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SPECIAL ISSUE ARTICLE

Neurophysiological and Neuroimaging Phenotypes in Schizophrenia Spectrum Disorders

Early and late contingent negative variation (CNV) reflect different aspects of deficits in schizophrenia

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Abstract

Abnormal reward processing and psychomotor slowing are well-known in schizophrenia (SZ). As a slow frontocentral potential, contingent negative variation (CNV) is associated with anticipatory attention, motivation and motor planning. The present study aims to evaluate the early and late amplitude and latencies of CNV in patients with SZ compared to healthy controls during a reward processing task and to show its association with clinical symptoms. We recruited 21 patients with SZ and 22 healthy controls to compare early and late CNV amplitude and latency values during a Monetary Incentive Delay (MID) Task between groups. Patients' symptom severity, levels of negative symptoms and depressive symptoms were assessed. Clinical features of the patients were further examined for their relation with CNV components. In conclusion, we found decreased early CNV amplitudes in SZ during the reward condition. They also displayed diminished and shortened late CNV responses for incentive cues, specifically at the central location. Furthermore, early CNV amplitudes exhibited a significant correlation with positive symptoms. Both CNV latencies were linked with medication dosage and the behavioural outcomes

Abbreviations: BNSS, Brief Negative Symptoms Scale; CNV, Contingent negative variation; CDSS, Calgary Depression Scale for Schizophrenia; EEG, Electroencephalography; MID, Monetary Incentive Delay; ηp^2, Eta-squared; PANSS, Positive and Negative Syndrome Scale; RM ANOVA, Repeated measures analysis of variance; SZ, Schizophrenia.

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of the MID task. We revealed that early and late CNV exhibit different functions in neurophysiology and correspond to various facets of the deficits observed in patients. Our findings also emphasized that slow cortical potentials are indicative of deficient motivational processes as well as impaired reaction preparation in SZ. To gain a deeper understanding of the cognitive and motor impairments associated with psychosis, future studies must compare the effects of CNV in the early and late phases.

KEYWORDS
contingent negative variation, EEG, motivation, motor preparation, reward processing, schizophrenia

1 | INTRODUCTION

Adaptive behaviour is a group of theoretical, interpersonal, and practical abilities that everyone learns in order to live their daily lives. Research has shown that the anticipation of earning monetary rewards and the anticipation of avoiding monetary losses are two of the most important elements that drive human behaviour (Flores et al., 2015; Frömer et al., 2021; Gueguen et al., 2021). Both gain and loss guide behaviour by manipulating attentional and cognitive resources (Choi & Cho, 2020; Kim & Anderson, 2021; Potts, 2011). This adaptive behaviour that makes individuals' lives practical, may be disrupted by the presence of mental disorders, and the breakdown of the gain and loss-related adaptive behaviour systems is increasingly recognized as a fundamental factor in several severe mental diseases including schizophrenia (Broyd et al., 2012).

Schizophrenia (SZ) is a debilitating disorder characterized by persistent functional impairment due to a gradual detachment from reality and a deterioration in neurocognitive functioning (de Oliveira Figueiredo et al., 2022). Also, motivational deficits and behavioural psychomotor slowing (i.e., reaction time) are prominent in patients with SZ (Morrens et al., 2007; Van Hoof et al., 1998). In the past two decades, the neural mechanisms of SZ-induced motivational and motor dysfunction have been the focus of numerous studies (for meta-analysis; Osborne et al., 2020). In this context, the contingent negative variation (CNV) stands out as it is associated with anticipatory attention, motivation, and prior expectation in sensory processing (Gómez et al., 2004, 2019; Gómez & Flores, 2011) and motor planning (Brunia et al., 2012; Zhang et al., 2017).

As a slow frontocentral potential, CNV refers to a negative electrical potential that progressively emerges during the period between the presentation of a warning stimulus and an urgent input (Miraglia et al., 2023; Tecce, 1972). It was pointed out that the CNV is associated with motivation (Cant & Bickford, 1967), effortful attention (Falkenstein et al., 2003; Gómez et al., 2007) and anticipation of motivationally salient stimuli (Baas et al., 2002), preparation for the target (Leuthold & Jentzsch, 2001). The CNV reflects the sustained attention required to convert sensory data into goal-directed actions (Brunia, 1993). CNV can be categorized into early and late phases (Brunia & van Boxtel, 2001) and these phases also differ by topography: early CNV shows more frontal distribution, while late CNV shows the centroparietal distribution (Brunia et al., 2011; Kirenskaya et al., 2011; Leynes et al., 1998; Pfabigan et al., 2014; Zhang et al., 2022). The early stage of CNV predominantly signifies cognitive processes related to orientation and anticipation in response to a warning signal, while the late stage generally indicates the preparation for an impending motor response and anticipatory attention (Brunia & van Boxtel, 2001; Gómez et al., 2019).

