ERP Biomarker Qualification Consortium

Magnitude and Repeatability of Ketamine Effects on ERP and QEEG Biomarkers in a Double-Blind, Randomized, Placebo-Controlled, Crossover Study in Healthy Volunteers

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Introduction

Ketamine is a drug of well-established pharmacology that has been used in clinical trials to model the symptoms of schizophrenia, and is increasingly used in the clinic to treat depression.

We present results from a study sponsored by the ERP Biomarker Qualification Consortium (https://erpbiomarkers.org) that investigated the effects of Ketamine on Event Related Potential (ERP) and Quantitative EEG (QEEG) measures.

The study had 3 main objectives:

- Measure the effect size of Ketamine-induced changes on ERP and QEEG measure collected and analyzed with standardized equipment and methods.
- Quantify the variability of the Ketamine effect on ERP and QEEG measures across two dosing sessions.
- Investigate a possible "disordinal effect" of Ketamine on ERP and QEEG feature parameters, where the direction and magnitude of Ketamine-induced changes could be predicted by the baseline value.

Here, we are presenting results related to the first 2 main study objectives. For results related to the third study objective, please see Poster #33, Fadem et al., 2023.

Materials and Methods

Study Design

The study was a randomized, double-blind, Placebo-controlled, 3-arm, 3-period crossover design performed at one study site in the United States (CenExel HRI, NJ, USA). Twenty-four study participants were administered Ketamine IV on two of the periods and Placebo on the remaining period in a counterbalanced order. The Ketamine dose was a 0.23 mg/kg bolus over 1 minute, followed by 0.58 mg/kg per hour for 30 minutes, and 0.29 mg/kg per hour for up to 29 minutes after that (Gunduz-Bruce et al., 2012). ERP and EEG data were collected during the infusions.

Study Participants

The study recruited male and female healthy volunteers aged 21 to 45 with a body mass index (BMI) between 18.5 and 30.0. Exclusion criteria were a positive alcohol/drug screen at any of the visits, a history of psychiatric and neurologic disorders, a history of severe renal or hepatic impairment, a history of significant cardiovascular condition, or an inability to detect a 1000 Hz tone at 40 dB in both ears. A detailed list of the inclusion/exclusion criteria for the study can be found at www.clinicaltrials.gov (NCT04928703).

ERP and EEG Testing

ERP and EEG data was collected using the COGNISION® System. Each testing session included 4 tests:

- Passive, duration-deviant mismatch negativity
- Eyes-closed resting state EEG
- One-deviant active oddball
- 40Hz auditory steady-state response

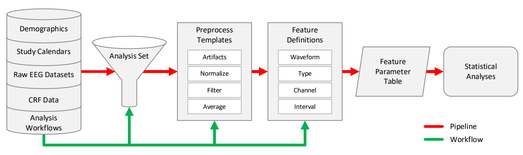
For a detailed description of the testing paradigms please see Cecchi et al., 2023.

At the end of each testing session, data was evaluated for quality against predefined objective quality metrics, and tests which passed quality review were flagged for automated data and statistical analysis.

Data and Statistical Analysis

Data preprocessing and extraction of ERP and QEEG parameters were automatically performed with the COGNISION® Software through a predefined data and statistical analysis pipeline.

Figure 1. Power data and statistical analysis workflows include predefined preprocess templates which determine how each ERP/EEG dataset is preprocessed, along with feature definition algorithms which define exactly how each feature will be extracted from the preprocessed ERP/EEG data. The statistical analyses are also predefined to act on the automatically generated feature parameter tables. To generate the feature parameter and statistical analysis output, the user tags the appropriate subjects as part of an "analysis set" predefined in the study protocol and initiates the analysis on those subjects to generate the output. The saved analysis workflows can be reused across studies to facilitate standardization and comparisons between different study cohorts.



The predefined preprocess templates for the ERP and EEG datasets, along with the feature definition algorithms which define how each ERP and QEEG parameters are extracted from the preprocessed ERP/EEG data are described in detail in Cecchi et al., 2023.

Statistical comparisons for the effects of Ketamine on ERP and QEEG measures were performed using a two-tailed *t*-test between the Placebo session and the average of the Ketamine sessions. Effect size was estimated as Cohen's *d*. Variability of the Ketamine effect across the two dosing sessions was calculated as intra-class correlation coefficient (ICC).

