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ERP Signature of the Visual Go/Nogo Task in Acute Schizophrenia

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Abstract

Background

Motor response inhibition deficits are a core feature of executive dysfunction in schizophrenia, with the N2 and P3 event-related potential (ERP) components during Go/Nogo task serving as key neural markers. While reductions in N2 and P3 amplitudes, as well as anteriorized P3 topography, have been documented in stable outpatients with schizophrenia, their presence in acute inpatients remains unexplored.

Methods

We collected high-density EEG in 23 inpatients with schizophrenia, recruited within 72 hours of admission in psychiatric hospital, and 23 healthy controls. We preprocessed data with MNE-Python, including filtering (0.2–40Hz), artifact rejection, and independent component analysis.

Results

Acute inpatients displayed a > 50% reduction in frontal Nogo N2 absolute amplitude compared to healthy controls (p=.003, g=-0.939). Inpatients also exhibited an anteriorized Nogo P3 (group*ROI interaction: p=.018, g = 0.78). In the Go condition, patients displayed more variable single-trial peak latency (N2: p<.001, g=-1.363; P3: p<.001, g=-1.086). Most ERP metrics correlated with task performance across both groups, but not with acute symptom severity.

Conclusion

We extended previously reported ERP alterations in stable outpatients to acute inpatients, with large effect sizes. This supports the potential use of visual Go/Nogo ERPs as diagnostic biomarkers of schizophrenia across different phases of the illness. Correlations between ERP components and behavioral performance highlight their functional relevance. These results provide the first characterization of the neural signature of visual Go/Nogo task in acute schizophrenia. Its neurobiological underpinnings and clinical relevance as biomarkers warrant further investigation.

1. Background

Schizophrenia is a severe, chronic psychiatric disorder, characterized by a relapsing-remitting course with recurrent acute psychotic episodes (American Psychiatric Association, 2013). Executive dysfunction is widely regarded as a core feature of the disorder, and is strongly associated with adverse outcome, including impaired global functioning and poor treatment response (Jonas et al., 2022; Kahn & Keefe, 2013; Mucci et al., 2021; Trampush et al., 2015). Consequently, elucidating its neurophysiological

underpinnings is highly relevant for the development of both reliable biomarkers and targeted, neuroscience-informed interventions (Kraguljac et al., 2021; Lesh et al., 2011).

Among executive functions, motor response inhibition has been extensively investigated in schizophrenia, as evidenced by impaired performance on the visual Go/Nogo task (Rahamim et al., 2024). In this paradigm, participants are sequentially presented with two types of visual stimuli: frequent Go cues, which require a behavioral response (e.g., pressing a key), and rare Nogo cues, which require motor response inhibition (e.g., withholding to press a key). However, the neural characterization of motor response inhibition during acute psychotic episodes in hospitalized inpatients remains understudied. Given that the large majority of patients with schizophrenia undergo recurrent hospitalizations for acute psychotic episodes (Baltazar et al., 2022; Geddes & Kendell, 1995), neuroimaging motor response inhibition during these acute phases is essential for a comprehensive understanding of the disorder across its different phases.

Electroencephalogram (EEG) event-related potentials (ERP) provide a fine-grained deciphering of the neural processes involved in motor response inhibition. EEG collected during a visual Go/Nogo task enables the examination of distinct ERP components called N2 and P3, each associated with specific executive subfunctions (Hong et al., 2017). Both Go and Nogo cues elicit a strong 200-300ms negative fronto-central deflection (N2). The N2 mainly reflects conflict monitoring between competing responses (Hong et al., 2017), lying at the crossroad between salience and executive networks (Kerns et al., 2005; Sheth et al., 2012). The N2 amplitude is sensitive to stimulus rarity, rare Nogo eliciting larger amplitude deflection compared to frequent Go targets. Furthermore, the N2 component depends on active cognitive engagement in a goal-directed task, involves dopaminergic transmission, and its main source lies in the anterior cingulate cortex (ACC) (Yeung et al., 2004).

In schizophrenia, previous studies have consistently reported a reduction of N2 amplitude with medium to large effect size (*d*=.50-.90) (Araki et al., 2016; Hong et al., 2021; Rentrop et al., 2011). One study found an increased single-trial variability of N2 peak latencies with *d*=.52 (Rentrop et al., 2011). Reduced N2 amplitude might also predict conversion to schizophrenia with medium effect size (*d*=.50-.58) (Hou et al., 2024).

The Go/Nogo task also elicits a positive ERP with peak latency around 300-450ms after stimulus onset (P3). While Go stimuli generate a parietocentral P3, Nogo cues elicit a stronger frontocentral P3 which reflects inhibitory and top-down selective attention processes (Albert et al., 2013; Hong et al., 2017). The neural generators of the Nogo P3 are widely distributed across fronto-parietal regions, including (but not restricted to) presupplementary motor area, midcingulate, inferior frontal, and precuneus cortice (Albert et al., 2013; Hong et al., 2017).

There have been mixed results concerning P3 morphology in schizophrenia. Several studies have reported a smaller P3 amplitude in schizophrenia with medium effect size (d = 0.45–0.47) (Devrim-Üçok et al., 2023; Ertekin et al., 2017; Weisbrod et al., 2000). Among these, Ertekin et al. (2017) and Weisbrod et al. (2000) reported a more pronounced deficit in Nogo P3 compared to Go P3, while Devrim-Üçok et al.

(2023) observed similar deficits for both. However, other studies found no significant P3 alterations in schizophrenia (Araki et al., 2016; Rentrop et al., 2011). Smaller Nogo P3 amplitude has been associated with acoustic-verbal hallucinations (Sun et al., 2021) and poorer global functioning (Araki et al., 2016). More consistently, topographical EEG studies have reported an anteriorized Nogo P3 in schizophrenia (Devrim-Üçok et al., 2023; Ertekin et al., 2017; Kleinlogel et al., 2007). This Nogo P3 anteriorization has also been observed in healthy siblings of patients with schizophrenia (Devrim-Üçok et al., 2023). In summary, the Nogo P3 anteriorization and amplitude reduction might serve as diagnostic biomarkers, as it has been suggested for P3 elicited by other tasks (Blackwood, 2000).

To our knowledge, none of cited studies have been conducted on acute inpatients with schizophrenia. Here, we use a cross-sectional design, recording high-density (128 electrodes) EEG during a visual Go/Nogo task in 23 acute inpatients with schizophrenia and 23 healthy participants, matched for age and parental education.

Our primary goal was to compare the N2 and P3 components between acute patients and healthy controls. We hypothesized to replicate differences previously reported between stable outpatients and healthy participants, but with a greater effect size since the neural mechanisms underlying motor inhibition might be more severely disrupted during acute psychosis. From the cited literature, we expected amplitude reduction in both N2 and P3 amplitude, increased variability of N2 single-trial latencies, and Nogo P3 anteriorization.

Our secondary aim was to test the associations between acute symptom severity (measured with the PANSS) and the N2/P3 morphologies. We expected to replicate the P3 amplitude inverse relation to symptom severity (Araki et al., 2016; Sun et al., 2021).

As an exploratory tertiary aim, we examined the associations between N2/P3 morphologies and behavioral performances across both groups. This analysis was preliminary in nature, and no *a priori* hypotheses were formulated.

