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Effects of Metformin on Resting-State EEG and Associations with Adaptive Behaviors in Fragile X Syndrome

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Abstract

Metformin has emerged as a candidate drug for Fragile X Syndrome (FXS) after promising results in animal studies and small-scale trials. A three-site registered clinical trial (RCT) demonstrated effects of metformin on behavioral symptoms in FXS in participants aged 6–11. Resting state electroencephalography (RS-EEG) was also collected during the RCT. We present results from analyses of RS-EEG and associated adaptive behavior measures. We observed significant metformin treatment effects on EEG measures associated with cortical excitation/inhibition balance (periodic gamma), brain maturation (periodic alpha), and signal complexity. Significantly affected EEG measures moved toward values associated with typical development. We also observed associations between more typical EEG activity and improved adaptive behavior scores in the treatment group. Additional significant effects and associations were observed when considering only participants without molecular mosaic. Results confirm metformin's potential as a treatment option and encourage further research into its effects on functional brain activity.

INTRODUCTION

Fragile X syndrome (FXS) is the leading known monogenic cause of autism spectrum disorder (ASD) and the leading known cause of inherited intellectual disability (ID), affecting an estimated one in 7,000 males and one in 11,000 females (1). FXS is associated with severe cognitive, attentional, and behavioral impairments and functional differences at the neural level, notably cortical hyperexcitability (2).

FXS is an X-linked genetic disorder caused by a triplet expansion of the *Fragile X Messenger Ribonucleoprotein 1* (*FMR1)* gene resulting in absent or impaired translation of FMRP, a selective mRNA-binding protein essential for synaptic development and plasticity (2). The *FMR1* gene is characterized by a polymorphic CGG triplet in the 5'-UTR region. Typical alleles have between 5 and 54 repeats of the triplet (3); alleles with 55–200 repeats are considered a premutation associated with FXS-related disorders including Fragile X-associated Tremor/Ataxia Syndrome (FXTAS); alleles with more than 200 repeats are considered full mutations and associated with FXS (3). Molecular mosaicism is also possible and has been associated with different and/or less severe symptom presentation of FXS due to generally higher FMRP levels (3, 4).

To date, treatment options for FXS have been limited to behavioral methods or drugs targeting specific symptoms and comorbid conditions. No pharmacological interventions have been approved. Metformin, a medication known to improve blood glucose levels, reduce obesity, and curb excessive appetite in type 2 diabetes, has emerged as a candidate drug for targeted FXS treatment based on animal studies showing rescue in FXS model organisms (5–7). Metformin may contribute to normalizing neural activity in FXS in part by reducing the activity of intracellular signaling proteins such as AKT and ERK (8, 9). Additionally, metformin is an upstream inhibitor of the mammalian target of rapamycin complex 1 (mTORC1). Reduced mTORC1 activity can impair translation of synaptic proteins such as Arc, αCaMKII, MAP1B, and MMP9 in an activity- and context-dependent manner. Increased Arc in FXS increases AMPA

receptor (AMPAR) internalization and reduces the level of AMPAR at the cell membrane. Overexpression of the other proteins is thought to dysregulate cytoskeletal remodeling and may contribute to atypical dendritic spine morphology. Dysregulated FMRP expression has also been associated with altered stability of the mRNA for a GABA receptor subunit and altered GABAergic signaling (10). Together, these mechanisms are thought to induce excitation-inhibition (E/I) imbalance consistent with cortical hyperexcitability (2).

Metformin is well-tolerated, even in very young patients, with a low risk profile (11). A 2018 clinical study of individuals with FXS from four to 58 years old reported that in addition to slowing weight gain and stabilizing appetite, doses of up to 1000 mg of metformin taken twice a day resulted in improvements on measures of language skills and aberrant behavior (12). A 2019 trial in nine children from 2–7 years demonstrated improvements in aberrant behaviors, expressive and receptive language, and motor skills (13). In a 2021 open-label trial with 15 participants, Proteau-Lemieux, *et al*. demonstrated the safety and tolerability of metformin in normoglycemic FXS patients, observing no serious adverse effects. Significant behavioral or cognitive effects were not observed. However, TMS results indicated improved corticospinal inhibition, which is mediated by $GABA_a$ and $GABA_b$ receptors, reflecting reduced neural excitability after treatment (11).

Based on promising preliminary results, a registered double-blind, placebo-controlled trial of metformin was conducted across three sites to assess physical, behavioral, cognitive, and neurophysiological effects of metformin in individuals with FXS over a four-month treatment period. In addition to diagnostic measures, behavioral scales, and molecular biomarkers, clinical effects of metformin were assessed in a subsample of the main study via electroencephalography (EEG). EEG is a functional neuroimaging method that measures electrophysiological activity at the cortical surface. EEG is noninvasive and flexible relative to other functional neuroimaging methods and offers very high time resolution. Thus, it is a common and vital tool for assessing neural correlates of cognitive development in children and clinical populations (14).

Resting state EEG (RS-EEG) is recorded in the absence of a specific task and measures intrinsic brain rhythms. Many features may be extracted from RS-EEG timeseries, some of which serve as indices of E/I balance and associated GABAergic activity. Many such indices differ between FXS and neurotypical (NT) participants. FXS participants exhibit increased delta, gamma, and theta activity (15, 16) and reduced alpha power and alpha peak frequency (APF) (5–7) relative to NT controls. FXS participants show decreased signal complexity, particularly in higher complexity scales (15). Alpha activity and signal complexity are markers of brain maturation (17–19), while gamma activity is an indicator of E/I balance and balance of GABAergic vs. glutaminergic activity in cortex (20).

Altered EEG biomarkers in FXS have also been associated with behavioral differences. Proteau-Lemieux, *et al.* (21) demonstrated associations between EEG and behavioral symptoms. Reduced alpha power in FXS was linked to higher social avoidance, and reduced high gamma power was associated with more

hyperactivity (21). Signal complexity in higher scales was linked to nonverbal intelligence quotient (NVIQ) (21).

Overall, prior results indicate metformin has the potential to modify E/I balance in FXS; EEG biomarkers of E/I balance and brain maturation are altered in FXS; and these alterations are associated with behavioral symptoms. However, the clinical effects of metformin on EEG are as yet unknown. The EEG portion of the metformin RCT aims to assess 1) whether a four-month treatment with metformin affected RS-EEG features in participants with FXS when compared to treatment with placebo and 2) whether metformin-related behavioral improvements found in the RCT and the EEG subsample were associated with metformin-related changes in EEG metrics. We hypothesized that EEG features known to be altered in FXS – e.g., alpha and gamma activity, signal complexity – would exhibit treatment-associated changes from baseline to post-treatment. We further hypothesized that these changes would move participants toward a more typical neural phenotype. We also hypothesized that treatment-associated changes in EEG features would correlate with changes in behavior, and these correlations would show a link between change toward a more typical EEG phenotype and improved FXS symptoms.

