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Associations between amygdala nuclei volumes, psychosis, psychopathy, and violent offending

Christina Bell [a,b,*], Natalia Tesli [b,c], Tiril P. Gurholt [b,c], Jaroslav Rokicki [b,d], Gabriela Hjell [b,e], Thomas Fischer-Vieler [a,b], Ingrid Melle [b,c,f], Ingrid Agartz [b,g], Ole A. Andreassen [b,c], Kirsten Rasmussen [h,i], Ragnhild Johansen [h,i], Christine Friestad [j,k], Unn K. Haukvik [b,f,j]

[a] Department of Psychiatry, Oslo University Hospital, Oslo, Norway
[b] Norwegian Centre for Mental Disorders Research (NORMENT), Institute of Clinical Medicine, University of Oslo, Oslo, Norway
[c] Norwegian Centre for Mental Disorders Research (NORMENT), Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway
[d] Department of Psychology, University of Oslo, Oslo, Norway
[e] Department of Psychiatry, Østfold Hospital Trust, Graalum, Norway
[f] Department of Adult Psychiatry, Institute of Clinical Medicine, University of Oslo, Norway
[g] Department of Psychiatric Research, Diakonhjemmet Hospital, Oslo, Norway
[h] St.Olavs Hospital, Forensic Research Unit, Brøset, Norway
[i] Norwegian University of Science and Technology (NTNU), Department of Psychology, and Department of Mental Health, Norway
[j] Centre of Research and Education in Forensic Psychiatry, Oslo University Hospital, Norway
[k] University College of Norwegian Correctional Service, Oslo, Norway

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ABSTRACT

The amygdala is involved in fear perception and aggression regulation, and smaller volumes have been associated with psychotic and non-psychotic violence. We explored the relationship between amygdala nuclei volumes in violent offenders with and without psychosis, and the association to psychopathy traits. 3T MRI scans (n = 204, males, 18–66 years) were obtained from psychotic violent offenders (PSY-V, n = 29), non-psychotic violent offenders (NPV, n = 19), non-violent psychosis patients (PSY-NV, n = 67), and healthy controls (HC, n = 89). Total amygdala and 9 amygdala nuclei volumes were obtained with FreeSurfer. Psychopathy traits were measured with the Psychopathy Checklist-revised (PCL-R). Multivariate analyses explored diagnostic differences in amygdala nuclei volumes and associations to psychosis, violence, and psychopathy traits.

PSY-V had a smaller basal nucleus, anterior amygdaloid area, and cortical amygdalar transition area (CATA), whereas PSY-NV had a smaller CATA than HC. Volumes in NPV did not differ from HC, and there were no associations between PCL-R total or factor scores and any of the nuclei or whole amygdala volumes. The lower volumes of amygdala nuclei involved in fear modulation, stress responses, and social interpretation may point towards some mechanisms of relevance to violence in psychosis, but the results warrant replication in larger subject samples.

1. Introduction

Violence covers a spectrum of aggressive behaviors with complex bio-psycho-social mechanisms (Anderson and Kiehl, 2014; Fjellvang et al., 2018). In forensic settings, violence is typically approached as a medical syndrome, categorized as either psychotic, impulsive (reactive), or proactive (psychopathic), based on the major symptom domains (Stahl, 2014). Psychotic violence is associated with positive psychosis symptoms, such as paranoid delusions of threat or persecution, command hallucinations, and grandiosity (Stahl, 2014). Impulsive violence is often precipitated by provocation and is characterized by high autonomic arousal (Stahl, 2014). Proactive (psychopathic)violence represents goal-directed, planned, or premeditated behavior, and is not necessarily accompanied by autonomic arousal (Stahl, 2014). Due to paranoid delusions, psychotic violence is often associated with fear (Kennedy et al., 1992), while proactive or psychopathic violence may be

* Corresponding author: Oslo Universitetssykehus, HF, Aker, Klinikk psykisk helse og avhengighet, Seksjon for psykosebehandling, Gaustad, Postboks 4959 Nydalen, 0424 Norway
E-mail address: chrbell@ymail.com (C. Bell).

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partly explained by callousness and a *lack of fear* (Poeppl et al., 2019). The different categories of violence are assumed to have distinct neurobiological bases with different malfunctioning brain circuits (Stahl and DA., 2014). Still, several forms of violence may be committed by the same individual (Fjellvang et al., 2018), like in individuals with psychopathy who often commit both psychopathic and impulsive aggression (Hecht et al., 2016). Regarding the diagnostic groups frequently seen in forensic practice, an increased understanding of the brain regions as well as the underlying brain circuits involved in the different forms of violent behavior is needed to optimize treatment.

