Revisiting the Ketamine 'Model' for Schizophrenia Through the Electrophysiology Looking Glass

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ERP Biomarker Qualification Consortium

Clinical Sciences by CenExel

Introduction

Glutamate dysfunction is thought to play a significant role in the underlying disease course and symptoms in Schizophrenia (SCZ). Recent data suggest that non-D2 modulating mechanisms, i.e., Muscarinic M1 and M4 agonists, demonstrate an efficacy signal. A unifying thread from preclinical studies is that NMDA antagonist's impairment i.e., ketamine or MK-801 are reversed by putative antipsychotics across a wide array of pharmacological targets. Following ketamine or phencyclidine exposure in healthy normal volunteers (HNVs) symptoms are observed which mimic some aspects of people with schizophrenia (SCZ).

STUDY AIM: In the current poster, we compare the changes in electrophysiology associated with SCZ as compared with Ketamine induced changes in healthy volunteers. We combine the data from two studies to achieve this comparison:
(supported by the ERP Biomarker Qualification Consortium erpbiomarkers.org)

- ERP/qEEG differences between stably treated SCZ and matched HNVs (repeated measures at least one week apart) in the EBS-A trial (NCT04025502; Cecchi et al., Schizophrenia Res. 2023). Reprint →
- ERP/qEEG differences in HNVs receiving ketamine (NHV-K) or saline infusions (replicate cross over design study) in the EBS-B (NCT04928703; Ereshefsky et al., 2023). Poster available →

For the evaluation of similarities/differences in the electrophysiology of the ketamine induced changes in HNVs against the differences between SCZ and HNVs, we compare the EEG spectral data as one group and the ERP data as a second group, using a Z-score transformation of the data, thereby evaluating the full profile of related tests within a single analyses.

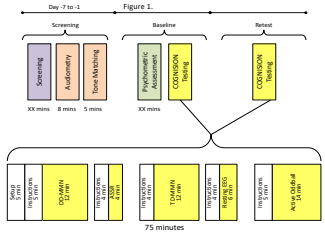
Methods

Study Design: All subjects refrained from caffeine or nicotine within 60 minutes of testing, and stopped any medications known to interfere with ERP/qEEG assessments for one week prior to testing, except for atypical antipsychotics in people with SCZ.

ERP and EEG Testing
ERP and EEG data were collected using the COGNISION® System.
EEG data is collected with eyes closed.
All data was evaluated for quality against predefined objective metrics.

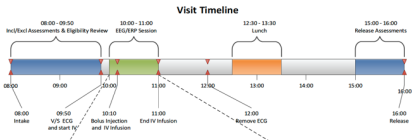
EBS-A: 81 HV and 80 SZ were tested at one of four study sites. Subjects were administered two ERP/EEG testing sessions on separate visits. Sessions included a mismatch negativity paradigm (duration deviant: 1000Hz standard 50 msec; deviant 100 msec), a 40 Hz auditory steady-state response paradigm, an eyes-closed resting state EEG, and an active auditory oddball paradigm. Visit schedule is displayed in Figure 1.

Figure 1.

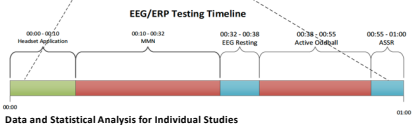


EBS-B: The study was a randomized, double-blind, placebo-controlled, 3-arm, 3-period crossover design performed at one study site in the United States (CenExel HRI, NJ, USA). 31 subjects were enrolled to complete 24 study participants (administered Ketamine IV on two of the periods and Placebo on the remaining period. 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. (See Figure 2, below).

Visit Timeline



EEG/ERP Testing Timeline



Data and Statistical Analysis for Individual Studies

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

EBS-A Analysis:

Group differences between HV and SZ subjects for ERP/QEEG endpoints were analyzed using a repeated measures ANOVA with group and visit as factors. Effect size was calculated as Cohen's *d*. 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 ERP/QEEG endpoints was calculated separately for HV and SZ groups as Intraclass Correlation Coefficients (ICCs). Half-way through the study we switched from a frequency-deviant (MMN FD) to a duration-deviant MMN (MMN DD), considered a more robust test, by our consultants (statistical analysis is reported only for MMN-DD). See definitions at the top right.