Given CNV's association with reward-induced motivation, previous studies revealed that the amplitudes of CNV were sensitive to punishment trials and reward valences such as gain and loss anticipation in healthy individuals (Pfabigan et al., 2014; Novak et al., 2016; Alt Qumeziane et al., 2017; Sun et al., 2023). Additionally, hedonic individuals showed higher CNV amplitudes to reward-associated stimuli, as opposed to anhedonic individuals (Pierson et al., 1987). This suggests that the ability to experience pleasure or positive emotions may influence how the CNV responds to reward and reward-conditioned stimuli (Pierson et al., 1987). One current meta-analysis showed abnormalities in CNV activity in SZ patients compared to controls (Osborne et al., 2020). Also, individuals with SZ exhibited significantly prolonged latencies, especially for late CNV (Li et al., 2015; Simlai et al., 2010). As is a neural marker of psychomotor processes including motor planning, and anticipatory attention, it is not unexpected that it results in reaction time slowing in SZ (Luck & Gold, 2008; Morrens et al., 2006). Osborne et al. (2020) and Simlai et al. (2010) suggested that a decrease in CNV amplitude at central electrode sites serves as a reliable indicator of SZ and primarily reflects motor preparation. On the other hand, a reduction in CNV amplitude at frontal sites is considered to be reliant on the current state of the individual (Smid et al., 2009; Verleger et al., 1999).

Clinical features of SZ showed associations with CNV components. Decrement in CNV was found to be correlated with the presence of both positive and negative symptoms of SZ, including avolition, attention deficits and blunted affect (Li et al., 2015; Oke et al., 1994; Verleger et al., 1999; Wagner et al., 1996; Zhang et al., 2016), and suggested CNV could serve as a valuable indicator of deficits (Pritchard, 1986). CNV was also responsive to dopaminergic regulation (Oishi et al., 1995; Tecce, 1991). Later studies suggested that CNV predominantly represents neural activity originating from a cortico-thalamo-striatal network that is influenced by dopamine (Brunia & van Boxtel, 2001; Fan et al., 2007). This suggestion was supported by showing that even a low dose of methylphenidate was sufficient to see changes in reaction time and late CNV amplitude (Linssen et al., 2011).

The monetary incentive delay (MID) task, which is an effective experimental paradigm, is run to evaluate the neural activity which includes reward and loss anticipation and outcome (Knutson et al., 2000). It is shown that sensitivity to reward or punishment influences motivated behaviour (Cooper et al., 2014; Corr & McNaughton, 2012; Unger et al., 2012) and is reported to be effective in showing differentiation between SZ patients and healthy controls (Akgül et al., 2023; Bedwell et al., 2016; Clayson et al., 2019; Leroy et al., 2020; Zeng et al., 2022). Additionally, researchers also investigated changes in motivational processing in terms of CNV in patients with SZ (Catalano et al., 2021, 2022; Lin et al., 2020) and reported blunted CNV in the patient group and altered motivation-related EEG activity. However, none of these studies investigated CNV by dividing it into early and late stages. It is thought that the frontally dominant early CNV may occur in response to a previously presented item, while the centrally dominant late CNV is linked to response and the anticipation of an event (Gaillard, 1976; Hamano et al., 1997; Mento, 2013). Therefore, early CNV may only reflect task-related cognitive processes and reward-related expectations that are not necessarily related to the action performed, whereas late CNV may reflect motor preparation and response-related activation (Bennett et al., 2015; Gómez et al., 2019; Mento, 2013; Rohrbaugh et al., 1986). It is possible that the differences that were shown in SZ patients might not be due to motivational deficits but to motor deficits.

Although its important role in effortful response preparation, it has not been studied well enough to evaluate the effect of reinforcement on the CNV. As aforementioned, CNV can reflect both motor and reward expectation-related processes, it can be an effective tool to demonstrate the motivational and motor deficits in SZ. Investigating these impairments is encouraging due to the lack of studies. Therefore, this study aimed to address neurophysiological aspects of both reward and motor preparation processing in SZ. In our study, it was hypothesized that during the MID task 1) the patient and healthy control groups would respond differently in terms of mean amplitudes and latencies of early and late CNV, 2) early and late CNV components would be related to different outcomes of the reward processing and 3) components of early and late CNV will be correlated with clinical symptoms, medication and response time, following earlier studies.

2 | MATERIALS & METHODS

2.1 | Participants

The study included 21 SZ patients who met the DSM-IV diagnostic criteria and demographically matched 22 healthy controls. Patients were recruited from the outpatient clinic at Dokuz Eylül University Hospital.

Inclusion criteria for the patient group included: (1) being age above 18 and under 55 years, (2) having no history of drug abuse or brain injury, (3) having no neurological disorders, (4) having education of five years or above, (5) having no electroconvulsive therapy in the last six months and (6) having no mental retardation or comorbid illnesses. All patients were receiving antipsychotic medication (chlorpromazine equivalent dose = 612.44 ± 350.65; Woods, 2003).

Inclusion criteria for the control group included: (1) having no neurological or psychological disorders, (2) having no family history of psychological disorders in first-degree relatives and (3) having no history of drug abuse or brain injury. All participants were right-handed and had normal vision.

This study conformed to the principles of the Declaration of Helsinki. All participants and/or their relatives provided informed consent for the study, which was approved by the local ethical committee of Dokuz Eylül University.

2.2 | Clinical measures

We evaluated patients' symptom severity, levels of negative symptoms and depressive symptoms that include the

Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), the Brief Negative Symptoms Scale (BNSS) (Kirkpatrick et al., 2011; Polat Nazlı et al., 2016), the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1993; Aydemir et al., 2000).