The amygdala complex is a key structure for understanding the neurobiology of violence (Adolphs, 2010), due to its involvement in the regulation of fear and aggression by rapid detection of threat and excitation of fight-or-flight responses (Stahl, 2014; Rosell and Siever, 2015; Gopal et al., 2013). Moreover, the amygdala is critical for emotional learning as well as cognitive processes such as memory and attention (Gallagher and Chiba, 1996; Zheng et al., 2019). The amygdala receives afferents from multiple brain regions, including neocortex, cingulate and hippocampal gyri (McDonald, 1998). Further, it is pivotal to the integration of motivationally salient stimuli and subsequent transmission of this information to a wide range of regions, including the brainstem, cortical and subcortical regions (Salzman and Fusi, 2010). Anatomically, the amygdala is divided into 9 nuclei, i.e., the lateral, basal, central, medial, cortical, paralaminar, and accessory basal nuclei, the cortico-amygdaloid transition area (CATA), and the anterior amygdaloid area (Z.M. Saygin et al., 2017). Based on animal studies, each nucleus appears to serve specific (but somewhat overlapping) functions (Stahl and DA., 2014).

The central nucleus is involved in fear learning and is the output region for innate emotional responses, and the basolateral complex acts as a sensory input gateway (Rosell and Siever, 2015; Wilensky et al., 2006). The basal nucleus is involved in fear memory, emotion, and cognition (Martijena and Molina, 2012; Asami et al., 2018). Hence, the central and the basal nuclei could be key structures for understanding the role of the amygdala in violence and aggression in psychosis and psychopathy.

Amygdala volume reductions have been replicated in two independent large-scale consortium studies of schizophrenia (van Erp et al., 2016; Okada et al., 2016). From a meta-analysis in 2017 both left, right, and total amygdala volumes were reduced in schizophrenia patients, compared to healthy controls and bipolar subjects, even when restricted to cohorts in the early stage of illness (Ho et al., 2019). A well-powered study has recently shown reduced volumes in the bilateral total amygdala, in addition to almost all its nuclei (except the medial nucleus) in patients with schizophrenia relative to controls (Barth et al., 2021).

In contrast, MRI studies of the amygdalae of *violent* offenders with schizophrenia have shown mixed results, ranging from smaller volumes (Barkataki et al., 2006), no differences (Del Bene et al., 2016), to larger volumes (Widmayer et al., 2018). Our group has previously reported smaller amygdala nuclei volumes in the basal and accessory-basal nucleus, CATA, and paralaminar nucleus in schizophrenia patients with a history of violence (Tesli et al., 2020). The different patterns in amygdala nuclei reductions between violent and non-violent schizophrenia patients may reflect a specific signature of psychotic violence and possible comorbidities.

Violence risk among persons with schizophrenia increases considerably with comorbid antisocial personality disorder (ASPD), psychopathy, or substance use, which are well-known comorbidities (Volavka, 2014). While ASPD and psychopathy are clinically overlapping and highly comorbid, they differ epidemiologically and etiologically and the distinction is often misunderstood in the clinical setting (Werner et al., 2015). The prevalence of ASPD (measured by SCID-II) is higher than the prevalence of psychopathy (measured by PCL-R) in forensic populations (50–70% vs 15–20%, respectively) (Hare, 2003). However, the most serious crimes are often committed by persons with high psychopathy scores (Hare, 2003).

Psychopathy is a multidimensional construct characterized by a constellation of personality traits such as grandiosity, impulsivity, lack of empathy and remorse (Fisher and Hany, 2019; Thomson et al., 2019), as well as manipulation of others, insincerity, lying, antisociality, and criminal offending (Wong and Olver, 2015). Psychopathy is associated with neuroanatomical abnormalities (Johanson et al., 2019) in specific brain circuits and areas, such as the amygdala and prefrontal cortex, and the uncinate fasciculus which reciprocally connects them (Fjellvang et al., 2018). In psychopathy, gray matter volume reductions have been found in most of the prefrontal cortex, the temporal cortex, several regions of the limbic system, the cingulate, and the insular cortices, as well as of the hippocampi and the amygdalae (Johanson et al., 2019; Yang et al., 2010; Vieira et al., 2015). Psychopathic violence has been associated with deficient fear conditioning (Stahl, 2014) and poor fear reactivity (Thomson et al., 2019), which have been linked to attenuated amygdala reactivity (Birbaumer et al., 2005).

