The Startle Response and Prepulse Inhibition in Psychosis and Violence: A Combined Electromyography and Electroencephalography Study

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There is a pressing need for biomarkers of violent behavior risk in psychosis. Previous research indicates that electrophysiological measures of automatic defensive reactions may have potential. The purpose of this study was to investigate associations between violent behavior in individuals with and without psychosis and electromyography (EMG) and electroencephalography (EEG) responses to startling auditory stimuli. Electromyography and EEG were recorded during an auditory startle paradigm from healthy controls (HC, $n = 211$), individuals with psychosis and a history of violent behavior (violent-PSY, $n = 18$), individuals with psychosis without a history of violence (nonviolent-PSY, $n = 32$), and individuals with a history of violence without psychosis (violent non-PSY, $n = 22$). We estimated the auditory startle response (ASR) and prepulse inhibition (PPI) using EMG (ie, EMG_{ASR} and EMG_{PPI}) and the auditory-evoked potential (ie, AEP_{ASR} and AEP_{PPI}) of the EEG. There were no significant effects of group on the EMG_{ASR} ($P = .10$) or the 30-, 60-, and 120-ms prepulse + pulse EMG_{PPI} amplitudes ($P = .11$, $P = .19$, and $P = .50$, respectively). The N1 amplitude of the AEP_{ASR} was reduced in the violent-PSY group ($P < .001$) and the nonviolent-PSY group ($P = .015$) compared with HC. The P2 amplitude of the AEP_{ASR} was reduced in violent-PSY relative to nonviolent-PSY ($P = .003$), violent non-PSY ($P = .016$), and HC ($P < .001$). Together, these results show that EEG-based neural responses to startling auditory stimuli are promising biomarkers of violence risk in psychosis.

Key words: schizophrenia; EEG; EMG; violence

Highlights

- There is an urgent need for biomarkers that can predict the risk of violent behavior in psychosis.
- This study investigated associations between electromyography and electroencephalography (EEG) measures and violent behavior in individuals with and without psychosis.
- EEG-based neural responses to startling auditory stimuli were reduced in patients with psychosis and violent behavior.
- EEG-based neural responses to startling auditory stimuli are promising biomarkers of violence risk in psychosis.

Introduction

While most individuals with psychotic disorders are not violent, the increased risk of violent behavior in this patient group represents a clinical challenge for mental healthcare providers.[1,2] However, the biopsychosocial mechanisms underlying this increased propensity for violent behavior need to be clarified due to significant limitations in developing effective treatments and evidence-based risk assessment. Current risk prediction models are based on clinical observations, with low to moderate predictive accuracy.[3-5] There is therefore a pressing need for identifying potential biomarkers to improve the ability to predict the risk of future violent behavior in individuals with severe mental disorders. Previous studies have suggested that electrophysiological markers of automatic defensive reactions may have potential.[6]

The auditory startle response (ASR) is a defensive physiological reaction to an unexpected and loud noise.[7] The most evident stimulus that triggers the defensive reflex is something abrupt, unpleasant, and unanticipated,[8] commonly assessed using eye-blink electromyography (EMG_{ASR}). Prepulse inhibition (PPI) is the reduction of this defensive eye-blink response when the startle-inducing stimulus (referred to as a "pulse") is preceded by a weaker "prepulse" stimulus, hereafter referred to as the EMG_{PPI}.[9] PPI is reliably elicited across species and reduces acoustic EMG_{PPI}, one of the most consistent electrophysiological findings in psychosis.[10-12] Defense-related functional and brain structural inhibition has also been associated with violent offenders compared with nonviolent control subjects.[13]

Several lines of evidence indicate that the neural circuits that mediate and modulate PPI and violent and aggressive behaviors overlap. In particular, frontotemporal lobe and brainstem deficits are linked to reduced PPI and the risk of violent behavior.[14-16] Moreover, a few studies have assessed the muscular $EMG_{startle}$ and EMG_{PPI} in individuals with mental disorders with a history of violence.[17] For instance, Kumari et al. investigated EMG_{PPI} in individuals with antisocial personality disorder (APD) or schizophrenia with or without a history of violence.[17]

Compared with healthy controls (HCs), EMG_{PPI} was reduced in all clinical groups, and high ratings of violence were associated with lower PPI across the entire sample. Another study assessed EMG_{PPI} in HC, men with a history of violence, comorbid psychosis, and dissocial personality disorder, violent men with psychosis, and men with a history of violence and APD.[18] Here, the comorbid group with a history of violence had a decreased PPI relative to controls, while antisocial personality traits were linked to impaired EMG_{PPI} across clinical groups. Together, these studies indicate an association between measures of PPI and violent behavior. Nevertheless, more research is needed to further clarify this relationship.

Most previous ASR and PPI research on humans has assessed the muscular eye-blink EMG response. Some studies have also employed electroencephalography (EEG)-based measures of the startle response and PPI by examining the auditory-evoked potential (AEP) elicited by acoustic "pulse" and "prepulse" stimuli.[19-21] Similar to the traditional, muscular eye-blink studies described above, these EEG studies have shown that AEP amplitudes induced by the startling pulse stimulus (AEP_{ASR}), particularly the N1 and the P2, were smaller when preceded by a weaker "prepulse" stimulus and these are hereafter referred to as the AEP_{PPI}. However, several studies have shown that the startle-related response and the PPI of the EMG and the AEP exhibited different changes during psychotropic drug treatments.[20,22] Moreover, some studies have suggested that the EMG- and the EEG-based approaches have varying sensitivities to personality traits and psychiatric diagnoses.[21,23] To our knowledge, no study has investigated the startle-related responses or PPI of the AEP in individuals with a history of violence, with or without severe mental illnesses.

Therefore, the current study aimed at investigating whether the startle-related response and PPI of the EMG- and the EEG-based AEP were associated with a history of violence in individuals with and without psychosis. Hence, 4 groups underwent assessments of EMG and EEG during an acoustic PPI paradigm: (1) HC, (2) individuals with psychosis and a history of violence, (3) individuals with psychosis without a history of violence, and (4) non-psychotic individuals with a history of violence. The primary hypothesis was that a history of violence is associated with reduced startle-related responses and PPI of the EMG and the AEP. If so, we expected the most distinctive effects in the participants with psychosis and history of violence. We also explored the relationships between EMG and AEP measures and clinical variables, including violence ratings and antisocial personality traits.