Results

Study Subject Demographic Data

Table 1. Demographics for the 24 study completers. An additional 7 subjects dropped out of the study.

Demographics for Study Completers	*Healthy Volunteers*
Sample Size	24
Age[1]	33.75 (1.07)
Gender	
Male[2]	19 (79.2%)
Female[2]	5 (20.8%)
Education[1]	12

Notes:
1. Mean (±SEM).
2. Total (% of Total).

Data Quality Review

Table 2. All tests were reviewed for quality for each testing paradigm. The "Comments" column shows findings for tests that were deemed "Not Valid" or "Other".

Testing Paradigm	*Tests*	*Valid*	*Not Valid*	*Other*	*Comments*
Passive DD-MMN	75	73	1	1	Data-Set 34757 (subject 0022, Dosing 1) has no EEG recorded from channel P4. Data-Set 33790 (subject 0006, Dosing 1) failed QC; subject 0006 was not part of the Analysis Set.
Resting-State EEG	75	74	0	1	Data-Set 34757 (subject 0022, Dosing 1) has no EEG recorded from channel F4.
Active Oddball	75	71	4	0	Data-Set 33561 (subject 0003, Dosing 1), Data-Set 34155 (subject 0010, Dosing 3), Data-Set 34757 (subject 0022, Dosing 1), and Data-Set 35360 (subject 0033, Dosing 1) failed QC.
40Hz ASSR	75	73	1	1	Data-Set 34757 (subject 0022, Dosing 1) has no EEG recorded from channel F3. Data-set 33616 (subject 0004, Dosing 1) failed QC; subject 0004 was not part of the Analysis Set.

Abbreviations: DD-MMN = Duration-Deviant Mismatch Negativity; ASSR = Auditory Steady-State Response.

Findings for Data Quality:

- Only 6 out of 300 tests (2%) did not meet Quality Review criteria and were deemed "Not Valid". "Not Valid" tests were excluded from all analyses.

Resting-State EEG

Figure 2. Power spectral density (PSD) for Placebo and average Ketamine administration from the eyes-closed resting state EEG. Data is shown at the Fz electrode.

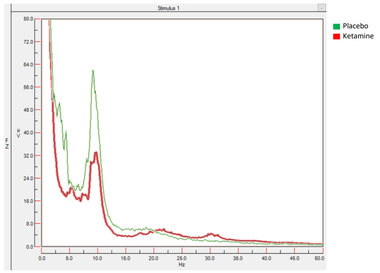


Table 3. QEEG feature parameters: significance, effect sizes and interclass correlation coefficients.

Feature[1]	*Channel*	*Frequency*	*Measure (units)*	*Placebo*[2]	*Avg Ketamine*[2]	*Cohen's d*	*ICC K1, K2*	*ICC K1-P, K2-P*
Delta-Absolute	AVG	[1.5-6]	Power (μV²/Hz)	98.874 (9.308)	71.031 (6.715)*	0.49	0.8554	0.9491
Delta-Relative	AVG	[1.5-6]	n/a	0.356 (0.029)	0.385 (0.029)	0.215	0.799	0.7814
Theta-Absolute	AVG	[6-8.5]	Power (μV²/Hz)	34.406 (4.481)	24.469 (2.385)*	0.565	0.7849	0.8989
Theta-Relative	AVG	[6-8.5]	n/a	0.112 (0.010)	0.127 (0.010)	0.33	0.6577	0.5688
Alpha1-Absolute	AVG	[8.5-10.5]	Power (μV²/Hz)	81.538 (16.15)	38.954 (8.874)**	0.586	0.7599	0.907
Alpha1-Relative	AVG	[8.5-10.5]	n/a	0.217 (0.025)	0.152 (0.02)**	0.673	0.6479	0.6369
Alpha2-Absolute	AVG	[10.5-12.5]	Power (μV²/Hz)	45.324 (8.629)	26.611 (4.718)*	0.529	0.8875	0.9504
Alpha2-Relative	AVG	[10.5-12.5]	n/a	0.13 (0.018)	0.114 (0.014)	0.169	0.8493	0.9158
Beta1-Absolute	AVG	[12.5-18.5]	Power (μV²/Hz)	28.479 (3.862)	17.730 (2.675)**	0.66	0.7122	0.8036
Beta1-Relative	AVG	[12.5-18.5]	n/a	0.093 (0.005)	0.086 (0.006)	0.273	0.6671	0.5817
Beta2-Absolute	AVG	[18.5-21]	Power (μV²/Hz)	10.099 (1.661)	7.932 (1.923)*	0.474	0.7673	0.2831
Beta2-Relative	AVG	[18.5-21]	n/a	0.033 (0.004)	0.035 (0.004)	0.118	0.6267	0.02658
Beta3-Absolute	AVG	[21-30]	Power (μV²/Hz)	17.203 (2.628)	22.66 (5.820)	0.272	0.8829	0.7763
Beta3-Relative	AVG	[21-30]	n/a	0.059 (0.006)	0.101 (0.012)**	0.879	0.5946	0.4652
Total Power	AVG	[1.5-30]	Power (μV²/Hz)	315.922 (38.708)	209.386 (23.567)**	0.638	0.8999	0.9509
Gamma-Absolute	AVG	[30-40]	Power (μV²/Hz)	8.123 (1.030)	16.398 (2.785)**	0.733	0.6245	0.4948
Alpha Peak Frequency	AVG	[6-12.5]	Frequency (Hz)	10.012 (0.141)	10.461 (0.196)**	1.148	0.8543	0.5672
Slow Wave Index	AVG		n/a	0.988 (0.131)	0.734 (0.116)~	0.412	0.6823	0.7213
Theta/Beta Ratio	AVG		n/a	1.017 (0.131)	1.294 (0.166)*	0.448	0.7516	0.6071