In the current study, we investigated the association between amygdala volumes and violence. At first, we compared volumes of the amygdala and its separate nuclei between psychotic violent offenders (PSY-V), non-psychotic violent offenders (NPV), non-violent psychosis patients (PSY-NV), and non-psychotic, non-violent healthy controls (HC). Secondly, we explored associations between psychopathy traits (PCL-R scores) and amygdala nuclei volumes in PSY-V and NPV. Based on previous findings we expected total amygdala volume to be smaller in at least PSY-V (Tesli et al., 2020), but also PSY-NV (Ho et al., 2019) and NPV (Johanson et al., 2019) compared to HC. Many individuals in the PSY-V group have psychopathic traits, besides psychosis, so this group has two conditions that are associated with lower GMW in their amygdalae. We hypothesized the basal and accessory basal nucleus, CATA and paralaminar nucleus to be associated with psychotic violence (also based on previous findings) (Tesli et al., 2020) and that the central nucleus and the basal nucleus would have smaller volumes in NPV, due to their association with fear processing. Higher levels of psychopathic traits were hypothesized to correlate with the smaller amygdala and nuclei volumes.

2. Methods and materials

2.1. Sample

The sample ($n = 204$) consisted of four groups of male participants. Diagnoses were based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).

The violent offenders with psychosis (PSY-V) group ($n = 29$) consisted of patients predominantly within the schizophrenia (SCZ) spectrum. Inclusion criteria were, in addition to diagnosis, a history of murder or attempted murder, or severe physical assault towards other people (including sexual assaults) according to the MacArthur criteria (Monahan et al., 2000). The PSY-V group were recruited from high-security psychiatric wards at Oslo University Hospital and Østfold Hospital, Norway, see supplemental information for diagnostics and medication use.

The violent offenders without psychosis (NPV) group ($n = 19$) consisted of imprisoned persons serving a preventive detention sentence in the Oslo region, Norway, following perpetration of a violent crime (according to the MacArthur criteria (Monahan et al., 2000)). They did not have a psychosis disorder at the time of the violent offense nor study inclusion. Preventive detention is a sanction imposed in cases where a time-limited prison sentence is deemed insufficient to protect society from the risk posed by the offender. Preventive detention is most commonly imposed in cases involving serious interpersonal violence (including sexual violence) and can involve life-long imprisonment as the sentence may be prolonged for periods of five years at a time, for as long as the person is considered to pose a risk to others/society. A total of 119 persons were in February 2020 serving a preventive detention sentence in Norway.

The non-violent psychosis patient (PSY-NV) group ($n = 67$) consisted of persons with a schizophrenia spectrum disorder without a history of violence. The PSY-NV were recruited from four major psychiatric hospitals and their affiliated outpatient clinics from the Oslo region, Norway, see supplemental information for diagnostics and medication use.

The non-violent, non-psychotic healthy control (HC) group ($n = 89$) consisted of persons with no history of severe mental disorder and was randomly selected from the Norwegian national population registry (https://www.ssb.no/en). All were residents in the Oslo region, Norway, and they were invited by a personal letter to participate in the study.

All participants were included as part of the ongoing multi-center TOP (Thematically organized psychosis) study in Oslo, Norway, between 2015 and 2019. Inclusion criteria for all groups were age between 18 and 65 years, Norwegian language knowledge to understand the study protocol and procedures, IQ scores above 65, and the ability to give informed consent to study participation. Additional inclusion criteria for the PSY-V and NPV participants were safety evaluations regarding study procedures and permission to leave the hospital ward/prison for the MRI acquisition. Exclusion criteria for all groups were head trauma leading to loss of consciousness more than 10 min and somatic illness that might have affected brain morphology. Due to low numbers of female PSY-V ($n = 2$) and NPV ($n = 0$) who completed the inclusion protocol, women were excluded from the study. Nine subjects were included in our previous study of hippocampal subfields and amygdala nuclei volumes in schizophrenia patients with a history of violence (Tesli et al., 2020)

The study was approved by the Norwegian Regional Committee for Medical Research Ethics, Norwegian Data Inspectorates, and relevant correctional agencies. Written informed consent was obtained from all participants after a complete description of the study and after the project physicians or the treating psychiatrist/psychologist had evaluated the subject's capacity to give informed consent to study participation. The study was conducted according to the Helsinki declaration.

2.2. Clinical assessment

Trained physicians, psychiatrists, and psychologists administered assessments of each study participant through clinical examination, including blood samples for clinical-chemical analyses to detect somatic illness.

The patients' psychiatric diagnoses were confirmed with the Structured Clinical Interview for DSM-IV Axis 1 disorders (SCID-1) (Spitzer et al., 1992) and supplementary information drawn from medical records. The PSY-V group had diagnostic evaluations based on detailed medical records and forensic reports. Psychosocial functioning was evaluated with the Global Assessment of functioning scale (GAF) scale. Alcohol and illicit substance use were evaluated with The Alcohol Use Identification Test (AUDIT) and The Drug Use Disorders Identification test (DUDIT), respectively. Current psychotic symptoms were rated using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Medication use was assessed and Defined Daily Dosages (DDD) of current antipsychotic medication use were calculated in line with the guidelines from World Health Organization (WHO; https://www.whocc/atc_ddd_index/).