METHODS

Participants and Recruitment

The study is a multisite project including Stollery Children's Hospital in Edmonton, University of Alberta (Canada); Centre Hospitalier Sainte-Justine in Montreal, Quebec (Canada); and the MIND Institute at the University of California, Davis (United States of America). The Health Canada- and FDA-approved clinical trial was registered (NCT03862950, Canadian sites; NCT03479476, US site).

Main inclusion criteria for participants were: FXS diagnosis with genetic confirmation of full *FMR1* mutation (> 200 CGG repeats) with or without molecular mosaic (size or methylation mosaic); age 6–35 years; not currently pregnant or lactating,; willing to use some form of birth control during the study if at risk of pregnancy; IQ not higher than 85 with overall age equivalent not higher than 13 as assessed at screening; and a parent or caregiver willing and able to attend all visits. See supplementary materials for full summary of inclusion/exclusion criteria and consent procedures.

Study Flow

Full study procedures are described in Bolduc, *et al.* (23). Treatment period was four months, with an optional open-label extension. Participants attended three in-person visits: screening (T0), two months (T1), and four months (T2). At T0, participants were tested for NVIQ via the Leiter International Performance Scale (Leiter-3: Roid, Miller, Pomplun, & Koch 2013, Stoelting Company, Wood Dale, IL 60191, USA) and for ASD via the Autism Diagnostic Observation Scale (ADOS) (24). Leiter-3 was chosen because it is a nonverbal test that can be used even with lower-functioning participants with few or no language skills and is valid for English- and French-speaking participants. Following IQ and ADOS

testing, participants or their guardians completed behavioral assessments, provided blood, stool, and urine samples, and were randomized into either the metformin or placebo condition.

Study medication was provided at T0 and T1. For patients weighing over 50 kg, initial dose of metformin was 500 mg taken orally with dinner. Dosage was increased by 500 mg/week until participants reached a maximum dose of 2000 mg/day. For patients under 50 kg, initial dose was 250 mg/day; if this dosage was well-tolerated, dosage was increased by 250 mg each week until a maximum dose of 1000 mg/day was reached.

Behavioral outcomes for the current analysis were based on behavioral measures administered to caregivers at T0 and T2. See supplemental materials for full information on behavioral variables.

EEG Acquisition and Processing

EEG data acquisition and preprocessing were conducted as previously performed in Proteau-Lemieux, *et al.* (21). Data were acquired at Canadian sites with a saline-based EGI 128-electrode dense array system and at the MIND Institute with a gel-based 32-electrode ActiCAP system. EEG was acquired in a soundproof booth with a caregiver and research staff member present at all times. Participants watched a muted movie without subtitles during EEG recording to increase compliance. RS-EEG recording continued until a total of four minutes of clean signal were acquired; the four minutes did not need to be sequential, as data were segmented for further analysis. RS-EEG was always acquired before task-based data collected in the same session. EEG recordings were preprocessed using the EEGLab toolbox (version 14.1.2) in MATLAB (version R2020b).

Sampling rate was set to 1000 Hz with an online bandpass filter of 0.1–500 Hz. Impedances were kept below 40 and 10 kΩ for the EGI and Brain Products system, respectively.

The Harvard Automated Preprocessing Pipeline for EEG (HAPPE Version3) (25) was used to automatically process EEG. First, outer electrodes in the 128-electrode cap most susceptible to artifacts and electrode movements were removed, resulting in the exclusion of twenty electrodes. A notch filter was applied to remove electrical noise of 60 Hz. Data was band passed through finite impulse response (FIR) between 1–80 Hz. Electrodes contaminated with artifacts due to high impedance, displacement, or inadequate scalp contact were identified and excluded from subsequent processing. An optimized wavelet-enhanced independent component analysis (W-ICA) was applied to attenuate artifacts related to participants' motion, electromyogenic activity, and ocular events (blinks/saccades), followed by an additional ICA step to remove remaining artifacts. Continuous data were then segmented into non-overlapping epochs of two, five, and 30 seconds. Epochs containing amplitudes exceeding ± 150 μV were rejected. Finally, each electrode was re-referenced to the common average, and removed electrodes were interpolated from neighboring electrodes using EEGLAB's spherical spline interpolation.

RS-EEG Feature Extraction

We quantified the effect of metformin treatment on EEG using a wide range of linear and nonlinear signal features. All features were calculated within each of seven ROIs, with exact configuration differing by recording setup as in (14). Epoch lengths were selected per feature to ensure they effectively captured the intended informational content of the time-series.

Absolute and relative power and periodic and aperiodic components were calculated in 2-second epochs. For these features, spectral power was first estimated using Welch method with a Hamming window of length 1000. Absolute power was calculated in frequency bands delta (1-3.5 Hz), theta (4–7 Hz), alpha (7.5–12.5 Hz), beta (3–30 Hz), low gamma (31–57 Hz), and high gamma (63–80 Hz). Relative power was estimated by dividing the absolute power of each frequency band by the broadband power (1–80 Hz). The power spectrum was parametrized into periodic (oscillatory) and aperiodic components using the one over f (FOOOF) method. Aperiodic exponent and offset were extracted using parameters of peak_width_limits = [0.5, 18], max_n_peaks = 10, and a frequency range between 1-55Hz. Periodic power in delta, theta, alpha, beta, and gamma (31–55 Hz), was computed as the integral of the curve resulting from subtraction of total spectrum from aperiodic fit (26).

Hurst exponent, a statistical measure indicating long-range dependence and fractal properties of a self-similar time series, was estimated using dispersional analysis in 2-second epochs (27) and Detrended Fluctuation Analysis in 30-second epochs (28). EEG signal irregularity was quantified using two entropy-based metrics in 5-seconds epochs: sample entropy (SE) (29) and multiscale entropy (MSE) with pattern length (m) of 2 and similarity criterion (r) of 0.5 in 40 scales (30). MSE, obtained by computing SE across multiple temporal scales, reflects multiscale spatiotemporal complexity of physiological signals. We derived the complexity index (CI) as the area under the multiscale entropy curve. To capture scale-specific contributions of this feature, CI was categorized into three components: CI across all scales (scales 1–40), CI at lower scales (scales 1–20; CI low-scale), and CI at higher scales (scales 21–40; CI high-scale).