2.3 | EEG recording, paradigm and "analysis"

EEG recordings were acquired using Easy-Cap comprising 30 Ag/AgCl electrodes replaced according to the international 10–20 system. Linked earlobe electrodes were used as reference electrodes. Two additional EOG electrodes were used to detect eye movement artefacts. All electrode impedances were kept below 10 kΩ. EEG and EOG were amplified utilizing a Brain Amp 32-channel DC system machine with a 500 Hz sampling rate with an online 0.1–70 Hz band-pass filter. All EEG recordings were obtained at 10.00 and 11.00 a.m.) and lasted ∼45 minutes. Participants sat in a sound-attenuated, electrically shielded, and dimly lit room during EEG recordings and evaluated the MID task (Knutson et al., 2000).

The task included three different conditions, where incentive and nonincentive cues were displayed. All recordings started with the control condition, and the other two conditions were randomized between participants. In the control condition, participants were asked to respond by clicking on the mouse to the target (white square), after the cue presentation, as soon as possible once it appeared on the screen. The purpose of this condition was to prepare the participants for the task and they did not receive a monetary reward. In the reward condition, participants had no money at the beginning of the task, yet they received a monetary reward if their responses were fast enough after the target cue (white square) that followed the incentive cues (orange square). If not, they did not gain monetary rewards. In the punishment condition, at the beginning of the task participants had 40₺, and if participants' answers were delayed to the target cue (white square) that follows the incentive cues (yellow square), they lost money. If not, they did not lose money. Nonincentive cues (blue square for reward and pink square for punishment conditions) did not make them lose or gain money. After every response, they received feedback regarding their response speed (Figure 1). Each condition consisted of 150 trials (40 for incentive and 110 for nonincentive cues). More detailed information about the task was given in our group's previous study (Akgül et al., 2023).

Brain Vision Analyzer v.2.2 program was used for offline data analysis. EEG preprocessing steps included: (1) A band-pass filter at 0.**1** with a 12 dB/octave slope and a 50 Hz notch filter was applied. (2) Vertical and horizontal ocular artefacts were corrected with independent component analysis (ICA) with the Infomax algorithm using default parameters. (3) A low-pass filter at 30 with a 12 dB/octave slope was applied. (4) Continuous EEG data were segmented into 500 ms before and 4500 ms after the cue onset. (5) The baseline of 200 ms was corrected. (6) Remaining artefacts were visually inspected and automatically rejected based on maximum voltage steps of 50 μV/ms, amplitudes exceeding ±70 μV, and activity below 0.5 μV parameters. (7) Maximum peaks and peak latencies between 600 and 2500 ms for early CNV, and between 2500 and 4500 ms for late CNV were automatically detected during the Delay period (Figure 1)

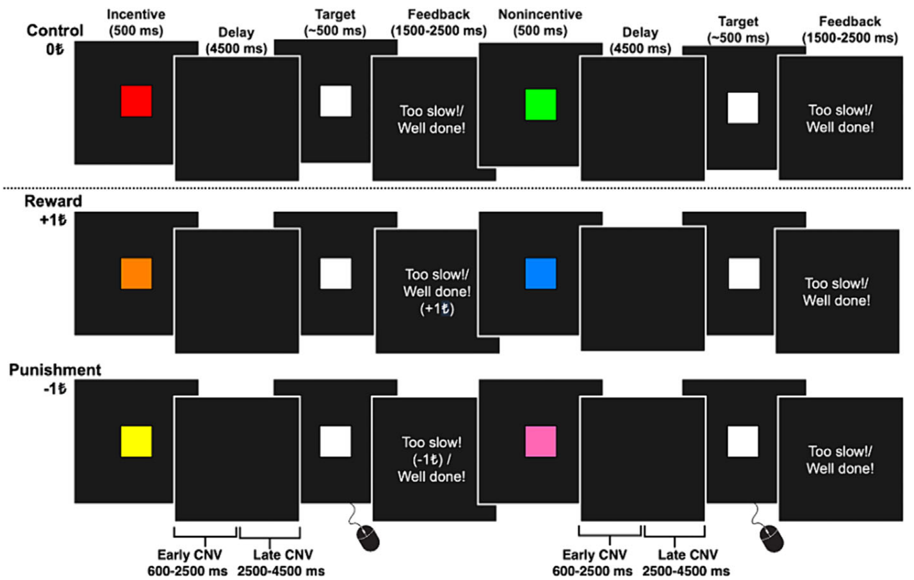

FIGURE 1 The MID task schema. Early CNV was measured within 600–2500 ms, and late CNV was measured within 2500–4500 ms in the delay period.

TABLE 1 Early CNV dependability as a function of conditions and stimulus.

