Effect of Demographics on EEG/ERP Biomarkers in Patients with Schizophrenia and Healthy Volunteers

EEG/ERP Biomarker Qualification Consortium
www.erpbiomarkers.org

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Introduction

Resting-state electroencephalography (EEG) and event-related potentials (ERPs) are increasingly recognized as sensitive, translatable biomarkers of central nervous system (CNS) dysfunction.

Previous studies have found varying effects of demographics on the electrophysiological activity in the brain during rest and in association with different types of cognitive, sensory, and motor tasks (e.g. see Ramos-Loyo et al., 2022; Yener et al., 2024; Zappasodi et al., 2015).

We analyzed data pooled across four pharma-sponsored CNS clinical trials involving healthy volunteers (HV) and patients with schizophrenia (SZ) to examine the effect of demographics on EEG/ERP biomarkers.

Specifically, we hypothesized that a subset of EEG/ERP measures will vary as a function of age and gender in both HV and SZ participants.

Materials & Methods

The pooled dataset consisted of EEG/ERP data from baseline and placebo arm sessions of 301 participants (164 HV and 137 SZ) recruited as part of four early-phase clinical trials (two interventional and two observational). Each clinical trial used the COGNISION® system (Neuronetrix Solutions LLC, dba Cognision) to collect data using three midline electrodes (Fz, Cz, Pz) and a standardized battery of validated EEG/ERP paradigms (**Figure 1**), including resting-state EEG (eyes closed; n = 301) and three cognitive / sensory ERP tasks (n = 240): auditory active oddball (P300); auditory passive oddball / duration-deviant mismatch negativity (MMN), and 40 Hz auditory steady-state response (ASSR). **Table 1** shows participant demographics. All data were processed using a validated, automated analysis pipeline. Statistical analysis was conducted using t-tests to examine the effect of gender and Pearson correlation coefficient to examine the effect of age on 25 EEG/ERP measures (biomarkers) (**Table 2**), with effect sizes calculated as Cohen's *d* and R^2, respectively. Data was visualized using power spectral density (PSD) plots for resting-state EEG; grand average ERP waveforms for active / passive oddball tasks; time-frequency plots of evoked power and intertrial coherence for ASSR; and age vs. EEG/ERP measure scatterplots. Outliers were removed using a modified z-score of 3.5. Data from HV and SZ participants were analyzed separately.

Table 1. Participant Characteristics

Demographic	HV (n = 164)	SZ (n = 137)
Age (years)	M = 36.4 SD = 9.8 Range = 20-56	M = 39.2 SD = 8.7 Range = 20-56
Gender (% male / female)	54.9% / 45.1%	69.3% / 30.7%

