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Clozapine is linked with altered EEG intertrial phase coherence compared to other second-generation antipsychotics in schizophrenia patients

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INTRODUCTION

- Event-Related Potential (ERP) studies in patients with schizophrenia often report reduced amplitudes of several ERP components, such as the Mismatch Negativity and P300 [1].
- Recent research has shown that the decreased ERP amplitudes in schizophrenia patients are linked to a larger temporal variability in neural processing [2].
- A recent model, the phase-based temporal imprecision model of psychosis (PTP), might explain these findings as it proposes that decreased phase coherence of neural oscillations in patients with psychosis reflects a temporal imprecision in neural synchronization that might be a core neuronal dysfunction of these disorders [3].
- The PTP proposes intertrial phase coherence (ITPC), a metric quantifying oscillatory phase coherence across repeated presentations of stimuli (Figure 1), as a potential biomarker for psychosis and schizophrenia given that it is consistently decreased in schizophrenic patients compared to healthy controls across several ERP paradigms [3].
- Animal studies have shown that Clozapine, an antipsychotic reserved for treatment-resistant schizophrenia, uniquely increases ITPC in Sprague Dawley rats, hinting at the fact that ITPC is sensitive to antipsychotic medication status [4]. Whether this is also true in patients with schizophrenia is currently unknown.
- In this study, we investigate whether ITPC differs by medication status (Clozapine vs. No Clozapine) in a cohort of patients with schizophrenia or schizoaffective disorder.

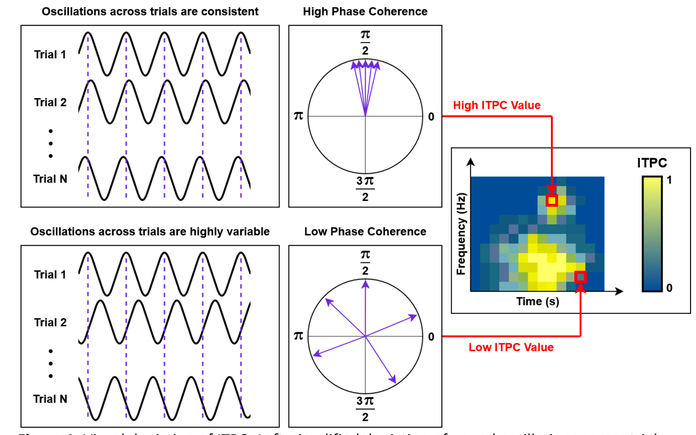

Figure 1: Visual depiction of ITPC. *Left:* simplified depiction of neural oscillations across trials. *Middle:* phase of individual trials (arrows). *Right:* Plot of ITPC values across time and frequency.

METHODS

- A publicly available EEG dataset of 45 patients with schizophrenia/schizoaffective disorder (22 prescribed Clozapine (37 ± 8.9 years; 3 females); 23 prescribed other second-generation antipsychotics (39.5 ± 9.5 years; 14 females)) was used [5].
- EEG was recorded from 64 channels while participants performed a modified Simon task (See Figure 2 for the visualization of a single trial). EEG data were filtered (60 Hz notch, 1–40 Hz bandpass), bad channels were interpolated, eye artifacts were removed using ICA, and signals were re-referenced to the average.
- Two event types were analyzed: *stimulus presentation*, when participants viewed a stimulus, and *response initiation*, when participants pressed a button (Figure 2). For each event type, epochs were extracted (-800ms to +1100ms from the stimulus). To avoid bias in the ITPC computation, the same number of epochs (N=273 for stimulus presentation, N=270 for response initiation) were used across all subjects, randomly selected from all epochs without artifacts.
- Time–frequency analysis (1–40 Hz, 1 Hz resolution, number of cycles = frequency/2) was performed using complex Morlet wavelets to extract average power and ITPC for three electrode groups: frontal left (electrodes Fp1, Af3, Af7, F3, F5, F7), frontal central (electrodes Afz, Fz, F1, F2), and frontal right (electrodes Fp2, Af4, Af8, F4, F6, F8).
- Group differences ("Clozapine" vs. "No Clozapine") in ITPC were assessed with cluster permutation tests (F-test, 10,000 permutations, threshold-free cluster enhancement), and power differences were additionally evaluated to control for their potential influence on ITPC [6]. Given the limitations of the dataset, F-tests were used to assess group differences, but no direction of any potential differences between groups was investigated.