EBS-B Analysis:

Group differences between placebo and mean Ketamine [(K1+K2/)2] for ERP/QEEG endpoints were analyzed using a two-tailed t-test. Effect size was estimated as Cohen's d. Variability of the Ketamine effect across the two dosing sessions was calculated as ICCs, (K1, K2) and for the differences K1-Placebo and K2-Placebo.

Comparison across EBS-A and EBS-B:

All data were transformed to Z-Scores (standardizing to a **mean value of 0** and a **standard deviation of 1)**. This process allows data comparison/analyses regardless of its original scale or actual numeric value. Data was assigned to two groups: **EEG spectral analyses** (eyes closed), Dominant Peak Frequency (DOM), Theta/Beta Ratio (TBR), and Alpha Slow wave Index (ASI). **ERPs passive and active oddball tasks,** included P50 amplitude, N100 amplitude, MMN amplitude, P3a amplitude, P3b amplitude, ASSR ITC 200-500, ASSR Evoked (gamma) Power, Button press Accuracy (BPA) and Median Response Time (MRT). Key comparisons are the Z-score differences between HNVs v. SCZ and PBO v. Ketamine. Repeated measure ANOVA was used to determine Group Effects (Wilks' Lambda) and pair-wise comparisons made by two sided t-Tests for the Equality of the Means, using an independent samples assumption, are shown in Tables assuming equal variances. Results were unchanged if unequal variances were assumed.

Results

Table 1 Study Participants	EBS-A HNVs	People w/ SCZ	EBS-B HNVs
Sample size	81	80	24 completer (7 drop outs d/t K AEs)
Age	37.3 (1.1)	38.4 (0.87)	33.75 (1.07)
Gender			
Male	45 (55.6%)	49 (61.3%)	19 (79.2%)
Female	36 (44.4)	31 (38.8%)	5 (20.8%)
Race			
White[3,4]	14 (17.3%)	9 (11.3%)	3 (12.5%)
African American[3,4]	31 (38.3%)	42 (52.5%)	18 (75.0%)
Other Race[3,4]	36 (44.4%)	29 (36.3%)	3 (12.5%)
Education[2]	13.9 (0.23)	12.2 (0.17)*	12 (median)
Duration of illness	NA	14.5 (0.85)	NA
BACS Verbal	43.4 (0.85)	35.3 (1.16)*	BMI = 27.0 (0.92) (kg/m²)
BACS Symbol coding	48.7 (1.1)	40.0 (1.33)*	

Notes: Mean (±SEM); Total (% of Total) * p < 0.01

Racial labels from FDA, 2016, Guidance for Industry, Collection of Race and Ethnicity Data in Clinical Trials (FDA, 2016).

EBS-A sites: CenExel-CNS (2 locations) CenExel-HRI And Columbia University

EBS-B was Conduct at CenExel-HRI (Marlton)

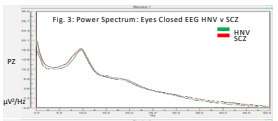
ICCs were good-to-excellent across most measures. QC process accepted 99% of all data attesting to procedural quality.

Results (cont'd)

Findings for Resting-State EEG HNV v SCZ

- Power spectral densities for HV and SZ subjects are shown in Figure 3.
- Several features showed significant changes (p<0.05) consistent with the literature including:
- Increased absolute Delta power.
- Lower relative Beta1, Beta2 power, and higher Theta/Beta ratio in SCZ.
- There was also a significant group × visit interaction for Theta relative power that, after subsequent post hoc analysis, revealed higher Theta relative power in SZ at Retest.