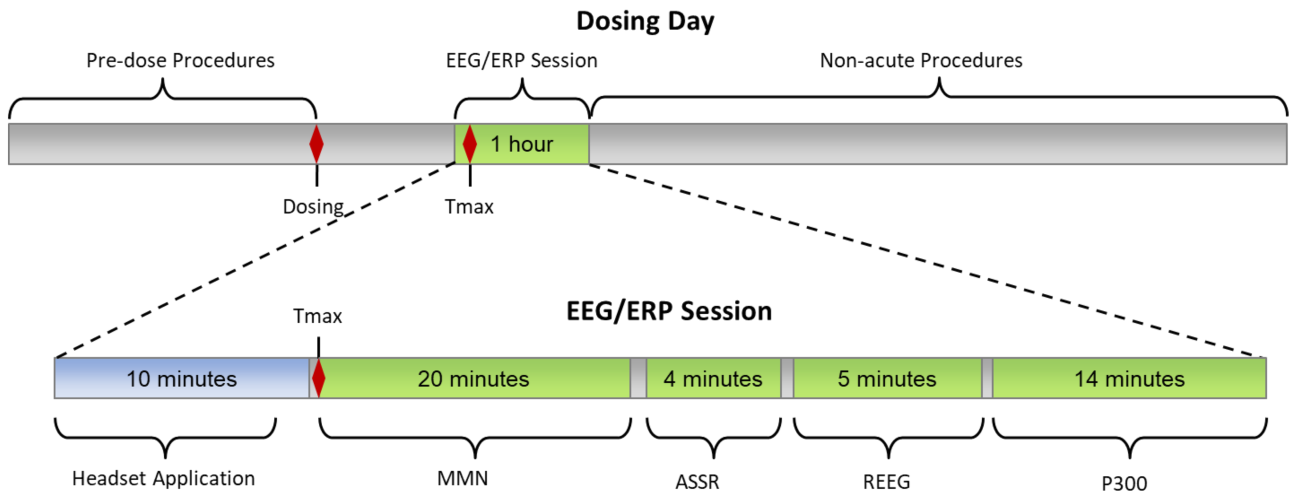

Fig. 1: Standardized EEG/ERP testing battery.

EEG/ERP Measures (Biomarkers)

Table 2. EEG/ERP Paradigms & Measures (Biomarkers)

Resting-state EEG (eyes closed)[a]	Theta / Beta Ratio [AV]
Delta Power (1.5-6.0 Hz) [Abs-AV]	Aperiodic Slope & Offset [AV]
Theta Power (6.0-8.5 Hz) [Abs-AV]	**Active Auditory Oddball (P300)[b]**
Alpha 1 Power (8.5-10.5 Hz) [Abs-AV]	P3b (P300) Amplitude & Latency [Pz]
Alpha 2 Power (10.5-12.5 Hz) [Abs-AV]	**Passive Oddball / Duration-Deviant MMN[c]**
Beta 1 Power (12.5-18.5 Hz) [Abs-AV]	N100 Amplitude & Latency [Cz]
Beta 2 Power (18.5-21.0 Hz) [Abs-AV]	MMN Amplitude & Latency [Fz]
Beta 3 Power (21.0-30.0 Hz) [Abs-AV]	P3a Amplitude & Latency [Cz]
Gamma Power (30.0-40.0 Hz) [Abs-AV]	**Auditory Steady-State Response (ASSR)[d]**
Total Power (1.5-30.0 Hz) [Abs-AV]	Evoked Power [Fz]
Dominant / Peak Alpha Frequency (6.0-12.5 Hz) [Pz]	Total Power [Fz]
Alpha Slow-Wave Index (Alpha / [Delta + Theta] Ratio)	Intertrial Coherence (1-500 ms) [Fz]

(NOTE: Abs = absolute power; AV = average across Fz, Cz, Pz electrodes)

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a. Jobert M, et al, Guidelines for the recording and evaluation of pharmaco-EEG data in man: the International Pharmaco-EEG Society (IPEG). Neuropsychobiology. 2012;66(4):201-220.
b. Polich J, et al, Neuropsychology and neuropharmacology of P3a and P3b. International Journal of Psychophysiology. 2006;60(2):172-185.
c. Light G, et al, Characterization of neurophysiologic and neurocognitive biomarkers for use in genomic and clinical outcome studies of schizophrenia. PloS one. 2012;7(7):e39434.
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Results

