Validation of a suite of ERP and QEEG biomarkers in a pre-competitive, industry-led study in subjects with schizophrenia and healthy volunteers

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Abstract

Objective: Complexity and lack of standardization in data acquisition and data analysis have mostly limited the use of event-related potentials (ERPs) and quantitative EEG (QEEG) biomarkers in schizophrenia drug development to small early phase trials. We present results from a clinical study on healthy volunteers (HV) and patients with schizophrenia (SZ) that assessed group differences, variance, and correlation with functional assessments for ERP and QEEG parameters collected at commercial and clinical trial sites with standardized methods and analyzed through an automated data analysis pipeline.

Methods: 81 HV and 80 SZ were tested at one of four study sites. Study subjects were administered two ERP/EEG testing sessions on separate visits. Each session included four tests conducted sequentially: a mismatch negativity paradigm, a 40Hz auditory steady state response, an eyes-closed resting state EEG, and an active auditory oddball task. SZ subjects were also tested on the Brief Assessment of Cognition (BAC), the Positive and Negative Syndrome Scale (PANSS), and the Virtual Reality Functional Capacity Assessment Tool (VRFCAT).

Results: Standardized ERP/EEG testing equipment and protocols ensured a low number of test failures. The automated data analysis pipeline allowed for near real-time assessment of results. Test-retest reliability was fair-to-excellent for most of the measures collected. SZ subjects showed significant deficits in ERP and QEEG parameters that were consistent with the published academic literature. A subset of ERP and QEEG parameters correlated with functional assessments administered to the SZ subjects.

Conclusions: With standardized equipment and methods, complex ERP/EEG testing sessions can be reliably performed at commercial and clinical study sites to produce high-quality data in near real-time. Data and methods from this study will inform the design of future interventional trials to enable accurate power analyses, scalability and reproducibility of results across studies, and ongoing monitoring of study results.

Keywords: ERP Biomarker Qualification Consortium, Event Related Potentials; Quantitative EEG; Schizophrenia; Test-Retest Reliability; Automated Data Analysis.

Abstract (250 words)

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1. Introduction

Event-related potentials (ERPs) and quantitative EEG (QEEG) have been established as important translational biomarkers in schizophrenia drug development. When properly implemented, ERPs and QEEG can detect target engagement and response to therapeutic intervention (Javitt et al., 2020; Kantrowitz et al., 2017; Luck et al., 2011; B. F. O'Donnell et al., 2013). ERPs in particular, also have the potential to predict response to registration endpoints for cognitive symptoms, negative symptoms, and global function (Thomas et al., 2017), and to possibly enable stratification of subjects with schizophrenia by "biotype" (Clementz et al., 2017).

Because of the complexity and lack of standardization for data acquisition and data analysis, the use of ERP and QEEG biomarkers in schizophrenia drug development has been mostly limited to university sites and a few small pharma-sponsored trials. Testing and validating reliable and scalable ERP and QEEG approaches will enable wider use of these measures in drug discovery and development (P. O'Donnell et al., 2019). An industry-led ERP Biomarker Qualification Consortium (https://erpbiomarkers.org) was constituted with the objective of bringing together industry, academic, and regulatory stakeholders in a spirit of pre-competitive cooperation to ensure that robust and reliable ERP and QEEG biomarkers can be collected in target clinical populations, such as patients with schizophrenia, thus ensuring scalability and consistency across studies. The explicit objectives of the Consortium are to: a) develop and document standardized methods and detailed operating procedures for performing ERP and EEG testing; b) develop a reliable and efficient data analysis pipeline methodology that can be used across study designs; c) establish normative ERP and QEEG biomarker metrics in healthy subjects reflective of the population used in Phase 1 safety trials and in a wide range of clinical populations, including schizophrenia; d) quantify and calibrate pharmacodynamic effects on ERP and QEEG biomarkers using well-replicated clinical pharmacological paradigms that mimic the impairment observed in those clinical populations, and e) formally qualify selected ERP and QEEG biomarkers for use in drug trials under the FDA Drug Development Tools Qualification Program. The accomplishment of those objectives will lead to reduced operational risk and trial cost, a more precise estimate of statistical power, and a streamlined regulatory process for trials leveraging qualified ERP and QEEG biomarkers.

This manuscript reports results from the first clinical study sponsored by the Consortium. This was an observational study that recruited healthy volunteers (HV) and subjects with clinically confirmed schizophrenia (SZ). The study a) established mean and variance across cohorts and repeated tests for ERP and QEEG measures collected with a standardized ERP/EEG device; b) validated a predefined, automated data analysis pipeline for ERP and QEEG measures; c) developed normative ERP/QEEG datasets representing SZ subjects and matched HV, and d) quantified the relationship between specific ERP and QEEG parameters and clinically important measures in SZ.

2. Material and Methods

2.1 Study Design

This was an observational, multicenter study on HV and SZ subjects performed at four study sites in the United States: Collaborative Neuroscience Network (CNS) Orange County (Los Angeles, CA), CNS South Bay (Los Angeles, CA), Hassman Research Institute (Marlton, NJ), and the New York State Psychiatric Institute (New York, NY).

The study included 3 visits: Screening, Baseline, and Retest (see Table 1 for an overview of the tasks performed at each visit).

Table 1
Study Calendar

Assessments	*Visit 1 Screening*	*Visit 2 Baseline*	*Visit 3 Retest*
Audiometry	X		
EEG/ERP			
Frequency-Deviant MMN[1]		X	X
Duration-Deviant MMN[2]		X	X
Auditory Steady-State Response		X	X
Resting-state EEG		X	X
Active Auditory Oddball		X	X
MINI	X		
BAC[3]	X		
PANSS[4]	X	X[5]	X[5]
CDSS[4]	X		
SAS[4]	X		
VRFCAT[4]	X		

Notes:
1. 1st part of study.
2. 2nd part of study.
3. Only symbol BAC Symbol Coding & Verbal Memory for HV.
4. SZ only.
5. To confirm eligibility.

2.2 Study Participants

Approximately 20 HV and 20 SZ subjects 21 to 50 years of age were tested at each of the four study sites, for a total of 81 HV and 80 SZ completers. The study (ClinicalTrials.gov number NCT04025502) was approved by institutional review boards for each site. Written informed consent was obtained from each study participant, after which subjects were screened for eligibility.

Eligibility criteria for HV subjects included normal cognitive function as determined by performing within two standard deviations of the mean of the normative sample on both the Brief Assessment of Cognition (BAC) Symbol Coding (BAC_SC) and BAC Verbal Memory (BAC_VM). Exclusion criteria included evidence or history of psychiatric illness as determined by The Mini International Neuropsychiatric Interview (MINI), or family history of schizophrenia spectrum disorders in first- or second- degree relatives.