Methods

Participants

The current study included 4 groups: (1) individuals with psychosis without a history of violence, (2) individuals

with psychosis and a history of violence, (3) non-psychotic individuals with a history of violence, and (4) HCs. The inclusion in the study was restricted to males since few females serve preventive detention in Norway. For all 4 groups, the inclusion criteria were ages between 18 and 70 years, male gender, IQ score above 65, the ability to give informed consent to participation, and a hearing threshold <40 dB. In addition, the inclusion criteria for the nonviolent-PSY group was a diagnosis based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) of SCZ spectrum disorder, psychotic BD, or psychosis not otherwise specified, and without a history of severe violence. For the violent-PSY group, the inclusion criteria were a DSM-IV diagnosis of SCZ spectrum disorder, psychotic BD, or psychosis not otherwise specified, and a history of severe violence (including murder, attempted murder, and severe assault toward other people classified using the McArthur criteria).[24] For all 4 groups, the exclusion criteria were neurological illnesses, brain injury or history of severe head trauma with loss of consciousness, and other significant medical illnesses affecting the brain. To ensure clarity on the exclusion criteria for participant selection in the groups with psychosis patients, demographic information regarding education, psychiatric- and somatic health conditions, living conditions, and heritability was recorded, and project physicians obtained somatic health status. For the participants in the violent non-PSY group, demographic information regarding criminal court records, education, lining conditions, heritability, and psychiatric- and somatic health conditions was recorded. Furthermore, subjects from the preventive detention facilities were reassessed for psychotic symptoms at study inclusion using the Structured Clinical Interview for the Positive and Negative Syndrome Scale (SCI-PANSS, see below) to ensure no development of psychotic disorder after sentence and confirm the requirement for criminal responsibility. Basic observation and conducted psychiatric evaluation did not recognize mental health issues in this group that would cause functional limitations in cognition, emotional regulation, or daily living that would interfere with participation in the project or daily living functioning. For violent non-PSY and HC, a history of psychosis was an exclusion criterion. For HC the exclusion criteria also included a history of psychosis, having a first-degree relative with a severe mental disorder, and current and prior substance abuse or addiction.

The individuals with psychosis but without a history of violence (nonviolent-PSY, *n* = 32) were recruited from psychiatric hospitals and affiliated outpatient clinics in the region of Oslo, Norway. The nonviolent-PSY group consisted of patients with the diagnosis of paranoid schizophrenia (DSM-IV 295.3, *n* = 18), schizoaffective disorder (DSM-IV 295.7, *n* = 2), schizophrenia (DSM-IV 295.9, *n* = 4), psychotic disorder NOS (DSM-IV 298.9, *n* = 4), brief psychotic disorder (DSM-IV 298.8,

n = 1), disorganized type (DSM-IV 295.1, *n* = 1), schizophreniform disorder (DSM-IV 295.4, *n* = 1), and residual type (DSM-IV 295.6, *n* = 1). Individuals with psychosis and a history of violence (violent-PSY, *n* = 18) were recruited from high-security forensic psychiatric wards at Østfold Hospital, Oslo University Hospital, and St. Olavs Hospital, Norway. The violent-PSY group included patients with the diagnosis of paranoid schizophrenia (DSM-IV 295.3, *n* = 10), undifferentiated schizophrenia (DSM-IV 295.9, *n* = 2), schizoaffective disorder (DSM-IV 295.7, *n* = 1), schizophreniform disorder (DSM-IV 295.4, *n* = 1), and bipolar 1 disorder (DSM-IV 296.4, *n* = 1). Non-psychotic individuals with a history of violence (violent non-PSY; *n* = 22) were incarcerated persons serving preventive detention sentences in the greater Oslo area and Trondheim, Norway. Healthy control without current or previous severe mental disorders and a history of violence (*n* = 211) were included through the Norwegian National Population Registry (https://www.ssb.no/en), thus resulting in a total sample of 283 participants. Eighteen participants were then excluded from the analyses of EMG and EEG measures due to technical issues of insufficient data quality, as outlined in EEG preprocessing. The remaining sample of 283 is described in Table 1. Two hundred and sixty-five of these had both EMG and EEG data that were included in the statistical analyses, whereas 275 and 265 had EMG or EEG data, respectively, after the exclusion of datasets with technical issues or insufficient data quality.

The Norwegian Regional Committee for Medical Research Ethics, the Norwegian Data Inspectorate, and relevant correctional agencies reviewed and approved the study. All subjects provided written informed consent after the procedure was fully explained.

Clinical Assessments

Trained clinicians assessed the participants using the Structured Clinical Interview for DSM-IV Axis 1 Disorders (SCID-I).[25] IQ was estimated using the Wechsler Abbreviated Scale of Intelligence (WASI) for all participants.[26] Alcohol and drug use were assessed using the Alcohol Use Disorders Identification Test (AUDIT)[27] and the Drug Use Disorders Identification Test (DUDIT).[28] Participants were also screened for tobacco use status.

Specifically, HC participants were interviewed to confirm no history of psychiatric disorder and screened with the Primary Care Evaluation of Mental Disorders questionnaire (Prime-MD).[29] Psychosocial functioning was measured with the Global Assessment of Function Scale (GAF),[30] and use of antipsychotic medication was calculated based on defined daily doses (DDD) per World Health Organization guidelines (https://www.whocc.no/atc_ddd_index/). Violent non-PSY, violent-PSY, and nonviolent-PSY groups were assessed for psychotic