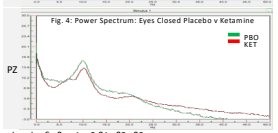
Fig. 3: Power Spectrum: Eyes Closed EEG HNV v SCZ



Findings for Resting-State EEG PBO v Ketamine

- Power spectral densities for HV and SZ subjects are shown in Figure 4.
- Several features showed significant changes (p<0.05) after Ketamine consistent with the literature including:
  - Decreases in absolute Delta, Theta power, and Beta 1.
  - Decreases in absolute Alpha 1, Alpha 2.
  - Increases in absolute Beta 3, and Gamma power.
  - Increases in Peak Alpha Frequency - Dominant (associated with clinical effects on depression).
  - Increased Theta/Beta ratio.

Fig. 4: Power Spectrum: Eyes Closed Placebo v Ketamine

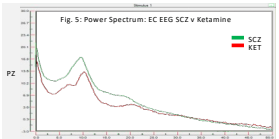


Freq bands: δ θ α1 α2 β1 β2 β3 γ

Findings for Resting-State EEG Ketamine v SCZ

- Power spectral densities of the untransformed data are shown as Figure 5.
- Z-Score transformed data of the differences between Ketamine in HNVs as compared to people with SCZ are shown as Figure 6. (ANOVA p<0.001). Note large effect sizes.

Fig. 5: Power Spectrum: EC EEG SCZ v Ketamine



δ θ α1 α2 β1 β2 β3 γ

Table 2 lists EEG parameters, Z-Score statistical analyses and Cohen's d

EEG Parameters[1]	t	df	Two sided t-Test	Mean Difference	Std Error	Cohen's d[2]
Absolute Delta	**3.635**	**102**	**<.001**	**1.25**	**0.34**	**0.85**
Absolute Theta	**2.808**	**102**	**0.006**	**0.77**	**0.27**	**0.65**
Absolute Alpha 1	**2.852**	**102**	**0.005**	**0.56**	**0.20**	**0.66**
Absolute Alpha 2	**1.977**	**102**	**0.051**	**0.54**	**0.27**	**0.46**
Absolute Beta 1	**2.282**	**102**	**0.025**	**0.63**	**0.28**	**0.53**
Absolute Beta 2	0.95	102	0.345	0.28	0.29	0.22
Absolute Beta 3	-0.647	102	0.519	-0.27	0.41	-0.15
Absolute Gamma	**-2.157**	**102**	**0.033**	**-1.22**	**0.57**	**-0.50**
Dominant Frequency (Alpha)	**-3.116**	**84**	**0.003**	**-0.96**	**0.31**	**-0.88**
Theta/Beta Ratio	0.467	102	0.641	0.18	0.39	0.11
Slow Wave Index	1.605	102	0.112	0.32	0.20	0.37

1. Spectral frequencies in μV²/Hz; 2. Cohen's d uses pooled standard deviation; **Bold rows ARE statistically significant**

Findings for ERPs HNV v. SCZ

- ERP measurements are combined into one statistical analyses.
- Z-Score transformed data of the differences between HNVs as compared to people with SCZ are shown as Figure 7. (ANOVA p<0.01)

Table 3 lists ERP parameters, Z-Score statistical analyses and Cohen's d.

Table 3: ERP Parameters[1] Lead specified	t	df	Two-Sided t-test	Mean Difference	Std. Error	Cohen's d[2]
P50 CZ	1.108	68	0.27	0.26	0.24	0.26
N100 CZ	**-2.656**	**68**	**0.010**	**0.56**	**0.21**	**-0.64**
MMN FZ	**-2.077**	**71**	**0.041**	**-0.43**	**0.21**	**-0.49**
P3a CZ	**2.777**	**71**	**0.007**	**0.56**	**0.2**	**0.65**
P3b PZ	**3.369**	**68**	**<.001**	**0.77**	**0.23**	**0.81**
ASSR40 ITC 200-500 FZ[3]	**3.205**	**70**	**0.002**	**0.70**	**0.22**	**0.76**
ASSR40 Evoked Power FZ	**2.42**	**70**	**0.018**	**0.48**	**0.20**	**0.57**
Button Press Accuracy (BP)	**4.105**	**68**	**<.001**	**1.11**	**0.27**	**0.98**
Median Response Time (MRT)	**-4.78**	**68**	**<.001**	**-1.29**	**0.27**	**-1.14**