Statistical Analyses

We conducted two analyses on features extracted from RS-EEG. All analyses were first applied to the entire sample of participants with valid EEG data (whole sample). Any measures emerging as significant in the whole sample were further tested within a sub-sample comprising only those participants without molecular mosaic (non-mosaic). We did not conduct tests within only participants with molecular mosaic due to the limited size of the mosaic sub-sample (see Table 1).

Table 1
Demographics of EEG sample by mutation type for participants with complete and incomplete datasets.

Whole EEG Subsample				
		All Participants	**Metformin**	**Placebo**
Full Sample (> 200 CGG Repeats)	N	84	41	43
	AMAB n (%)	67 (80%)	32 (78%)	35 (74%)
	Age, years, mean (min, max)	16.534 (6.182, 34.557)	16.375 (6.182, 34.557)	16.69 (6.745, 32.266)
	NVIQ, mean (min, max)	53.845 (30, 84)	54.927 (30, 84)	52.814 (31, 84)
Non-mosaic	N	60	28	32
	AMAB n (%)	44 (73%)	20 (71%)	22 (69%)
	Age, years, mean (min, max)	17.159 (6.182, 34.557)	17.3 (6.182, 34.557)	17.036 (6.735, 32.266)
	NVIQ, mean (min, max)	52.733 (31, 84)	54.464 (32, 81)	51.219 (31, 84)
Mosaic	N	24	13	11
	AMAB n (%)	23 (96%)	12 (92%)	11 (100%)
	Age, years, mean (min, max)	14.972 (6.705, 26.21)	14.384 (6.705, 26.21)	15.665 (8.885, 25)
	NVIQ, mean (min, max)	56.625 (30, 84)	55.923 (30, 84)	57.455 (32, 81)
Participants with Full Dataset (T0 + T2)				
		All Participants	Metformin	Placebo
Full Sample (> 200 CGG Repeats)	N	62	32	30
	AMAB n (%)	51 (82%)	26 (81%)	25 (83%)
	Age, years, mean (min, max)	17.196 (6.182, 34.557)	16.041 (6.182, 34.557)	18.427 (6.735, 32.266)
	NVIQ, mean (min, max)	54.177 (30, 84)	56.469 (30, 84)	51.733 (31, 845)
Non-mosaic	N	43	20	23
	AMAB n (%)	32 (74%)	14 (70%)	18 (78%)
	Age, years, mean (min, max)	17.646 (6.182, 34.557)	16.75 (6.182, 34.557)	18.426 (6.735, 32.266)

Whole EEG Subsample				
		All Participants	**Metformin**	**Placebo**
	NVIQ, mean (min, max)	54.372 (31, 84)	57.5 (33, 81)	51.652 (31, 84)
Mosaic	N	19	12	7
	AMAB n (%)	19 (100%)	12 (100%)	7 (100%)
	Age, years, mean (min, max)	16.175 (6.705, 26.21)	14.86 (6.705, 26.21)	18.43 (13.958, 25.873)
	NVIQ, mean (min, max)	53.737 (30, 84)	54.75 (30, 84)	52 (32, 81)

Treatment-Dependent Change

To assess whether metformin treatment had measurable effects on EEG, a linear mixed-effects (LME) regression model was fit for each feature. LME was selected because it is well-suited to the within-subjects longitudinal design of the clinical trial and because it could account for participants who did not have valid EEG data for either T0 or T2. LMEs were fit for each feature with raw feature value as outcome, fixed categorical predictors representing Session (T0/T2), Condition (metformin/placebo), and ROI, a fixed predictor representing interaction between Session and Condition, and random effects for participant ID and recording site (Montreal, Edmonton, or UCD). Additional fixed effects were included to control for age, NVIQ, and sex assigned at birth.

If an F-test on the model showed that ß was significant for the Session-Condition interaction, the feature was considered significantly affected by treatment. Multiple comparison correction (MCC) was conducted using the Benjamini-Hochberg (B-H) method (31) with a false discovery rate *Q* of 0.05. After assessing the significance of the interaction after MCC, data was pooled across all ROIs, and a paired t-test was used to test for significant change from T0-T2 within groups.

EEG and Behavioral Outcomes

After finding EEG features exhibiting a significant treatment effect, these features were tested for treatment-dependent associations with behavioral outcomes responsive to metformin in the RCT (23). Outcome measures of interest were: 1) Aberrant Behavior Checklist for Community (ABC-C), which was scored using an FXS-specific factoring system (ABC-FX) (32); and 2) a measure of vocabulary (number of different word roots) derived from Expressive Language Sampling (ELS) procedures in two contexts: narration and conversation (33). While significant treatment effects were not observed in the full RCT sample (N = 120), subscales of both ABC-C and ELS showed significant response to metformin treatment in the subsample of participants aged 6–11 (23). To identify further behavioral outcome

measures of interest within the RS-EEG subsample (N = 84), LMEs were fit for all behavioral measures administered at T0 and T2 (See supplemental materials). Each LME predicted score on a behavioral scale from condition (metformin/placebo), session (T0/T2), and session-condition interaction, with random effects of participant ID and recording site. All models controlled for sex at birth and NVIQ. If an F-test on the resulting model showed that ß was significant for the Session-Condition interaction, it was included as an additional outcome of interest.

For each behavioral measure of interest, MATLAB's *corr* function was used to test for significant correlations between the difference in each behavioral score between T2 and T0 (ΔBehavior) and the difference in each EEG feature's value (ΔEEG) within each treatment condition. ΔEEG was calculated within each ROI to capture localized effects associated with specific behavioral and sensory features of FXS. In the event of significant correlation between ΔBehavior and ΔEEG, direction of the correlation was used to determine whether ΔEEG was associated with symptom improvement on that measure. Due to the nature of the analyses, EEG/Behavior correlations were restricted to those participants who completed both T0 and T2 visits (see Table 1).

RESULTS

Demographic makeup of the EEG subsample is summarized in Table 1.

Treatment-Related Change in EEG

Linear mixed-effects model (LME) results are summarized in Table 2. In the whole sample, a significant Session-Condition interaction was observed in CI – total, high-scale, and low-scale – and periodic alpha and gamma power. Periodic alpha also exhibited significant main effects of Session and Condition. From T0 to T2, mean CI across all scales increased in the treatment but not placebo group (Fig. 1); t-tests showed this increase was significant only for low-scale and total. Periodic alpha increased from T0 to T2 in the treatment group (Fig. 2). T-tests showed significant change in treatment but not placebo. Periodic gamma decreased from T0 to T2 in treatment but not placebo (Fig. 2), but t-tests did not identify a significant pre/post difference in either group.

