-superior frontal) in the alpha band is also shared by males and females showing a significant group difference (FXS < TDC).

Executive Function

As expected, results from the KiTAP indicate that individuals with FXS have a lower performance overall across EF tasks as indicated by longer median response time and increased number of errors (Table 2).

Table 2
Summary of KiTAP performance for FXS and TDC participants

		FXS	TDC
Alertness	RT median	618.54 (372) ***	344.85 (103)
	RT SD	313.03 (344) ***	61.70 (44)
Distractibility	RT median	560.63 (227) **	464.10 (766)
	Errors	16.23 (13) ***	5.34 (7)
Flexibility	RT median	1168.38 (652) ***	699.79 (262)
	Errors	9.34 (5) ***	0.83 (1)
Go/NoGo	RT median	492.55 (140) *	444.39 (82)
	Errors	4.61 (6) ***	0.8 (2)

All values given in Mean (Standard Deviation); RT = reaction time, SD = standard deviation; p-value: * <0.05, ** <0.01, *** <0.001

Neural Connectivity and Executive Function Correlations

No significant correlations between IQ and dWPLI values in either frequency band were found in FXS. Table 3 gives Spearman correlations between dWPLI and KiTAP variables adjusted for non-verbal IQ.

Across FXS participants, we found significant relationships between increased error rates on the Distract and Go/NoGo tasks and increased gamma band connectivity strength in left posterior frontal and right posterior frontal regions (Fig. 3A). In alpha band, we found that reduced error rate during Flexibility related to increased dWPLI connectivity in right prefrontal regions (Fig. 3B).

Relationships between gamma band connectivity and error rates were primarily driven by males with FXS (Fig. 4A). We also found that increased connectivity strength in the gamma band were associated with shorter response times during the Flexibility task in males with FXS (Fig. 4B). Unexpectedly, in females

with FXS, we found that increased gamma band cross-hemispheric and right prefrontal connectivity strength were associated with fewer Flexibility errors (Fig. 4C). In contrast, increased alpha band connectivity in right posterior frontal and prefrontal regions was associated with reduced number of errors during Distractibility and Flexibility subtasks as expected in females with FXS (Fig. 4D).

Table 3
Significant Spearman's Partial Correlations (Accounting for Nonverbal IQ) between Connectivity Strength and Executive Function in FXS

Frequency Band	Regional Comparison	KiTAP Variable	FXS Group	rho	p
Gamma	Left Frontal	Distract Error	All	0.35	.009
			Male	0.50	.009
	Left Frontal	Go/NoGo Error	All	0.45	.001
			Male	0.53	.005
	Right Frontal	Go/NoGo Error	All	0.33	.02
			Male	0.49	.01
	Left Frontal	Flexibility Median RT	Male	-0.49	.02
	Cross-Hemisphere	Flexibility Error	Female	-0.44	.04
	Right Prefrontal	Flexibility Error	Female	-0.52	.01
Alpha	Right Prefrontal	Flexibility Error	All	-0.33	.02
			Female	-0.44	.04
	Right Frontal	Distract Error	Female	-0.43	.03

The regression models provided in Table 4 give the best fitting models for KiTap scores as a linear function of selected dWPLI measures after controlling for sex and Nonverbal IQ. Briefly, in the gamma band, for every 0.01 increase in dWPLI in the left frontal region, the Distractor Error increased by approximately 16%, and Flexibility median RT decreased by approximately 10%. For females only, every 0.01 increase in dWPLI in the left posterior frontal region corresponds to an increase in 1.90 errors during Flexibility and, simultaneously, every 0.1 increase in cross-hemispheric (i.e., more rightward) dWPLI corresponds to a decrease in 3.05 errors during Flexibility. Further, each 0.01 increase in dWPLI in the right prefrontal region in alpha band corresponded to a decrease in 0.62 errors during the Flexibility task, and every 0.01 increase in dWPLI in the right posterior frontal region Distractor Error decreased by approximately 9%.