Table 3. Statistics for HV – GENDER F/M (t-test)		AGE (Pearson correlation)
Delta Power	**124.0 (50.8) vs. 95.4 (32.3); d = 0.68*** **	r = -0.034, R^2 = 0.001
Theta Power	**61.5 (38.9) vs. 36.4 (19.3); d = 0.83*** **	r = 0.006, R^2 = 0.000
Alpha 1 Power	**112.1 (107.1) vs. 72.3 (64.9); d = 0.46** **	r = 0.033, R^2 = 0.001
Alpha 2 Power	**60.5 (58.8) vs. 38.1 (34.7); d = 0.47** **	r = -0.054, R^2 = 0.003
Beta 1 Power	**43.5 (22.8) vs. 29.6 (14.3); d = 0.75*** **	r = -0.105, R^2 = 0.011
Beta 2 Power	**12.1 (6.15) vs. 9.88 (4.96); d = 0.40* **	r = -0.081, R^2 = 0.007
Beta 3 Power	**20.1 (9.60) vs. 16.8 (8.45); d = 0.36* **	r = 0.118, R^2 = 0.014
Gamma Power	7.85 (4.00) vs. 8.42 (5.14); d = 0.12	r = 0.030, R^2 = 0.001
Total Power (EEG)	**484.0 (295.6) vs. 330.9 (152.8); d = 0.67*** **	r = -0.041, R^2 = 0.002
Dominant / PAF	**9.56 (1.34) vs. 9.98 (0.88); d = -0.37* **	r = -0.055, R^2 = 0.003
Alpha SW Index	**1.01 (0.80) vs. 0.77 (0.52); d = 0.36* **	r = -0.032, R^2 = 0.001
Theta / Beta Ratio	1.18 (0.60) vs. 1.03 (0.50); d = 0.28	r = 0.054, R^2 = 0.003
Aperiodic Slope	2.86 (0.12) vs. 2.85 (0.12); d = 0.11	**r = -0.197, R^2 = 0.039* **
Aperiodic Offset	2.42 (0.26) vs. 2.39 (0.27); d = 0.10	r = -0.129, R^2 = 0.017
P3b Amplitude	**9.62 (4.70) vs. 7.06 (2.75); d = 0.70** **	r = -0.018, R^2 = 0.000
P3b Latency	307.0 (46.5) vs. 319.0 (42.9); d = -0.27	r = -0.036, R^2 = 0.001
N100 Amplitude	-1.54 (1.45) vs. -1.69 (1.01); d = -0.12	r = 0.056, R^2 = 0.003
N100 Latency	93.7 (16.5) vs. 96.5 (15.7); d = -0.17	r = -0.064, R^2 = 0.004
MMN Amplitude	-5.32 (1.84) vs. -4.66 (2.28); d = 0.31	r = 0.119, R^2 = 0.014
MMN Latency	191.0 (36.0) vs. 189.1 (33.0); d = 0.06	r = -0.088, R^2 = 0.008
P3a Amplitude	**5.58 (4.10) vs. 3.69 (1.99); d = 0.62** **	**r = -0.238, R^2 = 0.057* **
P3a Latency	292.9 (32.1) vs. 297.6 (34.6); d = -0.14	r = 0.115, R^2 = 0.013
Evoked Power (ASSR)	**0.19 (0.14) vs. 0.14 (0.10); d = 0.42* **	r = 0.038, R^2 = 0.001
Total Power (ASSR)	0.68 (0.36) vs. 0.66 (0.43); d = 0.06	r = 0.133, R^2 = 0.018
Intertrial Coherence	0.45 (0.15) vs. 0.42 (0.15); d = 0.24	r = -0.176, R^2 = 0.031

