Identification and Prospective Replication of Electrophysiological Markers Linked to Cognitive Impairment in Schizophrenia (CIAS)

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1. Introduction

- Cognitive impairment associated with schizophrenia (CIAS) is a major driver of long-term outcomes
- Currently, there are no approved treatments for CIAS
- The search for effective therapies may benefit from translational pharmacodynamic markers such as electroencephalography (EEG)
- Prior work has examined EEG markers selectively or in small Ns. Here we compared all markers head-to-head in well-powered and clinically-broad samples
- This research focused on identifying the EEG markers best correlated with CIAS and sensitive to schizophrenia
- The findings are prospectively replicated, and are intended to guide future drug development for CIAS

2. Study Design

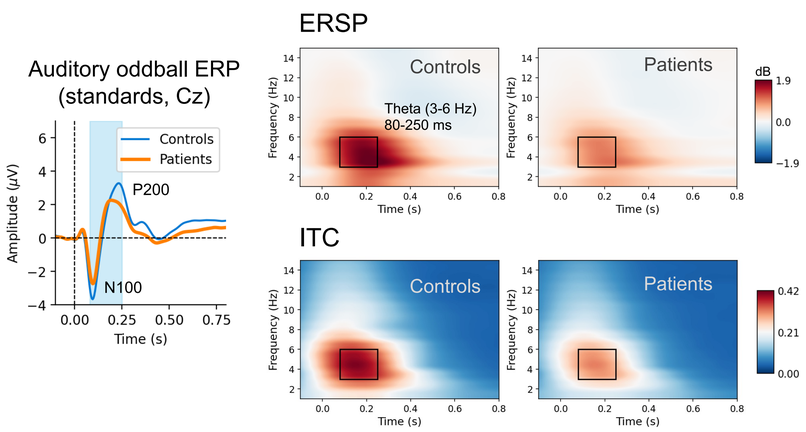
- Data from the Bipolar and Schizophrenia Network for Intermediate Phenotypes (BSNIP-1 and BSNIP-2) studies
- Patient group of interest were consistent with CIAS trial populations:
  - 18-55 years old with schizophrenia (SCZ) or schizoaffective disorder (SAD)
  - No more than a “moderate-severe” rating (<=5) on P1, P3-6, and a “moderate” rating (<=4) on P2 and P7 in PANSS
- EEG data were recorded from:
  - Eyes-open resting state
  - Active auditory oddball task
  - Auditory paired stimuli task
  - Auditory steady-state response (ASSR) task
- 641 healthy controls, 625 patients with EEG data from at least one task (93% also with cognition data)
- Cognition measured by the Brief Assessment of Cognition in Schizophrenia (BACS)
- We combined BSNIP-1 and BSNIP-2, and designated a random 50% of the patient data as a discovery set and the remaining 50% as a locked test set for prospective replication

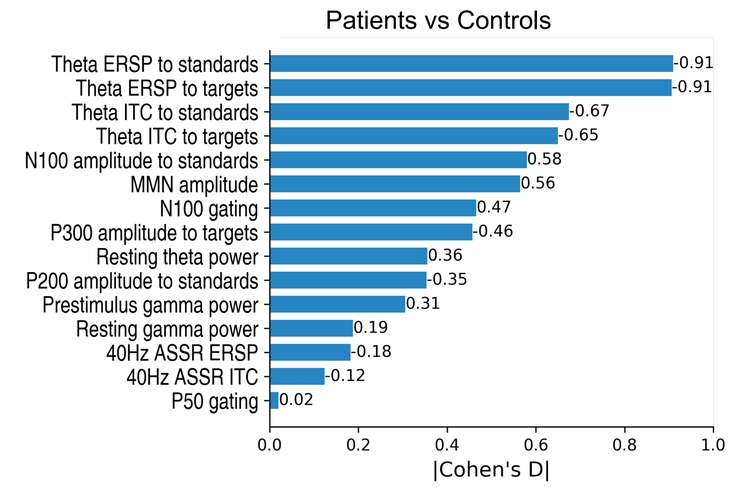
	N	Age	Male%	Edu years	Diagnosis (SCZ/SAD)	PANSS positive	PANSS negative
Discovery	305	36.0 (11.1)	58.0	13.1 (2.4)	175/130	16.0 (5.0)	15.0 (5.4)
Test	320	35.9 (11.4)	55.9	13.0 (2.3)	174/146	15.7 (5.0)	15.6 (5.5)

