ALTO-101 Modulates EEG Biomarkers Linked to Cognitive Impairment in Schizophrenia: Evidence from a Phase 1 Trial and BSNIP Studies

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1. Introduction

- Cognitive Impairment Associated with Schizophrenia (CIAS)
  - A key determinant of long-term functional outcomes
  - **No currently approved pharmacological treatments**
- EEG Biomarkers for CIAS Drug Development
  - Electroencephalography (EEG), including event-related potentials (ERPs), provides cost-effect, objective neural measures tied to cognition
  - Large-scale studies (e.g., BSNIP) can help pinpoint EEG/ERP markers that are both most affected in schizophrenia and strongly correlated with cognitive deficits
- PDE4 Inhibition: Promising Therapeutic Strategy
  - Enhancing intracellular cyclic adenosine monophosphate (**cAMP**) signaling has shown pro-cognitive effects in preclinical and clinical research
  - **Phosphodiesterase-4 (PDE4)** inhibitors raise cAMP levels by preventing its breakdown, representing a promising therapeutic strategy for CIAS
  - **ALTO-101** is a novel, selective PDE4 inhibitor with strong central nervous system penetration, potentially improving cognitive outcomes and modulating EEG biomarkers relevant to CIAS

2. Study Design and Analysis

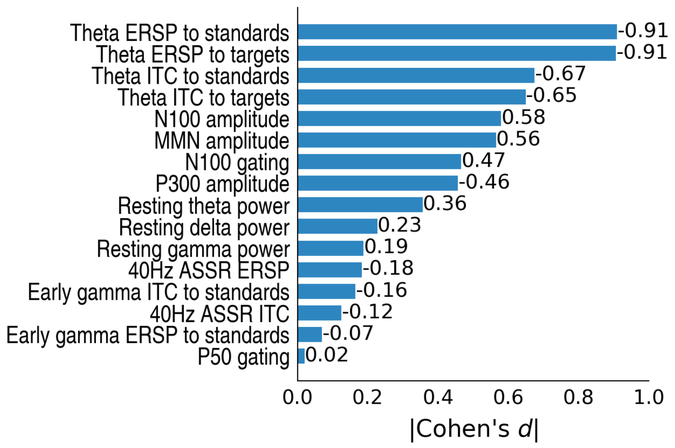
BSNIP Studies

- Participants:
  - BSNIP 1 and 2: **625 patients** with schizophrenia or schizoaffective disorder, **641 healthy controls**
  - Focus on individuals matching CIAS trial populations
- EEG Measures:
  - Resting-state spectral power
  - ERPs from
    - Active auditory oddball task
    - Sensory gating (paired auditory stimuli) task
    - Auditory steady-state responses (ASSR) task
- Cognition measured by the Brief Assessment of Cognition in Schizophrenia (BACS)
- **Discovery & Validation** Sets:
  - 50% discovery set
  - 50% locked validation set for prospective replication

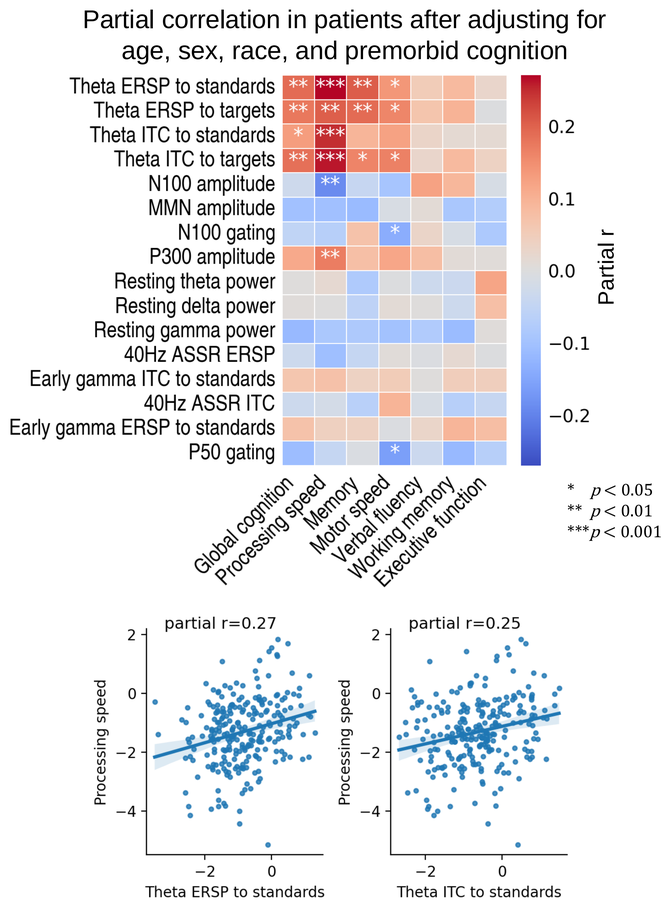
ALTO-101 Phase 1 Study

- Participants:
  - 40 healthy volunteers (age: 40-64)
  - Single oral dose of **placebo**, **0.5 mg ALTO-101**, and **1.5 mg ALTO-101** in a crossover, double-blind design
  - 7-day washout between doses
- EEG Measures:
  - Resting-state spectral power
  - Mismatch negativity (MMN) amplitude
  - Task-related theta and gamma responses
    - Inter-trial coherence (ITC)
    - Event-related spectral perturbation (ERSP)
- Mixed-effects models were used to evaluate the effects of ALTO-101 vs placebo

