# Neural Oscillatory Abnormalities During Gaze Processing in Schizophrenia: Evidence of Reduced Theta Phase Consistency and Inter-areal Theta-Gamma Coupling

## *Supplemental Information*

### Participants

All participants met the following criteria: aged 18-60, visual acuity at/above 20/30 according to a Snellen chart, no substance abuse/dependence in the past year, and no history of medical condition with neurological sequelae. Additional HC exclusion criteria were: history of psychiatric disorder, substance abuse in the past five years, and psychotic/bipolar disorders among first-degree relatives.

### Procedure

***Experimental task.*** The gaze discrimination task was programmed and presented using E-Prime software (Psychology Software Tools). Participants were presented with black-and-white images of faces and asked to indicate whether the person was looking at them or not. Face stimuli varied by gaze direction (direct or averted), emotion (neutral or fearful), and head orientation (forward or deviated). The task consisted of 512 total trials (64 trials x 8 conditions) presented in pseudo-random order across four blocks.

***EEG data acquisition and preprocessing***. EEG data were collected using a 32-channel lycra cap (EasyCap, BrainAnalyzer) with Ag/AgCl electrodes using the modified 10-20 system. We used a BrainAmp MR amplifier (Brain Products Gmbh) to record EEG with a low-pass filter of 250 Hz and high-pass filter of 0.016 Hz. Vertical electrooculogram was measured with an electrode placed below the right eye referenced to the Fp1 site. Electrode impedances were kept below 5 kΩ. EEG was referenced to FCz during recording. Data preprocessing began with importing raw EEG data into EEGLAB and downsampling from 5,000 to 500 Hz. Continuous data were filtered for line noise using Cleanline and then filtered with a high-pass (0.1 Hz) and low-pass filter (100 Hz). Next, visual inspection and manual rejection of non-stereotypical artifacts were performed on continuous data 250 ms pre-stimulus and 750 ms post-stimulus, as this was the data that were used for subsequent independent components analysis (ICA) and the time

window of interest for subsequent EEG measures. Then the continuous data was segmented in two ways: 1) into epochs of -250–750 ms relative to stimulus onset for ICA to remove non-neural artifacts, and 2) into epochs of -1,500–2,300 ms for subsequent time-frequency decomposition. ICA was then performed using the -250–750 ms epochs (time window containing stereotypical artifacts (e.g., ocular, muscular) in the data); components representing non-neural activities were identified. Then, these non-neural ICA components were removed from the -1,500–2,300 ms epochs, followed by re-referencing to common average, baseline adjustment (-250–0 ms), and automatic artifact rejection of ±100 μV. Finally, visual inspection and manual rejection were performed again to remove non-neural artifacts missed by ICA or automatic rejection.

*CFC*. KLMI was calculated with a ~0.5 Hz interval and included 10 frequencies for theta and 42 frequencies for gamma. In addition, KLMI values were multiplied by 10,000 for ease of interpretation.

**Statistical Analyses**

*ERSP and ITPC.* The time window of theta activity initially focused on ~0-400 ms, because increased post-stimulus theta was observed within that range at all sites. However, Fz showed a pattern of increased post-stimulus theta for a longer duration (~0-750 ms). We repeated the ANOVA and ANCOVA analyses using theta from this longer time window, and the results were almost identical as the results using a shorter time window for theta (Tables S3 and S4). The only exception was that, for the mixed ANOVA, group difference at P7 no longer reached statistical significance ($p$=0.053).

*Effect of condition on ERSP/ITPC group difference*. To examine the effect of different factors of the face (gaze direction, face emotion, or head orientation) on ERSP and ITPC during gaze processing, we used mixed ANOVAs. We focused this analysis on theta activity only. Three separate ANOVAs were conducted for each DV (ERSP, ITPC). Each ANOVA included scalp site, along with each of the three face factors, as within-subject factors, and group as a between-subjects factor.