Table 4
Significant Regression Models in FXS

Frequency Band	KiTAP Variable	Effect	Estimate	SE	DF	t	p
Gamma (Poisson)	Distractor Error	Intercept	0.801	0.240	51	3.34	0.002
		Sex (F)	0.102	0.081	51	1.26	0.213
		Nonverbal Z-score	-0.082	0.017	51	-4.92	< .0001
		dWPLI Left Frontal	15.766	2.236	51	7.05	< .0001
Gamma (Log normal)	Flexibility Median RT	Intercept	7.720	0.489	44	15.79	< .0001
		Sex (F)	0.222	0.180	44	1.23	0.225
		Nonverbal Z-score	-0.035	0.035	44	-1.00	0.321
		dWPLI Left Frontal	-10.376	4.844	44	-2.14	.0378
Gamma (Female only)	Flexibility Error	Intercept	13.574	6.804	20	2.00	0.060
		Nonverbal Z-score	-0.822	0.391	20	-2.10	0.048
		dWPLI Left Frontal	190.46	80.340	20	2.37	0.028
		dWPLI Cross-Hemi	-305.08	111.29	20	-2.74	0.013
Alpha	Flexibility Error	Intercept	13.664	3.146	44	4.33	< .0001
		Sex (F)	-0.770	1.234	44	-0.62	0.536
		Nonverbal Z-score	-1.132	0.250	44	-4.53	< .0001
		dWPLI Right Prefrontal	-62.307	18.165	44	-3.43	0.001
Alpha (Poisson)	Distractor Error	Intercept	3.463	0.222	51	15.62	< .0001
		Sex (F)	0.241	0.079	51	3.04	0.004
		Nonverbal Z-score	-0.082	0.017	51	-4.86	< .0001
		dWPLI Right Frontal	-8.867	1.547	51	-5.73	< .0001

Discussion

Resting state EEG phase connectivity within source-localized frontal regions in a well-powered sample of FXS and matched controls revealed in two key findings. First, individuals with FXS broadly demonstrated increased gamma and reduced alpha phase connectivity across frontal regions, both within and across hemispheres, compared to TDC. Second, significant associations between EF and frontal connectivity emerged in FXS, such that increased error rates were positively associated with gamma connectivity and inversely associated with alpha connectivity. Notably, these findings remained robust after accounting for general cognitive functioning. These latter findings document an important and not previously reported link between deficits in EF and the alterations in the coherence of specific frequencies of neural oscillations within the frontal cortices of individuals with FXS. Together, our study reveals a potential underlying neurophysiological basis for EF impairment in FXS that may represent a promising target for future intervention studies.

Phase Connectivity

Phase connectivity, when applied spatially, assesses the precise alignment neural oscillations at a specific frequency between brain regions. Phase connectivity, or coherence, between different brain regions is well known to support cognitive functions (41, 43, 47). Herein, we implemented source localization to examine point-to-point connectivity within frontal regions to clarify the source of previously reported alterations and their functional significance (14, 16, 22). Previous investigations into other neurodevelopmental and neurological disorders have linked alterations in resting frontal phase connectivity with impaired cognitive function, including EF (48–50).

Our primary results are consistent with previous electrode-level phase connectivity findings and further localize a subset of regions with gamma band hyper-connectivity and alpha band hypo-connectivity within frontal cortex in FXS (14, 16, 22). Specifically, gamma hyper-connectivity and alpha hypo-connectivity may reflect poor top-down regulation of local frontal circuits leading to hyperexcitability of local circuit function and subsequently to cognitive and behavioral dysfunction (51, 52). The observed alpha hypo-connectivity may represent deficient longer-range inhibitory mechanisms which down-regulate background neural excitability (40). From the perspective of an excitatory-inhibitory imbalance (E:I) model of neurodevelopmental disorders, these findings are consistent with a hyper-excitable phenotype that has been shown in FXS across in-vivo slice physiology and mouse model studies (17, 19, 21, 53).