2. Methods

2.1 Participants

Acute patients were recruited during an acute psychotic episode, defined by the presence of delusions, hallucinations, and/or behavioral/thought disorganization, within 72h after intake into an admission ward at the psychiatric hospital in *Hôpitaux Universitaires de Genève* (HUG, Switzerland). Ten patients were recorded in the first 24 hours following admission in the ward (43.5%), 5 in the 24-48h (21.7%), and 8 in the 48-72h (34.8%). Inclusion criteria comprised a schizophrenia diagnosis defined according to DSM-5 criteria, a Clinical Global Impression (CGI) score ≥ 4, an age comprised between 18 and 65 y.o., the exclusion of any concomitant substance use disorder according to DSM-5 criteria. Comprehensive inclusion and exclusion criteria are provided in supplementary materials (**Supplementary Table S1**).

Patients started antipsychotic medications at or shortly after the time of admission in the ward, with a maximum duration of 72h prior to EEG recording. Antipsychotic drugs taken by participants during EEG recording consisted in different molecules including first, second and third generation classes. Three participants were on a double antipsychotic medication. Risperidone dose-equivalents were calculated using the Defined Daily Doses (DDDs) method (Leucht et al., 2016). Antipsychotic medications are detailed in **Supplementary Table S2**. Given that antipsychotic drugs typically require more than six days to achieve clinically significant effects (Agid et al., 2003; Levine & Leucht, 2012; Suzuki et al., 2011), their influence on the EEG signal was expected to be minimal. However, we tested as a supplementary analysis the correlations between DDD and ERP measures (detailed below) in the inpatient group to rule out any unexpected confounding relationship.

Parental socio-economic status was estimated with the sum of parents' years of education, according to the Swiss education system (https://www.edk.ch/en/education-system-ch).

The acute symptom severity was measured using the Positive and Negative Syndrome Scale (PANSS) (Kay, 1991). We also derived subscales from 5 symptom dimensions: positive, negative, excited, disorganized, and depressed (Wallwork et al., 2012).

2.2 Stimuli and procedures

Participants performed a visual Go/Nogo task programmed in Eprime 3 (Psychology Software Tools, Pittsburgh, USA), carried out on a desktop computer. Stimuli comprised 270 standard (blue) circle image as Go trials, and 90 deviant (yellow) circle image as Nogo trials. Stimuli were presented in a pseudo-random order (sequences of 3 standard and 1 deviant images), with deviant stimuli displayed at minimum N + 2 from each other. All circle images were of identical diameter (10cm) and displayed centrally for 250 ms each on a black background. An interstimulus interval of random duration [800–1200 ms] with a white fixation cross was displayed on a black screen (Fig. 1). Before experiment, participants were instructed to press the space key on the keyboard with the index finger following any Go trial as quickly and accurately as possible. All stimuli were presented in one block without pauses, total experiment time was 8 minutes. Participants were seated in a dimly lit quiet room at the psychiatric hospital. Stimuli were presented at ~ 100cm from participants' face.

2.3 Behavioral measures

We computed the Hit rate (percentage of expected behavioral response to Go trials) and False alarm (percentage of non-inhibited behavioral response to Nogo trials). From these basic metrics, we derived the D-prime as z[hit rate] − z[false alarm rate] and the Beta-log as log(β) = log(False Alarm Rate / Hit Rate) (Ertekin et al., 2017; Weisbrod et al., 2000). D-prime reflects the participants' ability to discriminate signal from noise, with a D-prime equal to 0 corresponding to a chance level performance, and a highly positive D-prime reflecting a high capacity to discriminate between the two stimuli. The Beta-log is a marker of the participants' response strategy, with a Beta-log > 1 reflecting a conservative bias, i.e., a trend for motor inhibition in both Go and Nogo trials (favoring low False alarm at the cost of lower Hit

rate), while beta-log < 1 signals a liberal bias, i.e., a tendency for motor response in all trials (favoring higher Hit rate at the cost of higher False alarm). Both D-prime and Beta-log have been found decreased in patients with schizophrenia (Ertekin et al., 2017). Individual motor response latency was defined as the averaged response time to Go stimuli, latency variability as the standard error of single-trial response latency in Go condition, and number of perseverations as total occurrences of > 1 motor responses after a stimulus.

2.4 EEG recording and preprocessing

Electroencephalography (EEG) signals were recorded with a high-density 128-channel saline-soaked Waveguard net using an ANT Neuro (Enschede, The Netherlands) EEGO MyLab system with 2 amplifiers. Electrode impedances were kept below 10kΩ. The hardware signal was referenced to Cz-corresponding electrode, recorded with a 500Hz sampling rate. We conducted all EEG analyses in Python with MNE-Python v1.7 (Larson et al., 2026). We added a reference electrode Cz offline. Individual EEG data were band-pass filtered (0.2-40Hz, finite impulse response filtering). We conducted a careful visual inspection and marked bad segments and channels. We then conducted an ICA decomposition using the Picard method (Ablin et al., 2018). We manually rejected the ICA components corresponding to identifiable artifacts (e.g., eyeblinks, saccades, EKG, and facial muscle contractions) from the reconstructed signal. Channels marked as bad were then interpolated with the minimum-norm method using signal from neighbouring electrodes. Continuous data were segmented into epochs between [-500, 1000]ms from stimulus onset, applying a [-100, 0]ms baseline correction. Epochs containing EEG signals exceeding ± 150μV peak-to-peak amplitude in any electrode were automatically rejected. Remaining epochs were visually inspected and discarded from further analysis when contaminated by artifacts. The epoched data were average re-referenced. Eventually, trials were averaged by conditions (Go and Nogo). Importantly, we only included behaviorally successful trials, reflecting brain activity during active engagement in the task (Sun et al., 2021). Successful trials were defined by either the presence of a motor response after a Go stimulus, or the lack of motor response after a Nogo stimulus.

2.5 ERP analyses

We pre-defined two regions of interest (ROI) along the antero-posterior axis: a frontal and a central one. The frontal cluster consisted in the 6 electrodes surrounding Fz – corresponding to Z3, Z4, Z5, L4, L5, R4 and R5 in the ANT 128-channel WaveGuard internal electrode naming scheme. The central ROI comprised the 6 electrodes surrounding Cz (channels Z6, Z7, Z8, L7, L8, R7, R8). The N2 component in condition-averaged epochs was averaged in the frontal cluster, given its anterior distribution reported in previous studies. Since the P3 is typically observed in a broader central distribution (Albert et al., 2013) it was averaged in the central clusters. For each condition (Go and Nogo) and component (N2 and P3), the evoked-response mean amplitude and peak latency (most negative/positive voltage) were extracted in following time windows: 200-300ms for the N2 and 300–450 for the P3. As a supplementary measure, individual peak amplitude was computed by averaging the amplitudes from − 50 to + 50ms around the peak latency. Timings were based on previous literature (Araki et al., 2016; Hong et al., 2017; Weisbrod et al., 2000) and visual inspection of grand-averaged ERPs in the whole sample (**Supplementary Figure S1**).

Additionally, we computed single-trial peak latency variability using a filtering and peak-picking method (Jaśkowski & Verleger, 2000; Ouyang et al., 2017): epochs were low-pass filtered with a 4hz cut-off to remove irrelevant spiky peaks (prior to epochs averaging), and the standard error over single-trial peak latencies (defined as the amplitude maximum or minimum depending on the component's polarity) was calculated.

2.5 Statistical analyses

Normality distribution of the data was assessed with Shapiro-Wilks test. Demographic and behavioral variables were compared between groups using T-test or Chi-square with significance threshold of alpha=.05.