Table 2

Linear mixed-effects model statistics by feature and mutation type. Bold features exhibited a significant interaction between Session and Condition with results surviving multiple comparison correction.

Whole EEG Subsample						
Feature	Beta Condition	p	Beta Session	p	Beta Interaction	p
Complexity Interval	**-0.36**	**.543**	**-0.39**	**.078**	**1.03**	**< .001**
CI High-scale	**-0.24**	**.486**	**-0.27**	**.028**	**0.43**	**.01**
CI Low-scale	**-0.12**	**.703**	**-0.11**	**.396**	**0.56**	**.002**
DFA Alpha	-0.01	.1	0.01	.448	-0.005	.317
DFA Beta	-0.02	.263	-0.001	.668	-0.001	.796
1/f Exponent	0.02	.616	-0.01	.375	-0.03	.083
Hurst Exponent	0.004	.351	-0.01	< .001	0.003	.246
1/f Offset	0.02	.776	-0.14	< .001	0.05	.28
Periodic Alpha	**-0.3**	**.022**	**-0.08**	**.005**	**0.14**	**< .001**
Periodic Beta	-0.12	.615	-0.12	.134	0.14	.193
Periodic Delta	0.03	.285	0.01	.566	-0.03	.039
Periodic Gamma	**0.2**	**.269**	**0.11**	**.079**	**-0.27**	**.001**
Periodic Theta	-0.08	.483	0.02	.4	-0.06	.079
Sample Entropy	0.01	.38	< 0.001	.073	0.002	.684
Non-mosaic Only						
Feature	Beta Condition	p	Beta Session	p	Beta Interaction	p
Complexity Interval	**-0.96**	**.228**	**-0.63**	**.021**	**1.69**	**< .001**
CI High-Scale	**-0.5**	**.282**	**-0.31**	**.029**	**0.66**	**.001**
CI Low-Scale	**-0.44**	**.26**	**-0.28**	**.08**	**0.96**	**< .001**
Periodic Alpha	**-0.39**	**.02**	**-0.06**	**.084**	**0.14**	**.004**
Periodic Gamma	**0.51**	**.028**	**0.03**	**.719**	**-0.34**	**.001**

Whole EEG Subsample

In the non-mosaic sub-sample, interactions from the whole sample were replicated (Table 2) with some differing levels of significance. CI in all three scales increased from T0-T2 in the treatment but not placebo group, with t-tests showing significant change in treatment but not placebo in total and low-scale (Fig. 1). Mean periodic alpha increased in the treatment but not placebo group, but t-tests did not show a significant change in either condition (Fig. 2). Mean periodic gamma decreased, with t-tests showing significant decrease in the treatment but not placebo group (Fig. 2).

Relationships Between Change in EEG and Behavioral Phenotype

Full behavioral LME results are summarized in Supplemental Tables 1–2. In the whole sample, LMEs identified significant interactions between session and treatment condition for growth scale value scores on the Receptive and Expressive Communication subdomains of the Vineland Aberrant Behavior Scales (Vineland-3) (see supplemental materials) and the standard score of the Vineland-3 Daily Living Skills domain. These were added as additional measures of interest before continuing with further analyses.

Of the EEG features tested, periodic alpha and periodic gamma showed significant correlations between ΔEEG and ΔBehavior in the metformin group for at least one behavioral outcome. T0-T2 increase in periodic alpha was significantly associated with improvement on Vineland-3 Expressive Communication in left parietal and occipital ROIs in the treatment but not placebo group (Fig. 3). Decrease in periodic gamma activity in the left temporal ROI was associated with improvement on the ABC Irritability subscale and the Daily Living Skills domain of the Vineland-3 in treatment but not placebo (Fig. 3).

In the non-mosaic sub-sample, significant correlations with adaptive behavior outcomes were found for periodic gamma and alpha and CI high-scale in the treatment but not placebo group. Decreasing periodic gamma in occipital and left parietal ROIs was associated with improvement on Vineland-3 Daily Living Skills and Domestic (Fig. 4). Decreasing periodic gamma in the occipital ROI also correlated with improvement on the ABC Inappropriate Speech subscale (Fig. 4). Increasing periodic alpha in the left parietal ROI also correlated with improvement on Vineland-3 Daily Living Skills, Vineland-3 Domestic, and ABC Inappropriate Speech. Increasing periodic alpha in the occipital ROI correlated with improvement on Vineland-3 Expressive Communication (Fig. 4). Finally, increasing CI high-scale in the right temporal ROI correlated with improvement on Vineland-3 Daily Living Skills. Increased CI high-scale in the right parietal ROI correlated with improvement on ABC Hyperactivity and Inappropriate Speech (Fig. 4).

DISCUSSION

We investigated changes in RS-EEG activity in children and adults with FXS following a 16-week, placebo-controlled metformin treatment. Our findings revealed significant treatment effects on EEG measures associated with E/I balance, brain maturation, and signal complexity, all key features associated with FXS and related symptoms. Overall, we observed that EEG measures moved towards values found in TD participants in previous studies. We also observed associations between normalizing EEG measures and improved adaptive behavior scores in the treatment group, with additional significant associations observed when restricting analyses to only non-mosaic participants.

We observed changes to periodic gamma power differing by treatment group. Neural activity in the gamma band during resting state is closely associated with excitation-inhibition (E/I) balance, with elevated power suggesting increased E/I ratio (20). Mouse models have illustrated the relationship between absent or impaired FMRP production and imbalanced excitatory (glutaminergic) and inhibitory (GABAergic) cortical activity (5). Animal findings are replicated in FXS participants; gamma activity is reliably observed to differ in FXS vs. TD participants, with elevated gamma observed in FXS (15, 16) and ASD more broadly (34). Dysregulation of E/I balance and hyperexcitability have been

associated with increased oscillatory gamma power (20, 34). The reduction we observed in the treatment group indicates a shift toward a more typical phenotype. Reduction in periodic gamma was associated with clinically relevant improvements in symptoms related to irritability as measured by ABC-C and daily living skills as measured by Vineland-3. In the 6–11 year-old subsample of RCT participants, researchers observed significant reductions in problematic behaviors measured by most subdomains of the ABC-C and the ABC-FX composite score. Irritability in particular was significantly affected by metformin. An earlier case study also found a consistent reduction in ABC scores after metformin treatment (13). The Daily Living Skills domain of the Vineland-3 has been shown to be a comparative weakness in FXS, particularly for males (35). Scores show a downward trend with age (reflecting slower growth compared to TD participants) and have been linked to changes in cognition across the lifespan in children with FXS and other intellectual disabilities (35).