Table 4. Statistics for SZ – GENDER F/M (t-test)		AGE (Pearson correlation)
Delta Power	**156.3 (103.1) vs. 103.9 (47.5); d = 0.75*** **	r = 0.092, R^2 = 0.008
Theta Power	**66.1 (54.3) vs. 45.0 (30.8); d = 0.53** **	r = -0.121, R^2 = 0.015
Alpha 1 Power	94.8 (58.1) vs. 80.9 (69.1); d = 0.21	r = 0.068, R^2 = 0.005
Alpha 2 Power	**46.6 (42.9) vs. 30.3 (23.4); d = 0.53** **	r = 0.078, R^2 = 0.006
Beta 1 Power	37.0 (15.1) vs. 33.3 (20.2); d = 0.19	r = -0.010, R^2 = 0.000
Beta 2 Power	9.94 (4.28) vs. 8.53 (4.67); d = 0.31	r = -0.007, R^2 = 0.000
Beta 3 Power	21.6 (12.5) vs. 18.7 (10.8); d = 0.25	r = -0.065, R^2 = 0.004
Gamma Power	**13.2 (12.7) vs. 9.15 (6.14); d = 0.46* **	r = 0.094, R^2 = 0.009
Total Power (EEG)	**477.6 (236.7) vs. 379.0 (225.8); d = 0.43* **	r = -0.028, R^2 = 0.001
Dominant / PAF	9.48 (1.19) vs. 9.64 (1.10); d = -0.14	r = 0.070, R^2 = 0.005
Alpha SW Index	0.79 (0.47) vs. 0.74 (0.47); d = 0.12	r = 0.057, R^2 = 0.003
Theta / Beta Ratio	1.34 (0.79) vs. 1.19 (0.71); d = 0.22	r = -0.104, R^2 = 0.011
Aperiodic Slope	**2.94 (0.15) vs. 2.84 (0.15); d = 0.60** **	**r = 0.211, R^2 = 0.045* **
Aperiodic Offset	**2.57 (0.35) vs. 2.36 (0.31); d = 0.67*** **	r = 0.168, R^2 = 0.028
P3b Amplitude	**7.00 (3.71) vs. 5.63 (2.68); d = 0.45* **	r = -0.007, R^2 = 0.000
P3b Latency	321.0 (45.7) vs. 312.1 (42.5); d = 0.20	r = 0.159, R^2 = 0.025
N100 Amplitude	**-1.08 (1.31) vs. -1.87 (1.33); d = -0.60** **	r = -0.033, R^2 = 0.001
N100 Latency	97.2 (18.7) vs. 95.6 (16.7); d = 0.10	r = -0.046, R^2 = 0.002
MMN Amplitude	-4.15 (1.47) vs. -4.21 (1.96); d = -0.03	r = -0.018, R^2 = 0.000
MMN Latency	183.8 (31.8) vs. 177.0 (36.3); d = 0.19	r = -0.055, R^2 = 0.003
P3a Amplitude	3.99 (2.50) vs. 3.41 (2.02); d = 0.27	**r = -0.173, R^2 = 0.030* **
P3a Latency	296.1 (35.8) vs. 284.1 (35.0); d = 0.34	r = 0.061, R^2 = 0.004
Evoked Power (ASSR)	0.15 (0.16) vs. 0.13 (0.08); d = 0.20	r = 0.109, R^2 = 0.012
Total Power (ASSR)	1.10 (1.06) vs. 0.95 (1.02); d = 0.15	r = 0.028, R^2 = 0.001
Intertrial Coherence	0.34 (0.15) vs. 0.38 (0.15); d = 0.30	r = -0.027, R^2 = 0.001