1. All ERPs are amplitudes in μV; 2. Cohen's d uses the pooled standard deviation
3. ASSR 200-500 msec is considered highly sensitive to differences between HNV and SCZ; **Bold rows ARE statistically significant**

Fig. 6: Z Score Differences EEG Between Ketamine and Schizophrenia

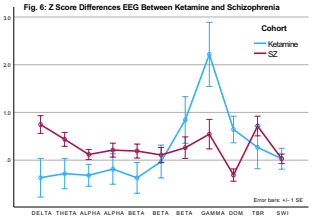
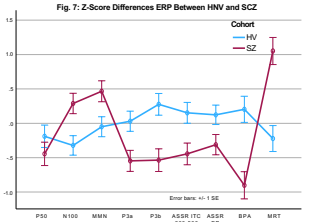


Fig. 7: Z-Score Differences ERP Between HNV and SCZ

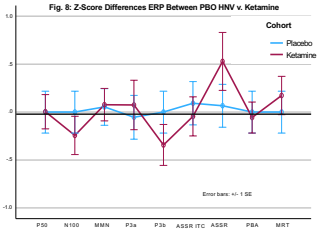


Findings for ERPs Ketamine v. SCZ

- ERP measurements are combined into one statistical analyses.
- Z-Score transformed data of the differences between HNVs as compared to subjects receiving Ketamine are shown as Figure 8. (NO significant difference by ANOVA).
- **These results are are in part due to the absence of an effect on Passive Auditory Oddball paradigm, MMN Duration Deviant:**
- ERP waves showed excellent morphology (comparable to the Active Oddball ERP, see Figure 9) and of large amplitude *(μV)* suggesting no methodological issues. ICCs were good to excellent.
- Ketamine's effects on MMN fit a disordinal effect where amplitude and direction of change are dependent on the subject's baseline amplitude values.
- We have presented (see QR code to the right) that the disordinal effect of ketamine is not regression to the mean by slope analyses.

Mathalon D, ERP Consortia, Disordinal Effect Analysis. CNS Summit 2023

Fig. 8: Z-Score Differences ERP Between PBO HNV v. Ketamine



Findings for Auditory Active Oddball:

These results for the active Auditory Oddball task and Passive Oddball task are reported in a prior poster presentation(Ereshefsky 2023, see QR code).

- ERP waves showed excellent morphology and large amplitude *(μV)*.
- ICC was good-to-excellent for most measures. See Table 4.
- "Active" means the subject is required to attend to the stimulus and press a button when he/she/they hear the different (deviant/oddball)
- Button-Press Accuracy was not different across conditions: Dose of ketamine selected to provide CNS effects with minimal impairment on behavioral tasks.
- N100 and P200 demonstrated differences in amplitude and longer latencies on Ketamine.
- Subjects showed impaired cognitive processing based on reduced P3b amplitude on Ketamine.

Fig. 9: Active Auditory Oddball Grand Average ERPs (from FZ, CZ, and PZ leads)

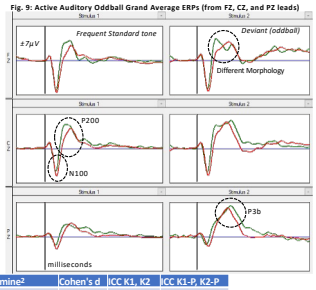


Table 4: Feature parameters from the Auditory Active Oddball: Ketamine was administered twice in a randomized 3 way cross over design with saline infusion (PBO)