Table 1. Sample Characteristics

	HC (*n* = 211)	Nonviolent-PSY (*n* = 32)	Violent-PSY (*n* = 18)	Violent non-PSY (*n* = 22)	Statistics
Age	48.5 (17.9; 19-89)	31.7 (10.1; 18-55)	35.4 (9.3; 21-58)	42.3 (14.5; 22-70)	*F* = 12.16; *P* < .001 (HC > nonviolent-PSY[*]; HC > violent-PSY[**])
WASI IQ	117.4 (11.1; 79-153)	102.4 (13.4; 69-122)	85.4 (12.3; 67-110)	101.9 (11.2; 82-128)	*F* = 56.86; *P* < .001 (HC > nonviolent-PSY[*]; HC > violent-PSY[*]; HC > violent non-PSY[*]; nonviolent-PSY > violent-PSY[*]; violent non-PSY > violent-PSY[*])
Daily tobacco use (y/n)	15/174	14/18	13/4	11/9	*P* < .001 (HC < nonviolent-PSY[*]; HC < violent-PSY[*]; HC < violent non-PSY[*]; nonviolent-PSY < violent-PSY[**])
PCL-R score			17.65 (7.88)	18.42 (6.95)	*F* = 0.10; *P* = 758
PANSS, total		57.50 (16.37)	64.00 (15.46)	36.23 (9.87)	*F* = 20.72; *P* < .001 (violent non-PSY < nonviolent-PSY[*]; violent non-PSY < violent-PSY[*])
Positive factor		8.38 (3.66)	9.93 (5.76)	5.23 (2.88)	*F* = 6.96; *P* < .002 (violent non-PSY < nonviolent-PSY[*]; violent non-PSY < violent-PSY[*])
Negative factor		12.13 (5.69)	14.93 (6.92)	6.82 (1.62)	*F* = 12.39; *P* < .001 (violent non-PSY < nonviolent-PSY[**]; violent non-PSY < violent-PSY[*])
Disorganized factor		5.53 (2.38)	6.14 (2.91)	3.41 (0.91)	*F* = 8.90; *P* < .001 (violent non-PSY < nonviolent-PSY[**]; violent non-PSY < violent-PSY[**])
Excited factor		5.59 (2.00)	6.86 (3.13)	4.32 (0.84)	*F* = 6.91; *P* = .002 (violent non-PSY < violent-PSY[**])
Depressive factor		7.13 (3.18)	6.43 (3.13)	5.27 (2.39)	*F* = 2.59; *P* = .083
GAF, symptom		52.38 (13.57)	46.21 (14.44)		*F* = 1.93; *P* = .172
GAF, function		53.06 (15.66)	45.26 (12.82)		*F* = 2.66; *P* = .110
Antipsychotics (DDD)		0.93 (0.68)	1.88 (0.92)		*F* = 8.87; *P* < .001 (nonviolent-PSY < violent-PSY[*])
Benzodiazepines (DDD)	0.00 (0.00)	0.063 (0.35)	0.40 (1.02)	0.00 (0.00)	*F* = 14.04; *P* < .001 (HC < violent-PSY[*]; nonviolent-PSY < violent-PSY[*]; violent non-PSY < violent-PSY[*])

Unless otherwise specified, the values indicate mean, SD, and range. Abbreviations: DDD, defined daily doses; GAF, Global Assessment of Function split version; HC, healthy control; nonviolent-PSY, nonviolent patients with psychosis; PANSS, Positive and Negative Syndrome Scale; PCL-R, Psychopathy Checklist-Revised; violent non-PSY, non-psychotic individuals with a history of violence; violent-PSY, individuals with psychosis and a history of violence; WASI, Wechsler Abbreviated Scale of Intelligence.
[*]*P* < .001;
[**]*P* < .05.

symptoms using the SCI-PANSS.[31] Psychopathy traits among violent non-PSY and violent-PSY were assessed using the Hare Psychopathy Checklist-Revised (PCL-R),[32] and violence history was classified using the McArthur criteria,[24] assessing variables critical for violence and evaluating medical records and forensic reports.

Experimental Procedure

The auditory startle paradigm was run with PsychToolbox-3[33–35] in MATLAB R2015a.[36] We employed a standard PPI paradigm that previously identified alterations in participants with psychosis and a history of violent behavior, which is highly relevant to our study's objectives.[17] The participants were instructed to focus on a red dot in the middle of the screen during the paradigm. The intensities of the auditory stimuli included white noise at 70 dB, prepulse stimuli at 85 dB, and pulse stimuli at 115 dB. Hearing threshold was tested binaurally using a pure sinusoidal 1000 Hz tone, and all participants had a threshold of <40 dB. The PPI paradigm included 90 trials and lasted for approximately 20 minutes. The experiment started with 3 pulse-alone (PA) trials, followed by 84 12 PA trials, 12 30-ms interval prepulse-pulse (PP) trials, 12

60-ms interval PP trials, 12 120-interval PP trials, and 12 PA trials (to estimate and remove the ERPs (event-related potentials) elicited by the prepulse stimuli). A PP trial involves a prepulse stimulus directly preceding a PA stimulus. These 84 trials were pseudo-randomized, with inter-trial intervals varying between 11 and 19 seconds. Three additional PA trials were at the end.

Data Acquisition

Continuous EEG and EMG recordings were acquired throughout the auditory startle paradigm using a 72-channel BioSemi ActiveTwo amplifier, with Ag-AgCl-sintered electrodes distributed across the scalp according to the international 10–5 system, using CMS (active electrodes) and DRL (passive electrodes) to replace reference and ground electrodes. External electrodes were placed at the outer canthi of both eyes and below and above the left eye to acquire horizontal and vertical electrooculograms for eye movement and eye-blink correction. Two electrodes were placed at a 1-cm horizontal distance on the orbicularis oculi muscle below the right eye to record EMG associated with the startle-evoked blinks. The ECG electrodes were placed over the right

clavicle and the left pelvic bone. Potentials at electrode sites were measured considering a common mode sense, with a driven right-leg electrode minimizing common mode voltages sampled at 2048 Hz.

EEG Preprocessing

Signal processing was conducted in MATLAB R2017a using EEGLAB version 2019.0.[37,38] Offline recordings were downsampled to 512 Hz. PREP (preprocessing) pipeline with default settings was used to remove noisy channels and remove artifacts before average referencing.[39] The data were then band pass-filtered between 1 and 40 Hz, and we rejected ±500 ms around data points exceeding 500 mV across the 64 scalp channels.[40] Independent component analysis and ICLabel were used to remove muscle, eye-blink, eye movement, and heart-related activity, as well as line and channel noise.[41] Separate epochs were extracted for each stimulus event with a time window of −100 to 500 ms. The data were then baseline corrected from −100 to 0 ms. Prepulse-corrected ERPs were created by removing "prepulse-alone" ERPs from each prepulse + pulse condition. Prior to the extraction of ERP voltages, the ERPs were re-referenced to linked mastoids in order to capture both the negative (on centrofrontal electrodes) and positive (on inferior temporal and posterior electrodes) polarity of the auditory ERP (inverting over the Sylvian fissure). The ERP components' peak latency and amplitude from channel Cz were extracted for the 30-, 60-, and 120-ms prepulse + pulse conditions. The time window for identifying the N1 amplitude peak was 100-140. The P2 was defined as the average within the 200-250-ms time window, given the longer duration of the P2. Two researchers (T.E. and N.B.) blinded to group status visually inspected the preprocessed EEG signals, and recordings without clear N1 and P2 peaks were excluded from the analyses.