Eligibility criteria for SZ subjects required a diagnosis of schizophrenia as determined by the MINI, excluding all other schizophrenia spectrum disorders. Patients had to be clinically stable, and on a stable regimen of antipsychotic medications for a minimum of 6 weeks, with up to 2 first or second-generation antipsychotics allowed. Exclusion criteria were scores of ≥ 5 for any of the Positive and Negative Syndrome Scale (PANSS) items P1 (delusions), P3 (hallucinatory behavior), G9 (unusual thought content), and P2 (conceptual disorganization), a score of > 6 for the Simpson Angus Scale (SAS), or a score of ≥ 6 for the Calgary Depression Scale for Schizophrenia (CDSS). Eligibility for the PANSS was confirmed at Baseline and Retest.

All study subjects were tested for hearing deficits at Screening and had to be able to detect a 1000Hz tone played at 40dB loudness in both ears. Subjects also had to pass a saliva drug/alcohol screen at all visits.

Finally, all study subjects were required to abstain from any medication known to interfere with ERP or EEG assessments within 1 week prior to Screening and throughout the study, and from products containing nicotine and/or caffeine for 60 minutes prior to ERP/EEG testing.

2.3 ERP and EEG Testing Sessions

ERP/EEG testing sessions were performed at Baseline and Retest visits and included four tests administered sequentially in rapid succession: 1) a mismatch negativity paradigm, 2) a 40Hz auditory steady state response, 3) an eyes-closed resting state EEG, and 4) an active auditory oddball. Each testing session lasted about 60min, including headset set up. About halfway through the study, the oddball stimulus in the mismatch negativity paradigm was changed from a frequency-deviant to a duration-deviant. See Table 2 for details of each ERP/EEG test protocol.

Table 2
EEG/ERP Test Descriptions

EEG/ERP Test	*Paradigm*	*Stimulus*	*Sequence*
Frequency-Deviant MMN	Auditory Oddball	Standard= 1000Hz, 100ms, 90%, 85dB Deviant= 2000Hz, 100ms, 10%, 85dB	Stimuli presented[1] in pseudorandom order so that between 6 and 12 standards were presented between deviants for a total of 1200 stimuli. The interstimulus interval was 600ms.
Duration-Deviant MMN	Auditory Oddball	Standard= 1000Hz, 50ms, 90%, 85dB Deviant= 1000Hz, 100ms, 10%, 85dB	Stimuli presented[1] in pseudorandom order so that between 6 and 12 standards were presented between deviants for a total of 2000 stimuli. The interstimulus interval was 600ms.
Auditory Steady-State Response	Stimulus Train	500ms duration, 40Hz white noise click trains, 85dB	Click trains presented[1] every 1000ms for a total of 200 repetitions.
Resting-state EEG	Eyes Closed	n/s	Subjects were instructed to rest with their eyes closed for 5 minutes of EEG recording.
Active Auditory Oddball	Auditory Oddball	Standard= 1000Hz, 100ms, 80%, 85dB Deviant= 2000Hz, 100ms, 20%, 85dB	Stimuli presented[1] in pseudorandom order so that between 2 and 5 standards were presented between deviants for a total of 300 stimuli. The interstimulus interval was randomized between 2500-3000ms. Subjects were instructed to press a button on the ERP/EEG testing device as soon as possible each time they heard the deviant (target) stimulus.

Notes:
1. All auditory stimuli were presented binaurally through medical grade insert earphones.

2.4 ERP/EEG Data Acquisition

ERP and EEG data were recorded using a COGNISION® Headset (Cognision) from channels Fz, Cz, Pz, F3, P3, F4, and P4 of the 10-20 electrode positioning system. All channels were referenced to linked mastoids M1 and M2. Data were digitized at 250Hz and bandpass filtered from 0.3 to 70Hz. Stimulus sequences were controlled using the COGNISION® Software. Auditory stimuli were presented binaurally through medical-grade insert earphones. Task responses were captured using the integrated response buttons on the COGNISION® Handset. All other test and data acquisition parameters were as described in Cecchi et al., 2015.

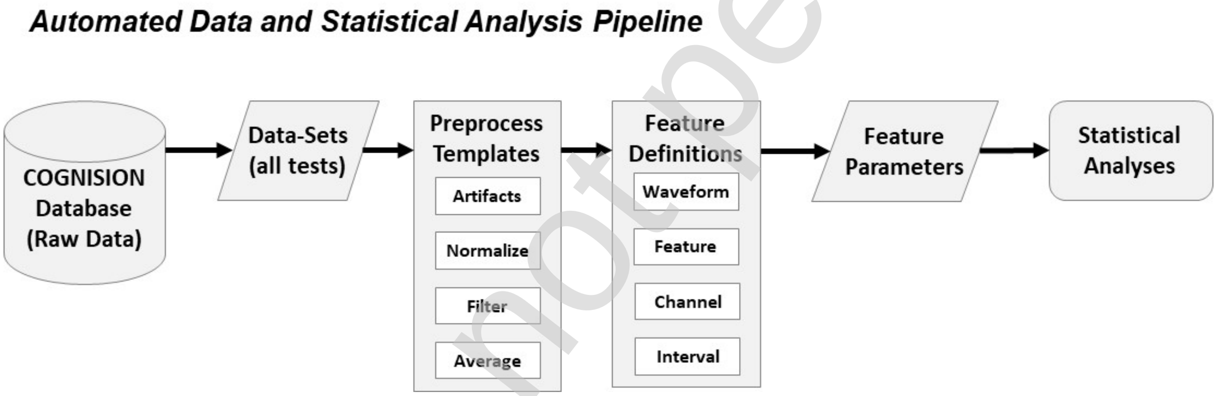
2.5 Data Quality Review

At the end of each testing session, data were immediately available for quality review through the web-enabled COGNISION® System software. Personnel blind to demographics and diagnostic information evaluated the data against predefined, objective quality metrics and those tests which passed quality control (QC) were flagged for automatic analysis.

2.6 Automated Data Cleaning, Preprocessing, and Feature Extraction

For tests that passed QC, data cleaning, preprocessing, and extraction of ERP and QEEG parameters were automatically performed with the COGNISION® Software through a predefined data analysis pipeline (see Figure 1).

Figure 1.



All subject test data from each test type were run through the data analysis pipeline at the same time using predefined preprocessing templates and feature definitions (see Table 3 for feature definition details). All feature parameters were provided in a format suitable for direct statistical analysis.