Mean (SD) for Females vs. Males; Cohen's *d*, Pearson *r*, R^2 values shown; * P < 0.05, ** P < 0.01, *** P < 0.001

Effect of Age

Healthy | Schizophrenia

Fig. 2: EEG Aperiodic Slope

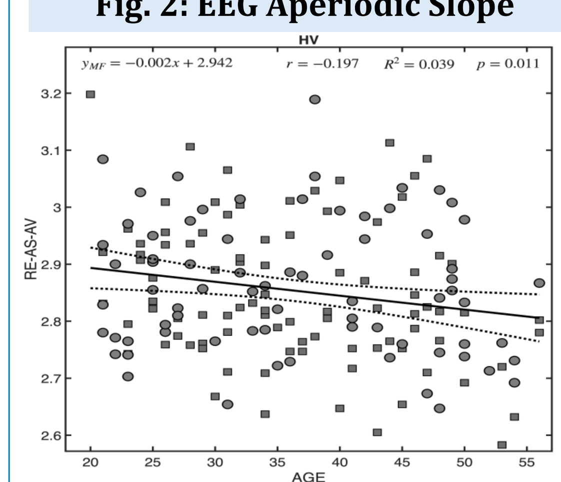


Fig. 3: P3a Amplitude

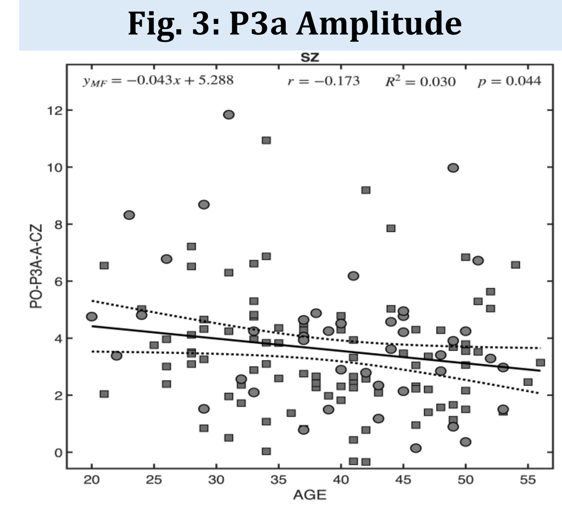


Fig. 4: EEG Aperiodic Offset

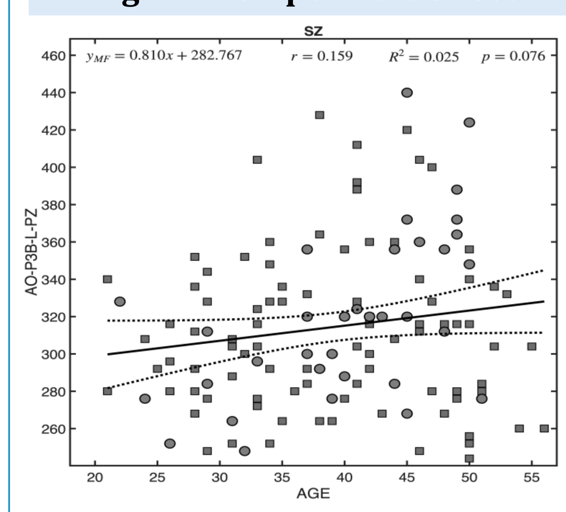


Fig. 5: P3b Latency

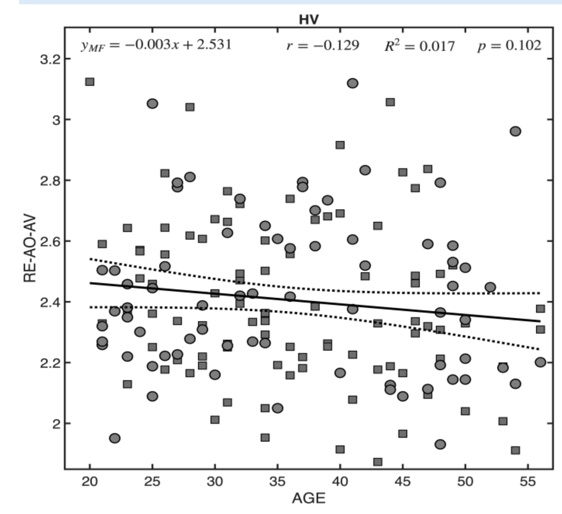


Fig. 2-5: Age Scatterplots

Pearson correlation analysis showed a statistically significant effect of AGE on only a few EEG/ERP measures (2 for HV and 2 for SZ out of 25) (**Tables 3 and 4**):

- 1 for HV and 1 for SZ out of 14 resting-state EEG measures
- 1 for HV and 1 for SZ out of 11 ERP measures

Associations were small in effect size, not exceeding R^2 = 0.03 to 0.06 (linear fit; see **Figures 2-5** for examples).

Effect of Gender

Healthy | Schizophrenia

Fig. 6: Active Oddball (P300)

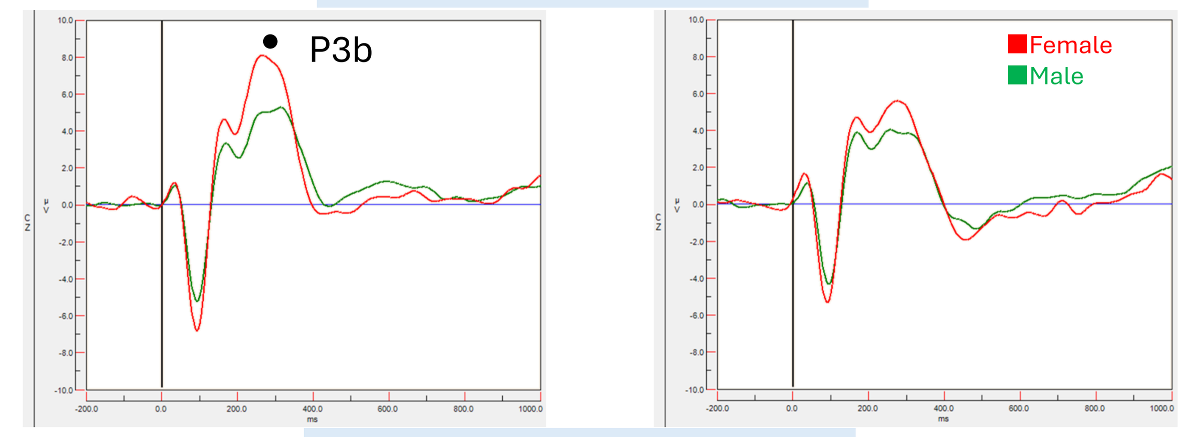


Fig. 7: Passive Oddball (MMN)