EMG Preprocessing

Electromyography analysis was performed following the guidelines established by Blumenthal et al.[42] First, we constructed a bipolar EMG channel by taking the difference between the 2 EMG channels. This channel was subsequently filtered within the frequency range of 28-500 Hz (by applying high- and low-pass filters successively). Next, we calculated the root-mean-square of this continuous signal using 40-point (20 ms) windows that moved with a 39-point overlap and zero padding.

Subsequently, we extracted epochs ranging from −0.5 to 0.7 seconds relative to stimulus onset (ie, prepulse or pulse), and baseline corrected these epoched data using a −200 to 0 ms baseline. Epochs containing excessive EMG activity during the baseline period, which indicates a spontaneous blink, were automatically detected and eliminated. This was done by applying a threshold of 3 SDs over the average EMG activity during the baseline period across all epochs.

Since raw EMG amplitudes vary considerably across subjects, partially reflecting slight differences in electrode placement or skin conductivity, we transformed them into z-scores. Importantly, this procedure preserves experimental effects of interest (ie, the relative amplitude differences between conditions), while controlling for the large inter-individual differences in raw EMG amplitudes. After the z-score transformation, the −200 ms to 0 baseline was removed once again, and re-epoched around the primary stimuli of interest (ie, the startle-inducing pulse in the prepulse conditions). Finally, peak amplitude and peak latency were determined within the time frame of 30-150 ms for each prepulse condition (30, 60, and 120 ms).

Statistical Analyses

Statistical analysis was performed using IBM SPSS Statistics version 29.0.

Analyses of variance and covariance were performed for continuous variables, and a chi-square test was run for categorical variables, to determine differences among the groups while controlling for the effect of age, IQ, smoking, and the DDD of antipsychotics and benzodiazepines. Group comparisons for the 30-, 60-, and 120-ms AEP_{PPI} and EMG_{PPI} were run with adjustments for stand-alone responses. Levene's test of equality of variances was conducted to assess the homogeneity of variance. Post hoc analyses with Bonferroni adjustments were used to compare all the groups at baseline, thus controlling the false positive rate. Pearson correlation was conducted to investigate the strength and direction of continuous data. Univariate linear regression was conducted for exploring the relationship between AEP and EMG, and PCL, GAF-S/F, and PANSS 5-factor model according to Wallwork-Fortgang.[43] Due to unequal sample sizes in our study with a larger number of controls than participants in the other groups, we also ran a sensitivity analysis by randomly selecting 105 HC out of the total sample of 211 participants. The main analyses were then repeated, and all results remained significant.

Results

#### Clinical and Demographic Characteristics

Table 1 details the clinical and demographic characteristics. Significant differences were found between groups in age, IQ, and smoking, with higher age in the non-psychosis participants, higher IQ in HC compared with the other groups, and significant group differences in the proportion of smokers. The proportion of antipsychotic medication users was higher in the violent-PSY than in the nonviolent-PSY group. Positive and Negative Syndrome Scale total score and the subscores Positive, Negative, Disorganized/Concrete, and Excited were higher in the psychosis compared with non-psychosis participants.

Table 2. Key Findings Across Groups for AEP Responses

	HC ($n = 211$)	Nonviolent-PSY ($n = 32$)	Violent-PSY ($n = 18$)	Violent non-PSY ($n = 22$)	Statistics
N1 amplitude of the AEP					
Auditory startle response	−30.47 (15.34)	−27.40 (18.75)	−17.80 (9.35)	−27.21 (15.74)	$F = 8.65$; $P < .001$ (HC > nonviolent-PSY[**]; HC > violent-PSY[*])
30 ms PPI	−12.02 (9.61)	−9.56 (11.38)	−8.08 (7.21)	−9.79 (8.79)	$F = 3.89$; $P = .10$
60 ms PPI	−15.70 (11.69)	−16.06 (17.11)	10.82 (10.22)	−15.44 (12.36)	$F = 3.01$; $P = .031$
120 ms PPI	−11.75 (10.45)	−12.17 (16.63)	−9.25 (8.63)	−12.14 (7.86)	$F = 1.46$; $P = .227$
P2 amplitude of the AEP					
Auditory startle response	16.26 (9.96)	18.71 (12.86)	7.65 (5.79)	15.37 (8.48)	$F = 7.24$; $P < .001$ (HC > violent-PSY[*]; nonviolent-PSY violent-PSY[**]; violent non-PSY > violent-PSY[**])
30 ms PPI	7.91 (7.46)	9.47 (8.37)	3.28 (3.57)	6.78 (6.22)	$F = 4.39$; $P = .005$
60 ms PPI	8.60 (7.63)	9.22 (8.26)	5.33 (5.44)	10.53 (5.82)	$F = 1.56$; $P = .199$
120 ms PPI	9.34 (8.19)	10.01 (9.90)	4.06 (4.81)	10.80 (6.55)	$F = 4.53$; $P = .004$