Table 3
ERP and QEEG Feature Parameters

EEG/ERP Test	*Feature*	*Filter*	*Stim*	*Chan*	*Int 1*^{1}	*Int 2*^{2}
Frequency-Deviant MMN	N100	50	1	Cz	56-153	52-164
	MMN	30	2-1	Fz	92-240	88-244
	P3a	30	2-1	Cz	196-352	192-356
Duration-Deviant MMN	N100	50	1	Cz	64-132	60-136
	MMN	30	2-1	Fz	104-260	100-264
	P3a	30	2-1	Cz	224-352	220-356
Auditory Steady-State Response	ITC000	38-42	1	Fz	-99-0	-
	ITC100	38-42	1	Fz	1-100	-

	ITC200	38-42	1	Fz	101-200	-
	ITC300	38-42	1	Fz	201-300	-
	ITC400	38-42	1	Fz	301-400	-
	ITC500	38-42	1	Fz	401-500	-
	EP	38-42	1	FZ	1-500	-
Resting-state EEG	See IPEG Guidelines (Jobert et al., 2012)					
Active Auditory Oddball	N100	50	1	Cz	68-140	64-144
	P3b	16	2	Pz	244-472	244-476
	BPA	-	2	-	-	-
	MRT	-	2	-	-	-

Abbreviations: BPA= Button Press Accuracy; MRT= Median Reaction Time

Notes:

1. An initial window interval for detecting a peak.
2. A secondary window interval if a peak was not detected in Int 1.

2.7 Functional Assessments

Functional assessments were administered by trained test administrators through the VeraSci Pathway platform (VeraSci). See Table 1 for a list of the assessments.

2.8 Statistical Analysis

Group differences between HV and SZ subjects for demographic characteristics and functional assessments were analyzed using a two-tailed *t*-test for continuous variables (age, education, BAC_SC and BAC_VM), and a chi-squared test for categorical variables (race and sex).

Group differences between HV and SZ subjects for study parameters from ERP and EEG testing were analyzed using a repeated measures ANOVA with group and visit as factors. When a significant group effect was present, a Cohen’s D effect size was calculated. When a significant group by visit interaction was found, a Bonferroni *post hoc* analysis was performed to test for possible group differences at each visit.

Baseline/retest variability for study parameters from ERP and EEG testing was calculated when a significant group effect was present. These values are reported separately for HV and SZ groups as Intraclass Correlation Coefficients (ICC).

Finally, correlations between study parameters from ERP and EEG testing and functional assessments in SZ were analyzed using Pearson correlation coefficients. To limit the number of comparisons, only parameters from ERP and EEG testing that showed HV vs SZ differences were included. Furthermore, Inter-Trial Coherence (ITC) correlation analyses were restricted to the 301-400ms latency block, as it was the latency interval with the largest SZ deficits. Parameters from functional assessments included in the correlation analyses comprised of Digit Sequencing (BAC_DS), BAC_SC, Tower of London (BAC_TL), Token Motor (BAC_TM), Verbal Fluency Total (BAC_VF) and BAC_VM from the BAC, Total Score (PANSS_TOT), Positive Symptoms Subscale (PANSS_PS), and Negative Symptoms Subscale (PANSS_NS) from the PANSS, and Adjusted Total Time (VRFCAT_AT), Total Forced Progressions (VRFCAT_FP), and Total Error Count (VRFCAT_TE) from the VRFCAT.

3. Results

3.1 Demographics and Clinical Characteristics

There were no significant differences in age, gender, and race between HV and SZ groups. As expected, SZ subjects had significantly fewer years of education (t=5.271, p<0.01). In addition, SZ subjects had significantly lower scores than HV in BAC_SC (t=4.848, p<0.01) and BAC_VM (t=5.657, p<0.01) (see Table 4 for subject demographics and clinical characteristics).

Table 4
Demographics and Clinical Characteristics

	Healthy Volunteers (HV)	Patients (SZ)
Sample Size	81	80
Age[1]	37.27 (1.08)	38.40 (.87)
Gender		
Male[2]	45 (55.6%)	49 (61.3%)
Female[2]	36 (44.4%)	31 (38.8%)
Race		
White[2,3]	14 (17.3%)	9 (11.3%)
African American[2,3]	31 (38.3%)	42 (52.5%)
Other Race[2,3]	36 (44.4%)	29 (36.3%)
Education	13.90 (.23)	12.21 (.17)**
Duration of Illness[1,4]	n/a	14.54 (.85)
CDSS[1,6]	n/a	1.24 (.18)
SAS[1,6]	n/a	.275 (.085)
BAC Verbal Memory[1]	43.36 (.85)	35.26 (1.16)**
BAC Symbol Coding[1]	48.67 (1.10)	40.03 (1.33)**
BAC Digit Sequencing[1,4]	n/a	15.48 (.49)
BAC Token Motor[1,4]	n/a	66.70 (3.23)
BAC Tower of London[1,4]	n/a	40.99 (1.18)
BAC Verbal Fluency[1,4]	n/a	12.56 (1.40)
PANSS Total Score[1,4]	n/a	61.38 (1.35)
PANSS Positive Symptoms[1,4]	n/a	14.89 (.50)
PANSS Negative Symptoms[1,4]	n/a	16.41 (.45)
VRFCAT Adjusted Total Time (sec)[1,4]	n/a	761.45 (21.08)
VRFCAT Total Error Count[1,4]	n/a	2.33 (.33)
VRFCAT Total Forced Progressions[1,4]	n/a	46.50 (1.83)

Abbreviations: CDSS= Calgary Depression Scale for Schizophrenia; SAS= Simpson-Angus Scale; BAC= Brief Assessment of Cognition; PANSS= Positive and Negative Syndrome Scale; VRFCAT= Virtual Reality Functional Capacity Assessment Tool

Notes:

1. Mean (±SEM).
2. Total (% of Total).
3. Racial labels from FDA, 2016, Guidance for Industry, Collection of Race and Ethnicity Data in Clinical Trials (FDA, 2016).
4. SZ only.
5. ** p<0.001

3.2 Data Quality

Data quality review resulted in the following number of tests that met quality control criteria: 176 out of 176 for frequency-deviant mismatch negativity; 145 out of 146 for duration-deviant mismatch negativity; 306 out of 322 for auditory steady state response; 321 out of 322 for resting EEG, and 299 out of 322 for auditory active oddball. The most common reason for test rejection was the inability of SZ subjects to perform the task associated with the active oddball as instructed.

3.3 ERP and QEEG Comparisons in HV vs SZ Subjects

Statistical significance, effect size, and test-retest reliability for parameters from ERP and EEG testing that showed significant group differences in HV vs SZ subjects are summarized in Table 5.