To compare ERP morphologies across groups and conditions, we ran two repeated measure ANOVAs (one for each component: N2 and P3) using the ERP metric as dependent variable. Group (inpatients *versus* controls) was used as between-subject factor and condition (Go *versus* Nogo) as within-subject factor. We looked at any significant group effect. However, when the condition*group interaction was significant, we ran a subsequent T-test to compare group within each condition (Go *versus* Nogo) in the tested component.

To test the anteriority of the Nogo P3 component between groups, we ran a repeated measure ANOVA on the Nogo P3 mean amplitude with clusters (frontal/central) as within-subject factor and group as between-subject factor, the spatial*group interaction term reflecting the difference in anteriority.

To test for relations between ERP components and acute severity, we ran Pearson (or Spearman when normality was not assumed) correlations between the PANSS total score and the three mean ERP measures. Correlations were run for each component and condition, in the patient group only.

To assess any potential confounding effects of illness chronicity, we repeated the same correlation analyses using illness duration instead of the PANSS, as an additional analysis.

To test if Nogo P3 anteriorization was related to acute symptom severity, we applied linear mixed models to predict mean amplitude from PANSS, contrasting with cluster (frontal versus central). We used the *my Mixed Model Trajectories* toolbox in MATLAB® R2024a: https://github.com/danizoeller/myMixedModelsTrajectories). PANSS and cluster were used as fixed effect (see Formula (1) in **Supplementary material**). We specifically looked at the Cluster*PANSS interaction term. The same analysis was repeated using illness duration instead of the PANSS to test any potential effects of chronicity.

To test for relations between ERP components and behavioral performance, we ran linear regressions to predict each of the three mean ERP measures from behavioral performance, contrasting by group, for each component and condition. To limit the number of analyses, we only used the D-prime (ability to discriminate between stimuli) parameter as a summary variable of individual performance in the task. Linear mixed models were applied on each ERP metrics, with D-prime and group as fixed effects, and

random slope varying by participant (*my Mixed Model Trajectories* toolbox in MATLAB® R2024a, see Formula (2) in **Supplementary material**).

In general, Bonferroni correction was applied for the three ERP metrics used, with a corrected significance threshold of alpha=.017. Repeated measure ANOVAs were conducted using IBM®SPSS® Statistics v26.0.0.0 for macOs (Armonk, NY: IBM Corp.). For all other statistical analyses and to generate illustrations we used in-built functions in Matlab® R2024a for MacOs (MathWorks).

3. Results

3.1 Demographic and clinical data

We recruited 23 adult acute inpatients with schizophrenia (1 woman and 22 men, 36.2 y.o. ± 8.5, range [23–52]), and 23 healthy controls (8 women and 15 men, 32.7 ± 9.6y.o., range [22–65]). Demographic and clinical characteristics of the sample can be found in Table 1. There were no significant differences between groups in age, parental education or handedness. A significant difference was found for biological sex (p=.009). Due to the presence of only one female participant in the patient group, we did not include sex as a covariate in the analyses to prevent unreliable effect estimates and the introduction of noise.

Inpatients' total score of the Positive and Negative Syndrome Scale (PANSS) administered within 72h after admission was 102.8 ± 16.7. The scores ranged from 62 to 130, indicating moderate to extreme illness severity (Leucht et al., 2005). Patients' mean illness duration was 15.5 ± 11.2 years, with an average number of hospitalizations (including the current one) of 6.2 ± 4.8. All patients had initiated an antipsychotic medication at time of recording, taken for less than 72h. Twenty patients were on an antipsychotic monotherapy, and 3 received an antipsychotic combination medication. In average, the risperidone dose equivalent (including double medication) was 6,1mg ± 3,7 (Leucht et al., 2016). For details about antipsychotic medication during recording, please see **Supplementary Table 2**.

Table 1

Demographic and clinical characteristics. Continuous variables as mean ± standard deviation, range in []; categorical variables as absolute number and percentage in (). Significant differences are highlighted in bold. PANSS: Positive and negative symptom scale.

Age (years)	**Controls (n = 23)**	**Schizophrenia (n = 23)**	***p***	***t* or *χ2***
	32.7 ± 9.6 [22–65]	**36.2 ± 8.5 [23–52]**	**0.201**	**-1.29**
Parents Cumulative Education (years)	34.1 ± 9.8 [12–60]	30.4 ± 6.7n[19–41]	0.213	1.27
Education (years)	20.0 ± 2.6 [15–27]	15.9 ± 3.6 [8–23]	**< 0.001**	4.43
Female (n)	8 (34.8%)	1 (4.3%)	**0.009**	6.77 (χ^2)
Left-handed (n)	0	1		
PANSS (total)		102.8 ± 16.7 [62–130]		
PANSS: Depression		7.1 ± 3.3 [3–18]		
PANSS: Disorganized		11.9 ± 3.0 [7–20]		
PANSS: Excited		16.6 ± 10.4 [6–54]		
PANSS : Negative		20.9 ± 6.5 [11–30]		
PANSS: Positive		14.9 ± 4.2 [8–25]		
Illness Duration (years)		15.5 ± 11.2 [2–45]		
Hospitalizations (n)		6.2 ± 4.8 [1–14]		

3.2 Behavioral data

Behavioral results are reported on Table 2. False alarm rate was greater for inpatients with schizophrenia (31.1% ± 19.8) compared to controls (13.5% ± 11.5), with t=-3.69 and p=.001. Inpatients also showed lower D-prime (t = 3.02 and p=.004) and Beta-log (t = 3.21, p=.003), reflecting poorer discrimination performances and more conservative bias in their response patterns respectively. The single-trial variability in motor response latency was higher in patients (t=-3.62, p=.001), as well as the number of perseverations (t=-3.04, p=.006). Importantly, all participants had individual D-prime values > 0 (range [0.6–6.2]), indicating that they all discriminated between stimuli above the chance level. We found no significant differences between groups in either Hit rate (p=.174) or Motor latency (p=.214).

Table 2

Behavioral data. Continuous variables as mean ± standard deviation, range in []. Significant differences are highlighted in bold. Hit rate indicates motor response in Go condition; False alarm rate indicates motor response in Nogo condition; D-prime estimates how well a participant discriminated between Go and Nogo targets (> 0 indicates above-chance level performance); Beta-log estimates the response pattern of the participant (> 1 indicates a conservative bias, i.e., favouring Nogo motor inhibition over Go motor response); latency indicates the motor response time in the Go condition; single-trial latency variability indicates the standard error in single-trial motor response latency in the Go condition; perseverations summarize the number of trials in which the participant responded > 1 time. W: Welch test used because of unequal variance of the data.

Hit Rate (%)	**Controls (*n* = 23)**	**Schizophrenia (*n* = 23)**	***p***	***t***	***g***
	93.9 ± 4.9 [83.2–100.0]	**89.4 ± 14.6 [38.0-100.0]**	**0.174**	**1.40 (W)**	
False Alarm (%)	13.5 ± 11.5 [0.0–43.0]	31.1 ± 19.8 [4.5–67.1]	**0.001**	**-3.69 (W)**	**-1.07**
D-Prime	3.2 ± 1.1 [1.7–6.2]	2.3 ± 1.0 [0.6–3.9]	**0.004**	**3.02**	**0.88**
Beta-log	2.7 ± 1.8 [0.8–6.9]	1.4 ± 0.8 [0.3–3.1]	**0.003**	**3.21 (W)**	**0.93**
Latency (ms)	173.3 ± 30.3 [133.2-257.4]	187.2 ± 43.1 [120.6-274.8]	0.214	-1.26	
Single-trial latency variability (ms)	40.8 ± 20.1 [18.1–96.6]	67.4 ± 28.9 [28.3-142.6]	**0.001**	**-3.62**	**-1.05**
Perseverations (n)	0.6 ± 1.3 [0–4]	4.9 ± 6.6 [0–26]	**0.006**	**-3.04 (W)**	**-0.88**

3.3 ERP results

For each ERP measure (mean amplitude, peak latency, and single-trial peak latency variability), we conducted repeated-measures ANOVAs for N2 and P3 separately, with group and condition (Go *versus* Nogo) as factors. Results are presented in Table 3. Significant group*condition interactions were followed by post-hoc *t*-tests. Figures 2A–C and 3A–C display the Go and Nogo components, respectively, along with their grand-averaged topographies. A more complete illustration of grand-averaged ERPs for each group is provided in **Supplementary Figure S1**.