Unless otherwise specified, the values indicate mean and SD in the parenthesis. Abbreviations: AEP, auditory-evoked potential; HC, healthy control; nonviolent-PSY, nonviolent patients with psychosis; PPI, prepulse inhibition; violent non-PSY, non-psychotic individuals with a history of violence; violent-PSY, individuals with psychosis and a history of violence.
[*]$P < .001$;
[**]$P < .05$.
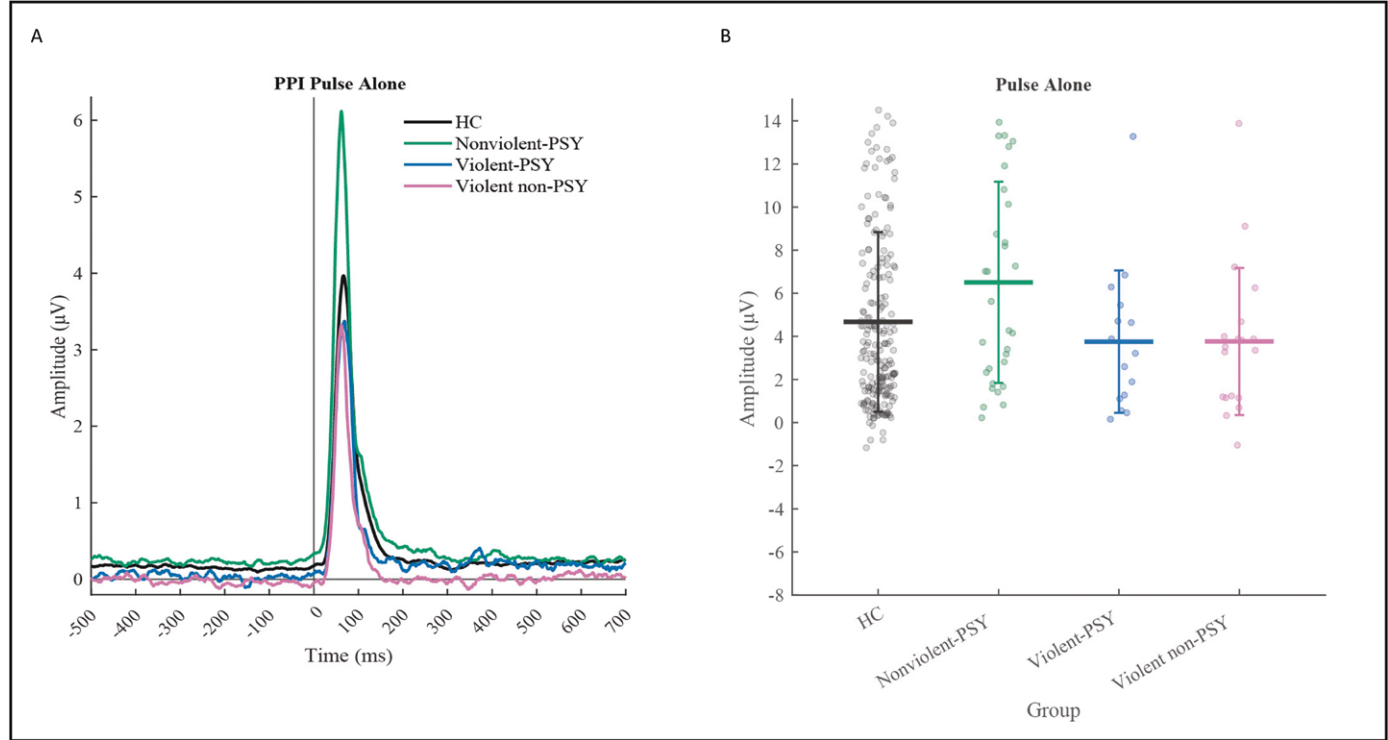
Figure 1. (A) Averaged Blink Electromyography (EMG) Startle Response to Pulse-Alone Trials by Group. EMG_{ASR} Was Measured by 2 Electrodes Over the Orbicularis Oculi Muscle Below the Right Eye. (B) Comparisons of EMG_{ASR} Between Healthy Controls (HCs), Individuals With Psychosis Without a History of Violence (Nonviolent-PSY), Individuals With Psychosis and a History of Violence (Violent-PSY), and Non-psychotic Individuals With a History of Violence (Violent Non-PSY). There Were No Significant Effects of Group on the EMG_{ASR} Amplitude ($P = .10$). Abbreviation: Nonviolent-PSY, Nonviolent Patients With Psychosis

Startle-Alone Response and PPI of the EMG

Table 2 provides key findings across all groups for EMG and AEP response. Figure 1 shows the EMG_{ASR} responses of the groups. First, we found a highly significant effect of the experimental condition on the EMG amplitudes ($F[1.7, 464.5] = 162.77$, $P < .00001$), with lower amplitudes for the 30-, 60-, and 120-ms prepulse + pulse conditions relative to the prepulse-alone condition (all

$P < .00001$) across the study participants. However, no significant effects were found in the EMG_{ASR} group or the 30-, 60-, and 120-ms prepulse + pulse EMG_{PPI} amplitudes ($P = .10$, $P = .11$, $P = .19$, and $P = .50$, respectively).

Startle-Related Response (*AEP_ASR*) and Prepulse Inhibition (*AEP_PPI*) of the AEP

The AEP_{ASR} of the groups is shown in Figure 2. First, we found a highly significant effect of the experimental condition on the N1 amplitude ($F[2.40, 656.3] = 568.50$, $P < .00001$), with less negative N1 amplitudes for the 30-, 60-, and 120-ms prepulse + pulse conditions relative to the prepulse-alone condition (all $P < .00001$) across the study participants. Likewise, a strong effect existed of the experimental condition on the P2 amplitude ($F[2.64, 723.2] = 304.03$, $P < .00001$), with less positive P2 amplitudes for the 30-, 60-, and 120-ms prepulse + pulse conditions relative to the prepulse-alone condition across the groups (all $P < .00001$).

A significant group effect was found on the N1 amplitude of the AEP_{ASR} ($F[3, 270] = 8.65$, $P \leq .0001$), while post hoc analysis with Bonferroni correction showed a significantly lower PA amplitude in the nonviolent-PSY group relative to HC ($P = .015$), lower amplitude in the violent-PSY group compared with HC ($P \leq .001$), and a trend toward lower amplitude in the violent-PSY group than the violent non-PSY group ($P = .057$). Adjustments for IQ, smoking, and DDD of antipsychotics and benzodiazepines did not change these findings.

Next, we found a significant group effect on the P2 amplitude of the AEP_{ASR} ($F[3, 270] = 7.24$, $P < .001$), while the post hoc analyses detected lower amplitude in the violent-PSY group than the nonviolent-PSY, the violent non-PSY, and the HC ($P = .003$, $P = .016$, and $P < .0001$, respectively). The $AEP_{startle}$ P2 amplitude difference between the violent-PSY and the nonviolent-PSY groups remained significant after adjusting for IQ, smoking, and the DDD of antipsychotics and benzodiazepines ($P < .05$). When correcting for smoking and IQ, the difference between the violent-PSY, and violent non-PSY and HC groups was no longer significant.

No significant effects of the group were found for the 30-, 60-, or 120-ms N1 AEP_{PPI} (all $P > .05$). A significant group effect was found for the 30-ms P2 AEP_{PPI} ($F[3, 270] = 4.38$, $P = .005$), where post hoc analyses showed reduced P2 AEP_{PPI} in the violent-PSY group compared with HC ($P = .003$). The latter difference was not significant after adjusting for IQ and smoking ($P = .28$). There was a significant effect of group for the 60-ms P2 AEP_{PPI} ($F[3, 270] = 2.81$, $P = .040$), where post hoc analyses showed reduced P2 AEP_{PPI} in the violent-PSY group compared with HC ($P = .031$). The latter difference was not significant after adjusting for IQ ($P = .27$). There was a significant effect of group for the 120-ms P2 AEP_{PPI} ($F[3,$ $270] = 4.53$, $P = .004$), where post hoc analyses showed reduced P2 AEP_{PPI} in the violent-PSY group compared with HC ($P = .003$), and violent non-PSY group. There was a trend toward significance after adjusting for IQ and smoking ($P = .052$).