More recently, a growing body of literature has raised the importance of increased variability in neural signals linked to enhanced cognition, basically because systems need to be tuned on-line to optimize them for behavioral demands (54–56). Our observations, when taken together with other EEG findings in FXS (e.g., decreased peak alpha frequency, decreased neural synchronization to the auditory chirp, reduction in global alpha power with concomitant increases in regional gamma power) suggest a diminished capacity or increased constraints on the expression of neural variability in the FXS cortex (15,

57–59). From a molecular standpoint, loss of FMRP results in a reduction of synaptic plasticity, defects in stimulus-induced synaptic protein synthesis, synaptic overgrowth, and changes in dendritic spine morphology in the FMR1-/- KO mouse and neurons derived from FXS patients (60–64). Such changes also would be predicted to dampen neural variability at the molecular and cellular levels (58).

Evolving Model of EF Physiology in FXS

The association between EF task performance and frontal lobe phase connectivity in the present study can be used to advance our understanding of higher-order cognitive processes in FXS and, for the first time, establish a neurophysiological model of impaired EF in this patient population. Importantly, the correlation and regression findings remained robust, even after correcting for general intellectual functioning. This suggests that frontal gamma hyper-connectivity and alpha hypo-connectivity may be specifically related to EF deficits rather than intellectual or general cognitive capacity more broadly. Alpha and gamma phase connectivity predicted increased error rates during the distractibility task as well as increased error rates and reduced reaction time during the cognitive flexibility task. Although faster reaction times are often thought to be better, this is not necessarily the case in the context of EF when slower reaction times can benefit participants in terms of the speed/accuracy tradeoff (46, 65). We speculate that functional consequences of connectivity abnormalities may include poorer local regulation of frontal activity and deficient inhibitory mechanisms, thus leading to difficulty in cognitive flexibility, attention shifting, ignoring distractions, and an increase in impulsivity.

Differences in Clinical Correlations between Males and Females with FXS

Contrary to our expectations, males and females with FXS had similar frontal gamma hyper-connectivity. As full-mutation males with FXS have significantly less expression of FMRP (66) and a higher burden of clinical symptoms (4), we had predicted increased gamma band phase connectivity in males than females. Previous studies have replicated the finding of increased resting local gamma power in males with FXS (15, 57, 58, 67). Phase-based measures, such as dWPLI, can show increases in phase synchronized neural oscillations across regions rather than just a parallel increase in the power at a given frequency band. Thus, our finding indicate high frequency activity in local circuits may be restricted to males with FXS, whereas high frequency activity in the mutual synchronized driving of excitability across widely distributed brain regions may be more broadly present across individuals with FXS.

Our findings indicated that associations of EF with alpha connectivity were primarily driven by females with FXS. Preserved regulatory capacity of long-distance inputs in the alpha band frequency, evident in variable degrees in female FXS participants, was related to more intact EF task performance. As full mutation females with FXS are obligate mosaics (one X chromosome still produces FMRP) it is not surprising that intermediate results (between full mutation males and controls) have been reported in resting state and event related EEG studies in FXS (15, 59, 68). Thus, greater FMRP expression in females may help to mobilize alpha band connectivity to support EF in a compensatory fashion. Our findings are consistent with the canonical role of alpha oscillations in attention and cognition, such that enhanced

alpha frontal connectivity may facilitate shifting attention and cognitive resources to support behavioral flexibility and inhibit distraction from sensory information that is not relevant to contextual demands (40). Previous fMRI studies have implicated compensatory mechanisms of increased activation in prefrontal regions to support inhibitory control and prevent distractor interference in FXS (13, 69). Complementing the general activation finding from fMRI work, our EEG study highlights the breadth and spatial distance of altered coherence of neural oscillation across regions that occurs in specific frequency bands that have their own functional significance.

Evidence of Atypical Lateralization

Lateralized substrates for distinct cognitive functions within frontal cortex have been consistently observed in typically-developing individuals. For example, right inferior and superior frontal gyri have been implicated in inhibitory control, specifically proactive control related to reaction time slowing (70, 71). Atypical brain lateralization of cognitive functions has been observed in other neurodevelopmental disorders, including ASD (72, 73). Our findings add to these previous studies by documenting atypical lateralization in individuals with FXS. For example, we found increased gamma band, but reduced alpha band, in right prefrontal regions in individuals with FXS compared to TDC. This finding suggests EF skills lateralized within these regions would be affected, which our partial correlation and regression findings support. Specifically, we observed reduced alpha connectivity within these atypically lateralized regions predicted impaired performance during cognitive flexibility and distractibility tasks. Yet, consistent with our compensatory hypothesis, our findings suggest that preserved lateralized right frontal alpha connectivity may facilitate inhibition of previously learned behavior (flexibility) and irrelevant sensory stimuli (distractibility) in individuals with FXS, especially among females.