Table 5
EEG/ERP Features, Significance, Effect Sizes, and Interclass Correlation Coefficients

EEG/ERP Assay	Feature	Measure (units)	HV_{AVG}	HV_{BL}	HV_{RT}	SZ_{AVG}^{1}	SZ_{BL}	SZ_{RT}	Cohen's D	ICC HV^{2}	ICC SZ^{2}
Frequency-Deviant MMN	P3a, Cz	Amplitude (µV)	3.26 (.19)	3.27 (.29)	3.24 (.26)	2.48 (.15)**	2.50 (.20)	2.45 (.21)	.491	.303	.092
	P3a, Cz	Latency (ms)	261 (4)	264 (6)	257 (6)	275 (4)*	277 (6)	272 (6)	.356	.228	.228
Duration-Deviant MMN	MMN, Fz	Amplitude (µV)	-5.58 (.31)	-5.79 (.46)	-5.50 (.41)	-4.44 (.27)*	-4.29 (.37)	-4.59 (.32)	.466	$.702^{\dagger\dagger}$	$.556^{\dagger}$
	P3a, Cz	Amplitude (µV)	6.72 (.47)	6.99 (.68)	6.57 (.67)	4.52 (.33)**	4.61 (.45)	4.44 (.49)	.609	$.762^{\dagger\dagger\dagger}$	$.826^{\dagger\dagger\dagger}$
Auditory Steady-State Response	ITC200, Fz	ITC	.341 (.013)	.332 (.019)	.350 (.016)	.290 (.011)*	.290 (.016)	.289 (.015)	.352	$.658^{\dagger\dagger}$	$.804^{\dagger\dagger\dagger}$
	ITC300, Fz	ITC	.403 (.014)	.396 (.02)	.410 (.018)	.337 (.013)*	.340 (.019)	.334 (.018)	.401	$.710^{\dagger\dagger}$	$.767^{\dagger\dagger\dagger}$
	ITC400, Fz	ITC	.363 (.013)	.361 (.019)	.365 (.018)	.294 (.012)*	.302 (.017)	.287 (.017)	.446	$.689^{\dagger\dagger}$	$.753^{\dagger\dagger\dagger}$
	ITC500, Fz	ITC	.350 (.012)	.345 (.018)	.354 (.017)	.292 (.012)*	.300 (.018)	.284 (0.017)	.379	$.612^{\dagger\dagger}$	$.720^{\dagger\dagger}$
Pharmaco-EEG	Delta, Absolute	Power (μV^2/Hz)	109.0 (4)	105.9 (5.5)	112.8 (5.6)	138.4 (6)**	144.9 (9.6)	131.8 (8.6)	.435	$.732^{\dagger\dagger}$	$.714^{\dagger\dagger}$
	Beta1, Relative	n/a	.104 (.003)	.103 (.004)	.105 (.005)	.090 (.003)*	.089 (.004)	.090 (.004)	.398	$.896^{\dagger\dagger\dagger}$	$.700^{\dagger\dagger}$
	Beta2, Relative	n/a	.033 (.001)	.034 (.002)	.032 (.002)	.028 (.001)*	.027 (.001)	.028 (.002)	.349	$.584^{\dagger}$	$.831^{\dagger\dagger\dagger}$
	Theta/Beta Ratio	Ratio	1.23 (.07)	1.24 (.10)	1.22 (.09)	1.71 (.18)**	1.71 (.17)	1.76 (.17)	.405	$.760^{\dagger\dagger\dagger}$	$.831^{\dagger\dagger\dagger}$
Active Auditory Oddball	P3b, Pz	Amplitude (µV)	9.57 (.34)	9.93 (.49)	9.31 (.50)	7.39 (.32)**	8.10 (.51)	6.80 (.41)	.544	$.547^{\dagger}$	$.524^{\dagger}$
	BPA	Total Accuracy (%)	96.5 (.7)	96.8 (1.0)	96.1 (1.0)	89.8 (1.2)**	90.2 (1.6)	91.00 (1.6)	.581	$.739^{\dagger\dagger}$	$.694^{\dagger\dagger}$
	MRT	Time (ms)	366 (8)	367 (12)	365 (12)	456 (11)**	456 (15)	443 (16)	.765	$.755^{\dagger\dagger\dagger}$	$.778^{\dagger\dagger\dagger}$

Abbreviations: HV_{AVG}= average of HV_{BL} and HV_{RT}; HV_{BL}= mean (±SEM) of all HV baseline tests; HV_{RT}= mean (±SEM) of all HV retests; SZ_{AVG}= average of SZ_{BL} and SZ_{RT}; SZ_{BL}= mean (±SEM) of all SZ baseline tests; SZ_{RT}= mean (±SEM) of all SZ retests; ICC= Interclass Correlation Coefficient; BPA= button-press accuracy; MRT= button-press median reaction time.

Notes:

1. * $p<0.05$ and ** $p<0.01$ compared to HV_{AVG}.
2. † = Fair; †† = Good; ††† = Excellent (Cicchetti and Sparrow, 1981)