Periodic alpha power also exhibited treatment-related changes, with an increase in periodic alpha in the metformin group corresponding to improvements in adaptive behavior. Alpha oscillations are a marker of brain maturity, increasing from infancy to adolescence and eventually becoming the dominant rhythm in the adult brain (17). Reduced alpha is a robust marker of FXS, indexing impaired brain maturation and thalamo-cortical and cortical-cortical information flow (36). Proteau-Lemieux, et al. found that oscillatory alpha activity did not correlate with age in FXS as it did in TD controls, and also found reduced alpha power in FXS vs. controls (15, 21).

We observed associations between shifts toward more typical EEG phenotypes and improvement on the Expressive Communication subdomain of the Vineland-3. Expressive communication – using speech, words, and sentences to express oneself – is a key deficit in FXS and ASD. Expressive language in FXS is significantly delayed relative to age-matched peers (35, 37), relating to global delays in functional and structural brain maturation (2, 37). Reduced alpha oscillations may reflect such delayed maturation (16).

These results are in line with previous studies of metformin treatment for FXS showing impacts on expressive communication and language skills. 2019 and 2020 case studies of seven and nine individuals, respectively, found that parents and caregivers reported more frequent and varied speech and improved conversation after metformin treatment (12, 13). The RCT also reported effects of metformin on ELS, an objective expressive language task, in 6–11-year-old participants (23). We observed no correlation between ELS and EEG measures in our sample. This discrepancy may relate to the broader age range in our sample and the constructs measured by each instrument: Vineland-3 provides a more general assessment of expressive communication, comprising a broad range of verbal and nonverbal communication skills, while ELS provides a highly specific vocabulary-based measure. Our results illustrate a link between more normalized alpha with metformin treatment and possible stabilizing effects on overall expressive communication skills. In previous studies (e.g., Proteau-Lemieux, et al., 2026), we found lower alpha power to be associated with social withdrawal in FXS. Although separate constructs, social and communication skills are developmentally linked. Notably, while authors urged caution in interpreting case study results due to possible placebo effects on parental self-report measures, we consistently observed significant correlations in the treatment but not placebo group. Therefore, associations between periodic alpha and improved communication are likely to represent true underlying treatment effects rather than placebo effects. Nevertheless, RS-EEG may not be as sensitive to specific changes in language skills as targeted task-based measures. Further analyses will focus on behavioral associations with task-based data acquired during the clinical trial, including an auditory oddball task that has previously shown sensitivity to alpha activity (38).

Our EEG results may support studies suggesting that metformin normalizes translation of proteins involved in membrane excitability and synaptic cytoskeletal structure. Globally, this manifests as reduced cortical excitability, consistent with reduced gamma activity. Kornfeld-Sylla, et al. suggest that such altered excitability in the absence of FMRP may be due to altered corticothalamic feedback dynamics (39). Metformin, by normalizing protein translation, may shift corticothalamic activity, and, as a consequence, alpha power toward more typical values. Kornfeld-Sylla, et al. recently developed a mouse model (*FMR1*$^{-/y}$) that recapitulates the reduced alpha phenotype (39). This model may prove valuable for molecularly dissecting the mechanism of altered alpha power and downstream behavioral effects.

Changes in complexity index at lower scales, at higher scales, and all scales also showed treatment-specific effects. Complexity increased from pre- to post-treatment. As in gamma and alpha features, we observed a shift toward a more typical phenotype with metformin treatment, in this case an increase from pre- to post-treatment. We did not find associations between this change in CI and behavioral outcomes in the whole sample. However, CI showed unique effects in the non-mosaic sub-sample alone. CI high-scale change in the treatment group was associated with improvement on the Vineland-3 Daily Living Skills subdomain and decreased hyperactivity and inappropriate speech as reported on the ABC-C. These associations are somewhat different from our expectation since, Lemieux, et al., (21) found a link between CI and NVIQ in FXS participants. We cannot speak to a possible association between EEG markers and NVIQ in this case, as the Leiter-3 was only administered at baseline. Complexity is an important index of brain maturation and cognitive function. EEG signal complexity increases with age, with the trajectory of this increase differing across sensory processing regions (15, 18). Lower signal complexity is associated with atypical development in ASD more broadly, in addition to other neurodevelopmental disorders like ADHD and Tourette Syndrome (40, 41). However, complexity has only recently been considered as an important biomarker of FXS. Lemieux, et al. (15) found reduced complexity in RS-EEG for FXS vs. TD participants. We observe that non-mosaic participants not only exhibited more pronounced effects of metformin on CI but exhibited correlations between increased CI and adaptive behaviors not present in the full sample. Non-mosaic participants exhibit more significant and pervasive developmental delays than those with the possible protective effects of a mosaic phenotype (4). These results underscore the utility of CI particularly in the more pronounced effects of metformin in those participants likely to experience the greatest challenges.

This study was subject to several limitations. First, while we investigated effects of metformin on all participants vs. non-mosaic participants, we did not have sufficient participants with molecular mosaic to conduct independent analyses comparing non-mosaic vs. mosaic participants. We hypothesize that effects of metformin treatment are more pronounced in non-mosaic participants. However, this should be confirmed by future analyses directly comparing double-blind results in equal samples of participants with and without and molecular mosaic.

In a related concern, we also note the unbalanced makeup of the sample with regard to biological sex. FXS is both more common and more pronounced in males (1, 42), contributing to the historic problem of unbalanced samples in studies and clinical trials related to FXS. Our sample did not include enough female participants with valid EEG data to conduct stratified analyses. 100% of participants with molecular mosaic were male, which contributed to our inability to conduct stratified analyses on non-mosaic vs. mosaic participants. We included biological sex as a control variable in our models to mitigate its influence on our results. However, we cannot rule out its role in treatment response. Future studies should prioritize validating these results, as well as those from the full metformin trial, in more balanced samples whose makeup allows for separate analyses of male vs. female participants.

Finally, we note that most results obtained in the RCT (23) were observed only in participants aged 6–11 years, with additional effects observed only in participants aged 12 and up. We controlled for age in all models but did not conduct stratified analyses in younger vs. older participants due to the unbalanced age range in the EEG subsample – less than 30% of RS-EEG participants fell into the 6–11 age group. With a mean age of 17 in the whole sample, our results may reflect additional influences of brain maturation throughout puberty and adulthood, potentially accounting for inconsistencies between the larger RCT results and the EEG results.