Dependability		Reward: incentive		Reward: nonincentive		Punishment: incentive		Punishment: nonincentive	
		TC	95% CI	TC	95% CI	TC	95% CI	TC	95% CI
F_3	HC	22	0.87 CI [0.78 0.94]	26	0.94 CI [0.90 0.97]	28	0.85 CI [0.73 0.93]	27	0.94 CI [0.90 0.97]
	SZ	19	0.89 CI [0.81 0.95]	10	0.98 CI [0.96 0.99]	15	0.92 CI [0.85 0.96]	9	0.98 CI [0.96 0.99]
F_z	HC	19	0.89 CI [0.81 0.95]	18	0.96 CI [0.93 0.98]	16	0.91 CI [0.84 0.96]	16	0.96 CI [0.94 0.98]
	SZ	15	0.91 CI [0.85 0.96]	11	0.98 CI [0.96 0.99]	16	0.91 CI [0.85 0.96]	9	0.98 CI [0.97 0.99]
F_4	HC	29	0.84 CI [0.72 0.93]	20	0.95 CI [0.92 0.98]	20	0.88 CI [0.80 0.95]	23	0.95 CI [0.91 0.98]
	SZ	14	0.92 CI [0.86 0.96]	8	0.98 CI [0.97 0.99]	10	0.94 CI [0.89 0.97]	7	0.98 CI [0.97 0.99]
C_3	HC	25	0.86 CI [0.76 0.94]	21	0.95 CI [0.92 0.98]	16	0.91 CI [0.84 0.96]	15	0.97 CI [0.94 0.98]
	SZ	9	0.94 CI [0.90 0.97]	9	0.98 CI [0.96 0.99]	14	0.92 CI [0.86 0.96]	12	0.97 CI [0.95 0.99]
C_z	HC	14	0.92 CI [0.85 0.96]	12	0.97 CI [0.95 0.99]	9	0.95 CI [0.91 0.98]	10	0.98 CI [0.96 0.99]
	SZ	13	0.92 CI [0.87 0.96]	11	0.98 CI [0.96 0.99]	18	0.90 CI [0.82 0.95]	20	0.96 CI [0.92 0.98]
C_4	HC	24	0.87 CI [0.77 0.94]	14	0.97 CI [0.94 0.98]	11	0.93 CI [0.88 0.97]	12	0.97 CI [0.95 0.99]
	SZ	9	0.95 CI [0.90 0.97]	8	0.98 CI [0.97 0.99]	11	0.93 CI [0.88 0.97]	10	0.98 CI [0.96 0.99]

Notes: n = 43; TC = Trail cut-off; CI = Credible interval.

TABLE 2 Late CNV dependability as a function of conditions and stimulus.

Dependability		Reward: incentive		Reward: nonincentive		Punishment: incentive		Punishment: nonincentive	
		TC	95% CI	TC	95% CI	TC	95% CI	TC	95% CI
F_z	HC	25	0.86 CI [0.75 0.93]	19	0.96 CI [0.92 0.98]	14	0.92 CI [0.85 0.96]	17	0.96 CI [0.93 0.98]
	SZ	15	0.91 CI [0.85 0.96]	12	0.97 CI [0.95 0.99]	16	0.91 CI [0.84 0.95]	11	0.98 CI [0.96 0.99]
C_z	HC	16	0.90 CI [0.83 0.96]	12	0.97 CI [0.95 0.99]	9	0.95 CI [0.91 0.98]	10	0.98 CI [0.96 0.99]
	SZ	12	0.93 CI [0.87 0.96]	12	0.97 CI [0.95 0.99]	22	0.88 CI [0.79 0.94]	19	0.96 CI [0.93 0.98]
P_z	HC	11	0.93 CI [0.88 0.97]	7	0.98 CI [0.97 0.99]	8	0.95 CI [0.92 0.98]	7	0.98 CI [0.97 0.99]
	SZ	9	0.95 CI [0.91 0.98]	10	0.98 CI [0.96 0.99]	9	0.94 CI [0.90 0.97]	10	0.98 CI [0.96 0.99]

Notes: n = 43; TC = Trail cut-off; CI = Credible interval.

and visually checked. Following the earlier studies, early CNV peak amplitudes and latencies were extracted from frontal (F_3, F_z, F_4) and central (C_3, C_z, C_4), and late CNV peak amplitudes and latencies were extracted from midline frontal (F_z), central (C_z) and parietal (P_z) locations (Osborne et al., 2020). Since the control condition was only for the preparation, only the reward and punishment conditions were compared between groups. For each participant, the minimum trial number of 30 for incentive cues, and 30 for nonincentive cues was set.

Lastly, reliability via internal consistency values was calculated using the ERP Reliability Analysis (ERA) toolbox v.0.5.2 (Clayson & Miller, 2017a) for early and late CNV components to ensure there was a reliable signal. The ERA toolbox output provides overall dependability estimates of the data. The number of channels was set to 6 for early and to 3 for late CNV, the number of iterations was set to 10.000 and the a priori dependability threshold was set to 0.80 (Clayson & Miller, 2017b). Results suggested that both CNV components had good-to-excellent dependability for both cues and conditions (0.72 to 0.99 dependability; Clayson & Miller, 2017b). Final dependability estimates, 95% credible intervals (CI), and trial cut-off (TC) values for early and late CNV are presented in Table 1 and Table 2.

2.4 | Statistical analysis

To determine the sample size that is needed to detect a difference between the two groups, power calculation was conducted by using G*Power v.3.1.9 software. A priori sample-size estimations were performed using a criterion of $\alpha = 0.05$, $1\text{-}ß = 0.80$, and medium effect size Cohen's $f = 0.25$, resulting in 48 participants. However, due to the pandemic, the required number of participants could not be included in the study.

All statistical analyses were carried out with IBM SPSS Statistics 26.0 software. Separate repeated measures (RM) ANOVAs were performed for the early and late

TABLE 3 Groups' demographic and clinical profiles.

