Translational Utility of ERP and Time-Frequency Features for Cognitive Impairment in Schizophrenia: Preclinical Evaluation of MK-801 Deficits and Rescue by ALTO-101

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1. Introduction

- Cognitive Impairment Associated with Schizophrenia (CIAS) remains an area of major unmet need, with no approved medications specifically targeting these deficits.
- Electroencephalography (EEG) signals, including event-related potentials (ERPs), are promising translational pharmacodynamic (PD) tools in schizophrenia (SCZ).
- Previously, we identified theta response, measured by theta inter-trial coherence (ITC), to be a promising neural marker of CIAS, as it is consistently disrupted in patients with SCZ and strongly correlates with their cognitive impairments.
- A leading hypothesis posits that N-methyl-D-aspartate receptor (NMDAR) hypofunction plays a key role in CIAS pathophysiology.
- This study used a rat model to assess (1) the effect of MK-801, an NMDAR antagonist, on theta ITC and other schizophrenia-related ERP markers and (2) whether ALTO-101, a novel phosphodiesterase-4 (PDE4) inhibitor, could rescue the MK-801 induced deficits.

2. Study Design

- We conducted two separate crossover studies in male Sprague-Dawley rats that were implanted with wireless EEG transmitters. Transcranial screw recordings were performed in a frontal channel.
  (1) In the MK-801 study, rats received vehicle and each of two doses of MK-801.
  (2) In the MK-801 + ALTO-101 study, all rats received a fixed dose of MK-801 and were additionally treated with three doses of ALTO-101 and vehicle.
- ERP responses were captured at multiple timepoints using two paradigms— Auditory oddball and Auditory Steady-State Response (ASSR).

	MK-801	ALTO-101 + MK-801
Doses tested	Vehicle; MK-801 at 0.1 or 0.3 mg/kg	Vehicle; ALTO-101 at 0.003, 0.03, or 0.1 mg/kg; MK-801 at 0.1 mg/kg in all arms
Sample size	N = 15	N = 14

PD markers of interest:

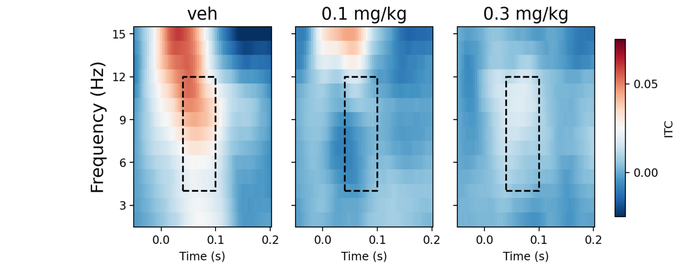
- Theta inter-trial coherence (ITC)
  - Passive auditory oddball task (standard trials)
  - Blunted in SCZ, related to cognitive impairment
- ASSR Gamma inter-trial coherence (ITC)
  - Blunted in SCZ
- Mismatch Negativity (MMN)
  - Blunted in SCZ, related to cognitive impairment
- N1
  - Blunted in SCZ, related to auditory processing

3. Data Analysis

- We utilized mixed-effects analyses to model EEG features as a function of treatment, time, and dosing sequence, while adjusting for baseline values and accounting for each animal's unique characteristics.

4. MK-801 decreases theta ITC

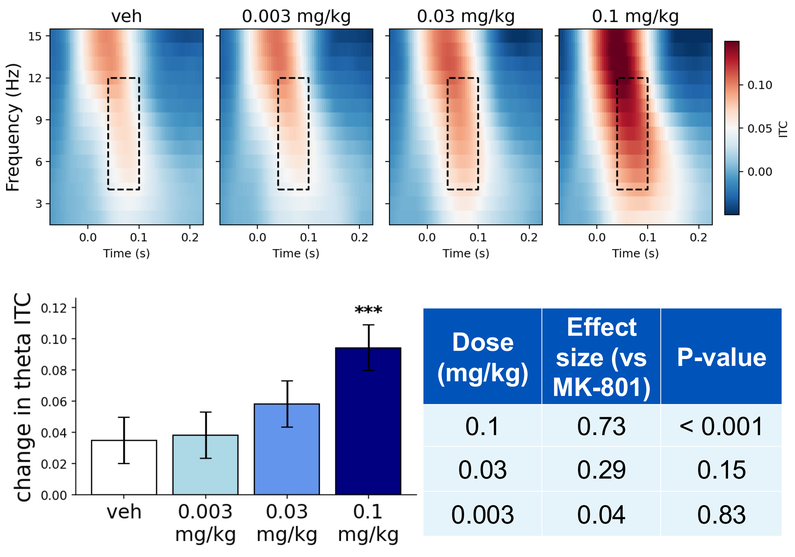
Strong dose dependent decrease in theta ITC



Dose (mg/kg)	Effect size (vs vehicle)	P-value
0.3	-1.25	< 0.001
0.1	-1.16	< 0.001