**Table S1.** Inter-correlations (Spearman rho) between theta power (ERSP), theta phase consistency (ITPC), and theta-gamma cross-frequency coupling (KLMI) across all participants (*N*=62)

|  | P7 theta ERSP | P8 theta ERSP | Fz theta ERSP | P7 theta ITPC | P8 theta ITPC | Fz theta ITPC | P7→Fz KLMI | P8→Fz KLMI | Fz→P7 KLMI |
|---|---|---|---|---|---|---|---|---|---|
| P8 theta ERSP | 0.78*** | | | | | | | | |
| Fz theta ERSP | 0.87*** | 0.86*** | | | | | | | |
| P7 theta ITPC | 0.80*** | 0.48*** | 0.66*** | | | | | | |
| P8 theta ITPC | 0.62*** | 0.82*** | 0.75*** | 0.60*** | | | | | |
| Fz theta ITPC | 0.70*** | 0.65*** | 0.80*** | 0.79*** | 0.84*** | | | | |
| P7→Fz KLMI | 0.67*** | 0.47** | 0.59*** | 0.73*** | 0.56*** | 0.65** | | | |
| P8→Fz KLMI | 0.57*** | 0.62*** | 0.64*** | 0.55*** | 0.73*** | 0.69*** | 0.88*** | | |
| Fz→P7 KLMI | 0.65*** | 0.55*** | 0.66*** | 0.73*** | 0.71*** | 0.74*** | 0.83*** | 0.80*** | |
| Fz→P8 KLMI | 0.48*** | 0.57*** | 0.59*** | 0.48*** | 0.72*** | 0.64** | 0.71*** | 0.78*** | 0.82*** |

Note. ERSP = event-related spectral perturbation. ITPC = inter-trial phase consistency. KLMI = Kullback-Leibler Modulation Index. **$p<0.01$. ***$p<0.001$.

**Table S2:** Mixed ANOVA for theta ERSP and ITPC by gaze direction, face emotion, or head orientation

| | | A) Theta ERSP | | | | B) Theta ITPC | | | |
|---|---|---|---|---|---|---|---|---|---|
| **GAZE DIRECTION** | | | | | | | | | |
| | df | F | p | $\eta_p^2$ | Post-hoc | F | p | $\eta_p^2$ | Post-hoc |
| Group (HC, SZ) | 1, 60 | 18.39 | <0.001 | 0.20 | HC>SZ | 18.62 | <0.001 | 0.18 | HC>SZ |
| Site (P7, P8, Fz) | 2, 300 | 24.31 | <0.001 | 0.02 | P8>P7/Fz | 120.02 | <0.001 | 0.12 | P8>P7>Fz |
| Gaze (Averted, Direct) | 1, 300 | 0.05 | 0.829 | 0.00 | -- | 0.01 | 0.926 | 0.00 | -- |
| Group x Site | 2, 300 | 4.71 | 0.010 | 0.00 | HC > SZ* | 0.18 | 0.839 | 0.00 | -- |
| Group x Gaze | 1, 300 | 0.03 | 0.859 | 0.00 | -- | 0.05 | 0.822 | 0.00 | -- |
| Site x Gaze | 2, 300 | 0.18 | 0.837 | 0.00 | -- | 0.12 | 0.891 | 0.00 | -- |
| Group x Site x Gaze | 2, 300 | 0.28 | 0.757 | 0.00 | -- | 0.01 | 0.989 | 0.00 | -- |
| | | | | | | | | | |
| **FACIAL EMOTION** | | | | | | | | | |
| | df | F | p | $\eta_p^2$ | Post-hoc | F | p | $\eta_p^2$ | Post-hoc |
| Group (HC, SZ) | 1, 60 | 18.38 | <0.001 | 0.20 | HC>SZ | 18.49 | <0.001 | 0.17 | HC>SZ |
| Site (P7, P8, Fz) | 2, 300 | 22.80 | <0.001 | 0.02 | P8>P7/Fz | 116.58 | <0.001 | 0.12 | P8>P7>Fz |
| Emotion (Fearful, Neutral) | 1, 300 | 0.01 | 0.911 | 0.00 | -- | 0.08 | 0.774 | 0.00 | -- |
| Group x Site | 2, 300 | 4.53 | 0.012 | 0.00 | HC > SZ* | 0.19 | 0.831 | 0.00 | -- |
| Group x Emotion | 1, 300 | 0.52 | 0.472 | 0.00 | -- | 0.01 | 0.942 | 0.00 | -- |
| Site x Emotion | 2, 300 | 0.08 | 0.923 | 0.00 | -- | 0.04 | 0.963 | 0.00 | -- |
| Group x Site x Emotion | 2, 300 | 0.21 | 0.811 | 0.00 | -- | 0.11 | 0.896 | 0.00 | -- |
| | | | | | | | | | |
| **HEAD ORIENTATION** | | | | | | | | | |
| | df | F | p | $\eta_p^2$ | Post-hoc | F | p | $\eta_p^2$ | Post-hoc |
| Group (HC, SZ) | 1, 60 | 18.23 | <0.001 | 0.20 | HC>SZ | 18.69 | <0.001 | 0.17 | HC>SZ |
| Site (P7, P8, Fz) | 2, 300 | 23.18 | <0.001 | 0.02 | P8>P7/Fz | 114.03 | <0.001 | 0.12 | P8>P7>Fz |
| Head (Deviated, Forward) | 1, 300 | 6.12 | 0.014 | 0.00 | D>F | 5.80 | 0.017 | 0.00 | D>F |
| Group x Site | 2, 300 | 4.57 | 0.011 | 0.00 | HC > SZ* | 0.15 | 0.860 | 0.00 | -- |
| Group x Head | 1, 300 | 2.23 | 0.136 | 0.00 | -- | 1.01 | 0.316 | 0.00 | -- |
| Site x Head | 2, 300 | 0.16 | 0.849 | 0.00 | -- | 0.39 | 0.680 | 0.00 | -- |
| Group x Site x Head | 2, 300 | 0.06 | 0.946 | 0.00 | -- | 0.23 | 0.795 | 0.00 | -- |