Abbreviations: ICC K1, K2 = Intraclass Correlation Coefficients (ICC) for first Ketamine administration and second Ketamine administration; ICC K1-P, K2-P = ICC for first Ketamine administration minus Placebo, and second Ketamine administration minus Placebo; AVG = Average of all electrode locations.

Notes:
1. The frequency bands selected for Pharmaco-EEG analysis were taken from an International Pharmaco-EEG Society (IPEG) guidance document intended to standardize Pharmaco-EEG analysis methods for the pharmaceutical industry (Jobert et al., 2012).
2. Values are mean (±SEM)
3. *p < 0.05, **p < 0.01, and ~p < 0.1 compared to Placebo.

Findings for Resting-State EEG:

- ICC was good-to-excellent across most measures.
- Several features showed significant changes after Ketamine that were consistent with published literature.
- Decreases in Delta and Theta power and increases in Peak Alpha Frequency may explain clinical effect on depression.

40Hz Auditory Steady-State Response (ASSR)

Figure 3. Grand average waves for Placebo and average Ketamine administration from the 40Hz ASSR test. Data is shown at the midline electrodes.

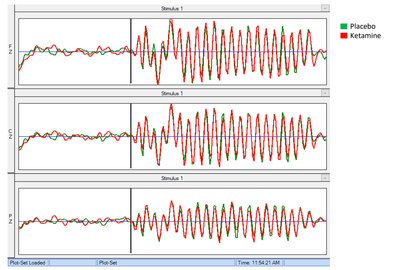


Table 4. Feature parameters from the 40Hz ASSR: significance, effect sizes and interclass correlation coefficients

Feature	*Channel*	*Frequency*	*Interval (ms)*	*Measure (units)*	*Placebo*[1]	*Avg Ketamine*[2]	*Cohen's d*	*ICC K1, K2*	*ICC K1-P, K2-P*
ITC000	Fz	38-42	-99-0	n/a	0.07 (0.008)	0.071 (0.005)	0.011	0.2152	0.7205
ITC100	Fz	38-42	1-100	n/a	0.182 (0.013)	0.169 (0.014)	0.182	0.2305	0.3016
ITC200	Fz	38-42	101-200	n/a	0.335 (0.026)	0.317 (0.028)	0.187	0.6122	0.3591
ITC300	Fz	38-42	201-300	n/a	0.409 (0.031)	0.39 (0.029)	0.148	0.7235	0.6697
ITC400	Fz	38-42	301-400	n/a	0.332 (0.032)	0.337 (0.028)	0.045	0.6385	0.4696
ITC500	Fz	38-42	401-500	n/a	0.318 (0.031)	0.32 (0.027)	0.019	0.6457	0.5091
ITC1500	Fz	38-42	1-500	n/a	0.44 (0.026)	0.419 (0.029)	0.21	0.734	0.5579
EP	Fz	38-42	1-500	μV²/Hz	0.156 (0.018)	0.189 (0.025)~	0.411	0.5537	0.2205
TP	Fz	38-42	1-500	μV²/Hz	0.559 (0.048)	0.788 (0.093)**	0.577	0.4927	0.7679