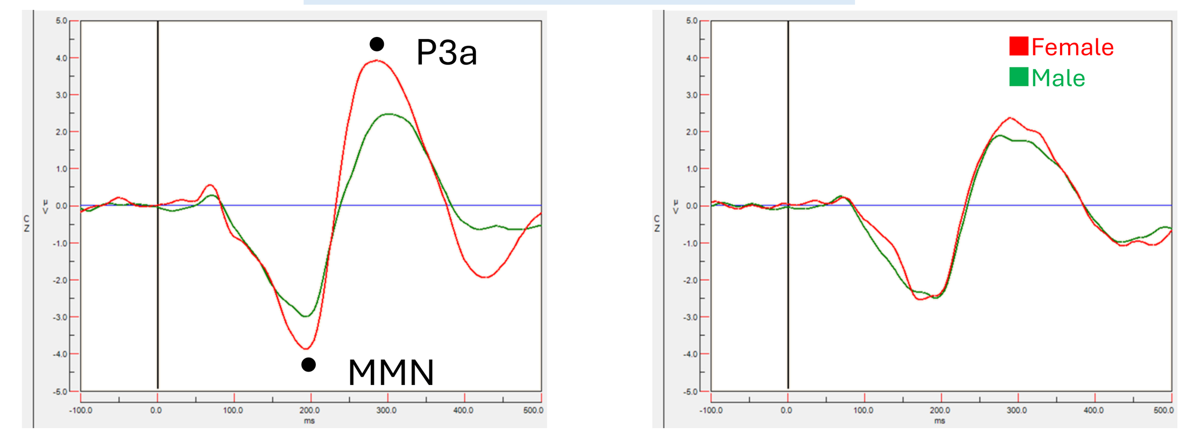


Fig. 8: Resting State EEG (PSD)