Note. Since group difference in the effects of the face factors (gaze direction, face emotion, or head orientation) were the effects of interest here, the results representing the Group x Condition interaction are highlighted (shaded).

*There was a significant Group x Site interaction, where HC showed a pattern of greater theta power at P8 relative to P7/Fz but this pattern was weaker in SZ than HC.

ERSP = event-related spectral perturbation. ITPC = inter-trial phase consistency. HC = healthy control. SZ = schizophrenia. False Discovery Rate (FDR) correction was applied to each ANOVA.

**Table S3:** Mixed ANOVA for theta ERSP and ITPC measured with a longer time window (2-742 ms post-stimulus)

**A) ERSP**

| | df | $F$ | $p$ | $\eta_p^2$ | Post-hoc |
|---|---|---|---|---|---|
| Group (HC, SZ) | 1, 60 | 12.61 | 0.001 | 0.15 | HC>SZ |
| Site (P7, P8, Fz) | 2, 120 | 22.60 | <0.001 | 0.03 | Fz>P7/P8 |
| Group x Site | 2, 120 | 1.61 | 0.204 | 0.00 | -- |

**B) ITPC**

| | df | $F$ | $p$ | $\eta_p^2$ | Post-hoc |
|---|---|---|---|---|---|
| Group (HC, SZ) | 1, 60 | 19.35 | <0.001 | 0.19 | HC>SZ |
| Site (P7, P8, Fz) | 2, 120 | 52.36 | <0.001 | 0.11 | P8>P7>Fz |
| Group x Site | 2, 120 | 0.03 | 0.975 | 0.00 | -- |

Note. Post-hoc tests were conducted using Tukey HSD. HC had greater theta power or inter-trial phase consistency than SZ at all sites except P7 ($p$=0.053). ERSP = event-related spectral perturbation. ITPC = inter-trial phase consistency. HC = healthy control. SZ = schizophrenia.
False Discovery Rate (FDR) correction ($p$<0.05) was applied to each ANOVA.