The results reported here can serve as crucial evidence for hypothesis generation, identifying key RS-EEG markers as indicators of metformin's effects and possible treatment targets. Overall, future research should focus on replicating these results in larger samples allowing for stratified analyses by age, sex, and molecular status. This will require larger trials with more ambitious recruitment goals in younger age groups. The results of our analyses demonstrate that further trials are merited and should incorporate EEG as an outcome measure.

Recent research has suggested that EEG can provide valuable insight for clinical trials, identifying potential treatment targets and elucidating effects not discernable from behavioral results alone.

Whole EEG Subsample

EEG measures have previously been shown not only to correlate with development of cognitive and social function in children, but also to predict future development (14, 22). Combining EEG measures and clinical outcomes therefore builds a robust proof-of-concept and enables an early signal detection of efficacy, accelerating clinical solution development.

Here, we demonstrate for the first time the value of EEG in a large RCT in FXS. More precisely, we show that metformin affects RS-EEG measures associated with key elements of FXS, including cortical E/I dysregulation and global delays in neurodevelopment. We show a change toward a more typical EEG phenotype with metformin treatment. We further demonstrate change associated with treatment-specific improvement on adaptive behaviors like expressive communication, irritability, and daily living skills. Our results are consistent with recent research showing that EEG features like periodic gamma, periodic alpha, and complexity differ systematically in FXS vs. TD individuals. Improvements in adaptive behavior echo findings of the larger metformin RCT and previous smaller trials, linking them to changes in functional brain activity. RS-EEG results provide a foundation for future hypothesis generation and treatment evaluation, suggesting that metformin could be a valuable treatment option for FXS and illustrating the merit of future research into the relationship between metformin's clinical effects and underlying functional brain activity.

Declarations

Ethics approval and clinical trial registration

FXS participants were recruited via a multi-site, large-scale clinical study taking place at the CHU Sainte-Justine and the University of Alberta in Canada and the MIND Institute at the University of California, Davis, in the United States. The study protocol was approved by the ethics committees of all the three sites, and informed consent was obtained from all participants and parents/guardians of participants. The study was monitored by a DSMB at each site and registered at Clinicaltrials.gov (ID NCT03862950 for Canadian and ID NCT03479476 for U.S. sites).

Availability of data and materials

Data supporting the findings of this study are available from the corresponding authors upon reasonable request.

Competing interests

The authors have no conflict of interest to disclose.

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Figures

Whole EEG Subsample

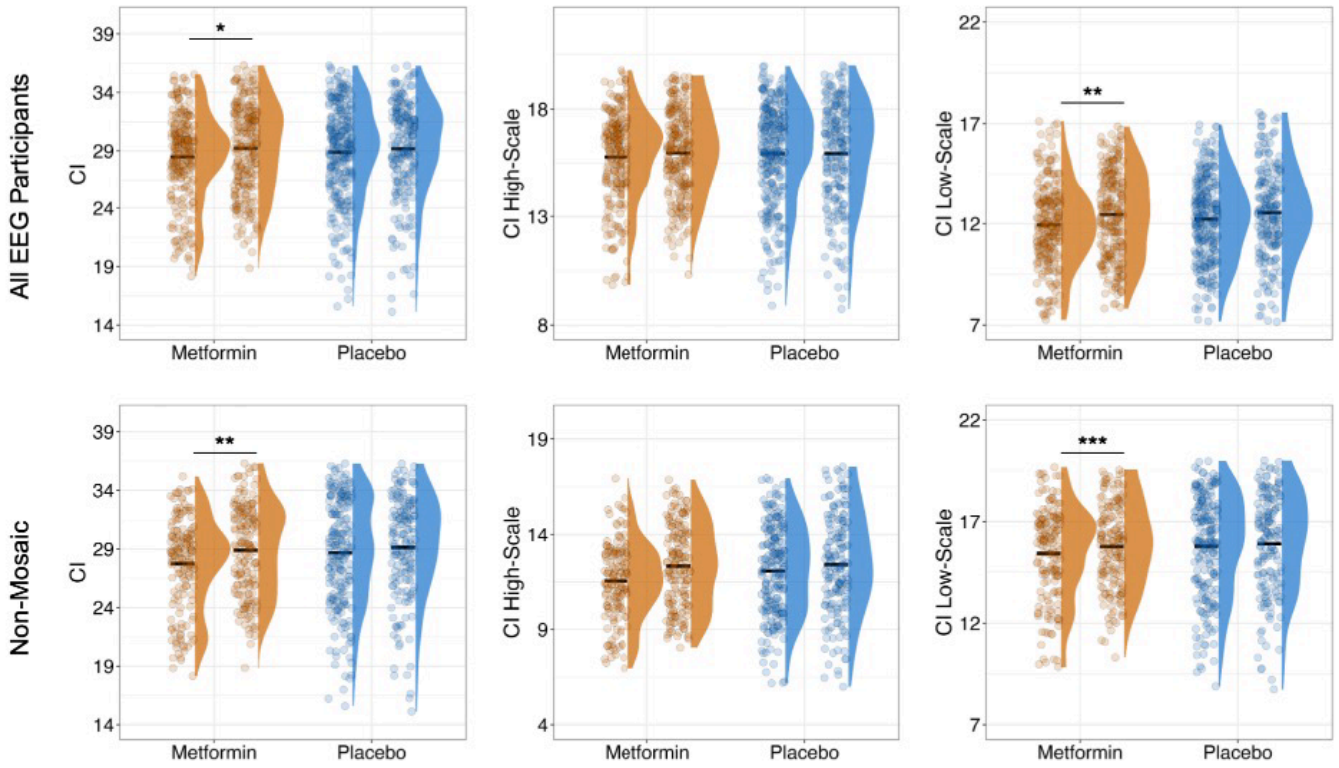


Figure 1

EEG feature values at pre-treatment and post-treatment for complexity features exhibiting a significant interaction between session and condition (metformin/placebo). First row shows results for entire pooled sample; second row shows results for non-mosaic only. First column denotes complexity in all scales, second column denotes complexity in high scales, third column denotes complexity in low scales. Within each treatment group, left distribution denotes T0, right distribution denotes T2. Increasing complexity from pre- to post-treatment indicates a change toward a more typical phenotype. Markers indicate significance of t-test results. * p<.05; ** p<.01; *** p<.005.

