ERP Biomarker Qualification Consortium

Baseline Mismatch Negativity Amplitude Predicts Direction and Magnitude of Ketamine Effect in Healthy Volunteers: a "Disordinal" Effect

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Introduction

The mismatch negativity (MMN) is neurophysiological response elicited during a passive oddball ERP paradigm where an occasional deviant stimulus is presented in a stream of more frequent standard stimuli. MMN is a negative deflection in the difference wave generated by subtracting the brain response to the standard stimulus from the response to the deviant stimulus, and it is thought to be linked to activity of the NMDA receptor (NMDAr).

Though numerous studies have generally reported that NMDAr antagonists such as Ketamine reduce the amplitude of the MMN peak, recent data suggests that the link between NMDAr function and mismatch negativity amplitude (MMN-A) is not as clear as once thought, with low dose and low affinity NMDAr antagonists observed to facilitate MMN (Harms, L. et al, 2021).

In our hands, Ketamine seems to show a bidirectional effect on MMN-A where Ketamine administration can suppress or augment MMN-A response based on the baseline level of NMDAr activation.

In here, we analyze results from four independent ERP studies to test the hypothesis that Ketamine has a disordinal effect on MMN-A, where the direction and magnitude of the Ketamine effect is dependent on, and can be predicted by the amplitude of the MMN response at baseline.

Materials and Methods

Study Design

We report the results from three double-blind, placebo-controlled clinical trials in healthy volunteers. For these studies (KET1 n=8, NCT04928703; KET2 n=19, NCT05049343; KET3 n=27, Hamilton HK et al. Schizophr Res. 2018 Jan;191:87-94), MMN-A was assessed during IV placebo/saline and during active Ketamine administration. IV Ketamine was administered at a dose of 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.

These Ketamine samples were used to assess the relationship between "baseline" MMN-A assessed during placebo and the change in MMN-A produced by Ketamine. Because baseline MMN-A may predict Ketamine-induced MMN-A change due to regression to the mean, we separately estimated the regression to the mean effect using a drug-free test-retest study (TR n=35) by examining the Time 1 MMN-A as a predictor of the change in MMN-A at Time 2.

ERP Data Collection and Analysis

ERP testing was performed using the COGNISION System for KET1, KET2 and TR, and a Neuroscan System for KET3. For all studies, the ERP paradigm included a duration-deviant oddball stimulus that was 50ms longer than the standard tone. To minimize the influence of attention on MMN, participants were instructed to ignore auditory stimuli while performing a primary visual task. Stimulus-locked EEG epochs were preprocessed for artifact removal, baseline-corrected, averaged to generate the ERP waves, and low-pass filtered at 30Hz. MMN-A was calculated as the amplitude of the most negative post-stimulus peak in the deviant minus standard difference wave.

Statistical Analysis

MMN-A data from each study were separately Z-score normalized with respect to the mean and standard deviation (SD) of the data from the placebo session (for Ketamine studies) or Time 1 session (for test-retest study) before statistical analyses were conducted. Specifically, each MMN-A value was subtracted from the placebo or Time 1 mean and divided by its SD. As a result, MMN-A data had a mean of zero and SD of 1 for each Ketamine study placebo session and for the test-retest study's Time 1 session. Time 2 and active Ketamine MMN-A were expressed as z-score deviations from the Time 1 or Placebo sessions.

Using these z-scored data, a linear regression model was run in which MMN-A z change-scores (Ketamine-Placebo or Time 2-Time1) were regressed on Study (dummy coding to represent 4 studies), MMN-A baseline/placebo or Time 1 z-scores, and the Study x MMN-A interaction. The interaction effect was of primary interest, providing a test of the slope differences of the regression lines between the studies.

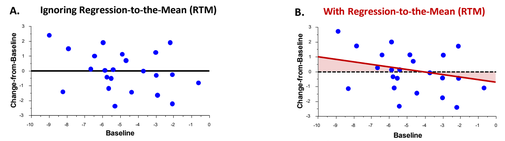
Based on the hypothesis that prediction of Ketamine-induced MMN-A change by placebo MMN-A reflected more than a regression to the mean effect, we expected the slopes of the Ketamine studies to be significantly steeper than the slope estimated from the test-retest study. A significant interaction effect was followed up with pairwise comparisons of the slopes between studies. Further, for differences in slopes between the test-retest study and the Ketamine studies, we conducted the Johnson-Neyman procedure to identify the range of MMN-A z-score values where the change induced by Ketamine is significantly larger or significantly smaller than the test-retest change.

For all comparison, threshold for statistical significance was set at p=0.05.

Regression to the Mean or Disordinal Effect?