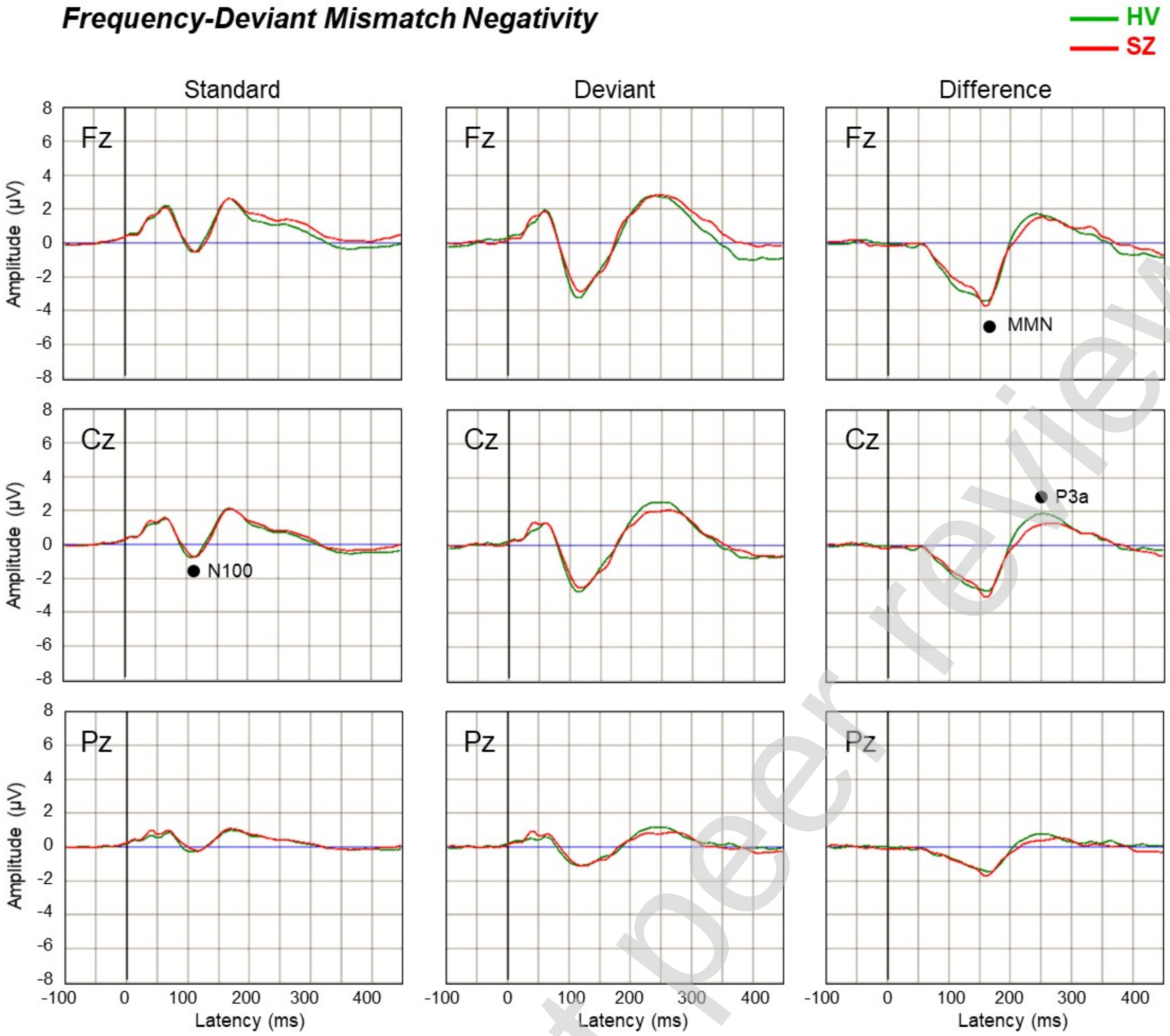
3.4 Frequency-Deviant Mismatch Negativity

Grand average waves for standard and deviant stimuli and the grand difference wave (deviant-standard) for the passive, frequency-deviant auditory oddball in HV vs SZ subjects are shown in Figure 2.

Statistical comparisons for the N100 from the standard stimulus showed a lower peak amplitude at Baseline than at Retest ($F_{1,86}$=4.86, $p<0.05$) with no group effects or significant interactions.

Statistical analyses of ERP parameters from the difference wave revealed a reduced P3a amplitude ($F_{1,86}$=8.531, $p<0.01$), and a prolonged P3a latency ($F_{1,86}$=4.474, $p<0.05$) in SZ subjects compared to HV.

Figure 2.



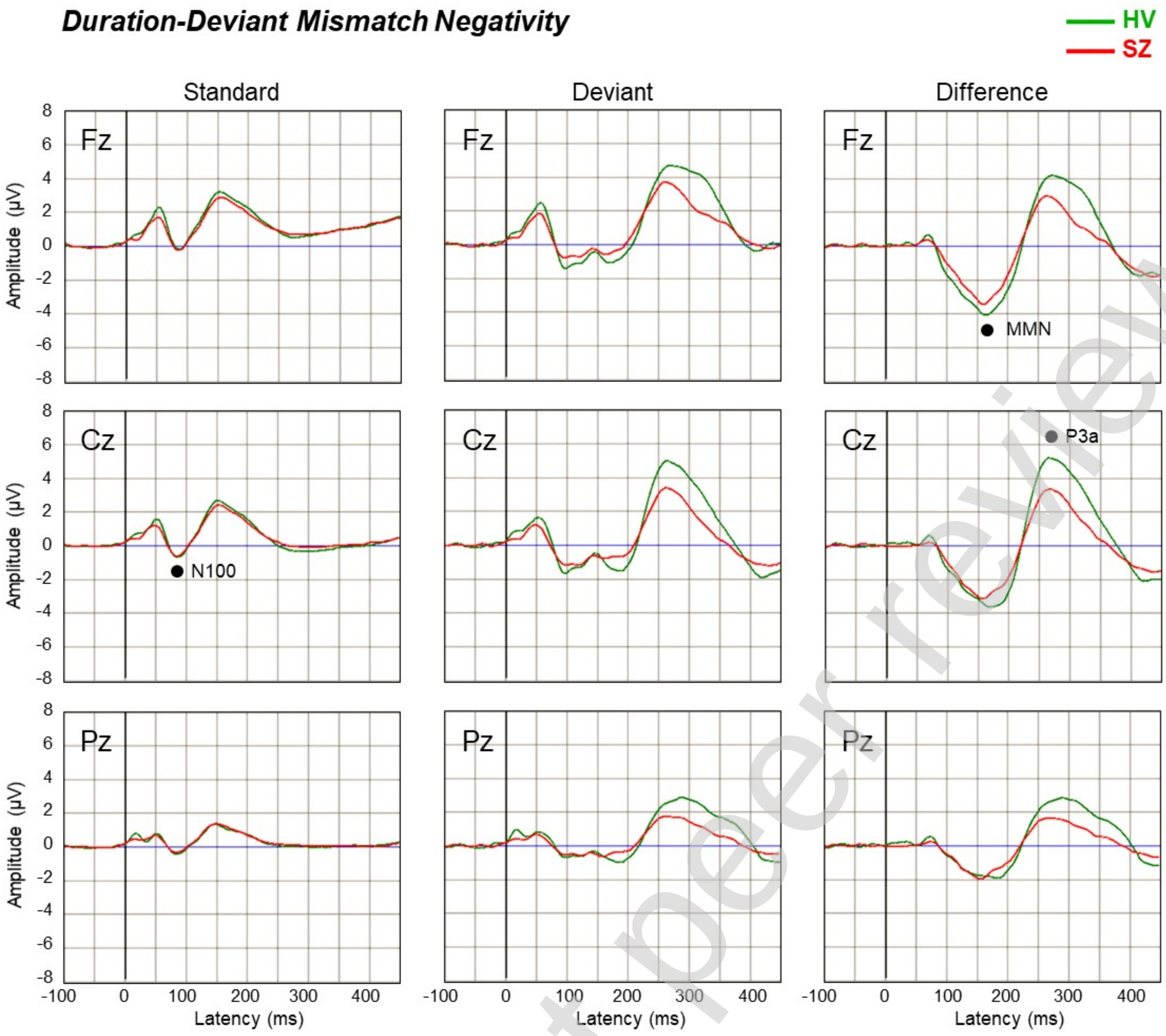
3.5 Duration-Deviant Mismatch Negativity

Grand average waves for standard and deviant stimuli and the grand difference wave (deviant-standard) for the passive, duration-deviant auditory oddball in HV vs SZ individuals are shown in Figure 3.