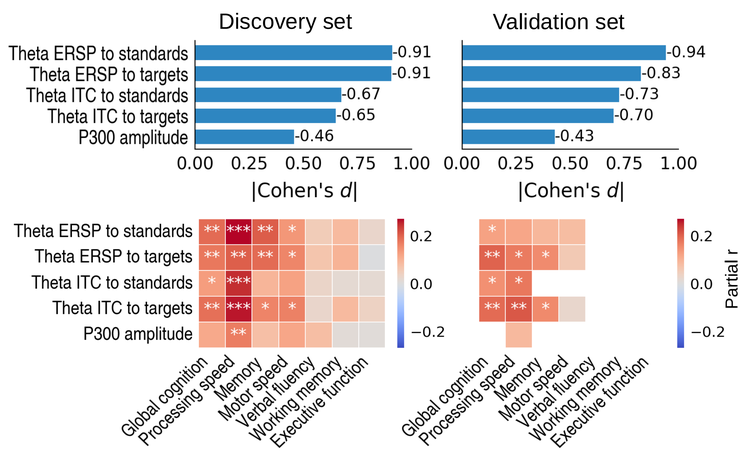
3. BSNIP: Patients vs. Controls in Discovery Set



4. BSNIP: Cognitive Association in Discovery Set

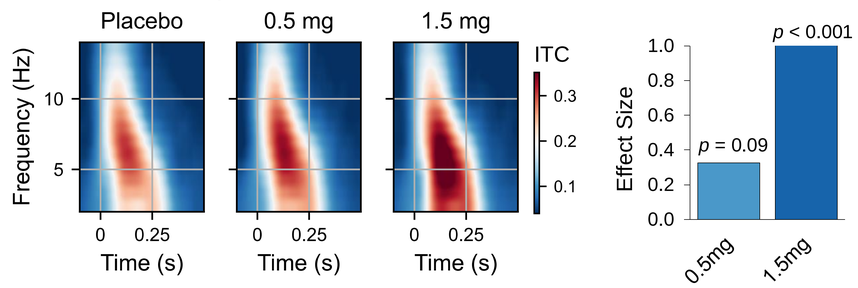


5. BSNIP: Replication Analysis

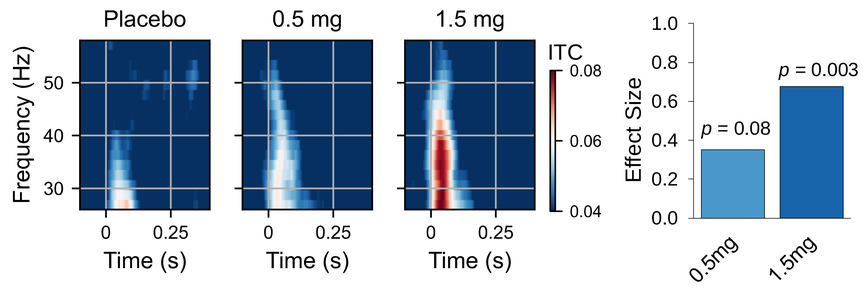


6. ALTO-101 Phase 1 Findings

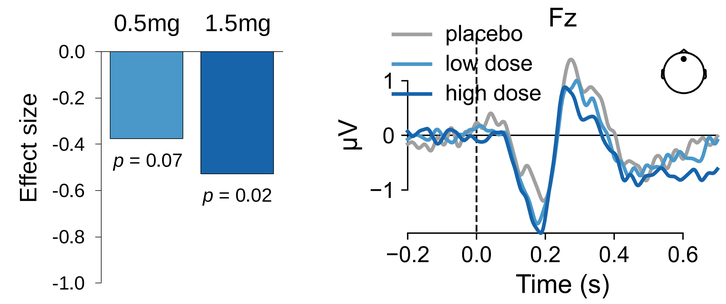
- Dose-dependent increase in **theta response** to standard stimuli (measured by theta ITC at Cz, with a similar effect for theta ERSP)



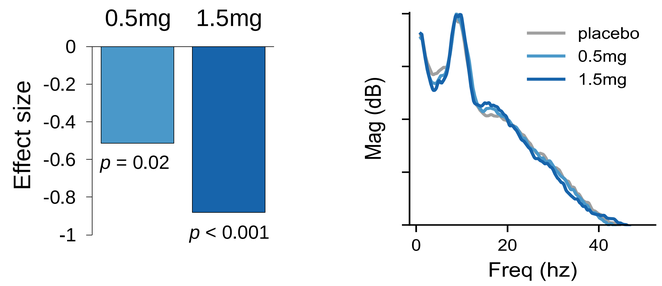
- Dose-dependent increase in gamma response to standard stimuli (measured by gamma ITC at Pz)



- Dose-dependent increase in MMN amplitude (Fz)



- Dose-dependent decrease in relative theta power (Fz)



7. Conclusions

- BSNIP findings indicate theta responses are the EEG features most disrupted in schizophrenia and correlate strongly with cognitive performance
- ALTO-101 significantly enhances theta responses, suggesting potential cognitive benefits for patients with CIAS
- A Phase 2 proof-of-concept study of ALTO-101 in CIAS is currently underway

8. Acknowledgments

- We thank all participants and study staff involved in the ALTO-101 Phase 1 trial and the BSNIP consortium.
- All authors receive salary and equity compensation from Alto Neuroscience. A. Savitz holds equity in J&J.