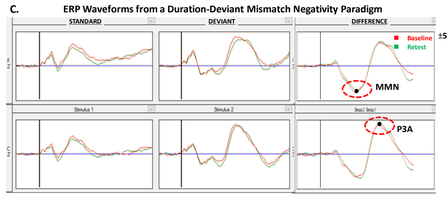
Regression with Perfect Correlation of the Means

When plotting a regression of Baseline vs Change-from-Baseline, if the means are perfectly correlated there are 2 possible regression slopes: (A) One in which Regression-to-the-Mean (RTM) is ignored and (B) one in which RTM is considered. When RTM is considered the regression will have a small, non-zero, slope. This RTM effect must be factored into any study design using a "no-drug" condition and a "drug" condition within the same subject. These studies include pre-dose vs post-dose studies and placebo vs drug in cross-over designs.

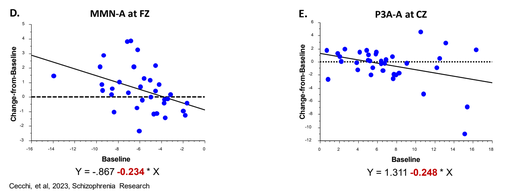


Regression-to-the-Mean with "No-Drug" Condition

The image below (C) shows the grand average waves from 80 healthy subjects tested at Baseline then again at Retest. When a Baseline vs Change-from-Baseline regression analysis is performed for the MMN amplitude (D) and the P3A amplitude (E) an RTM slope will emerge. NOTE that the red numbers are the RTM slope.

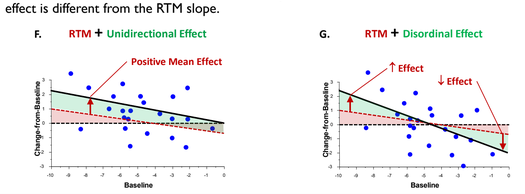


The two images below (D) show results from a published study in which participants where tested twice under "NO-DRUG" conditions. In these examples, the slopes (0.234 and 0.248) represent only RTM.



Baseline vs Change-from-Baseline with an Active Drug

An active drug can have 2 possible effects on the parameter of interest: (F) The drug could have a "unidirectional" effect (post-drug) in which the regression line would be offset from the baseline (pre-drug) RTM slope; (G) The drug could also have a "disordinal" effect (post-drug) in which the magnitude AND direction of the effect is dependent upon and can be predicted by the baseline (pre-drug) value. This effect can be detected by an increased rotation of the regression slope over the baseline RTM slope. This disordinal effect can be difficult to identify when the rotation of the effect slope is in the same direction as the RTM slope. In this case, a statistical comparison of slopes analysis must be performed to demonstrate that the disordinal effect is different from the RTM slope.



Results

Study Subject Demographic Data

Table 1. Demographics for study completers.

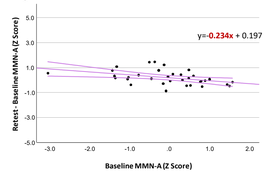
Study	*TR*	*KET1*	*KET2*	*KET3*
Sample Size	35	8	19	27
Age[1]	38.11 (1.91)	35.25 (1.82)	42.56 (2.06)	25.78 (1.2)
Gender				
Male[2]	17 (48.6%)	6 (75%)	13 (68.4%)	15 (55.6%)
Female[2]	18 (51.4%)	2 (25%)	6 (31.6%)	12 (44.4%)
Race				
White[2]	8 (22.9%)	2 (25%)	8 (42.1%)	21 (77.8%)
African American[2]	4 (11.4%)	5 (62.5%)	11 (57.9%)	1 (3.7%)
Other[2]	23 (65.7%)	1 (12.5%)	0 (0%)	5 (18.5%)
Education[1]	13.83 (0.32)	12		15.52 (0.51)
BMI[1]		26.99 (0.92)	27.21 (0.5)	23.88 (0.96)

Abbreviations: BMI = Body Mass Index.
Notes:
1. Mean (±SEM).
2. Total (% of Total).

Regression-to-the-Mean (RTM)

Linear regression for MMN-A Z-scores at Baseline vs. Retest Change from Baseline. Lines are linear fit with confidence intervals (95% of mean). Statistical analyses for the regression showed p=0.012 and R^2=0.176. The slope of the regression is 0.234.

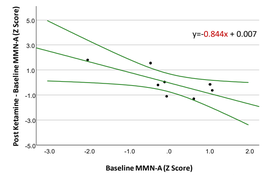
TR Study



Linear regression for MMN-A Z-scores at Baseline vs. Retest Change from Baseline for KET1. Lines are linear fit with confidence intervals (95% of mean). Statistical analyses for the regression showed p=0.035 and R^2=0.549. The slope of the regression is 1.844.