Notably, among males with FXS, we found gamma hyper-connectivity in left pars opercularis and pars triangularis, areas within the inferior frontal gyrus critical for speech and language. This suggests increased phase synchronized frontal gamma activity also may contribute to language impairments and delays in FXS, which are nearly universal among male patients (74, 75). Our previous work showed increased frontal gamma power prior to the onset of speech production in individuals with FXS compared to controls, and greater gamma increases were associated with more unintelligible speech in FXS (76). Taken together, these findings implicate increased local and synchronized high frequency frontal activity may have widespread disruptive role in FXS that is not necessarily specific to EF or speech production. Future studies are needed to determine the extent to which high frequency activity within frontal cortices more broadly affects learning and development in FXS.

Limitations

Frontal connectivity findings are limited to brain activity at rest and thus should not be equated with task-based connectivity findings. Similarly, resting connectivity findings may not generalize to neural activity during real world function. Thus, future work is needed to study dynamic changes in neural oscillation during EF task performance. Findings further are limited to short-range frontal connectivity and do not consider longer-range connectivity relevant to EF (e.g., fronto-parietal connections). Still, findings remain

the first of their kind in FXS and represent a critical step to better understanding neurophysiological mechanisms underlying impaired EF in FXS. It also is important to note that only certain aspects of EF were measured using KiTAP, indicating the need to replicate findings in a broader battery of neuropsychological tests (e.g., NIH Cognitive Toolbox). We did not have an IQ- and age-matched control group. However, given that our analyses controlled for IQ, we believe our findings are specific to specific relations of EF skills to frontal lobe EEG features independent of the level of intellectual ability. Last, we note that FMRP expression is not dichotomous based on sex as presently described. Future work examining frontal connectivity in relation to a continuous measure of FMRP (66) is needed to better understand the role of FMRP in EF impairments in FXS.

Conclusions

In the first study of its kind using high-density source localized resting state EEG, we documented increased gamma band connectivity and reduced alpha band connectivity in frontal brain regions in individuals with FXS relative to TDC, and these connectivity abnormalities were predictive of executive function deficits in FXS, independent effects on general cognitive ability. Our findings implicate gamma hyper-connectivity within frontal brain regions, and thus support and extend previous findings demonstrating E:I imbalance in FXS. Given the directions of correlation, we hypothesize that increased gamma connectivity may impair EF performance via its relation to hyperexcitability of cortex whereas increased alpha connectivity may provide compensatory support for EF in individuals with FXS by supporting adaptive shifts is brain state needed for context-relevant behavioral demands. Our findings suggest that frontal phase connectivity may be an important measure of target engagement and target for future intervention trials. Together, our findings provide novel insight into potential mechanisms of deficit in EF in FXS.

List Of Abbreviations

ASD
Autism spectrum disorder
CGG
Cysteine-guanine-guanine
CH
Cross Hemisphere
cMFG
Caudal middle frontal
dWPLI
debiased weighted phase lag index
EEG
Electroencephalography
EF

Executive function
E:I
Excitatory:inhibitory
FP
Frontal pole
FMR1
Fragile X messenger ribonucleoprotein 1 (*FMR1*)
fMRI
Functional magnetic resonance imaging
FMRP
Fragile X protein
FXS
Fragile X Syndrome
IAPF
Individual alpha peak frequency
ID
Intellectual disability
IQ
Intelligence quotient
KiTAP
Test of Attentional Performance in Children
LF
Left Frontal
lme
linear mixed effect
LOF
Lateral orbito frontal
LPF
Left Prefrontal
MOF
Medial orbito frontal
MRI
Magnetic resonance imaging
PCR
Polymerase chain reaction
pORB
Pars orbitalis
pOPER
Pars opercularis
pTRI

Pars triangularis
RF
Right Frontal
rMFG
Rostral middle frontal gryus
RPF
Right Prefrontal
RT
response time
SB-5
Stanford-Binet-5th Edition
SD
Standard deviation
sFG
Superior frontal
TDC
Typically developing control

Declarations

Ethics approval and consent to participate

The studies involving human participants were reviewed and approved by Cincinnati Children's Hospital Medical Center. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Consent for publication

Not applicable

Availability of data and materials

The dataset used for the current is are available from the corresponding author on reasonable request.