Relationships Between Startle-Related Responses and PPI and Antisocial Personality Traits, Global Functioning, and Psychotic Symptoms

There were no significant correlations between PCL-R scores and the N1 amplitudes of the AEP_{ASR} or the 30, 60, or 120 ms AEP_{PPI} (all $P > .30$). Likewise, there were no significant correlations between PCL-R scores and the P2 amplitudes of the AEP_{ASR} or the 30, 60, or 120 ms AEP_{PPI} (all $P > .26$). Moreover, there were no significant correlations between PCL-R scores and the EMG_{ASR} or the 30, 60, or 120 ms EMG_{PPI} (all $P > .16$). We also explored the relationships between the GAF function domain (GAF-f), and GAF symptom domain (GAF-s), and found no significant associations (all $P > .05$). There were, however, significant correlations between the PANSS subscore disorganized factor and the P2 amplitude of AEP_{ASR} ($P = .011$), and between EMG_{ASR} and PANSS disorganized factor ($P = .024$). To further explore this, we ran the analysis in each of the psychosis groups and found that the correlation coefficient was comparable in these groups.

The Relationship Between EMG- and AEP-Based Assessments of the Startle-Related Response and PPI

We then investigated the relationships between the startle-related responses and the PPI of the EMG and the AEP across the entire sample. There was a significant correlation between the EMG_{ASR} and N1 AEP_{ASR} amplitudes, with a greater EMG amplitude in those with larger N1 ($r = -0.25$, $P < .0001$). Furthermore, we found a positive correlation between the EMG_{ASR} and the P2 AEP_{ASR} amplitude ($r = 0.39$, $P < .00001$). There was a significant association between the EMG_{PPI} and N1 AEP_{PPI} of the 30 ms prepulse + pulse condition ($r = 0.12$, $P < .048$), significant correlations between the EMG_{PPI} and N1 ($r = 0.21$, $P < .0001$) and P2 ($r = 0.27$, $P < .00001$) AEP_{PPI} of the 60 ms prepulse + pulse condition, and a significant association between the EMG_{PPI} and P2 AEP_{PPI} of the 120 ms prepulse + pulse condition ($r = 0.26$, $P < .00001$).

Discussion

The present study examined defensive reflexes and their modulations using EMG and EEG in individuals with and without a history of violence and psychosis. There were 3 main findings. First, the P2 amplitude of the EEG-based AEP_{ASR} was reduced in violent-PSY compared with the other groups. Second, the N1 amplitude of the AEP_{ASR}
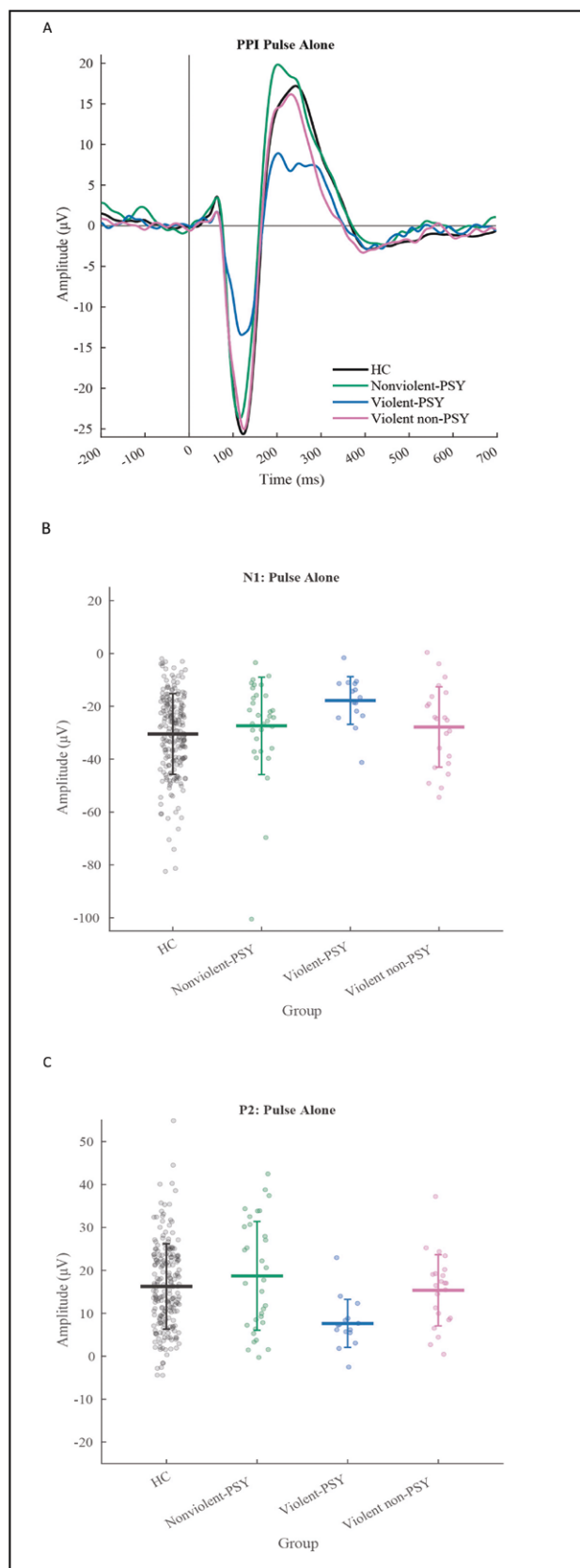
was reduced in both psychosis groups (ie, violent-PSY and nonviolent-PSY) compared with HCs. Finally, there were weak correlations between the EEG- and the EMG-based startle-related responses and PPI. Together, these findings demonstrate the most pronounced alterations in the EEG-based startle-related response in the psychosis group with a history of violence, and that the EEG and the EMG measures may reflect at least partly distinct neural processes.