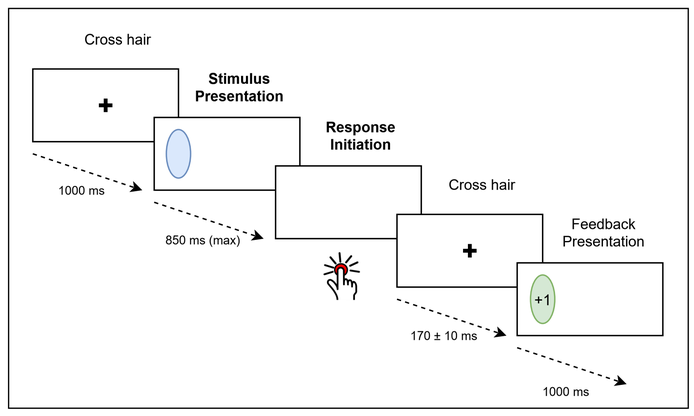

Figure 2: Single trial of the modified Simon Task. The two event types (stimulus presentation; response initiation) which were analyzed are highlighted in bold.

RESULTS

Stimulus Presentation

- In the average ERP plots of the stimulus presentation events, no clear visual difference between the Clozapine and No Clozapine group can be identified (Figure 3, upper row).
- In the average ITPC plots, cluster permutation testing identified no large clusters in any of the three electrode groups within the range of stimulus presentation.
- A significant cluster was identified in the frontal right group around 800-1000 ms post stimulus in the beta range (±25-30 Hz), but its occurrence lies outside of the presentation duration of the stimuli (Figure 2).

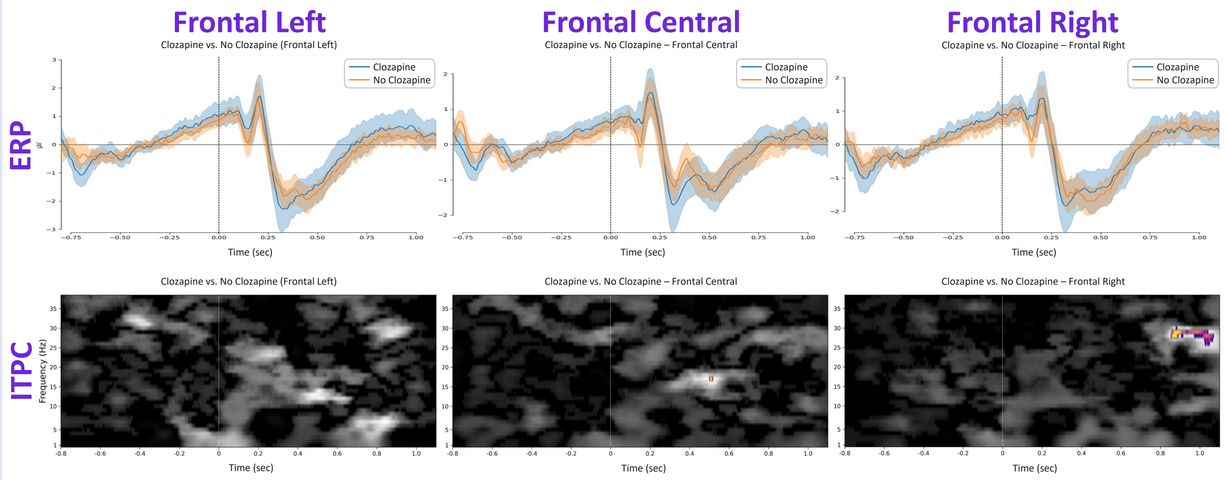

Figure 3: average ERP plots with confidence interval (upper row) and ITPC difference plots (lower row) for the stimulus presentation events for the frontal left, central, and right electrode groups (left, middle, and right column). Colored regions in the ITPC plots denote clusters where ITPC values are statistically significant between groups.