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest for the current manuscript.

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Authors' contributions

L.M.S interpreted data and wrote full draft of the manuscript. J.L. and R.L. analyzed the dWPLI data and assisted with manuscript draft. P.H. analyzed the correlation and regression data. J.A.S, C.A.E, E.V.P. assisted with data interpretation and edited the manuscript. J.A.S and C.A.E. participated in the initial conceptualization of the broader study, and L.M.S., J.L., and E.V.P. conceptualized the specific sub-study. All authors reviewed the manuscript and approved the submitted version.

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Figures

Figure 1

Frontal Connectivity Across FXS and TDC Participants. Gamma band connectivity summary at subject level (A). Upper alpha band connectivity summary at subject level (B). dWPLI values were averaged over connections of each region, and over frequencies within gamma band.

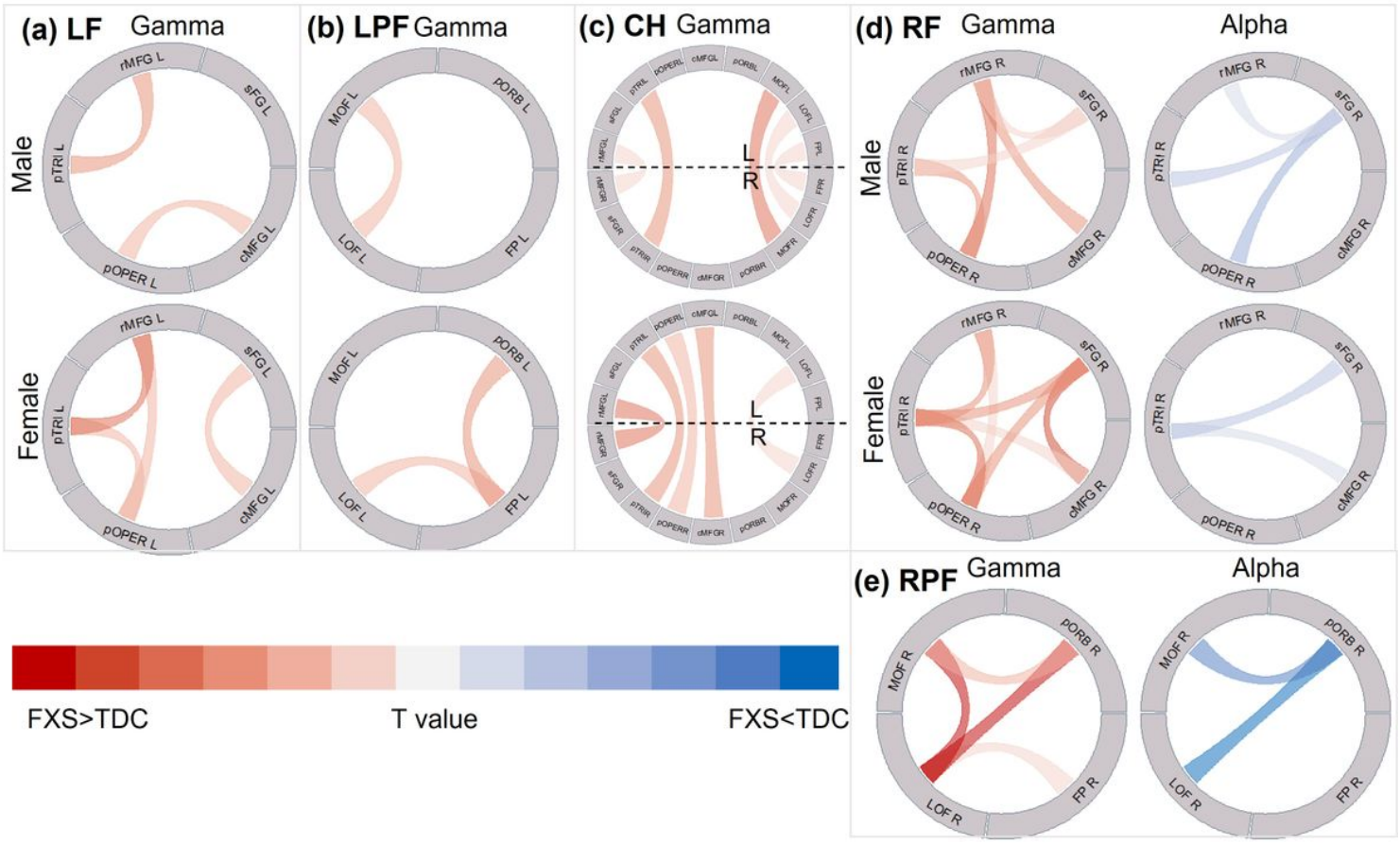

Figure 2

Circular Chart of Connections with Significant Group Differences in Connectivity. Statistically significant group differences (multiple comparisons were FDR corrected per model) for gamma band connectivity depicted in left posterior frontal (a) and prefrontal (b) regions as well as cross-hemisphere (c). Right posterior frontal (d) connectivity group differences depicted for gamma, and right prefrontal connectivity group differences depicted for gamma (e) band. Male and females are shown separately when sex reached significance for the model. Blue ribbon denotes significant FXS>TDC connections and red ribbon denotes significant FXS<TDC connections. Darker colors represent higher T values.