5. ALTO-101 increases theta ITC in MK-801 treated rats

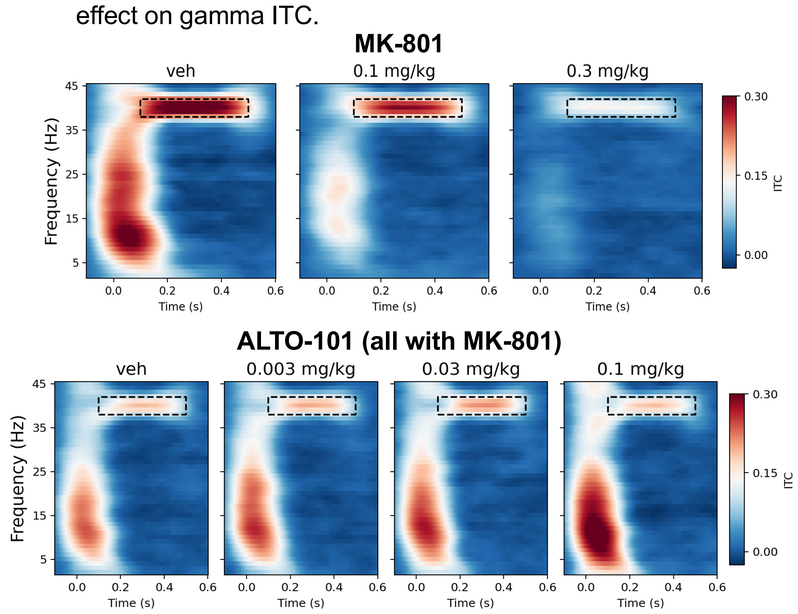
Dose dependent increase in theta ITC (all with 0.1mg/kg MK-801)



Dose (mg/kg)	Effect size (vs MK-801)	P-value
0.1	0.73	< 0.001
0.03	0.29	0.15
0.003	0.04	0.83

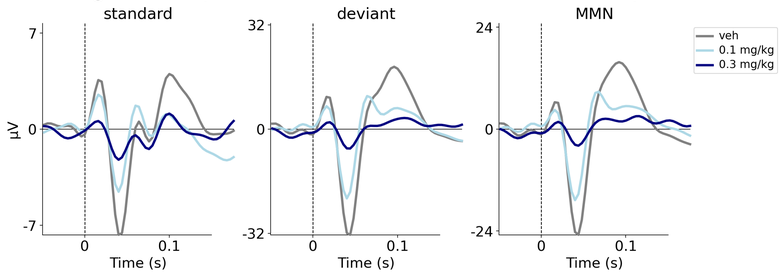
6. Time-frequency response to ASSR click trains

- MK-801 decreases theta and gamma ITC (boxed).
- ALTO-101 increases theta ITC in MK-801 treated rats. No effect on gamma ITC.



7. MK801 decreases MMN and N1 amplitudes

Strong dose dependent decrease in N1 and MMN amplitudes

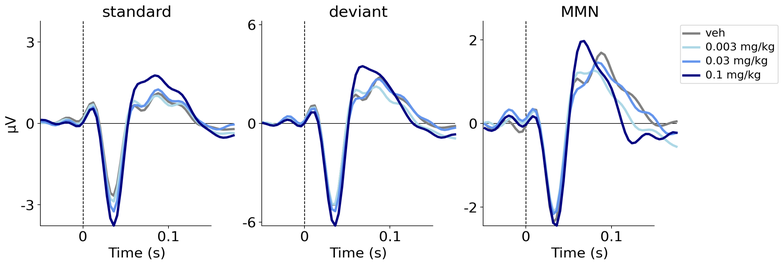


Summary table of 0.1 mg/kg MK-801 effects

	N1 (standard)	N1 (deviant)	MMN
Effect size (vs vehicle)	-0.86	-0.82	-0.69
P-value	< 0.01	< 0.01	< 0.01

8. ALTO-101 increases N1 amplitudes

Dose dependent increase in N1 amplitudes



Summary table of 0.1 mg/kg ALTO-101 effects (all with MK-801)

	N1 (standard)	N1 (deviant)	MMN
Effect size (vs MK-801)	0.49	0.33	0.09
P-value	0.01	0.06	0.58

9. Conclusions

- MK-801 reduces EEG theta response in rodent model, thereby modeling aspects of CIAS-related pathophysiology.
- ALTO-101 led to a dose-dependent rescue of theta response from deficits induced by MK-801.
- This result is consistent with Alto's Phase 1 trial, where ALTO-101 increased theta ITC compared to placebo in healthy human volunteers - as previously reported at the Schizophrenia International Research Society (SIRS) in 2025.
- These results underscore the therapeutic potential of ALTO-101 to rescue blunted EEG theta response in a preclinical model of CIAS.

10. Acknowledgments

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