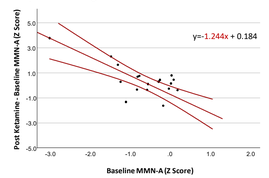
Change from Baseline after Ketamine

KET1 Study



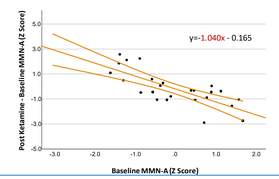
Linear regression for MMN-A Z-scores at Baseline vs. Retest Change from Baseline for KET2. Lines are linear fit with confidence intervals (95% of mean). Statistical analyses for the regression showed p<0.001 and R^2=0.584. The slope of the regression is 1.244.

KET2 Study



Linear regression for MMN-A Z-scores at Baseline vs. Retest Change from Baseline for KET3. Lines are linear fit with confidence intervals (95% of mean). Statistical analyses for the regression showed p<0.001 and R^2=0.564. The slope of the regression is 1.040.

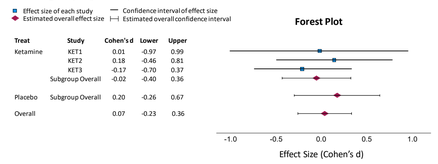
KET3 Study



Across Studies Comparisons

Ketamine Group Effects

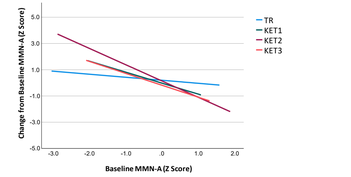
The forest plot illustrates the effect sizes for the KET studies compared to TR. Positive effect sizes indicate smaller MMN-A than at Baseline. Overall, there was no significant difference between Ketamine and Placebo subgroups (p=0.46).



Treat	Study	Cohen's d	Lower	Upper
Ketamine	KET1	0.01	-0.97	0.99
	KET2	0.18	-0.46	0.81
	KET3	-0.17	-0.70	0.37
	Subgroup Overall	-0.02	-0.40	0.36
Placebo	Subgroup Overall	0.20	-0.26	0.67
Overall		0.07	-0.23	0.36

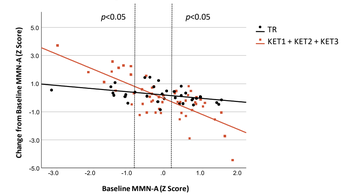
Slope Comparisons Across the 4 Separate Studies

Linear regressions for MMN-A Z-scores at Baseline vs Retest Change from Baseline for the 4 separate studies. Statistical analyses showed a significant overall difference for slopes across studies (p<0.001). Relative to TR, significantly steeper slopes were observed for KET2 (p<0.001) and KET3 (p<0.004) with a trend towards significance for KET1 (p=0.082). Slopes for the 3 Ketamine studies did not differ from each other (p=0.502).



Slope Comparisons for Test-Retest vs Combined Ketamine Studies

Linear regressions for MMN-A Z-scores at Baseline vs Retest change from Baseline for TR vs the combined data from the KET studies. Relative to TR, KET (beta = -1.087) showed a significant difference in slope (p<0.001). Subsequent Johnson-Neuman analysis indicated that Ketamine significantly decreased MMN-A for Z-scores lower than -0.7727 (21.84% of the distribution; p=0.05), and significantly increases MMN-A for Z-scores higher than 0.1781 (44.83% of the distribution; p=0.05).



Conclusions

- Ketamine produces a "disordinal" effect on MMN amplitude, inducing decreases in subjects with larger MMNs at baseline and increases in subjects with smaller MMNs at baseline, that is distinct from regression-to-the-mean.
- These findings suggest fundamentally new approaches for precision medicine in the treatment of CNS disorders.

References

- Effects of Ketamine on ERP/EEG Measures in healthy volunteers. (NCT04928703).
- Study of SAGE-904 using a Ketamine challenge to evaluate electrophysiology, safety, tolerability, and pharmacokinetics in healthy participants (NCT05049343).
- Hamilton, H.K. et al. (2018) Interactive effects of an N-methyl-d-aspartate receptor antagonist and a nicotinic acetylcholine receptor agonist on mismatch negativity: Implications for schizophrenia. Schizophr Res. 2018 Jan:191:87-94.
- Cecchi, M. et al. (2023) Magnitude and repeatability of Ketamine effects on ERP and QEEG biomarkers in a double-blind, randomized, placebo-controlled, crossover study in healthy volunteers. Poster presentation. CNS Summit, Boston, MA.