For the N2 Mean amplitude, the repeated measure ANOVA revealed a significant group*condition interaction ($F(1,44) = 12.16$, $p=.001$). Post-hoc *t*-tests showed that, in the Nogo condition, inpatients exhibited a reduced N2 amplitude (-1.1uV ± 1.8) compared to controls (-2.7uV ± 1.6), with $t=-3.18$, $p=.003$, and Hedge's $g=-0.939$. The same comparison using peak instead of mean amplitude revealed a similar result ($p=.003$, $t=-3.18$, Hedge's $g=-.938$). No group difference was found in the Go N2 mean amplitude ($p=.286$, $t=-1.08$).

For N2 peak latency, no group differences were found ($p=.096$), and the group*condition interaction was non-significant ($p=.820$). However, for single-trial peak latency variability, the group*condition interaction

was significant ($F(1,44) = 25.98$, $p<.001$). Post-hoc *t*-tests revealed no group difference in the Nogo condition ($p=.890$), but in the Go condition, inpatients showed increased single-trial peak latency variability compared to controls ($t=-4.71$, $p<.001$, Hedges' $g=-1.363$; Fig. 2D, left panel).

For the P3 component, no significant group effects ($F(1,44) = 0.81$, $p=.374$) or group*condition interactions ($F(1,44) = 0.74$, $p=.112$) were observed for mean amplitude. The P3 peak latency also showed no group effect ($F(1,44) = 0.13$, $p=.717$) or group*condition interaction ($F(1,44) = 0.00$, $p=.984$). However, single-trial peak latency variability ANOVA revealed a significant group*condition interaction ($F(1,44) = 22.02$, $p<.001$). Post-hoc *t*-tests showed no group difference in the Nogo condition ($t = 0.55$, $p=.584$), but in the Go condition inpatients displayed a higher single-trial peak latencies variability compared to controls ($t=-3.75$, $p<.001$, Hedge's $g=-1.086$; Fig. 2D, right panel).

Additionally, the Nogo P3 in acute patients with schizophrenia was more anterior (frontal) distribution, as indicated by a significant spatial*group effect on mean amplitude ($F(1,44) = 6.87$, $p=.012$, Hedge's $g=.777$; Fig. 3D). Neither the within-subject spatial effect ($p=.058$) nor the between-subject group effect ($p=.731$) reached significance. Full results of this repeated ANOVA are reported in **Supplementary Table 3**.

As an additional analysis, we examined potential correlations between risperidone dose-equivalent antipsychotic medication (using the defined daily dose method, DDD, Leucht et al, 2016) and the three ERP metrics in each condition and component. No significant relationships were found (smallest $p=.160$). Detailed results are provided in **Supplementary Table 4**.

Table 3

ERP results. Repeated measure ANOVAs with group (inpatients *versus* controls) as between-subject factor, and condition (Go *versus* Nogo) as within-subject factor. Continuous variables as mean ± standard deviation, range in []. Significant effects highlighted in bold. Subsequent *t*-tests between groups for measures with significant group*condition are presented in the main text.

Controls (*n* = 23)		**Schizophrenia (*n* = 23)**		**Group Effect**		**Condition Effect**		**Group x Condition Interaction**	
Go	**NoGo**	**Go**	**Nogo**	***p***	**F(1,44)**	***p***	**F(1,44)**	***p***	**F(1,44)**
N2 (Fz)									
Mean Amplitude (uV)									
-1.7 ± 1.1 [-5.5–0.5]	-2.7 ± 1.6 [-6.7–0.9]	-1.2 ± 1.7 [-3.9-2.3]	-1.1 ± 1.8 [-4.5-2.8]	**.022**	**5.63**	**.015**	**6.47**	**.001**	**12.16**
Peak Latency (ms)									
239.0 ± 21.6 [200–282]	242.4 ± 22.0 [200–292]	250.6 ± 30.7 [202–300]	252.0 ± 29.3 [200–300]	.096	2.89	.595	0.29	.820	0.05
Single-trial peak Latency variability (ms)									
3.9 ± 1.0 [2.5–6.1]	6.6 ± 1.6 [4.5–10.6]	5.6 ± 1.4 [3.2–11.1]	6.6 ± 1.3 [4.4–9.4]	**.031**	**4.98**	**< .001**	**119.70**	**< .001**	**25.98**
P3 (Cz)									
Mean Amplitude (uV)									
1.0 ± 1.8 [-5.1-4.0]	1.4 ± 1.6 [-2.7-4.3]	0.7 ± 1.4 [-0.9-4.0]	1.0 ± 1.4 [-1.2-4.1]	.374	0.81	.028	5.17	.112	0.74
Peak Latency (ms)									
360.2 ± 48.8 [300–450]	388.3 ± 44.6 [310–450]	356.0 ± 42.6 [300–450]	383.8 ± 47.2 [300–450]	.717	0.13	**< .001**	**18.01**	.984	0.00
Single-trial peak Latency variability (ms)									
5.5 ± 1.4	9.2 ± 2.1	7.5 ± 2.1	8.9 ± 1.6	.088	3.05	**< .001**	**108.28**	**< .001**	**22.02**

Controls (*n* = 23)		Schizophrenia (*n* = 23)		Group Effect		Condition Effect		Group x Condition Interaction	
Go	**NoGo**	**Go**	**Nogo**	***p***	**F(1,44)**	***p***	**F(1,44)**	***p***	**F(1,44)**
N2 (Fz)									
[3.5-9.0]	[6.4–13.9]	[5.4–15.5]	[6.4–12.9]						

3.4 Correlations between ERP and clinical variables within acute inpatients

We found no significant correlations between the total PANSS and any of the ERP metrics (detailed results in **Supplementary Table S5**). For the Nogo P3 mean amplitude, the linear mixed model found no significant interaction between cluster (frontal versus central) and total PANSS (interaction effect: *beta*=.0232, *p* = .212).

Our supplementary analyses testing for potential confounding effects of the chronicity on ERP metrics revealed no significant correlation between illness duration and either mean amplitude or peak latency (smallest *p*=.127; **Supplementary Table S6**). However, single-trial peak latency variability was significantly correlated with illness duration in the Nogo P3 (*r* = 0.667, *p*<.001), Go N2 (*r* = 0.580, *p*=.005), and Go P3 (*r* = 0.735, *p*<.001), but not in the Nogo N2 (*r*=-0.051, *p*=.823). Additionally, the anteriority of Nogo P3 mean amplitude showed no significant association with illness duration (linear mixed model, chronicity*cluster interaction effect: *beta*=.0219, *p* = .442).