	SZ	HC	p
Age	37.71 ± 9.01	36.64 ± 9.11	0.699
Gender	6F/15M	8F/14M	0.747
Education	11.33 ± 3.37	11.68 ± 4.19	0.766
PANSS sum score	68.24 ± 17.03		
PANSS factor scores			
Positive	14.19 ± 5.66		
Negative	21.10 ± 6.03		
General psychopathology	32.95 ± 9.31		
BNNS sum score	39.90 ± 13.19		
BNNS subscales' scores			
Anhedonia	8.90 ± 4.05		
Asociality	8.48 ± 3.50		
Avolition	6.38 ± 2.16		
Blunted affect	9.62 ± 3.67		
Alogia	6.24 ± 2.53		
Lack of distress	2.43 ± 1.33		
CDSS	2.63 ± 4.26		

Notes: Data is presented as mean ± standard deviation. PANSS = Positive and Negative Syndrome Scale; BNSS = The Brief Negative Symptom Scale; CDSS = Calgary Depression Scale for Schizophrenia.

CNV amplitudes and latencies. RM ANOVAs included a 2-level *Group* [SZ and controls] as a between-subjects factor. For early CNV calculations; 2-level *Condition* [reward and punishment], 2-level *Cue* [incentive and nonincentive], 2-level *Location* [frontal and central] and 3-level *Laterality* [left, mid, right] were included as within-subject factors. For late CNV calculations; 2-level *Condition* [reward and punishment], 2-level *Cue* [incentive and nonincentive] and 3-level *Location* [frontal, central, parietal] were included as within-subject factors.

Statistical analyses of demographic information and clinical measures were carried out with one-way ANOVA. When Mauchly's test indicated that the assumption of sphericity had been violated, the Greenhouse–Geisser correction was applied where $\varepsilon < 0.75$, and the Huynh-Feldt correction was applied where $\varepsilon > 0.75$.

The Pearson correlation analysis was conducted to reveal the possible relation between early and late CNV components and the clinical features (i.e., PANSS negative and positive score, BNSS sum score, and medication dosage) of patients and behavioural data (i.e., total gain and reaction time) of both groups. The Benjamin-Hochberg false discovery rate (FDR) was applied for multiple comparisons correction to control the type-I error. Levels of $p < 0.05$ were considered significant for all comparisons.

3 | RESULTS

3.1 | Group characteristics

Demographic, clinical and psychometric information for both groups is presented in Table 3. The demographic features did not show any difference between groups ($p > 0.050$).

Regarding the reaction time, the SZ group had longer reactions in both conditions and to both cues (all, $p < 0.030$). Likewise, reaction time was lower in the SZ group for reward and punishment conditions (all, $p < 0.008$). Patients with SZ gained significantly less than controls in the reward condition (SZ: 24.14 ± 13.61; HC: 36.45 ± 9.76, $p = 0.002$), and lost more in the punishment condition (SZ: 21.19 ± 15.36; HC: 36.36 ± 11.12, $p < 0.001$).

3.2 | EEG results

3.2.1 | Early CNV

Amplitude measures showed interaction effects of *Group and Condition* ($F_{1,41} = 4.441$; $p = 0.041$, $\eta p^2 = 0.098$), and *Group, Condition and Cue* ($F_{1,41} = 4.113$; $p = 0.049$, $\eta p^2 = 0.091$). Further analysis indicated lower amplitudes

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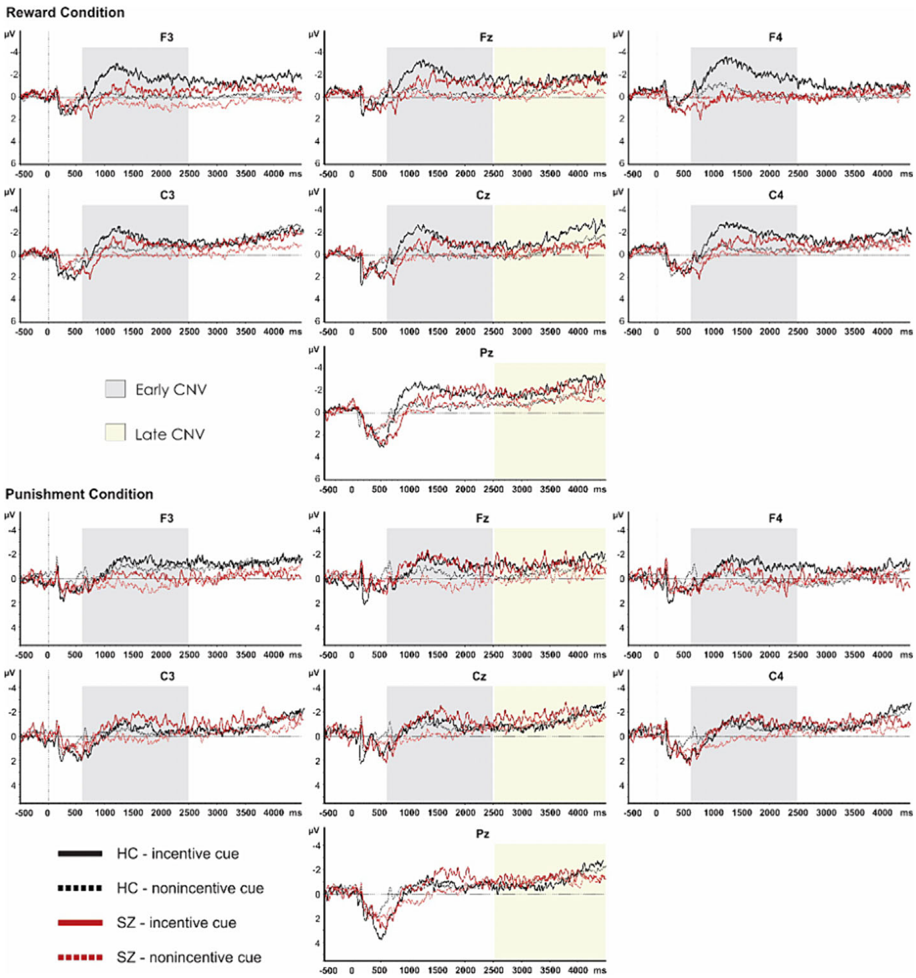