Whole EEG Subsample

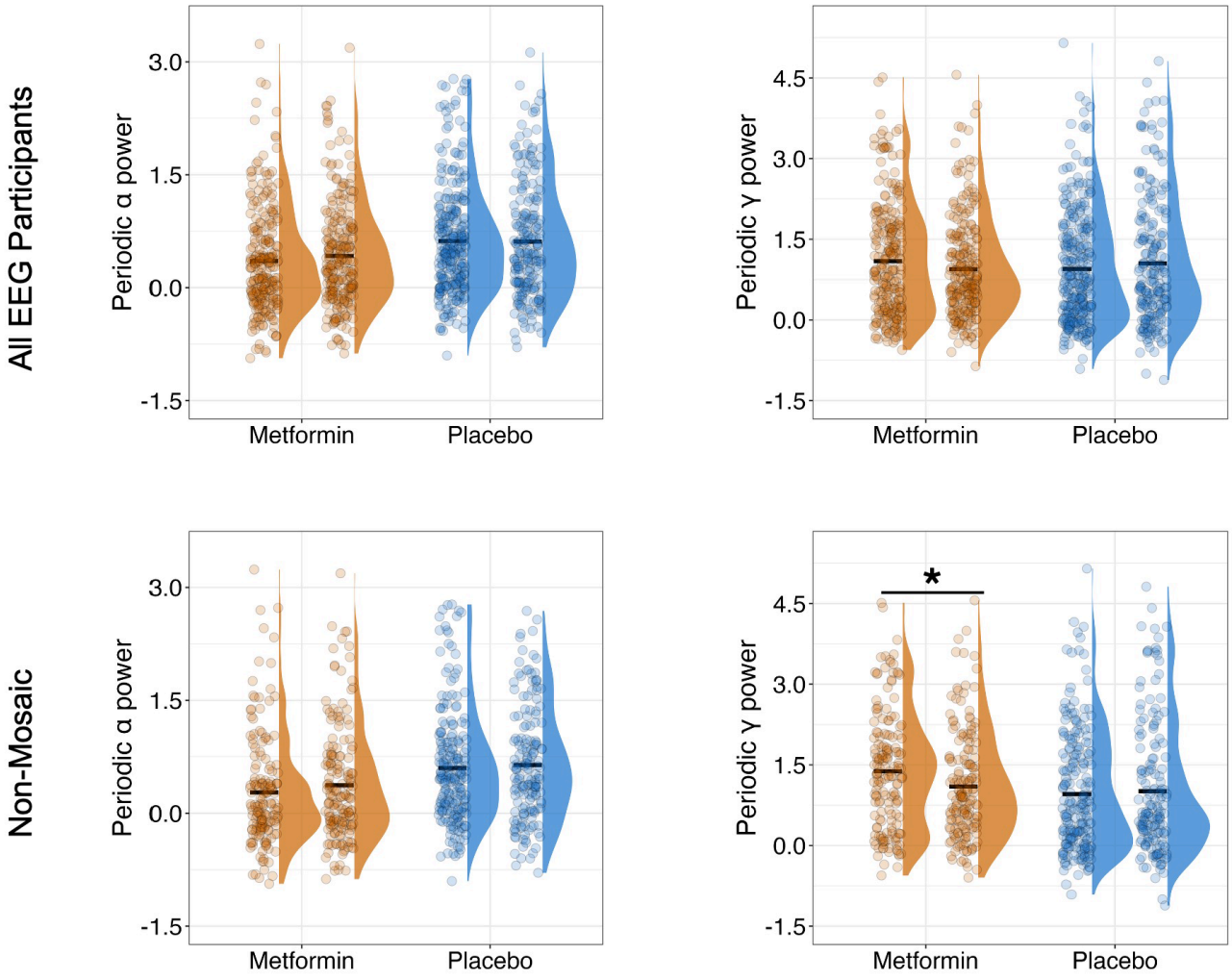


Figure 2

EEG feature values at pre-treatment and post-treatment for power features exhibiting a significant interaction between session and condition (metformin/placebo). First row shows results for entire pooled sample; second row shows results for non-mosaic only. First column denotes periodic alpha, second column denotes periodic gamma. Within each treatment group, left distribution denotes T0, right distribution denotes T2. Markers indicate significance of t-test results. * p<.05; ** p<.01. Increasing periodic alpha and decreasing periodic gamma are consistent with change toward a more typical phenotype.