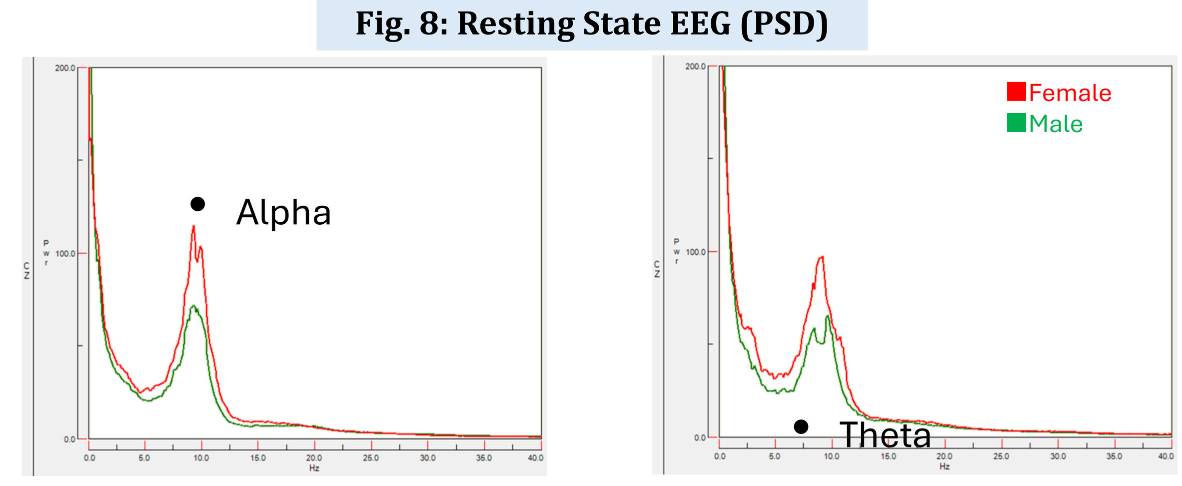


Fig. 9: ASSR Evoked Power

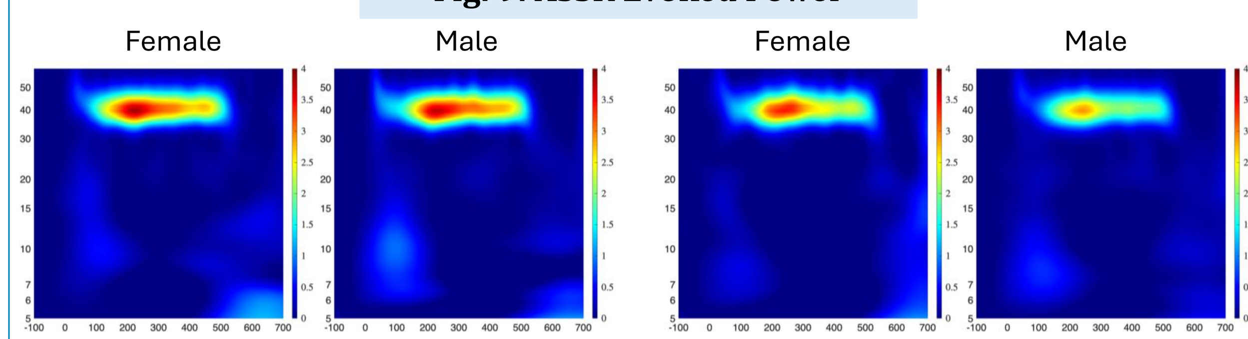
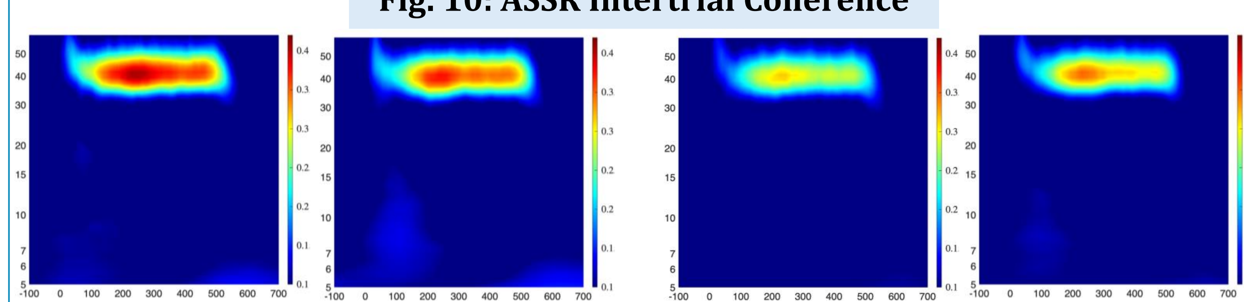


Fig. 10: ASSR Intertrial Coherence



T-tests showed a statistically significant effect of GENDER on several EEG/ERP measures (13 for HV and 9 for SZ out of 25) (**Tables 3 and 4**):

- 10 for HV and 7 for SZ out of 14 resting-state EEG measures
- 3 for HV and 2 for SZ out of 11 ERP measures

Females showed larger P3a / P3b but smaller N100 (SZ only) amplitudes than males during active / passive oddball ERP tasks, with medium to moderately large effect size (d = 0.45 to 0.70) (**Figures 6 and 7**).

Females showed greater spectral power than males across multiple frequency bands during resting-state EEG and 40 Hz ASSR (HV only) tasks, with medium to large effect size (d = 0.36 to 0.83) (**Figures 8-10**).

Discussion / Conclusions

The present work demonstrates the feasibility of implementing EEG/ERP biomarkers in early-phase, pharma-sponsored CNS clinical trials and the ability to analyze pooled data across trials based on standardized and scalable testing, data acquisition, and analytic methods.

A comprehensive analysis of 25 different EEG/ERP measures across resting-state EEG and three cognitive / sensory ERP tasks showed a robust effect of gender across several measures. The effect of age was substantially less robust in our dataset and participant sample.

Our findings highlight the importance of considering gender in the study design and analysis of EEG/ERP data from HV and SZ participants.

Clinical trials collecting EEG/ERP data in HV and SZ participants must ensure balanced participant recruitment in terms of gender across study arms. Alternatively, covariate adjustment approaches could be used as part of statistical analysis when analyzing EEG/ERP data.

Future work should confirm and extend these findings in larger, more diverse groups of participants (e.g. with other CNS conditions; across a wider age range). Effect of other demographic factors such as education and race / ethnicity on EEG/ERP measures should also be examined.