Statistical comparisons for the N100 from the standard stimulus showed a significant group by visit interaction for the peak amplitude ($F_{1,70}$=5.061, $p<0.05$) with no significant differences observed in the subsequent *post hoc* analysis.

Statistical analyses of ERP parameters from the difference wave revealed significantly reduced MMN amplitude ($F_{1,70}$=5.573, $p<0.05$) and P3a amplitude ($F_{1,70}$=8.529, $p<0.01$) in SZ subjects compared to HV.

Figure 3.



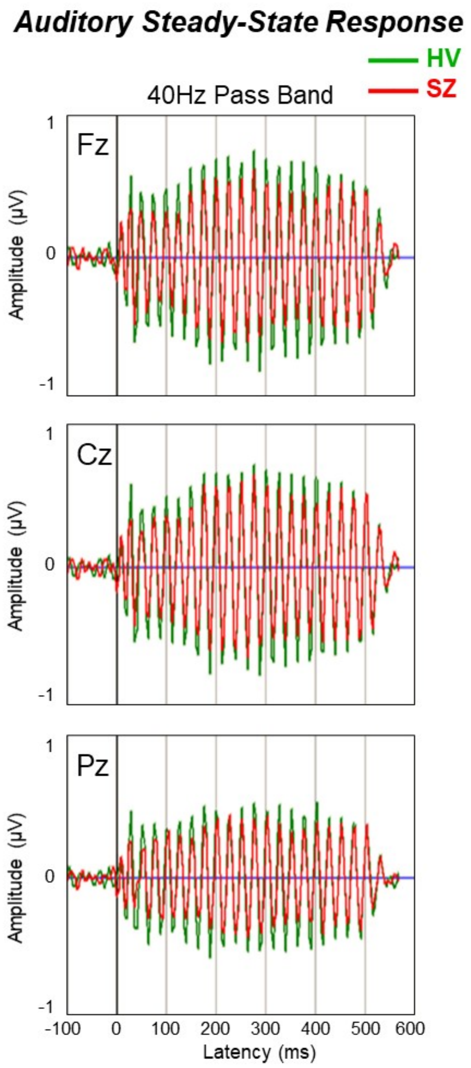
3.6 Auditory Steady-State Response

Grand average waves generated during the ASSR paradigm in HV and SZ subjects are shown in Figure 4.

Statistical analyses revealed lower ITC for SZ at latency intervals 101-200ms ($F_{1,145}$=4.057, p<0.05), 201-300 ($F_{1,145}$=5.171, p<0.05), 301-400 ($F_{1,145}$=6.497, p<0.05), and 401-500 ($F_{1,145}$=4.461, p<0.05). There was also a trend toward significance for the 1-100ms interval ($F_{1,145}$=3.738, p=0.055).

Evoked Power (EP) showed a mild decrease in SZ that was not statistically significant ($F_{1,145}$=1.859, p=0.175). Finally, no significant group differences were found for ITC at the prestimulus interval (-99-0ms).

Figure 4.

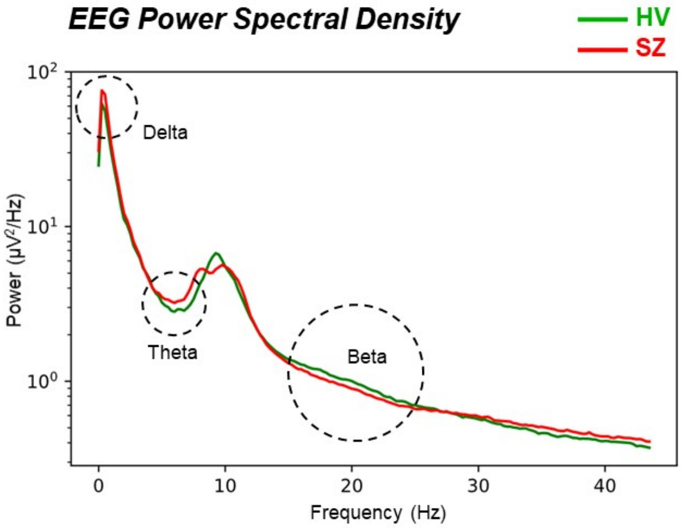


3.7 Eyes-closed Resting EEG

Power spectral densities for HV and SZ subjects are shown in Figure 5.

Statistical analyses for the QEEG parameters showed higher absolute Delta power ($F_{1,158}=8.527$, $p<0.01$), lower relative Beta1 ($F_{1,158}=6.581$, $p<0.05$) and Beta2 ($F_{1,158}=5.691$, $p<0.05$) power, and higher Theta/Beta ratio ($F_{1,158}=7.065$, $p<0.01$) in SZ subjects. There was also a significant group x visit interaction for Theta relative power that, after subsequent *post hoc* analysis, revealed higher Theta relative power in SZ at Retest.

Figure 5.