Response Initiation

- In the average ERP plots of the response initiation events, no clear visual difference between the Clozapine and No Clozapine group can be identified (Figure 4, upper row).
- In the average ITPC plots, cluster permutation testing identified significant clusters ($p < 0.05$) between the Clozapine and No Clozapine group in all three electrode groups (Figure 4, bottom row).
- Identified clusters all lie around the response trigger (± -100 to 200 ms) and are in the delta and theta range (±1 to 8 Hz).
- No significant clusters in the corresponding time-frequency power values were identified, so no strong evidence is present that ITPC differences are driven by power differences [6].

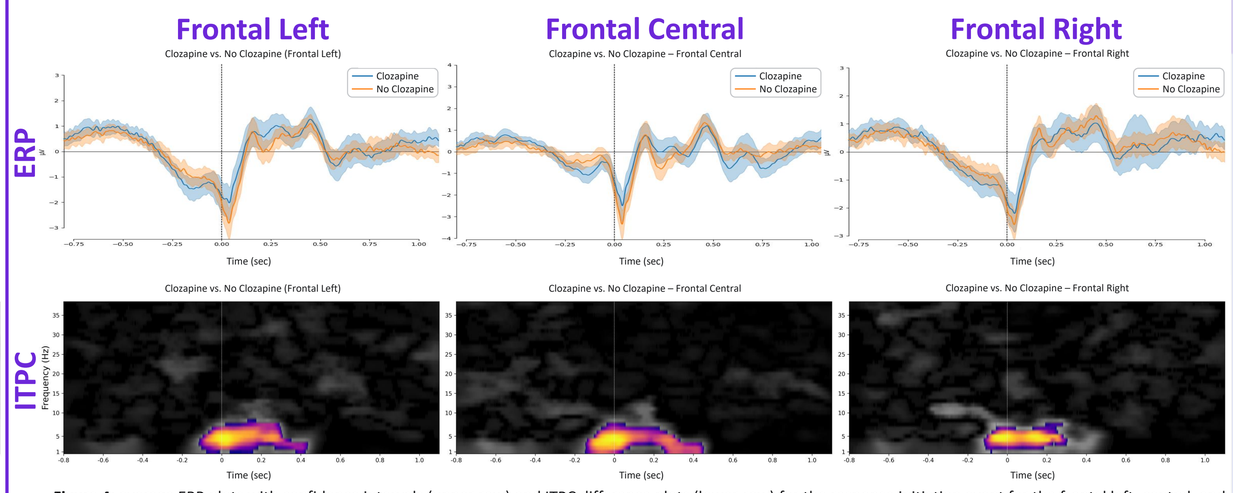

Figure 4: average ERP plots with confidence intervals (upper row) and ITPC difference plots (lower row) for the response initiation event for the frontal left, central, and right electrode groups (left, middle, and right column). Colored regions in the ITPC plots denote clusters whare ITPC values are statistically significant between groups.

CONCLUSION

- No differences in average ERPs can be identified when comparing patients with schizophrenia or schizoaffective disorder who were either administered Clozapine or other second-generation antipsychotics, suggesting that commonly employed ERP metrics such as amplitude or latency are not sufficient to capture the effect of antipsychotic medication on neural processing in patients with schizophrenia or schizoaffective disorder.
- Using ITPC to investigate potential differences in neural processing due to medication status, significant clusters were identified around the response initiation events (± -100 to 200 ms) in the delta and theta range (± 1-8Hz), highlighting the capability of ITPC to capture medication-dependent differences in neural processing.
- Clusters were identified in all three electrode groups, showing that the difference is not limited to a single electrode but can be identified in all frontal electrodes.
- Limitations of the employed dataset such as differences in disease phenotype (Clozapine is reserved for treatment-resistant schizophrenia), differences in gender distribution across groups, and the limited sample size makes further interpretation of the identified differences difficult. Future studies should further elucidate the precise effect of distinct antipsychotics on ITPC in patients with schizophrenia or schizoaffective disorder.
- This study provides support for the phase-based temporal imprecision model of psychosis and further highlights the potential of ITPC as a biomarker for schizophrenia and schizoaffective disorder given that it is both sensitive and specific to these disorders [3], can reliably be investigated across multiple ERP paradigms [3], and can capture medication-specific differences in neural processing within the patient population.

References

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