**Table S4:** ANCOVA for theta ERSP measured with a longer time window (2-742 ms post-stimulus) for each site

|  | df | P7 THETA ERSP | | | P8 THETA ERSP | | | FZ THETA ERSP | | |
|---|---|---|---|---|---|---|---|---|---|---|
|  | | $F$ | $p$ | $\eta_p^2$ | $F$ | $p$ | $\eta_p^2$ | $F$ | $p$ | $\eta_p^2$ |
| Covariate | | | | | | | | | | |
| Site's Theta ITPC[a] | 1, 59 | 34.73 | <0.001 | 0.37 | 41.88 | <0.001 | 0.41 | 53.26 | <0.001 | 0.46 |
| Fixed Factor | | | | | | | | | | |
| Group (HC, SZ) | 1, 59 | 0.88 | 0.351 | 0.01 | 1.36 | 0.249 | 0.01 | 2.45 | 0.123 | 0.02 |

Note. [a] For each model, theta ITPC site is the same as theta ERSP site.
ERSP = event-related spectral perturbation. ITPC = inter-trial phase-consistency. HC = healthy control. SZ = schizophrenia.
False Discovery Rate (FDR) correction ($p<0.05$) was applied to each ANCOVA.
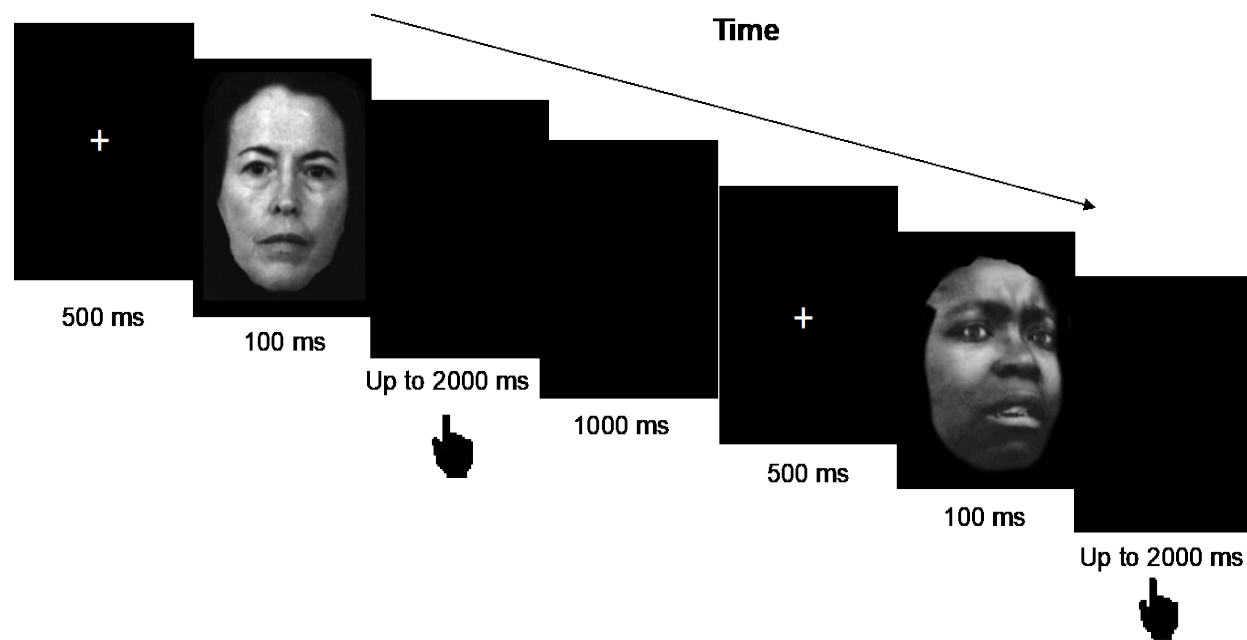
**Figure S1.** Gaze discrimination task. Participants pressed a button to indicate whether the face was "looking at" them (Yes/No). Faces varied in gaze (direct or averted), facial emotion (neutral or fearful), and head orientation (forward or deviated with a rotation of 30° left/right).
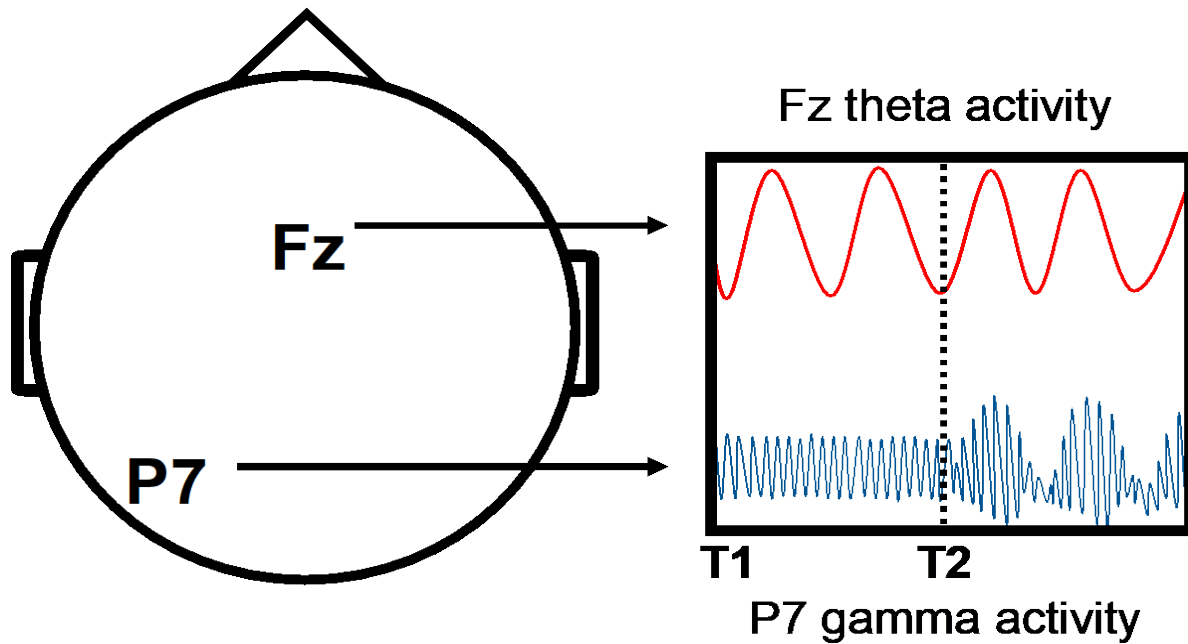
**Figure S2.** Illustration of a hypothetical inter-areal cross-frequency coupling (CFC) between theta phase and gamma amplitude. Theta