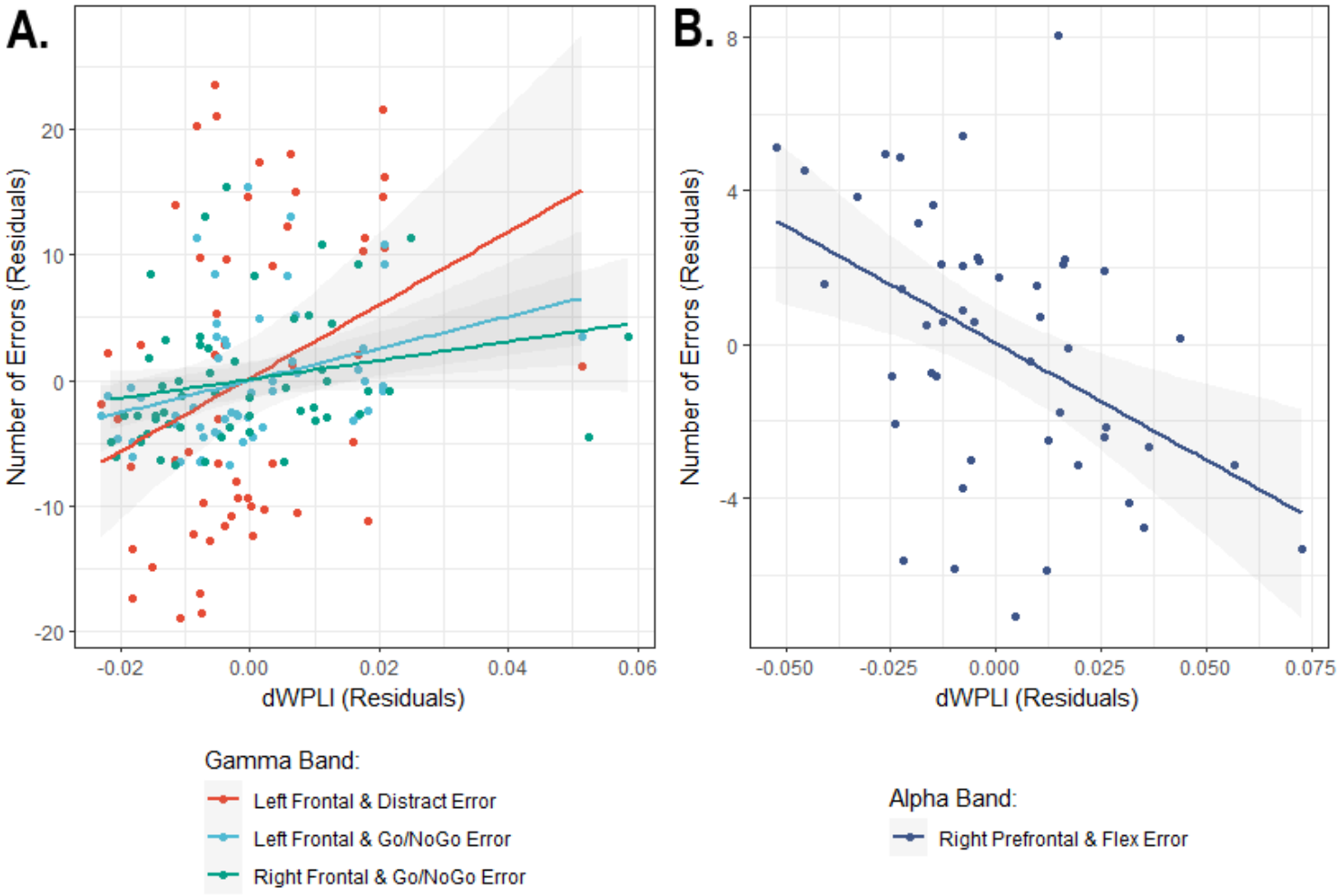

Figure 3

Correlations between Frontal Connectivity and Executive Function Measures Across FXS. Spearman's correlations showing positive correlation in the gamma band (A) and negative correlation in alpha band (B) between connectivity strength and number of errors