3.5 Linear associations between behavioral performance and ERP

Linear mixed models found that in the Nogo condition, higher discrimination performance (D-prime measure) was significantly correlated with greater absolute mean amplitudes in N2 (*beta*=-0.593, *p*=.009) and P3 (*beta* = 0.800, *p*=.007) (Fig. 4A). A similar association was found for the Go P3 mean amplitude (*beta* = 0.779, *p*=.015). These D-prime associations with ERP amplitudes were also significant when peak amplitude was used instead of mean amplitude. In the Nogo condition, D-prime was associated with shorter peak latency in P3 (*beta*=-25.5, *p*=.004). In the Go condition, an association between D-prime and single-trial peak latency variability was found in both the N2 (*beta*=-0.190, *p*<.001) and P3 (*beta*=-0.306, *p* = .001; Fig. 4B). Group*D-prime interactions were not significant for any of the ERP measures, suggesting that patterns of associations between behavioral performance and ERP components were similar across both groups. Detailed results are presented in **Supplementary Table S7.**

4. Discussion

Here, we recorded the neural activity of inpatients with schizophrenia during an acute psychotic episode, while performing a motor response inhibition task, known as the visual Go/Nogo paradigm. This study revealed novel insights into the neural correlates of executive dysfunction in acute schizophrenia, with implications for understanding the pathophysiology of executive function deficits in this population.

4.1 Reduced Nogo N2 amplitude and impaired conflict monitoring

The study revealed a substantial reduction in N2 absolute amplitude among acute inpatients with schizophrenia, specifically in the Nogo condition, with a large effect size (Hedge's *g*=-0.939). The reported effect size falls within the upper range of previously reported values (*d* = 0.5–0.9) in stable outpatients with schizophrenia (Araki et al., 2016; Hong et al., 2021; Rentrop et al., 2011), underscoring a pronounced N2 amplitude deficit during the acute phase of the illness. The amplitude reduction showed no correlation with either acute symptom severity or illness duration within the patient sample, suggesting a relative stability across illness stages and phases. However, our inpatient sample did not cover the full spectrum of severity and chronicity, and the N2 might be sensitive to more extreme ends of these clinical dimensions.

In contrast to previous literature, the reported N2 absolute amplitude reduction was specific to Nogo stimuli. However, direct comparisons across studies are challenging due to methodological differences, particularly regarding the specificity of the condition (Go *versus* Nogo). For instance, Rentrop et al. (2011) used two different tasks and merged epochs across Go and Nogo stimuli, while Hong et al. (2021) focused solely on the Go condition. Although Araki et al. (2016), like our study, analyzed Go and Nogo stimuli separately, their task was simpler, with stimuli and cross-fixation timings approximately twice as long. Thus, the differences between Araki and colleagues' findings and ours may reflect variations in illness phase, task difficulty, or an interaction of both factors.

Here, the Nogo N2 amplitude was associated with task performance (as indexed with D-prime), underscoring the functional relevance of this neural marker. Importantly, no significant differences were found between acute inpatients and controls in their single-trial variability of Nogo N2 peak latencies. This suggests that the observed difference in Nogo N2 amplitude didn't arise from a peak latency jitter blurring the averaged ERP and artificially reducing its amplitude (Polich, 2007), but rather from a reduction in the neural generator strength or synchrony underlying the N2 component.

At the neurophysiological level, the Go/Nogo N2 mainly reflects conflict monitoring – an active error-detection process mediated by dopaminergic signaling in the anterior cingulate cortex (ACC) (Yeung et al., 2004). Given the previously reported ACC dysfunction in treatment-resistant schizophrenia (Chan et al., 2026; Liu et al., 2023), N2 amplitude reduction may theoretically serve as a predictor of acute psychosis response to antipsychotic treatment – a hypothesis that warrants further confirmation through longitudinal studies.

At this stage, our findings combined with previous literature (Araki et al., 2016; Hong et al., 2021; Rentrop et al., 2011), support the phenomenon of a large and persistent N2 absolute amplitude reduction across different phases of the disorder, pointing to its potential as a categorical diagnostic biomarker. If confirmed, this would contrast with the mismatch negativity (MMN), another biomarker candidate that is also linked to error detection, but involving earlier, pre-attentive, and glutamatergic/NMDA-mediated processes. Unlike what our results and previous studies suggest about the N2, MMN alterations in schizophrenia are strongly correlated with chronicity (Erickson et al., 2016). Future studies on the Go/Nogo N2 in schizophrenia should directly test the effects of clinical stage and phase, while ensuring that Go and Nogo epochs are averaged separately.

4.2 Anteriorized Nogo P3 and altered automatic attentional orienting

Although we did not replicate the P3 amplitude reduction previously reported in clinically stable schizophrenia, we confirmed the anteriorization of the Nogo P3 component in acute inpatients, a pattern previously documented in stable outpatients and first-episode schizophrenia (Devrim-Üçok et al., 2023; Ertekin et al., 2017; Kleinlogel et al., 2007). The observed effect size (*g*=.777) falls within a similar medium-to-large range as that reported in comparisons between first-episode psychosis and healthy controls (*g*=.64) (Devrim-Üçok et al., 2023). Furthermore, P3 anteriorization in schizophrenia has been also demonstrated when using visual oddball paradigms (Oribe et al., 2013). Consequently, this topographical phenomenon may represent a stable neural marker of the disorder, consistently observed across different P3-eliciting tasks (Go/Nogo and oddball) and illness phases (acute inpatients and stable outpatients). Notably, Nogo P3 anteriorization was not affected by symptom severity or illness duration in our study, further supporting its possible role as a categorical diagnostic biomarker.

The Go/Nogo P3 component reflects both motor inhibition *per se* and allocation of attentional resources (Albert et al., 2013; Hong et al., 2017). Either of these mechanisms could account for the positive correlation between P3 amplitude and behavioral performance observed in our sample, a finding consistent with previous reports (Ertekin et al., 2017). Regarding the neural correlates of the Nogo P3 anteriorization, previous authors have suggested that a more frontal P3 may indicate increased neural activity in frontal sources, functionally reflecting automatic attentional orienting to infrequent stimuli – here, Nogo stimuli (Barry & Rushby, 2006). If the P3 anteriorization observed in our inpatients is reflecting enhanced automatic orienting to Nogo targets, this may directly arise from altered conflict monitoring already discussed in 4.1., possibly via a late compensatory recruitment of the ACC. Such compensatory mechanisms have been previously described in healthy adults with impulsive traits, as evidenced by a simultaneous EEG/fMRI paradigm showing delayed ACC recruitment (Schmüser et al., 2016). If confirmed, such an imbalance in the recruitment of frontal and parietal circuits generating the P3 would align with prior findings of fronto-parietal network disruptions in schizophrenia (Guo et al., 2014).

4.3 Single-trial jitter in Go peak latencies and imprecise motor response

The present study revealed significantly elevated intra-participant variability in single-trial peak latency for both the N2 and P3 components, specifically in the Go condition, in patients compared to healthy controls, with very large effect sizes (g = -1.363 for Go N2 and − 1.086 for Go P3). Importantly, our supplementary analyses revealed that in the Go condition, both N2 and P3 single-trial peak latency jitter were significantly associated with illness duration in the patient sample, but not with symptom severity.

On the functional and neurophysiological level, increased jitter of single-trial peak latency during motor responses (i.e., the Go condition) has been previously associated with increased reaction time variability (Bender et al., 2015; Jung et al., 2001). We tested this association *post-hoc* in our inpatient sample and found a significant positive correlation (p=.033, r=.449, Spearman correlation). The neural mechanism underlying this association has yet to be fully elucidated, although Bender et al. (2015) reported a significant mediating effect of the dopamine transporter genotype (*DAT1*) (Bender et al., 2015).