The first finding was a lower amplitude of AEP_{ASR} P2 in the violent-PSY group compared with the other groups. Previous studies of brain potentials elicited by auditory stimuli have indicated distinct functional roles for the N1 and P2 components. P2 corresponds to late attentive stages engaged in allocating attention to protect higher-order functions, whereas N1 is associated with early attentive stages reflecting filter mechanisms involved in the activation of attention.[44-47] One of the most important aspects of behavior that helps manage distracting stimuli to optimize performance is allocating attentional resources and cognitive control.[48] Attention problems, often associated with social and emotional processes, have been used to explain aggressive behavior. They are also considered crucial in distinguishing individuals prone to violent behavior.[49]

Studies of the startle magnitude employing EEG and EMG techniques have shown a direct relation to amygdala activity, which has a fundamental role in fear-associated responses to threat and involvement in chronic stress responses as well as the core of emotional processing.[50–52] Previous research has found deficits in the muscular startle response in adolescents with conduct disorder and emotional deficits related to antisocial behavior.[53] Moreover, studies of amygdala lesions have shown startle reflex disruption, supporting the linkage between the startle response and amygdala activity.[54] The amplitude of the startle response has exhibited intra-individual stability across time and may be partly heritable, making it a promising biomarker for individual differences in psychopathology and premorbid vulnerability.[55–57]

Figure 2. (A) Auditory-Evoked Potentials (AEPs) by Diagnostic Group Extracted From Midline Site (Cz). (B) There Was a Significant Effect of Group on the N1 With Lower Pulse-Alone Amplitude in Individuals With Psychosis Without a History of Violence (Nonviolent-PSY) Relative to Healthy Controls (HCs) ($P = .015$), and Lower Amplitude in Individuals With Psychosis and a History of Violence (Violent-PSY) Compared With HCs ($P < .001$). (C) There Was a Significant Effect of Group on the P2 With Lower Amplitude in the Group of Violent-PSY Compared With Nonviolent-PSY, the Violent non-PSY, and the HC ($P = .003$, $P = .016$, and $P < .0001$, respectively). Abbreviations: Nonviolent-PSY, Nonviolent Patients With Psychosis; Violent Non-PSY, Non-psychotic Individuals With a History of Violence

A study by da Cunha-Bang et al. found reduced amygdala-prefrontal and striato-prefrontal connectivity in violent individuals compared with non-offenders.[58] This finding was consistent with studies showing that violent offenders have significantly reduced amygdala-medial prefrontal functional connectivity and increased amygdala connectivity with paralimbic regions. These patterns suggest that aggression results from impaired emotion processing and decreased prefrontal cortical control.[59,60]

Some evidence suggests that individuals' brain structural correlates of aggressive behavior vary. For example, they can be characterized by developmental abnormalities and deficits in executive function linked to dorsolateral prefrontal dysfunctions. In contrast, the risk of violence in individuals with neuropsychiatric disorders is often associated with damage to the orbital and ventromedial prefrontal cortex.[61,62] According to previous studies, focal orbitofrontal injury notably affects social judgment, risk aversion, and empathy skills, brain structures associated with aggression and psychosis.[61,63–66] These findings have indicated separate subgroups of violent offenders based on distinct neural circuits.

Results from neuroimaging studies have indicated more severe impairment in the prefrontal and frontal cortex in schizophrenia patients with a history of aggression and violence compared with schizophrenia patients without a history of violence.[67] These findings may have clinical significance. Deficits in the early stages of AEP_{ASR} may constitute a marker of sensitivity to mental disorders related to sensory-based pre-attentive functions. In contrast, deficits at a later stage may involve higher functions related to cognition and personality traits. Distinguishing between these 2 groups during clinical decision-making guided by knowledge of the underlying condition may support prognostic evaluation and preventative treatments.

Our study did not find a significant group effect in the analysis of EMG, contrary to the findings of Kumari et al., who investigated EMG_{PPI} in clinical groups with APD, violence, and schizophrenia. Kumari et al. found significantly reduced PPI in clinical groups compared with HC, although PPI did not distinguish the 3 clinical groups.[17] Factors responsible for differences among these studies may be the sample sizes, methodological approaches, and population characteristics. Indeed, the final sample in Kumaris' study consisted of fewer participants ($N = 46$) than our sample ($N = 283$). Our study consisted of participants with psychotic disorders, with or without a history of violence.

Moreover, schizophrenia was a criterion for 2 of the clinical groups in Kumari et al.'s study, and the APD group had a diagnosis of APD and varying assessments of violence, which may have led to differences among participants. Our study did not find a significant group effect in the analysis of $EMG_{startle}$ alone. However, our results revealed a correlation between $EMG_{startle}$ and $AEP_{startle}$ N1 and P2 in the groups with psychosis, with and without violent history, respectively. Correlation between $EMG_{startle}$ and $AEP_{startle}$ N1 in the violent-PSY group may indicate that both EMG and EEG detect early sensory processing in a defensive reaction, while EEG may be an independent measure, detecting higher cognitive processing reflected in distinct $AEP_{startle}$ P2 but not reflected in EMG.

The current study found reduced $EEG_{startle}$ N1 in violent-PSY and nonviolent-PSY compared with HC. Subgroups of schizophrenia have exhibited altered baseline startle reactivity.[68] Reductions in the generation of N1 have been well recognized in patients with schizophrenia, and research of first-degree relatives of schizophrenia has suggested a genetic risk of the disorder.[69] The $EEG_{startle}$ N1 is mainly associated with primary and secondary auditory cortices. Previous findings have indicated that deficiencies at this early stage of sensory processing may contribute to the impairment of higher-order functions also subserved by other brain areas, such as the prefrontal cortex.[70]

Moreover, a negative correlation was found between the auditory cortex volume and hallucination severity.[71] Anatomical research has shown a reduction in terminal density in the deep layers of the auditory cortex in schizophrenia, indicating that abnormalities within this area may partially cause symptoms.[72] Overall, our study indicated lower $AEP_{startle}$ N1 among the groups with psychosis, suggesting potential impairments in early sensory processing. Additionally, lower N1 may indicate a genetic vulnerability associated with the disorder.[69]

Research on auditive hallucinations in schizophrenia has shown structural deficits in the primary auditory cortex, potentially explained by changes in cerebral blood alterations and reduced dendritic arborization. Thus, these structural findings can be viewed as part of a broader pathological condition affecting multiple sensory systems, reflected in neural activity and EEG measures.[70,73,74] In our study, $AEP_{startle}$ P2 differentiated the groups with psychotic disorder with and without a history of violence, indicating differences in later attentive stages in these groups related to higher cognitive functions and personality traits. Previous studies on startle magnitude, known to affect behavior through bilateral projections between auditory pathways and amygdala activity, have shown distinct brain activity related to violent behavior and psychosis.