Feature	Channel	Measure	Placebo[1]	Avg Ketamine[2]	Cohen's d	ICC K1, K2	ICC K1-P, K2-P
BPA	n/a	%	89.841 (2.918)	89.087 (2.168)	0.075	0.6758	0.7282
False Alarm (FA)	**n/a**	**%**	**0.377 (0.095)**	**0.705 (0.184)***	**0.493**	**0.607**	**0.436**
MRT	n/a	ms	414.857 (23.717)	433.667 (21.730)	0.22	0.6974	0.5907
P50-Amp	Cz	mcV	1.536 (0.278)	1.541 (0.229)	0.005	0.8338	0.6
P50-Lat	Cz	ms	41.714 (2.183)	43.048 (2.377)	0.133	0.4429	0.265
N100-Amp	**Cz**	**mcV**	**-5.190 (0.480)**	**-5.725 (0.430)***	**0.463**	**0.8929**	**0.6747**
N100-Lat	**Cz**	**ms**	**92.571 (1.996)**	**97.429 (2.466)***	**0.568**	**0.851**	**0.7663**
P200-Amp	**Cz**	**mcV**	**6.345 (0.535)**	**4.651 (0.396)****	**0.814**	**0.7924**	**0.8573**
P200-Lat	**Cz**	**ms**	**195.81 (6.575)**	**214.286 (4.667)****	**0.705**	**0.3382**	**0.473**
N200-Amp	Cz	mcV	2.306 (0.582)	2.563 (0.47)	0.096	0.5869	0.5314
N200-Lat	Cz	ms	236.444 (9.439)	239.000 (7.082)	0.05	0.3305	0.6702
P3B-Amp	**Pz**	**mcV**	**6.976 (0.588)**	**6.051 (0.577)***	**0.466**	**0.6309**	**0.5437**
P3B-Lat	**Pz**	**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.
1. Values are mean (±SEM); 2. **'p < 0.01, and ~p < 0.1 compared to Placebo. **Bold rows ARE statistically significant**

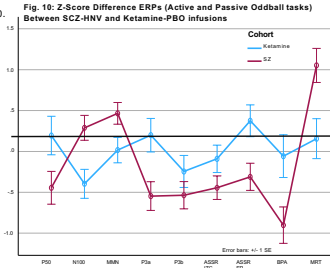
Findings for ERPs Ketamine v SCZ

- Z-Score transformed data of the differences in ERP measures between Ketamine in HNVs as compared to people with SCZ are shown as Figure 10.
- The group statistic ANOVA p<0.001, is highly significant including keeping MMN in the model. Note the large effect sizes observed.
- Table 5 lists ERP parameters, Z-Score statistical analyses and Cohen's d.

ERP Parameters[1] Lead specified	t	df	Two-Sided t-Test	Mean Difference	Std. Error Difference	Cohen's d[2]
P50 CZ	**-2.067**	**55**	**0.043**	**-0.64**	**0.31**	**-0.56**
N100 CZ	**2.932**	**55**	**0.005**	**0.68**	**0.23**	**0.79**
MMN FZ	**2.073**	**58**	**0.043**	**0.41**	**0.20**	**0.55**
P3A CZ	**-2.943**	**58**	**0.005**	**-0.76**	**0.26**	**-0.78**
P3B PZ	-1.129	55	0.264	-0.29	0.26	-0.30
ASSR40 ITC200-500 (ms) FZ [3]	**-2.041**	**58**	**0.046**	**-0.46**	**0.22**	**-0.54**
ASSR40 Evoked Power FZ	**-2.952**	**58**	**0.005**	**-0.73**	**0.25**	**-0.78**
Button Press Accuracy	**-2.458**	**55**	**0.017**	**-0.84**	**0.34**	**-0.66**
Median Response Time	**2.789**	**55**	**0.007**	**0.90**	**0.32**	**0.75**

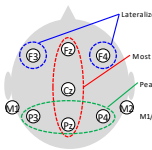
1. All ERPs are amplitudes in μV; 2. Cohen's d uses the pooled standard deviation; 3. ASSR 200-500 msec is considered sensitive to differences between HNV and SCZ; Bold rows ARE statistically significant

Fig. 10: Z-Score Difference ERPs (Active and Passive Oddball tasks) Between SCZ-HNV and Ketamine-PBO infusions