3. Data Analysis

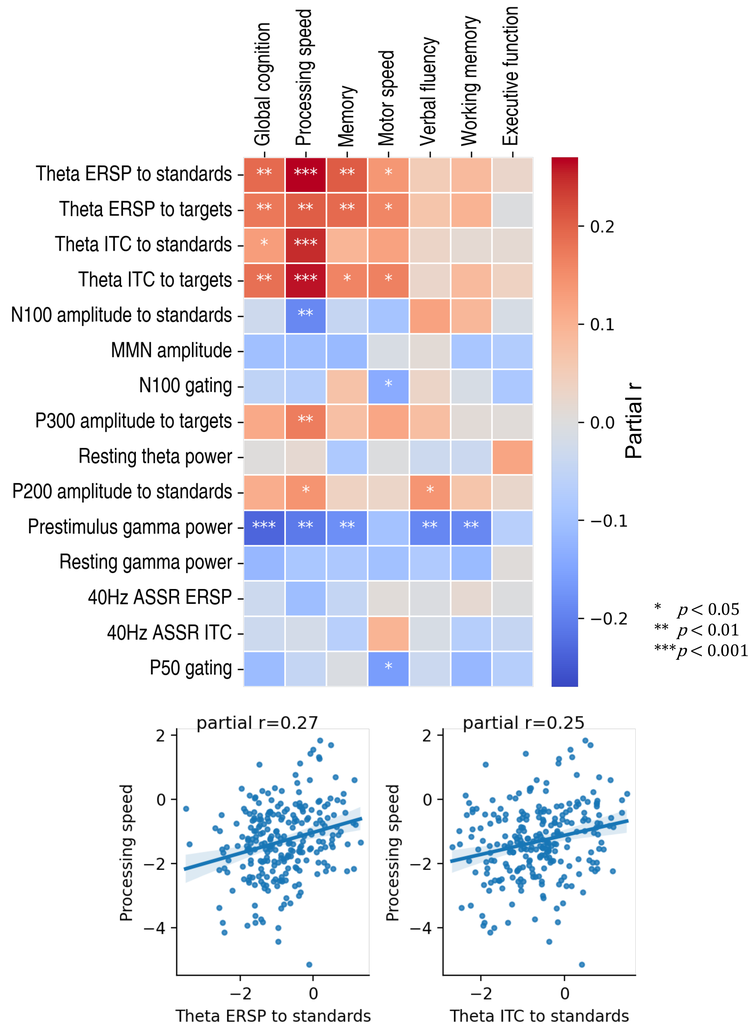
- Band powers, event-related potentials (ERPs), and time-frequency markers including event-related spectral perturbation (ERSP) and inter-trial coherence (ITC) were extracted from EEG data
- EEG markers were normed by age and sex based on the BSNIP1/2 healthy control data
- Norms were applied for BACS (Keefe et al., 2008)
- Correlations between EEG markers and cognition were assessed using partial correlations, adjusting for age, sex, race, and premorbid functioning (as measured by WRAT-4 reading subtest)
- Successful replication in test set was determined by one-sided $p < 0.05$ after false discovery rate (FDR) correction

4. Case-control Difference in Discovery Set



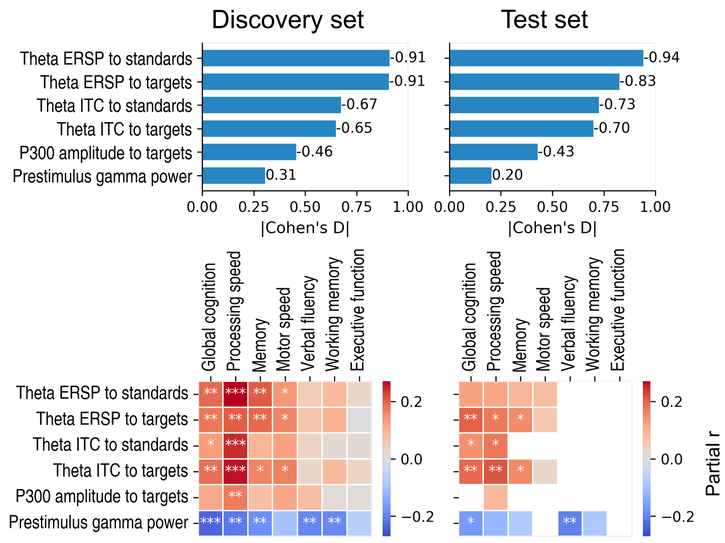


5. Associations with Cognition in Discovery Set



6. Prospective Replication

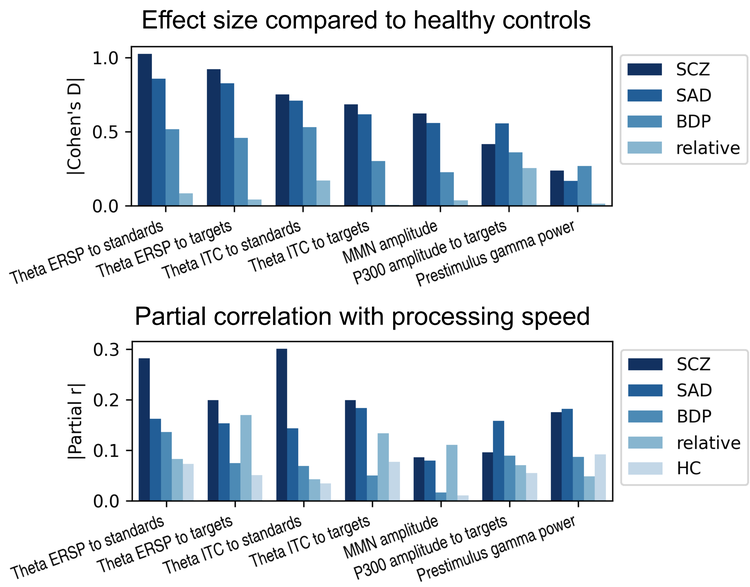
Candidates for replication were predefined based on statistical significance and consistency before unlocking the test set



7. Results in Different Participant Groups

Sample size for all available subjects with oddball data

	Healthy controls	SCZ	SAD	Bipolar with psychosis (BDP)	Relatives of probands
N	487	411	295	251	519



8. Conclusions

- Conventional ERP markers, including P300 and MMN, show weak correlations with cognition in SCZ patients
- Reduced theta responses (ERSP and ITC) linked to poorer processing speed likely reflect disrupted neural synchronization that underpins efficient sensory processing – a core cognitive deficit in SCZ
- Theta ERSP and ITC may serve as pharmacodynamic markers for candidate CIAS drugs
- These markers hold potential for translational applications across different species

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