Abbreviations: ICC K1, K2 = Intraclass Correlation Coefficients (ICC) for first Ketamine administration and second Ketamine administration; ICC K1-P, K2-P = ICC for first Ketamine administration minus Placebo, and second Ketamine administration minus Placebo; ITC = Intertrial Coherence; EP = Evoked Power; TP = Total Power.

Notes:
1. Values are mean (±SEM)
2. **p < 0.01, and ~p < 0.1 compared to Placebo.

Findings for the 40Hz Auditory Steady-State Response:

- Data showed high SNR and excellent morphological concordance between conditions.
- Ketamine had a minimal effect on ITC, consistent with Sivarao, 2016, when test_time is considered.
- The increase in 40Hz power (EP and TP) after Ketamine was mostly driven by non-timelocked increase in Gamma power, consistent with Resting-State EEG.

Auditory Active Oddball

Figure 4. Grand average waves for Placebo and average Ketamine administration from the Auditory Active Oddball test. Data is shown at the midline electrodes.

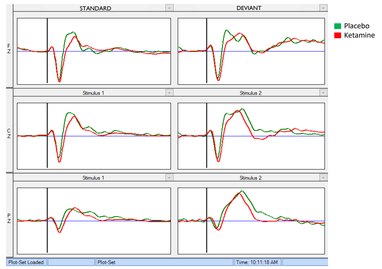


Table 5. Feature parameters from the Auditory Active Oddball: significance, effect sizes and interclass correlation coefficients.

Feature	*Channel*	*Interval 1 (ms)*	*Interval 2 (ms)*	*Measure (units)*	*Placebo*[1]	*Avg Ketamine*[2]	*Cohen's d*	*ICC K1, K2*	*ICC K1-P, K2-P*
BPA	n/a	n/a	n/a	%	89.841 (2.918)	89.087 (2.168)	0.075	0.6758	0.7282
FA	n/a	n/a	n/a	%	0.377 (0.095)	0.705 (0.184)*	0.493	0.607	0.436
MRT	n/a	n/a	n/a	ms	414.857 (23.717)	433.667 (21.730)	0.22	0.6974	0.5907
P50-Amp	Cz	28-76	24-80	μV	1.536 (0.278)	1.541 (0.229)	0.005	0.8338	0.6
P50-Lat	Cz	28-76	24-80	ms	41.714 (2.183)	43.048 (2.377)	0.133	0.4429	0.265
N100-Amp	Cz	68-140	64-144	μV	-5.190 (0.480)	-5.725 (0.430)*	0.463	0.8929	0.6747
N100-Lat	Cz	68-140	64-144	ms	92.571 (1.996)	97.429 (2.466)*	0.568	0.851	0.7663
P200-Amp	Cz	136-256	132-260	μV	6.345 (0.535)	4.651 (0.396)**	0.814	0.7924	0.8573
P200-Lat	Cz	136-256	132-260	ms	195.81 (6.515)	214.286 (4.667)**	0.705	0.3382	0.473
N200-Amp	Cz	176-320	172-324	μV	2.306 (0.582)	2.563 (0.47)	0.096	0.5869	0.5314
N200-Lat	Cz	176-320	172-324	ms	236.444 (9.439)	239.000 (7.082)	0.05	0.3305	0.6702
P3B-Amp	Pz	248-472	244-476	μV	6.976 (0.588)	6.051 (0.577)*	0.466	0.6309	0.5437
P3B-Lat	Pz	248-472	244-476	ms	310.476 (10.204)	288.286 (5.170)~	0.425	0.2994	0.8778

Abbreviations: ICC K1, K2 = Intraclass Correlation Coefficients (ICC) for first and second Ketamine administration; ICC K1-P, K2-P = ICC for first Ketamine administration minus Placebo, and second Ketamine administration minus Placebo; BPA = Button Press Accuracy; FA = False Alarms; MRT = Median Reaction Time; Amp = Amplitude; Lat = Latency.