Nomenclature and EEG and ERP Descriptions

7 Leads Matching to International 10-20 Standard



Nomenclature	Frequency range Hz
δ^2	1.5 to <6.0
θ^2	6.0 to <8.5
α_1^2	8.5 to <10.5
α_2^2	10.5 to <12.5
β_1^2	12.5 to <18.5
β_2^2	18.5 to <21.0
β_3^2	21.0 to <30.0
Total power	1.5 to <30.0
γ	30.0 to <40.0
Dominant frequency	6.0 to <12.5
ASI	$\frac{\alpha_1^2 + \alpha_2^2}{\delta^2 + \theta^2}$
TBR	$\frac{\theta^2}{\beta_1^2 + \beta_2^2}$

FD-MMN Frequency Deviant Mismatch Negativity	Auditory Oddball Standard – 1000 Hz, 100 ms, 90 %, 85 dB Deviant = 2000 Hz, 100 ms, 10 %, 85 dB	Stimuli presented in pseudorandom order so that 6 to 12 standards were presented between deviants for a total of 1200 stimuli. The interstimulus interval was 600 ms.
DD-MMN Duration Deviant Mismatch Negativity	Auditory Oddball Standard = 1000 Hz, 50 ms, 90 %, 85 dB Deviant = 1000 Hz, 100 ms, 10 %, 85 dB	Stimuli presented in pseudorandom order so that 6 to 12 standards were presented between deviants for a total of 2000 stimuli. The interstimulus interval was 600 ms.
ASSR Auditory Steady-State Response 40 Hz	Stimulus Train 500 ms duration, 40 Hz white noise click trains, 85 dB	Click trains presented every 1000 ms for a total of 200 repetitions.
Active Oddball Single Deviant Infrequent Stimulus	Auditory Oddball Standard = 1000 Hz, 100 ms, 80 %, 85 dB Deviant = 2000 Hz, 100 ms, 20 %, 85 dB	Stimuli presented in pseudorandom order so that 2 to 5 standards were presented between deviants for a total of 300 stimuli. The interstimulus interval was randomized between 2500 and 3000 ms. Subjects were instructed to press a button on the ERP/EEG recording device as soon as possible each time they heard the deviant (target) stimulus.

Discussion and Conclusions

- It is constructive to look at (un)expected findings as well as the differences and similarities in electrophysiology between HNV Ketamine treated subjects and people with Schizophrenia.
- The use of the same acquisition paradigms, equipment, and data pipeline (for analyses) via the Cognision system, facilitates the combination of data from different studies with high reliability and reproducibility.

EEG

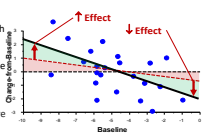
- **People with SCZ demonstrated expected EEG changes as did HNVs on Ketamine.**
- The differences between SCZ and Ketamine HNVs on EEG are striking (Z-Scores).
- Ketamine decreases lower frequency and dramatically increases gamma Power as compared to SCZ.
- Ketamine increases Dominant Alpha Frequency in HNVs and decreases alpha power, reflective of a potential EEG signature for antidepressants.
- Cohen's d for the statistically significant differences between people with SCZ and Ketamine in HNVs for findings (in 7 measures) range from ~0.5 to >0.8.
- **Power Spectrum EEG and calculated EEG ratio/parameter differences between SCZ and Ketamine subjects suggest that these measures do not reflect a substantial 'commanality' in brain surface electrical activity.**
- Other measures such as EEG coherence, connectivity analysis, task-based EEG, or sleep EEG are not addressed in this study.
- EEG is particularly well suited (reproducible, short sampling time of 5-10 minutes) for exploratory medicine and early phase pharmacologically focused studies.