activity at Fz and gamma activity at P7 are independent between time points T1 and T2. Starting from T2 and through T3, gamma amplitude at P7 becomes coupled with (modulated by) theta phase at Fz. This is one example of CFC site-pairing indexing feedback connectivity from Fz to P7. Other site-pairings indexing feedforward or feedback connectivity are not shown in this illustration.
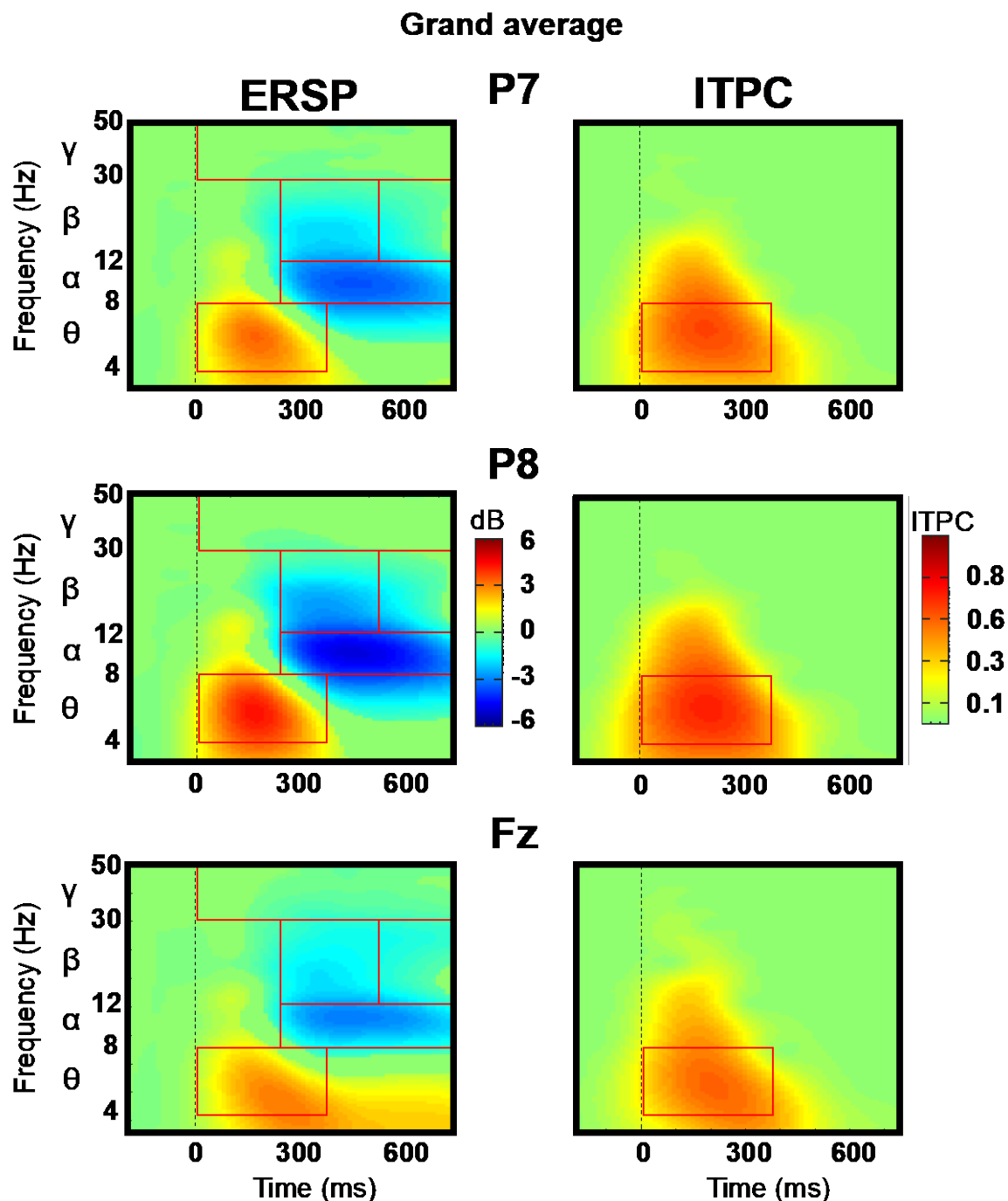
**Figure S3.** ERSP (left) and ITPC (right) values across all participants. Values not significantly different from zero (FDR-corrected *p* > 0.01, based on one-sample *t*-tests using 10,000 permutations) appear green. Boxes with red outline indicate the