Notes:
1. Values are mean (±SEM)
2. **p < 0.01, and ~p < 0.1 compared to Placebo.

Findings for the Active Oddball:

- ERP waves showed excellent ERP morphology.
- ICC was good-to-excellent for most measures.
- Button-press Accuracy was not different across conditions: subjects were minimally impaired on behavioral task.
- Subjects showed impaired cognitive processing based on reduced P3b amplitude.

Duration-Deviant Mismatch Negativity

Figure 5. Grand average waves and grand difference waves for Placebo and average Ketamine administration from the Duration-Deviant Mismatch Negativity test. Data is shown at the midline electrodes.

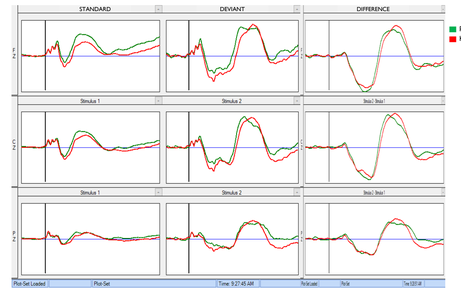


Table 6. Feature parameters from the Duration-Deviant MMN: significance, effect sizes and interclass correlation coefficients.

Feature	*Channel*	*Interval 1 (ms)*	*Interval 2 (ms)*	*Measure (units)*	*Placebo*[1]	*Avg Ketamine*	*Cohen's d*	*ICC K1, K2*	*ICC K1-P, K2-P*
P50-Amp	Cz	24-76	20-80	μV	1.595 (0.249)	1.356 (0.226)	0.207	0.5187	0.6277
P50-Lat	Cz	24-76	20-80	ms	47.833 (2.587)	47.583 (2.102)	0.02	0.3098	0.5734
N100-Amp	Cz	64-132	60-136	μV	-1.608 (.0251)	-2.089 (0.279)	0.287	0.6685	0.7652
N100-Lat	Cz	64-132	60-136	ms	93.667 (3.43)	93.583 (2.629)	0.005	0.3745	0.5759
P200-Amp	Cz	108-220	104-224	μV	2.649 (0.307)	2.167 (0.27)	0.291	0.6836	0.7851
P200-Lat	Cz	108-220	104-224	ms	171.667 (4.121)	174.417 (4.449)	0.083	0.4319	0.7057
MMN-Amp	Fz	104-260	100-264	μV	-5.098 (0.496)	-5.060 (0.386)	0.02	0.677	0.6799
MMN-Lat	Fz	104-260	100-264	ms	171.833 (4.8)	170.500 (4.865)	0.053	0.5134	0.55
P3A-Amp	Cz	224-352	220-356	μV	4.143 (0.371)	4.503 (0.480)	0.152	0.8136	0.816
P3A-Lat	Cz	224-352	220-356	ms	279.167 (6.185)	287.083 (5.256)	0.247	0.5163	0.6581

Abbreviations: ICC K1, K2 = Intraclass Correlation Coefficients (ICC) for first Ketamine administration and second Ketamine administration; ICC K1-P, K2-P = ICC for first Ketamine administration minus Placebo, and second Ketamine administration minus Placebo; MMN = Mismatch Negativity; Amp = Amplitude; Lat = Latency.

Notes:
1. Values are mean (±SEM)

Findings for the Duration-Deviant Mismatch Negativity:

- ERP waves showed excellent ERP morphology.
- ICC was good-to-excellent for most measures.
- Morphology for the ERP wave from the Standard stimulus was similar to the one from Active Oddball, suggesting consistent results across testing paradigms.
- No group effects of Ketamine on the ERP parameters from the paradigm. Ketamine did affect MMN-A in a direction and magnitude that was dependent on the baseline amplitude values. See discussion of "Disordinal" data on Poster #33, K.C. Fadem et al., 2023.

Conclusions

- With standardized equipment and methods, high quality EEG/ERP biomarkers can be reliably measured in Ketamine-challenge studies (2% of tests did not pass quality).
- Data quality and reliability (as measured by ICC) were good-to-excellent even with Ketamine administration.
- Ketamine showed significant effects on various ERP and QEEG measures that are generally consistent with the published literature.

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