Whole EEG Subsample

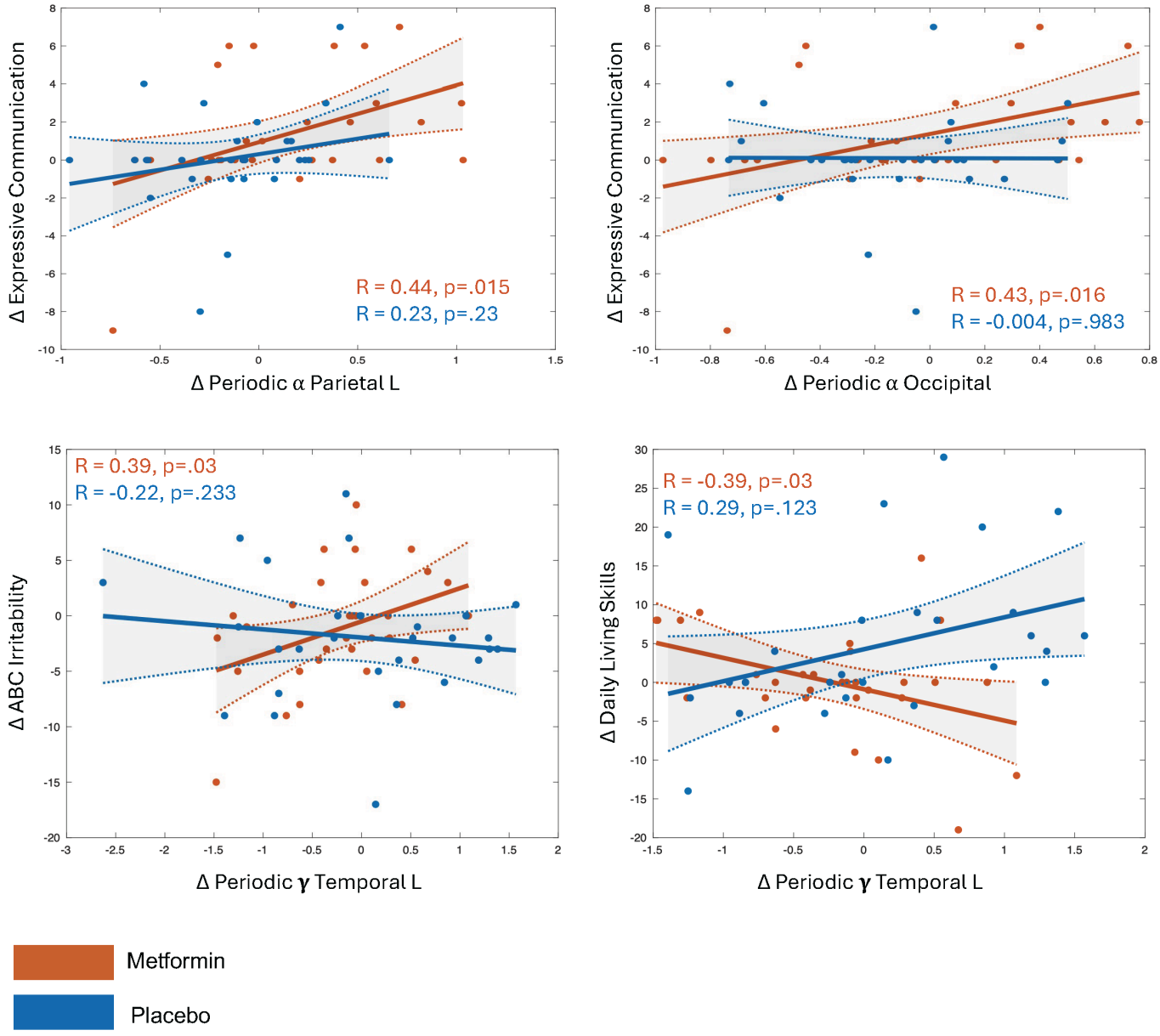


Figure 3

Significant relationships between change in EEG from pre- to post-treatment and change in behavioral measures in all EEG participants with complete data. Expressive Communication and Daily Living Skills are subdomains of Vineland-3; a positive change from pre- to post-treatment indicates improved adaptive behavior. For ABC measures, a negative change from pre- to post-treatment indicates fewer symptoms. Increased periodic alpha activity (positive change) from pre- to post-treatment indicates a move toward a more typical phenotype; decreased periodic gamma activity (negative change) indicates a move toward a more typical phenotype.

Whole EEG Subsample

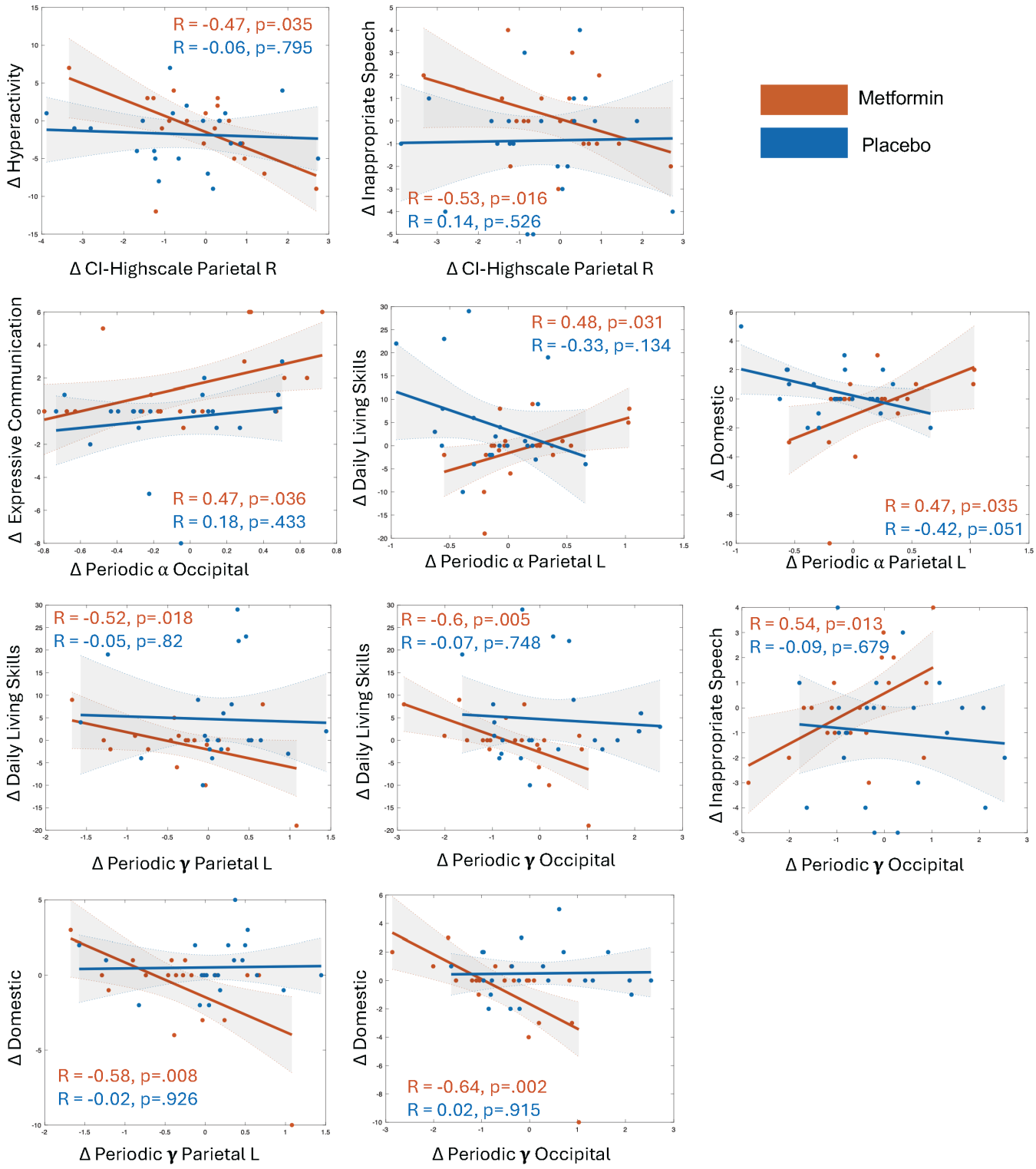


Figure 4

Significant relationships between change in EEG from pre- to post-treatment and change in behavioral measures in non-mosaic EEG participants with complete data. Expressive Communication, Daily Living Skills, and Domestic are subdomains of Vineland-3; a positive change from pre- to post-treatment indicates improved adaptive behavior. For ABC measures, a negative change from pre- to post-treatment indicates fewer symptoms. Increased periodic alpha activity (positive change) from pre- to post-treatment indicates a move toward a more typical phenotype;

decreased periodic gamma activity (negative change) indicates a move toward a more typical phenotype; increased signal complexity (CI) indicates a move toward a more typical phenotype.

Supplementary Files

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