time-frequency windows for extraction of ERSP and ITPC values for subsequent ANOVA analyses to test for group differences. Note that the time-frequency window for theta-band ITPC (right) was set to match that of theta ERSP. Time-frequency window for theta = 4-8 Hz across 2–392 ms (24 frequency points x 30 time points); alpha = 8-12 Hz across 244–742 ms (14 frequency points x 38 time points); beta = 12-30 Hz across 244–554 ms (33 frequency points x 24 time points); and gamma = 30-50 Hz across 2–742 ms (18 frequency points x 56 time points).
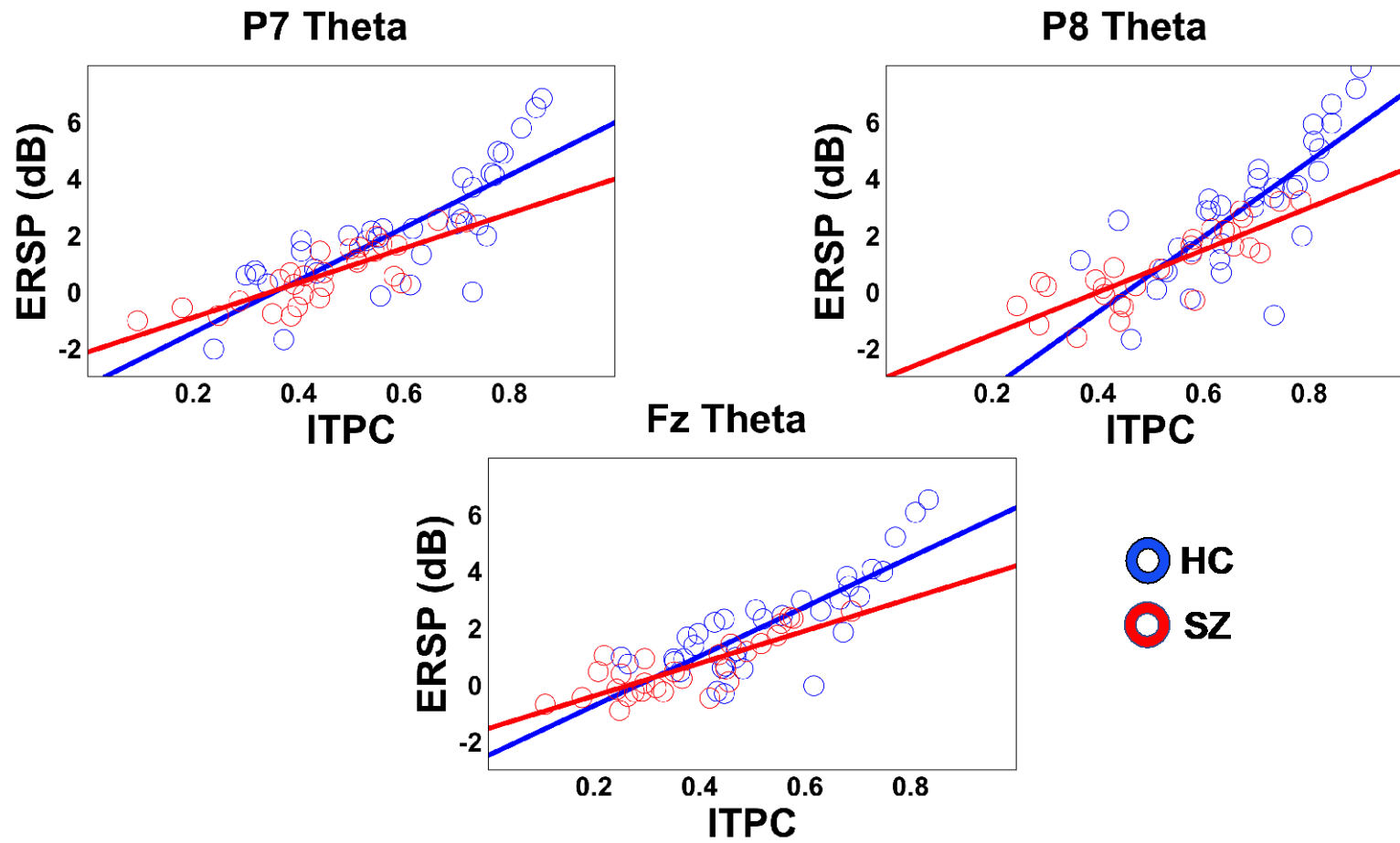
**Figure S4.** Scatterplots of the relationship between theta ITPC and theta ERSP at each site.