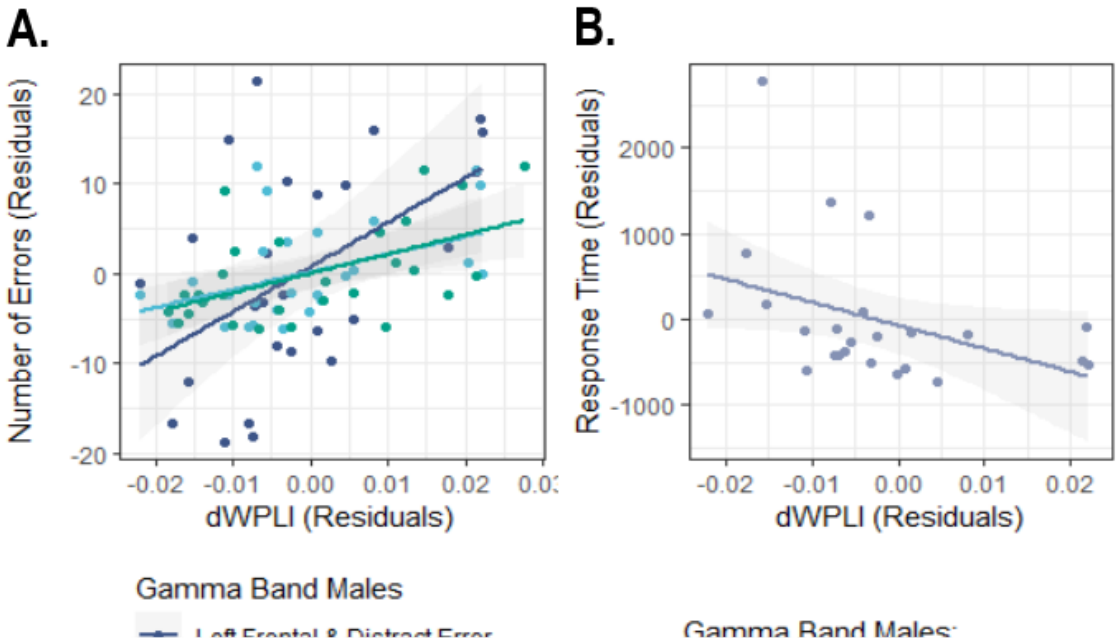

Figure 4

Correlations between Frontal Connectivity and Executive Function Measures by Sex. Sex-specific significant Spearman's correlations are shown separately for males (A-B) and females (C-D) for both gamma and alpha bands.

Supplementary Files

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