One previous study has suggested that ERP single-trial latency jitter elicited by different types of tasks may serve as potential biomarkers in schizophrenia (Trenado et al., 2019). In the context of visual Go/Nogo ERPs, Rentrop et al. (2011) also reported increased single-trial peak latency variability in both N2 (d=.52) and P3 (non-significant trend, p=.09, d=.47) (Rentrop et al., 2011). The smaller effect sizes compared to ours may be attributable to the merging of Go and Nogo epochs in the cited study – a methodological limitation already discussed in the above section, which could have obscured condition-specific effects. Alternatively, our small ample size may also be vulnerable to overestimation of effect sizes, despite our correction using Hedge's g.

Finally, the correlation we observed between illness chronicity and single-trial peak latency jitter warrants caution in interpreting our finding solely in the light of the acute phase of our patient sample. Future studies should disentangle the effects of illness phase and stage on ERP latency jitter in motor response tasks to clarify its potential use as a biomarker of the disorder.

5. Limitations

Several limitations of the present study warrant consideration. First, the absence of replication of previous findings regarding P3 amplitude differences between groups, as well as the lack of associations between ERP components and symptom severity, may stem from limited statistical power and the restricted heterogeneity in PANSS scores within our acute patient sample.

Additionally, some demographic and clinical characteristics of our sample require cautious interpretation. The imbalance in biological sex between groups, unaddressed due to regression constraints, may have introduced confounding effects and limits the generalizability of our findings, particularly to patients with female biological sex. Furthermore, the inclusion of both first-episode and

chronic patients may have introduced variability related to illness stage, although we conducted supplementary analyses to assess this potential confounding effect. While the recent initiation of antipsychotic treatment minimized direct drug effects, and even though we tested for relationships between ERP measures and risperidone dose-equivalents, the cognitive side effects of some antipsychotics (e.g., from antihistaminic or antimuscarinic properties) could have influenced task performance and related neural processes.

Finally, our cross-sectional design limits the possibility to distinguish between trait and state biomarkers, as the phase and stage of the disorder were not directly tested. Nevertheless, the consistency of Nogo N2 absolute amplitude reduction and Nogo P3 anteriorization with prior findings, combined with the lack of significant associations with symptom severity and illness duration, supports their trait-like nature. However, the limited prior literature on increased single-trial latency jitter in schizophrenia, as well as its observed association with chronicity in our study, limits immediate interpretation of its precise clinical and neural correlates.

6. Conclusion

This study extends previous ERP findings in stable outpatients to acute inpatients with schizophrenia, thereby confirming and expanding the characterization of neural signature in the Go/Nogo visual task. The pronounced N2 absolute amplitude reduction and anteriorized Nogo P3 in acute patients support their potential role as trait biomarkers across different phases of the illness. The correlations between ERP components and behavioral performance further underscore the functional relevance of these neural measures. The observed alterations may theoretically be mediated by impaired conflict monitoring and atypical automatic attentional orienting, though simultaneous EEG/fMRI studies could further elucidate the exact underlying mechanisms. The heightened single-trial jitter in N2/P3 peak latencies during motor response suggests its potential role as an additional diagnostic biomarker, though its neural and clinical correlates must be elucidated. Longitudinal studies involving larger and clinically more heterogeneous samples, with repeated intra-participant EEG recordings across distinct illness phases (e.g., acute vs. stable), are necessary to clarify the specificity of our findings to acute schizophrenia. Such designs would enable a finer distinction between state- and trait-biomarkers and assess the clinical relevance of visual Go/Nogo ERP alterations for predicting clinical outcomes in acute schizophrenia.

Declarations

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Author Contributions Statement

M.G.: Writing – original draft, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. C.P.: Writing – review & editing, Resources, Project administration. V.R.: Methodology, Data curation, Conceptualization. M.E.: Writing – review & editing, Resources, Project administration. M.S.: Writing – review & editing, Supervision. M.K.: Writing – review & editing, Validation, Supervision, Methodology. S.K.: Writing – review & editing, Visualization, Resources, Project administration, Methodology, Conceptualization. M.D.P.: Writing – review & editing, Resources, Project administration, Methodology, Funding acquisition, Data curation, Conceptualization. All authors read and approved the final manuscript.

Data Availability Statement

Data supporting the results of the present study will be made available upon reasonable request to the corresponding author.

Clinical trial number

Not applicable.

Ethics declarations

Ethics approval and consent to participate

All procedures involved in this study were carried out in strict compliance with the Declaration of Helsinki. Before or after EEG recording, we obtained written informed consent from all participants, following the Swiss national guidelines for observational research in acute settings. The Ethics Committee of the Geneva Canton (Switzerland) approved the research protocol (ID 2023–0535).

Consent to publish

Not applicable.

Competing interests

SK received advisory board honoraria from Boehringer and Exeltis as well as royalties for cognitive test and training softwares from Schuhfried. MK received advisory board honoraria from Otsuka. The other authors declare no competing interest.

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Figures

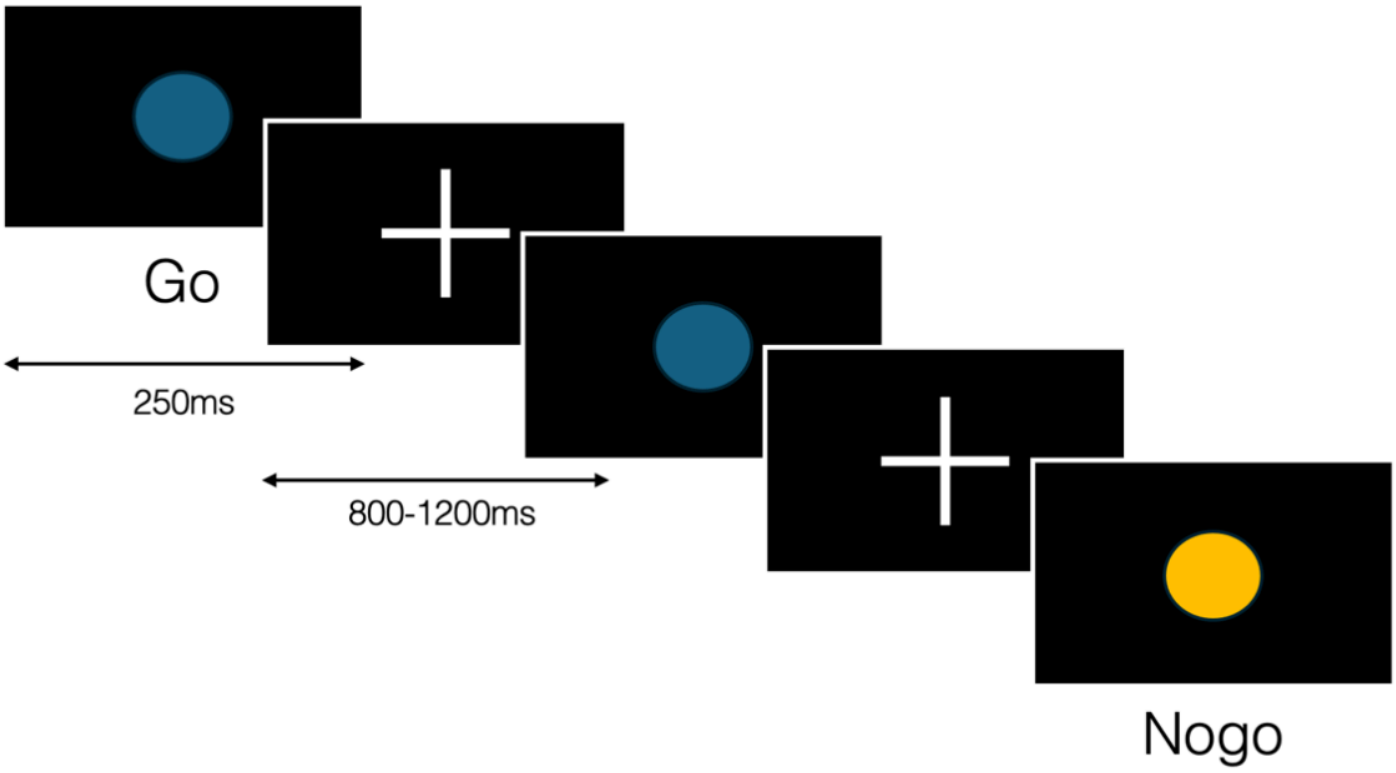


Figure 1

Schematic illustration of stimuli presented to participants during EEG recording.