Aggressive behavior in individuals with psychosis is often associated with impaired impulse control and emotional dysregulation; this, in turn, was linked to alterations in neural circuitries associated with both aggression and psychosis.[75–77] Imaging studies demonstrate that the brain activity associated with these 2 processes is interconnected, where the emotional input and attentional impairment may disrupt response inhibition by

imposing additional demands on already limited brain resources.[78] Although speculative, these mechanisms could contribute to the results of the present study showing reduced EEG responses in the violent-PSY group. The current study also found an association between the disorganized factor of PANSS, EMG_{ASR}, and P2 AEP_{ASR}, but further exploration did not show specificity according to psychotic groups with or without violence. Despite the lack of specificity, the disorganized factor may be studied in future studies since the item reflects disorganized conception, alterations in abstract thinking, disorientation, and attention impairments which could be connected to alterations in neural circuits and higher-order functioning in schizophrenia with violence history.[79] This factor is also strongly connected to daily activities and social functions, and is found to have some conceptual overlap with neuropsychological facets such as abstract thinking and attention.[80] PPI is connected to sensory gating, that is, an adaptive mechanism involved in information processing, which prevents overstimulation of higher cortical areas.[81] Because sensory gating helps filter incoming sensory information, this mechanism is key for learning and memory processes, and the treatment of patients with psychosis and violent behavior requires an integrated approach that addresses both issues, as well as awareness among clinicians about the central roles of information processing in mental health therapies.[82]

Some studies have found a significant correlation between EMG and EEG, while others have not.[83–85] A finding in our study indicated that EMG may be less sensitive to clinically relevant changes in the startle response compared with EEG. A moderate correlation was found between $EMG_{startle}$ and $AEP_{startle}$ but not between EMG_{PPI} and $AEP_{PPI,}$ suggesting overlapping basic neurobiological mechanisms in the startle response/reflex, while its modulation (ie, PPI) demanded a greater degree of cognitive evaluation, colored by individual personality traits, emotional status, and behavioral patterns. No group differences existed between $EMG_{startle}$ and AEP_{PPI}, but $AEP_{startle}$ measures had significant findings.

Subgroup analysis revealed correlations between $EMG_{startle}$ and $AEP_{startle}$ P2 in nonviolent-PSY and the violent-PSY group correlation between $EMG_{startle}$ and $AEP_{startle}$ N1. Additionally, the violent-PSY sample was smaller than the violent non-PSY sample, yet there was still a significant association between EMG and AEP in the violent-PSY group. However, we found no correlation between $EMG_{startle}$ and $AEP_{startle}$ for the violent non-PSY.

Future research with larger groups is needed to investigate if there is a distinct neurological basis for violent behavior in the violent-PSY group compared with the violent non-PSY group. Studies have suggested different pharmacological sensitivities and distinct neurological pathways.[22] For instance, studies of PPI_{EMG} and the N1/P2 auditory-evoked response have shown that EMG_{PPI} but not the N1/P2 complex was reduced by bromocriptine, although tricyclic antidepressant amitriptyline reduced PPI of the N1/P2 complex, without modifying EMG_{PPI}.[20,86] In our study, approximately 90% of both psychosis groups used psychotropic medications. The violent-PSY group used larger doses of antipsychotic medication than the nonviolent-PSY group. However, the main group differences remained significant after adjustments for daily doses of antipsychotic medications, and it is therefore unlikely that medications underlie those group differences. Hence, our findings suggest that EMG and EEG indices of the startle response and PPI are relatively independent measures, potentially indexing partially independent neurobiological systems.[22,85]

Limitations

This study was limited by small sample sizes in the clinical groups, reflecting recruitment challenges from high-security forensic wards and prisons. This limitation could have hindered our ability to detect significant differences in PPI among the clinical groups. Another limitation was the sample size imbalance, with a larger sample of HC compared with the other groups. Unequal sample size may lead to unequal variances between samples and this may affect statistical power and type 1 error rates. Furthermore, there is only a limited increase in statistical power if the size of the largest group is increased beyond 4-5 times that of the smallest group.[87] Notably, we reran the main analyses after randomly selecting half of the control participants and found that the group differences—as found in the main analyses where all HC were included—remained significant. Another limitation was that the sample consisted of only male participants, so future research should also investigate female violent offenders. Finally, our study was cross-sectional. Hence, by applying a longitudinal approach, future researchers can investigate neurodevelopment antecedents and trajectories of violence in psychosis.

Conclusion

To conclude, this study showed that amplitude reductions of the EEG-based N1 AEP response to startle-inducing auditory stimuli are associated with psychotic disorder. In contrast, amplitude reductions of the later P2 component AEP (associated with cognition and higher-order functions) may be more specific to individuals with both psychosis and a history of violent behavior. Our finding of the most pronounced effects in the violent-PSY group may suggest that the EEG-based startle response is a promising biomarker of violence risk among persons with psychosis. Hence, its predictive value should be investigated in future studies by including female violent offenders. By applying a longitudinal approach with larger sample sizes, future studies could clarify whether measurements of the EEG-based startle response can predict the risk of violence in psychosis.

Author Contributions

Nina Bang (Conceptualization, Formal analysis, Investigation, Writing—original draft, Writing—review & editing), Johanne H. Pettersen (Software, Formal analysis, Visualization, Writing—review & editing), Merete Berg Nesset (Writing—review & editing, Supervision), Kirsten Rasmussen (Writing—review & editing, Supervision), Hilde Dahl (Writing—review & editing, Investigation, Project administration), Natalia Tesli (Writing—review & editing, Investigation), Christina Bell (Writing—review & editing, Investigation), Anja Vaskinn (Writing—review & editing, Investigation), Thomas Fischer-Vieler (Writing—review & editing, Investigation), Christine Friestad (Writing—review & editing, Project administration, Investigation), Ole A. Andreassen (Writing—review & editing, Conceptualization, Project administration), Erik G. Jönsson (Writing—review & editing, Project administration), Unn K. Haukvik (Writing—review & editing, Project administration, Supervision, Investigation), Torgeir Moberget (Writing—review & editing, Conceptualization, Methodology, Supervision), and Torbjørn Elvsåshagen (Conceptualization, Methodology, Investigation, Writing—original draft, Writing—review & editing)

Conflicts of Interest

Torbjørn Elvsåshagen is a consultant to BrainWaveBank and Sunovion and received speaker's honoraria from Lundbeck and Janssen Cilag. Ole Andreassen is a consultant to HealthLytix and received the speaker's honoraria from Lundbeck. The other authors declare no competing interests.

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