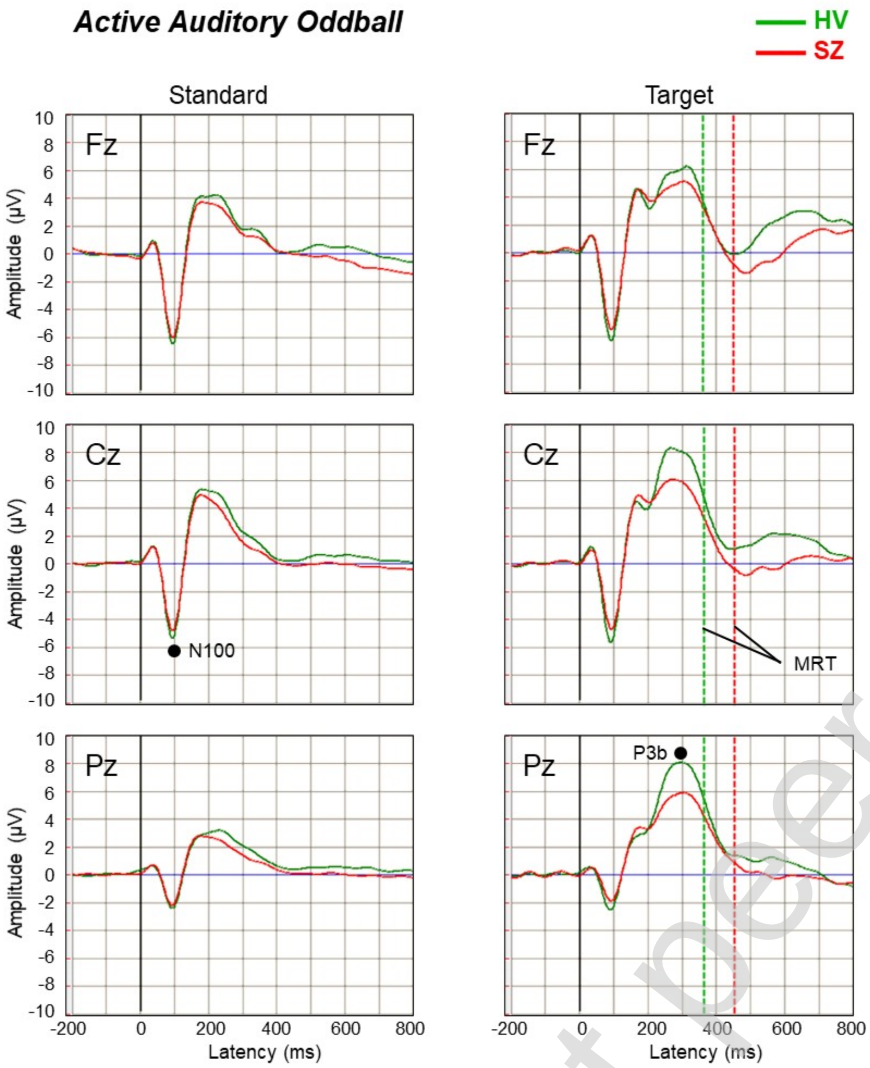
3.8 Active Auditory Oddball

Grand average waves for standard and deviant stimuli from the active auditory oddball in HV vs SZ individuals are shown in Figure 6.

Statistical comparisons for ERP parameters showed significant group ($F_{1,140}$=13.148, $p<0.01$) and visit ($F_{1,140}$=8.945, $p<0.01$) effects for P3b amplitude. The peak amplitude was lower in SZ subjects than HV, and at Retest when compared to Baseline.

When performance in the behavioral response was analyzed, SZ subjects showed lower button press accuracy ($F_{1,142}$=12.030, $p<0.01$) and delayed median reaction time ($F_{1,142}$=21.052, $p<0.01$) compared to HV. Finally, false alarms were lower overall at Retest ($F_{1,142}$=21.052, $p<0.05$) than at Baseline.

Figure 6.



3.9 Correlation of Parameters from ERP and QEEG Testing with Functional Assessments in Subjects with schizophrenia

Table 6 summarizes significant correlations between ERP and QEEG Parameters that showed changes in SZ subjects, and functional assessments.

For the passive, frequency-deviant auditory oddball, P3a amplitude correlated with PANSS_PS, P3a latency correlated with BAC_SC and VRFCAT_FP. For the passive, duration-deviant auditory oddball, MMN and P3a amplitude correlated with BAC_SC. For the auditory steady state response, ITC in the 301-400ms latency block correlated with BAC_DS and BAC_VF. For the resting EEG, Delta absolute power correlated with PANSS_PS, while Theta/Beta ratio correlated with BAC_VF and VRFCAT_FP. Finally, for the active oddball median reaction time correlated with PANSS_NS, and button press accuracy with VRFCAT_AT.

Table 6
EEG/ERP Parameter Correlations with Standard Psychometric Measures.

EEG/ERP Assay	EEG/ERP Feature	Psychometric Measure	Correlation Coefficient
Frequency-Deviant MMN	P3a, Amplitude, Cz[1]	PANSS_PS	-.320*

	P3a, Latency, Cz[1]	BAC_SC	-.349*
	P3a, Latency, Cz[1]	VRFCAT_FP	.304*
Duration-Deviant MMN	MMN, Amplitude, Fz[2]	BAC_SC	-.386*
	P3a, Amplitude, Cz[2]	BAC_SC	.340*
Auditory Steady-State Response	ITC400, Fz	BAC_DS	.242*
	ITC400, Fz	BAC_VF	.240*
Pharmaco-EEG	Delta, Absolute, Avg	PANSS_PS	.249*
	Theta/Beta Ratio	BAC_VF	-.221*
	Theta/Beta Ratio	VRFCAT_FP	.305**
Active Auditory Oddball	BPA	VRFCAT_AT	-.277*
	MRT	PANSS_NS	.254*

Abbreviations: PANSS_PS= Positive Symptoms Subscale; BAC_SC= Symbol Coding; VRFCAT_FP= Total Forced Progressions; BAC_DS= Digit Sequencing; BAC_VF= Verbal Fluency; VRFCAT_AT= Adjusted Total Time; PANSS_NS= Negative Symptoms Subscale.
Notes:
1. Frequency-Deviant MMN Paradigm.
2. Duration-Deviant MMN Paradigm.
3. * $p<0.05$; ** $p<0.01$

4. Discussion

The current study provides evidence that, with standardized equipment and methods, complex ERP/EEG testing sessions can be reliably performed across commercial and clinical study sites to produce high-quality data with few test failures. In our study, group differences matched results reported in the academic literature, and test-retest reliability was fair-to-excellent for most of the measures collected. Also, several ERP and QEEG measures exhibited significant correlations with functional measures.

4.1 Automated Pipelined Data Analysis and Data Quality

ERP and QEEG parameters were obtained through a predefined, automated data analysis pipeline. This analysis approach contributed to the high quality of the data collected by ensuring that data cleaning, preprocessing, and feature extraction were consistent across datasets and free from subjective interpretation. The analysis pipeline output is available immediately at the end of each testing session. Rapid data throughput and analyses for interventional trials will enable quality assurance and training interventions, as well as facilitate study protocol changes in adaptive trial designs.

Because early phase clinical trials of experimental compounds are usually performed on small cohorts of subjects, it is important that the ERP/EEG testing sessions be performed with very few test failures. In the current study, the number of ERP and EEG tests that did not meet quality criteria was very low, even when compared to similar studies performed at specialized ERP academic labs (see for example Light et al., 2014, and Turetsky et al., 2015). The most common reason for test rejection was the inability of a subset of SZ subjects to correctly perform the task associated with the active oddball test, a factor that should be taken into account when designing SZ clinical trials that include an active oddball ERP paradigm.

A second requirement for an accurate assessment of the effects of experimental drugs is adequate test-retest reliability. The large majority of ERP and QEEG parameters analyzed in this study had a test-retest reliability score that was good or excellent (Cicchetti and Sparrow, 1981), again with no loss of quality when compared to similar studies performed at specialized ERP academic labs (see for example Roach et al., 2020; 2019). Exceptions were the P3b amplitude from the active oddball that had “fair” test-retest reliability, likely because of the habituation observed at Retest, and P3a amplitude and latency from the frequency-deviant MMN paradigm. While the frequency-deviant MMN paradigm was sensitive enough to resolve group differences in P3a, it is possible that the total test length was not sufficient to provide optimal test-retest reliability across visits. Test duration was increased from 1200 to 2000 total stimuli for the duration-deviant MMN paradigm, and ICC for the P3a significantly improved.