ERPs

- **There are several ERPs frequently associated with Schizophrenia**
  - Mismatch Negativity as well as earlier post-odd ball stimulus measurements such as P50, N100, P200, and P3a are pre-attentive measurements of information/cognitive/working memory processing and are useful in subjects with active psychosis.
  - The ASSR 40 measures entrainment to a 40Hz 'click' (gamma range).
  - Active oddball tasks require attention and response to stimuli by the subject. When the odd ball variant tone is heard, the subject is instructed to press a button as soon as they hear the tone. This allows estimation of the P3b as well as functional parameters such as False Alarm (FA) Button presses, Button Press Accuracy (BPA), and Median Reaction Time (MRT).
  - **We see significant differences in our Z-score measurements for Patients with SCZ when compared with HNVs:**
    N100 CZ; MMN FZ; P3a CZ; P3b PZ
    ASSR40: ITC 200-500 msec FZ; ASSR40 Evoked Power FZ
    BPA and MRT
    Cohen's d range from an absolute value of 0.5 to > 1.1 for these measures.
- **Ketamine when compared with baseline or PBO** data showed significant effects on various ERP measures, consistent with the literature, including changes in N-100, P-200, and P3b (active oddball task).
- There were small decreases in performance on the active oddball task, i.e., increases in FA presses, however, BPA and MRT were unaffected, indicating that the dose of ketamine used did not significantly impair the subjects.
- Ketamine also demonstrated some differences (See poster QR code in intro):
  - ASSR40 usually demonstrates robust changes with Ketamine. However, our 1-hour long evaluation paradigm had ASSR at the 'end' of the ketamine infusion, where attenuation of effects as compared to earlier in the infusion are reported. (Sivarao, 2016)
  - Ketamine produced a "disordinal" effect on MMN amplitude: inducing larger changes with smaller MMNs at baseline and smaller changes with larger MMNs at baseline, not simply a regression to the mean (See our Poster for additional information using the QR code in the Intro section).

Fig 11: Regression to the Mean (RTM) vs Disordinal Effect Model Differences

Ketamine regression analysis fits a 'steeper' slope that is consistent with a disordinal effect. The test-retest ketamine trials (EBS-B) shows a statistically significantly steeper slope than RTM, i.e., the subjects with a positive Z-score at baseline (low MMN-A) have a negative Z-score for change: the peak goes more negative; the MMN-A gets larger.



  - The baseline MMN amplitude predicted the magnitude and direction of the on Ketamine MMN; a possible precision medicine approach?
- **Ketamine effects in HNVs when compared to people with SCZ** demonstrated statistically significantly different results (with the exception of P3b):
- People with SCZ were more 'impaired' than Ketamine HNV subjects on P50, P3a, ASSR40 ITC200-500, ASSR40 Evoked Gamma Power, and BPA; whereas
- HNVs on Ketamine were more impaired than People with SCZ on N100, MMN, and BPA.
- **These data suggest that even though we might assume similarities in electrophysiology based on the Ketamine Glutamate model for Schizophrenia, the reality as reflected in Z-Scores (the differences from HNVs in Schizophrenia and for HNVs receiving ketamine) is not clear.**
  - It is apparent that there are many measures that are significantly different between both groups with substantial Cohen's d values signifying substantial effect sizes.
- **There are several limitations** to this combined study strategy to evaluate similarities/differences in Schizophrenia (EBS-A) and HNVs on Ketamine (EBS-B).
  - Statistical evaluation of the data set was performed with repeated measures ANOVA, where missing values result in the subject being dropped. When the ANOVA was significant, we ran the t-test with all data included. We plan reanalyzing using a NLME model.
  - Patients with SCZ were clinically stable and on atypical antipsychotic medications, so EEG and ERPs do not reflect the untreated disease state. EEG effects from other medications were addressed.
  - MMN DD was conducted in ~ ½ of subjects in EBS-A; the first ½ of HNVs and people with SCZ had MMN FD performed.
  - The Ketamine infusion exposures were based on published recommendations, but dose and duration of infusion affect the readouts.
  - The MMN response to Ketamine was smaller then expected…likely due to a disordinal effect resulting in no significant differences from PBO. Details are provided in the poster QR code provided.
  - We did not analyze ERP latencies for this poster, nor used any visual stimuli ERPs.

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