FIGURE 2 Grand averages of the groups' early and late CNV during incentive and nonincentive cues in the reward and punishment conditions.

for incentive cues in the SZ group in the reward condition ($p = 0.043$) (Figure 2, Supplementary Figure S1).

Regarding the latency, there was an interaction effect of *Group, Cue and Location* ($F_{1,41} = 4.346$; $p = 0.043$, $\eta p^2 = 0.096$), yet post-hoc analysis revealed insignificant results ($p > 0.050$). No other main or interaction effects were found ($p > 0.05$).

3.2.2 | Late CNV

We found interaction effects of *Group and Location* ($F_{2,82} = 3.449$; $p = 0.036$, $\eta p^2 = 0.078$), and *Group, Cue and Location* ($F_{2,82} = 3.699$; $p = 0.041$, $\eta p^2 = 0.083$), indicating lower amplitudes in the patient group at the central location (C_z) ($p = 0.039$). These lower amplitudes over the central electrode were in response to incentive cues in the SZ group ($p = 0.019$) (Figure 2 Supplementary Figure 3).

Latency calculations showed the main *Group* effect ($F_{1,41} = 8.423$; $p = 0.006$, $\eta p^2 = 0.170$), indicating shortened responses in the patient group. There was also an interaction effect of *Group and Location* ($F_{2,82} = 4.110$; $p = 0.020$, $\eta p^2 = 0.091$). Further analysis indicated these shortened responses of patients were over central (C_z) and parietal (P_z) locations (respectively, $p = 0.013$; $p = 0.001$) (Supplementary Figure 3). No other main or interaction effects were found ($p > 0.05$).

3.2.3 | Correlation analysis

During the reward condition, early CNV amplitudes in response to incentive cues were positively correlated with PANSS positive scores (F_z: $r = 0.555$, $p = 0.009$; C_z: $r = 0.458$, $p = 0.037$). Also, CNV latencies were positively correlated with antipsychotic medication dosage (F_z: $r = 0.529$, $p = 0.024$). In addition, the SZ group's latency values showed a negative correlation with total gain (C_4: $r = -0.537$; $p = 0.012$), while healthy controls' latencies showed a positive correlation (F_3: $r = 0.480$; $p = 0.024$; C_z: $r = 0.501$; $p = 0.017$). After the FDR correction, only the correlation of early CNV amplitudes at the F_z electrode and PANSS positive scores remained significant (Figure 3, top row).