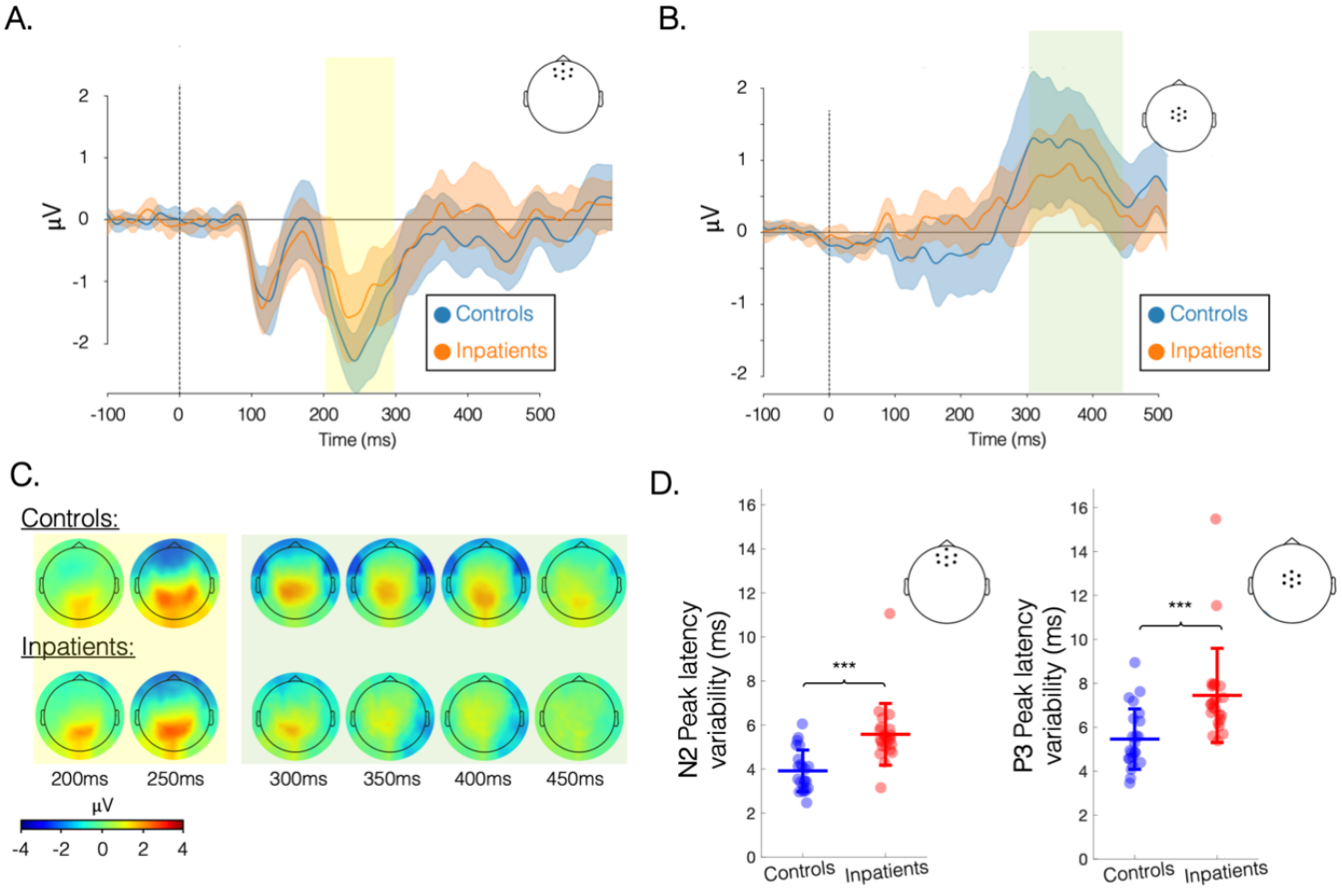


Figure 2

Event-related potentials (ERP) in the Go condition. A. Time-course of the frontal cluster ERP in the Go condition. Group-averaged ERP (controls in blue, inpatients in orange), with 95% confidence interval, yellow shading indicates the time-window for the N2 component. Topography indicates the electrodes positions of the predefined spatial cluster. **B.** Time-course of the group-averaged ERP in the central cluster for the Go condition. **C.**Topographical grand-averaged maps by group in the Go condition. Yellow shading: time window for N2, green shading: P3. **D.** Group differences in single-trial peak latency variability for the N2 (left panel) and the P3 (right panel) components. Controls in blue and patients in red, mean and standard deviation are plotted. *** *p* <.001.