4.2 ERP and QEEG Comparisons in HV vs SZ Subjects

Our findings closely match published results from academic labs.

SZ subjects showed a reduction in MMN amplitude from the duration-deviant paradigm but not from the frequency-deviant. Patient functional status is an important determinant of the pattern of MMN dysfunction in SZ, such that deficits in duration MMN appear to be present across all SZ subjects, whereas deficits in frequency MMN are restricted to a subgroup of low-functioning subjects drawn primarily from supervised residential-care settings (see for example Lee et al., 2017), and may index reductions in auditory cortex volume that are observed during initial years of the disease (Salisbury et al., 2007). The bimodal distribution of tone matching impairments in SZ suggests that these may represent an etiologically distinct subgroup (Dondé et al., 2019). Our results add to the evidence that relatively high functioning patients drawn from outpatient settings show deficits in duration MMN but relatively intact frequency discrimination. The differential MMN findings may also reflect the differential structural correlations of the different MMN types (Curtis et al., 2021).

While group differences in MMN amplitude were dependent on the kind of deviant, P3a amplitude was decreased in SZ subjects for both frequency and duration-deviant paradigms. Deficits in P3a amplitude have been a consistent finding in SZ, and are present even at the early stages of the disease (Ford et al., 2010; Light et al., 2014; Mathalon et al., 2000; Nagai et al., 2013). Interestingly, SZ subjects in our study also showed a significant increase in P3a latency for the frequency-deviant. Though similar data have been previously reported (Frodl et al., 2001; Li et al., 2013), this is a relatively novel finding, and its specificity to the frequency-deviant paradigm further suggests differential patterns of dysfunction according to deviant type.

ASSR test results showed a significant decrease in ITC in SZ subjects for most latency blocks collected during stimulus presentation. Similar to Light et al., 2006, the largest group difference was observed for the 301–400ms latency interval.

ASSR EP was not significantly different between groups. Roach and Mathalon have reported that ASSR ITC and EP do not necessarily covary (Roach and Mathalon, 2008).

Indeed, though most of the studies reported in the literature show a decrease for ITC in SZ, published results are less homogeneous for EP, with some of the studies that have reported an increase or no change (Hirano et al., 2015; Kirihara et al., 2012). Using a well-established preclinical model of acute NMDA hypofunction, Sivarao and colleagues have shown that EP is highly-sensitive to the level of NMDA receptor hypofunction (Sivarao et al., 2016). Thus, differences in the level of NMDAR receptor hypofunction across studied populations could contribute to differences in reported EP deficits.

For the eyes-closed resting EEG, a large published literature reports power increases across lower frequencies and decreases across higher frequencies in patients with SZ (for review, see Newson and Thiagarajan, 2019). Consistent with those findings, our results show an increase in Delta absolute power, a decrease in Beta1 and Beta2 relative power, and a significantly higher Theta/Beta ratio in the SZ group.

Finally, in the active oddball paradigm P3b amplitude was significantly decreased in SZ subjects. P3b deficits in SZ have been widely reported throughout the course of illness (see Onitsuka et al., 2013 for a review), and manifest since the early stages of the disease (Hamilton et al., 2019). In our study, P3b amplitude was also decreased at Retest when compared with Baseline regardless of subject group, suggesting possible habituation of the brain response to target deviants across repeated testing. Subjects with SZ showed longer reaction time and lower button press accuracy in the behavioral task associated with the active oddball. A delay in reaction time is already present early in SZ (Hamilton et al., 2019). Luck and colleagues have proposed that such deficit is the consequence of impairments in the response selection that lies between stimulus evaluation and response initiation (Luck et al., 2009).

4.3 Correlations with Functional Assessments

A subset of the parameters from ERP and EEG testing that showed a deficit in SZ patients also correlated with functional assessments. Significant correlations were found with cognitive domains such as attention and speed of information processing, working memory, verbal fluency, and functional capacity (Keefe et al., 2016; 2004), as well as the PANSS Positive and Negative Symptoms subscales. Correlations with functional assessments further underscore the utility of ERP and QEEG measures, suggesting that they might provide insight on the severity of the impairment in SZ at the subject level while tracking responses to treatments that improve function in this population.

Correlations for P3a amplitude from the frequency-deviant and the duration-deviant MMN paradigms did not overlap, suggesting again that these deviant types might engage distinct brain circuits (Curtis et al., 2021; Lee et al., 2017).

4.4 Study Limitations

All patients were medicated. Thus, the study cannot distinguish effects of medication from those of the illness. Nevertheless, the critical issues were the effect-size and test-retest reliability of our measures in a patient sample that is likely representative of subjects who would participate in clinical trials of new cognition-targeted therapies in SZ.

4.5 Conclusions

The current study reports findings from a precompetitive, industry-led, collaborative research program. Our findings match published results from academic labs, and show that complex ERP/EEG testing sessions can reliably be performed across commercial and clinical study sites. The metrics reported on test-retest reliability can be leveraged for accurate power analyses in future interventional trials. The use of standardized equipment and protocols will allow scalability and ensure high data reproducibility across studies. The implementation of a fully automated ERP/EEG data analysis pipeline will facilitate ongoing study monitoring and adaptive study designs that can improve the likelihood of success and reduce costs.

5. Figure Legends

Figure 1. All subject information and ERP/EEG test session metadata are stored in the online COGNISION Database. As ERP/EEG test sessions are completed, the raw data (Data-Sets) are automatically uploaded to the database and associated to the appropriate subject. Also in the database are predefined Preprocess-Templates which specify the data cleaning, preprocessing, and epoch averaging methods for each test type. Feature Definitions are also predefined which specify the algorithm that will be used to extract each Feature Parameter from the specific ERP/EEG test. Upon initiation of the automated data analysis pipeline, all defined Feature Parameters, from each test for all study subjects, are streamed for Statistical Analysis.

Figure 2. Grand average and grand difference waves from midline electrodes for the frequency-deviant mismatch negativity paradigm.

Figure 3. Grand average and grand difference waves from midline electrodes for the duration-deviant mismatch negativity paradigm.

Figure 4. EEG synchronization at midline electrodes in response to 40-Hz click trains.

Figure 5. Power spectral density for HV and SZ subjects from the eyes-closed resting state EEG test. Data is average of all electrodes.

Figure 6.Grand average waves from midline electrodes for the active auditory oddball. Dotted lines show median reaction time (MRT).

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