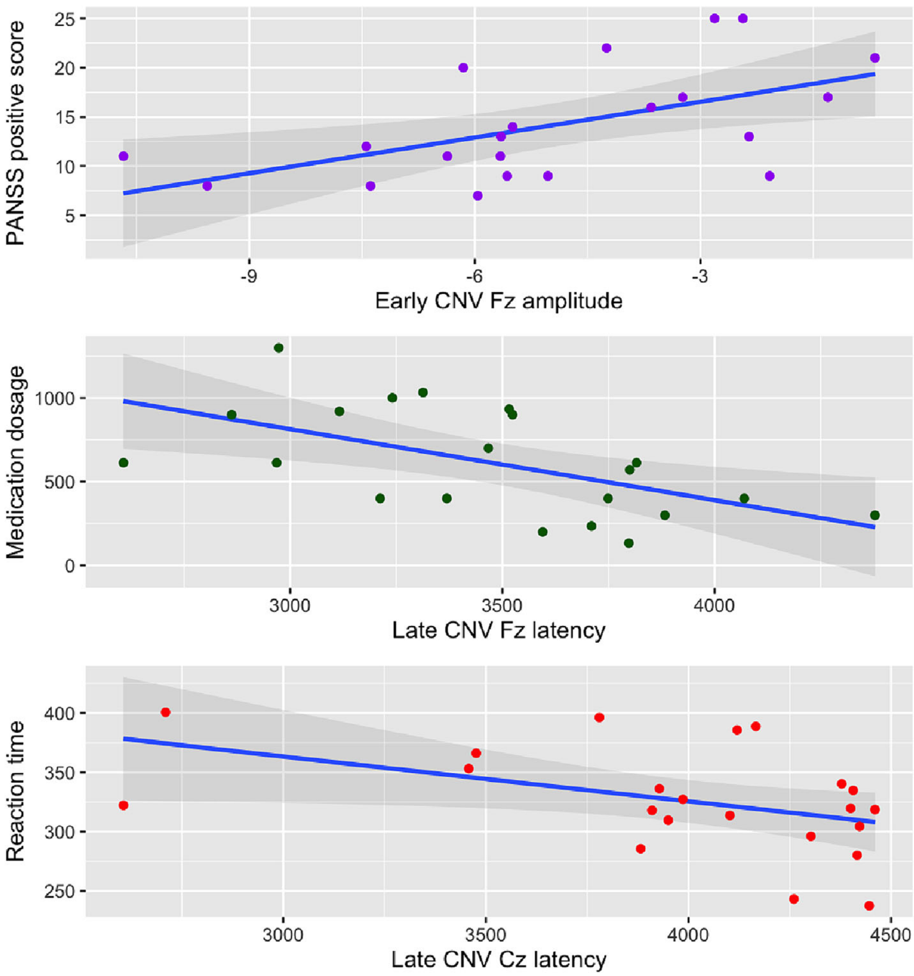

FIGURE 3 Scatter plots of correlations that remained significant after FDR correction. Top row shows relations between patients group's amplitudes and PANSS positive scores; middle row shows relations between patients group's latencies and antipsychotic medication dosage; and bottom row shows relations between healthy controls' latencies and reaction time.

Late CNV latency values showed negative correlations with antipsychotic medication dosage (F_z: $r = -0.687$, $p = 0.002$; C_z: $r = -0.553$, $p = 0.017$; P_z: $r = -0.543$, $p = 0.020$). Late CNV latency values of the control group for incentive cues showed negative correlations with reaction time (C_z: $r = -0.552$; $p = 0.008$; P_z: $r = -0.436$; $p = 0.043$). After the FDR correction, correlations between late CNV latency at the F_z electrode and antipsychotic medication dosage, and latency at the C_z electrode and reaction time remained significant (Figure 3, middle and bottom rows, respectively).

4 | DISCUSSION

The present study aimed to investigate deficits in reward-related motivation and motor processing of patients with SZ using neurophysiological aspects. With this aim, we compared the SZ and control groups' early and late CNV components that were evoked during the MID task. Additionally, we sought the relationship between CNV components and the clinical profiles of the patients and behavioural data of both groups. We demonstrate that the SZ group had lower early CNV amplitudes in the reward condition for incentive cues, and lower and shortened late CNV amplitudes for incentive cues at the central location. Also, early CNV amplitudes were related to positive symptoms, and both latencies were associated with medication dosage and behavioural outcomes of the MID task.

The CNV has received less attention in reward processing, although it is important in anticipatory attention and motor preparation (Falkenstein et al., 2003). Earlier results in healthy individuals showing the relationship between CNV amplitudes and reward or loss anticipation are a little mixed: some did not show any effect of cues anticipating monetary gain and loss (Broyd et al., 2012); others indicated a larger CNV amplitude in the reward condition (Schevernels et al., 2014). This inconsistency between the findings might be due to paradigm differences or CNV measurements.

On the contrary, there seems to be a consensus on reward processes in SZ. Most findings point out disruptions in cortico-striatal-thalamic-cortical networks, which is the brain circuit that controls reward, movement execution and habit formation (Bracht et al., 2013; Mittal et al., 2017; Rădulescu et al., 2017; Walther et al., 2017). Regarding the CNV activity, several studies have shown reductions in patients' amplitudes compared to controls (Wynn et al., 2010; Zhang et al., 2016). Therefore, we hypothesized to find group differences in both early and late CNV components and our results reporting diminished amplitudes in the patient group for both CNVs confirmed our hypothesis. Hence, we showed that CNV is evidently sensitive to reward outcomes.

More specifically, the patient group had lower early CNV responses in the reward condition for incentive cues. As mentioned in the Introduction, early CNV is thought to be related to motivation. It has been proposed that early CNV provides top-down information about ventral striatum activity (Cohen et al., 2012; Plichta et al., 2013) via signifying neuronal activity originating from a cortical-thalamic-striatal network mediated by dopamine (Fan et al., 2007). SZ patients display hypofrontality, which results from decreased dopamine receptor density, and this reduced activity in this region causes learning difficulties regarding reward-predictive cues (Millard et al., 2022; Slifstein et al., 2015) and is associated with avolition (Taylor et al., 2020). In light of these, our early CNV results may indicate impaired frontal activity in SZ during the reward process possibly due to alterations in the mesolimbic dopamine pathway (Brunia & van Boxtel, 2001; Fan et al., 2007).

We further found an association indicating that less activation in early CNV amplitudes for reward anticipation was related to positive symptom severity, which complements theearlier studies showing that diminished frontal CNV amplitudes relied on the individual's current state (Smid et al., 2009; Verleger et al., 1999). More recently, Zeng et al. (2022) indicated an association between the neural processing of reward outcomes in the medial prefrontal cortex and the underlying mechanisms of positive symptoms in SZ. The development and severity of positive symptoms appear to be influenced by reward anticipation (Esslinger et al., 2012; Kapur, 2003; Murray et al., 2008; Nielsen et al., 2012). Taken together, we can conclude that early CNV amplitudes indeed imply reward-related motivational processes, and may reflect the activity of dopamine-related frontal impairments within the reward circuitry, as well as positive symptom severity. Yet, these assumptions should be confirmed with other imaging techniques, before making further conclusions.