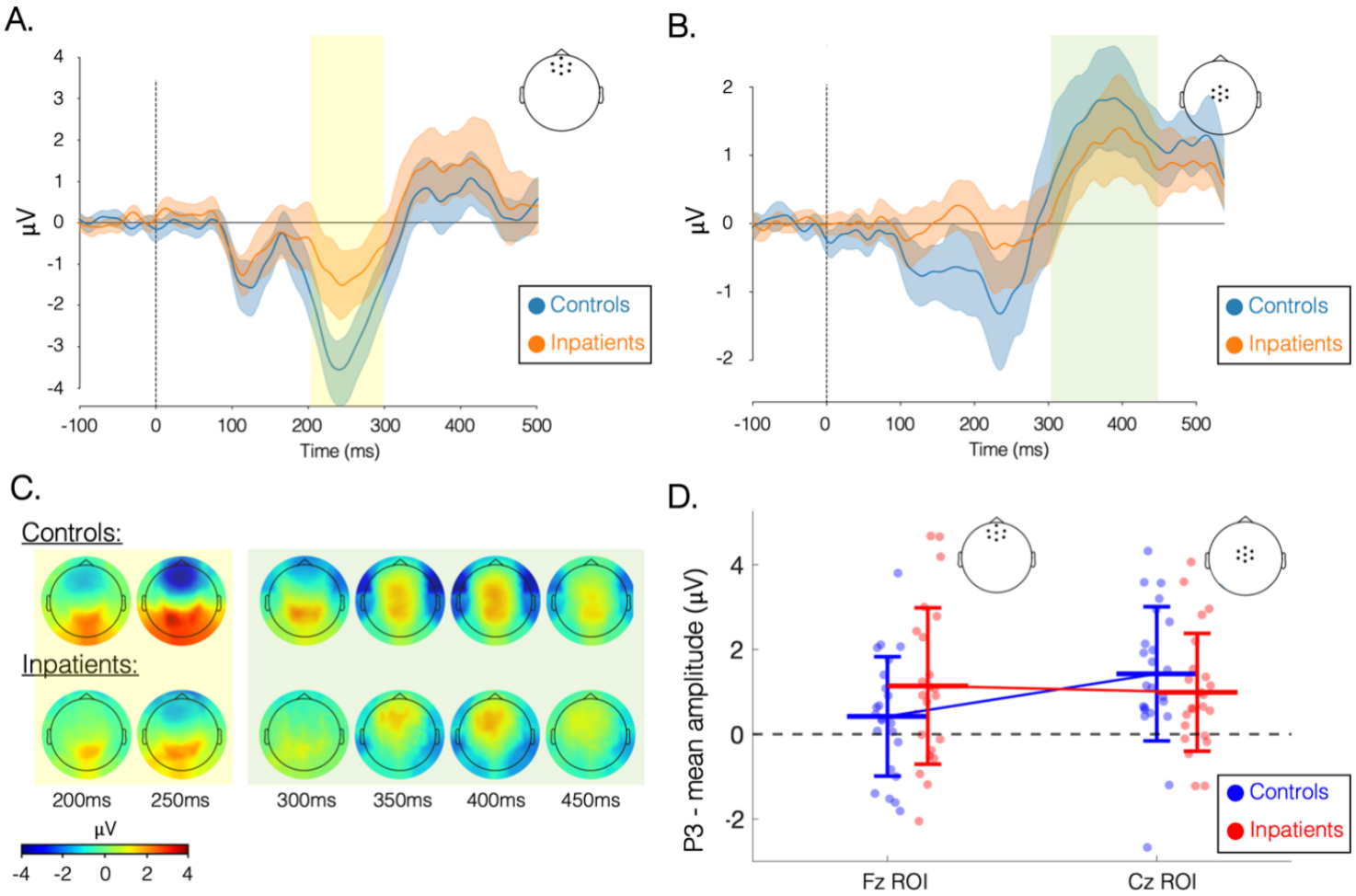


Figure 3

Event-related potentials (ERP) in the Nogo condition. A. Time-course of the frontal cluster ERP in the Nogo condition. Solid-line represents group-averaged ERP (controls in blue, patients in orange), with 95% confidence interval. Yellow shading indicates the time-window for the N2 component. Topography indicates the electrodes positions of the predefined spatial cluster. **B.** Time-course of the group-averaged ERP in the central cluster for the Nogo condition. **C.** Topographical grand-averaged maps by group. Yellow shading indicates the time window for N2, and green shading for P3. **D.** Repeated measure ANOVA of the Nogo P3 mean amplitude with cluster (frontal Fz *versus* central Cz) as within-subject factor and group as between-subject factor. Individual data are plotted, with group mean and standard deviation in each spatial cluster. Spatial*group effect: p=.012. Controls in blue and inpatients in red. Cz: cluster around the central electrode. Fz: cluster around the frontal electrode. ROI: Region of interest.

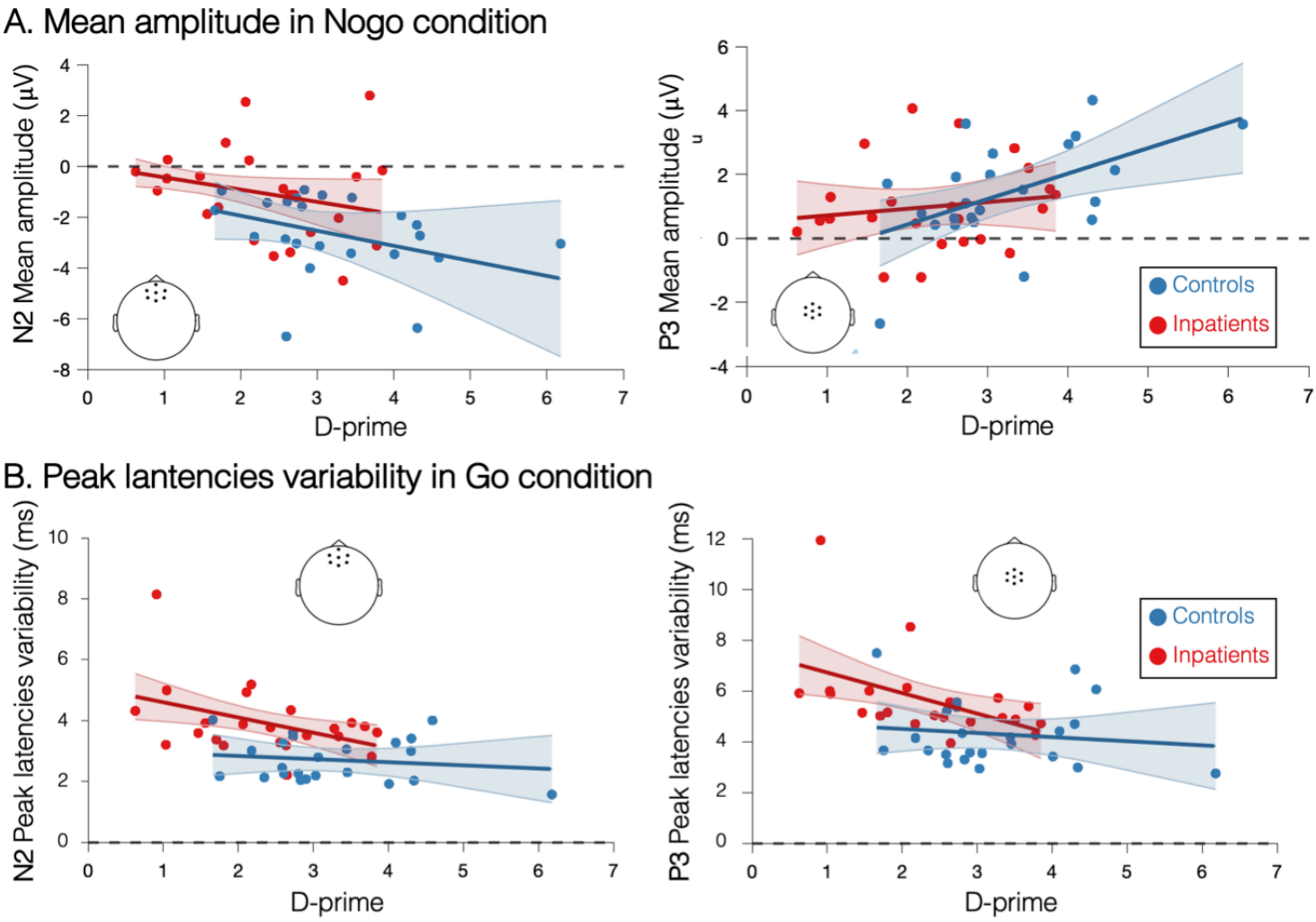


Figure 4

Event-related potentials (ERP) relations with behavioral performance. A. Linear mixed model effects in the Nogo condition for N2 (left panel) and P3 mean amplitudes (right panel) with group and D-prime as fixed-effects. D-prime reflects participants' behavioral discrimination performance during the task. Solid lines show linear regressions with 95% confidence interval in shaded areas. Acute inpatients in red, and controls in blue. D-prime effects were significant, D-prime*group interaction were not, see main text for detailed results. Topographies display the cluster of electrodes in which EEG data were spatially averaged. **B.** Linear mixed model effects in the Go condition, with single-trial peak latency variability in the N2 (left panel) and P3 (right panel) components, with D-prime and group as fixed-effects. D-prime effects were significant, D-prime*group interactions were not. PANSS: Positive and negative symptom scale.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymaterials.docx