Regarding the late CNV, the patient group showed lower amplitudes for incentive cues over the central and shortened latencies over the central and parietal locations in SZ. The late CNV has a greater concentration in the central region and affects a posterior cortical network for perceptual-motor tasks (Berchicci et al., 2016; Brunia & Damen, 1988; De Kleine & Van der Lubbe, 2011; Gómez et al., 2003; Leynes et al., 1998). It has been associated with two specific functions of the parietal–frontal motor system: the preservation of the stimulus–response connections and the stimulation of the hand-motor region (Verleger et al., 2000). Complementing these results, we showed a relation between reaction time and central late CNV latency values in the control group. The most common finding in the literature is that individuals with SZ have smaller CNV amplitudes, which, when compared to delayed responses, indicates a lack of improved action readiness (Smid et al., 2009; Verleger et al., 1999; Wynn et al., 2010). Therefore, deficits in preparatory motor performances may cause patients to be more vulnerable in giving responses reactively to stimuli rather than preparing for planned actions.

On the other hand, human intracerebral measurements showed that late CNV is not merely associated with motor responses (Hamano et al., 1997): it is a mixture of expectancy-related attention processes and response readiness motor preparation (Berger et al., 2018; Brunia & van Boxtel, 2001). Indeed, CNV was found to be related to attention, and lower responses in SZ patients were thought as an indicator of impaired sustained attention (Catalano et al., 2021; Lin et al., 2020; Zhang et al., 2016). Even though altered responses to incentive cues can be thought of as attentional processes (Chiew & Braver, 2016), since this study did not evaluate attention directly, we can only make speculation on the SZ group's lower responses which were only for incentive cues, independently from the conditions. Since latency is computed based on the time at which peak amplitudes are obtained, shortened late CNV latencies in SZ patients could be interpreted as a result of diminished amplitudes which might result in SZ patients' difficulty in sustaining attention for extended periods. Therefore, we can suggest that late CNV responses may be associated with motor and attentional deficits rather than directly related to reward-induced motivation. When patients were presented with the target stimuli after incentive cues, they may have displayed an impaired allocation of mental resources. Consequently, this might result in equal or lower cognitive input, leading to smaller amplitudes when they get the incentive stimuli. However, future studies are needed to show a direct link between late CNV and attention, to make further assumptions.

Lastly, we found that the frontal latency values of late CNV were associated with medication dosage. Multiple evidence indicates that dopamine availability may have a role in modulating CNV (Oishi et al., 1995; Rizzo et al., 1983; Simlai et al., 2010; Tecce, 1991; Tecce et al., 1975; Tecce & Cole, 1974). The CNV may serve as a dependable indicator of the status of SZ which is characterized by an excessive amount of dopamine in the acute phase, which can be counteracted by antipsychotic medication (Linssen et al., 2011; Simlai et al., 2010). Yet, regarding the location, where the late CNV is the most pronounced, this association can be unexpected. Considering there is no difference in frontal late CNV latencies between groups, this relation may reflect compensation in SZ. Nonetheless, this association should be investigated in a more comprehensive manner and with a larger sample, since this is the first study that showed such a relation.

5 | CONCLUSION

Abnormal reward processing and psychomotor slowing are well-known phenomena in SZ. Particularly, psychomotor slowing is accepted as "the closest thing to a north star in schizophrenia research" (Cancro et al., 1971; Osborne et al., 2020). Additionally, reduced reward anticipation has been suggested as a core symptom of SZ. By extending these findings, we demonstrate that early and late CNV play different roles in neurophysiology and reflect different aspects of the mentioned impairments in individuals with SZ. To be more specific, while both early and late CNV amplitudes decreased in SZ, only the early CNV amplitude decrements were related to reward conditions and correlated with positive symptoms. Meanwhile, late CNV showed more general alterations independently from the task conditions.

These results should be read with caution due to the relatively small sample size and broad age range. Even though the broad age range is typical in the studies on SZ, the smaller variance of age would be better for controlling subtle changes that can be elicited with age. Nonetheless, our study was well-powered enough to detect a small to medium effect size and CNVs exhibited good reliability, confirming that the results were not due to error. In this study, we provide more support for the hypothesis that slow cortical potentials reflect inadequate reward-induced motivational processes, as well as response preparation and possible attention deficits in patients with SZ.

It can be emphasized that CNV is suitable both for evaluating reward mechanisms and as a good indicator for showing SZ-related impairments, medication effects and clinical symptoms. Subsequent investigations should prioritize the analysis of CNVs in drug-naive patients since medication dosage has an impact on the latency values. Additionally, recruiting SZ patients according to their symptoms (i.e., SZ patients with deficits vs. non-deficits) would provide more understanding of symptom-related reward processing differences. To gain a deeper understanding of the cognitive and motor impairments associated with psychosis, future studies must compare the effects of CNV in the early and late phases.

AUTHOR CONTRIBUTION

Emre Bora, **Berna Binnur Akdede**, **Görsev Yener**, **Köksal Alptekin**, **Özge Akgül**: Conceptualization. **Özge Akgül**, **Ezgi Fide**, **Fatih Özel**: Methodology. **Özge Akgül**, **Ezgi Fide**: Formal analysis; visualization; writing—original draft. **Görsev Yener**: Writing—reviewing and editing; supervision.

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CONFLICT OF INTEREST STATEMENT

All authors declare no conflict of interest.

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DATA AVAILABILITY STATEMENT

Data is available on reasonable request.

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