Among PSY-V and NPV, a history of violence was assessed based on court documents, hospital records, and the self-report instrument Life history of aggression (Coccaro et al., 1997). Psychopathy traits were assessed with the Hare Psychopathy Checklist-Revised (PCL-R) (Hare, 2003), based on interviews, court documents, and/or medical records. The PCL-R is a 20-item scale for the assessment of psychopathy in research, clinical and forensic settings. It uses a semi-structured interview, file, and collateral information to measure personality traits and behaviors related to a widely understood conception of psychopathy (Hare, 2003). To address PCL subdomains, the scores were computed following the two-factor model for affective interpersonal and anti-social psychopathy traits (Hare, 2003).

To confirm the non-violent history in the PSY-NV group, their medical records were carefully inspected. This procedure encompassed evaluation of all study inclusion protocols which are based on comprehensive information obtained from medical records, including data from clinical journals and detailed interviews with the patient. All patients in the PSY-NV group who had scores above 4 on PANSS item G14 (i.e. poor impulse control) were excluded from the study.

HC subjects were screened with the Primary Care Evaluation of Mental Disorders (Prime-MD) questionnaire (Spitzer et al., 1994) and interviewed by specially trained clinical psychologists or neuroscientists to confirm no history of severe psychiatric disorder.

Current IQ was measured in all participants with the Norwegian version of the Wechsler Abbreviated Scale of Intelligence (WASI) by specially trained psychologists. For each participant, the number of completed years of formal schooling was used as an estimate for years of education.

2.3. MRI acquisition and post-processing

MRI data were collected on a 3T GE 750 Discovery scanner using a 32-channel head coil at Oslo University Hospital. T1-weighted volumes were acquired using a sagittal 3D BRAVO sequence with the following parameters: repetition time (TR) 8.2 ms, echo time (TE) 3.2 ms, flip angle 12°, slice thickness 1.0 mm, voxel size $1 \times 1 \times 1$ mm^3, 192 slices, a field of view (FOV) 256×256 mm^2. All participants were scanned on the same MRI scanner interchangeably across groups to avoid differences based on scanner drifting. There were no major scanner upgrades during the study period. A neuroradiologist evaluated all the MRI scans to ensure no brain pathology affecting the analyses. The quality of the neuroimaging data was assessed with an automated MRI quality control algorithm (MRIQC) (Esteban et al., 2017), which is a machine learning algorithm that applies a Random Forests Classifier, and assigns values from 0 (excellent quality of data) to 1 (poor quality of data) to each image. All images with values exceeding the a priori chosen cut-off at 0.7 were discarded from subsequent analyses.

T1-weighted MRI volumes were pre-processed using the standard FreeSurfer recon-all pipeline (version 6.0.0; http://surfer.nmr.mgh.harvard.edu/). Subsequently, amygdala nuclei volume estimates were obtained using a joint hippocampal subfields and amygdala nuclei segmentation algorithm (Iglesias et al., 2015; Z.M. Saygin et al., 2017) released with FreeSurfer v6.0.0, developmental version. This tool implements a probabilistic atlas based on Bayesian inference and is built with ultra-high-resolution *ex vivo* MRI data to generate an automated segmentation of the amygdala. From the FreeSurfer segmentation stream, we obtained the total intracranial volume, volumes for the whole amygdala and the nine amygdala nuclei, i.e., lateral, basal, accessory basal, central, medial, cortical, and paralaminar nucleus, the anterior amygdala area (AAA) and the cortico-amygdaloid transition area (CATA). After segmentation errors, one subject (healthy control) was excluded from subsequent analyses. Fig. 1 shows the automated amygdala nuclei volume delineations.

2.4. Statistical analyses

For the descriptive analyses, we used analyses of variance (ANOVA), t-tests, or Mann-Whitney U tests, to assess group differences in demographic and clinical characteristics. All statistical tests were two-tailed with statistical significance reported at the 0.05 level.

All analyses were performed with a diagnostic group (PSY-V, PSY-NV, NPV, HC) as the independent variable, and age, and intracranial volume (ICV) as covariates in a full factorial model. Group differences in the whole amygdala were analyzed in two steps. First, we conducted an analysis of covariance (ANCOVA) for the whole amygdala, followed by pair-wise analyses. Nine amygdala nuclei volumes were analyzed using multiple analyses of covariance (MANCOVA). Followed, by the ANCOVA and pair-wise analyses. Homogeneity of covariance in the

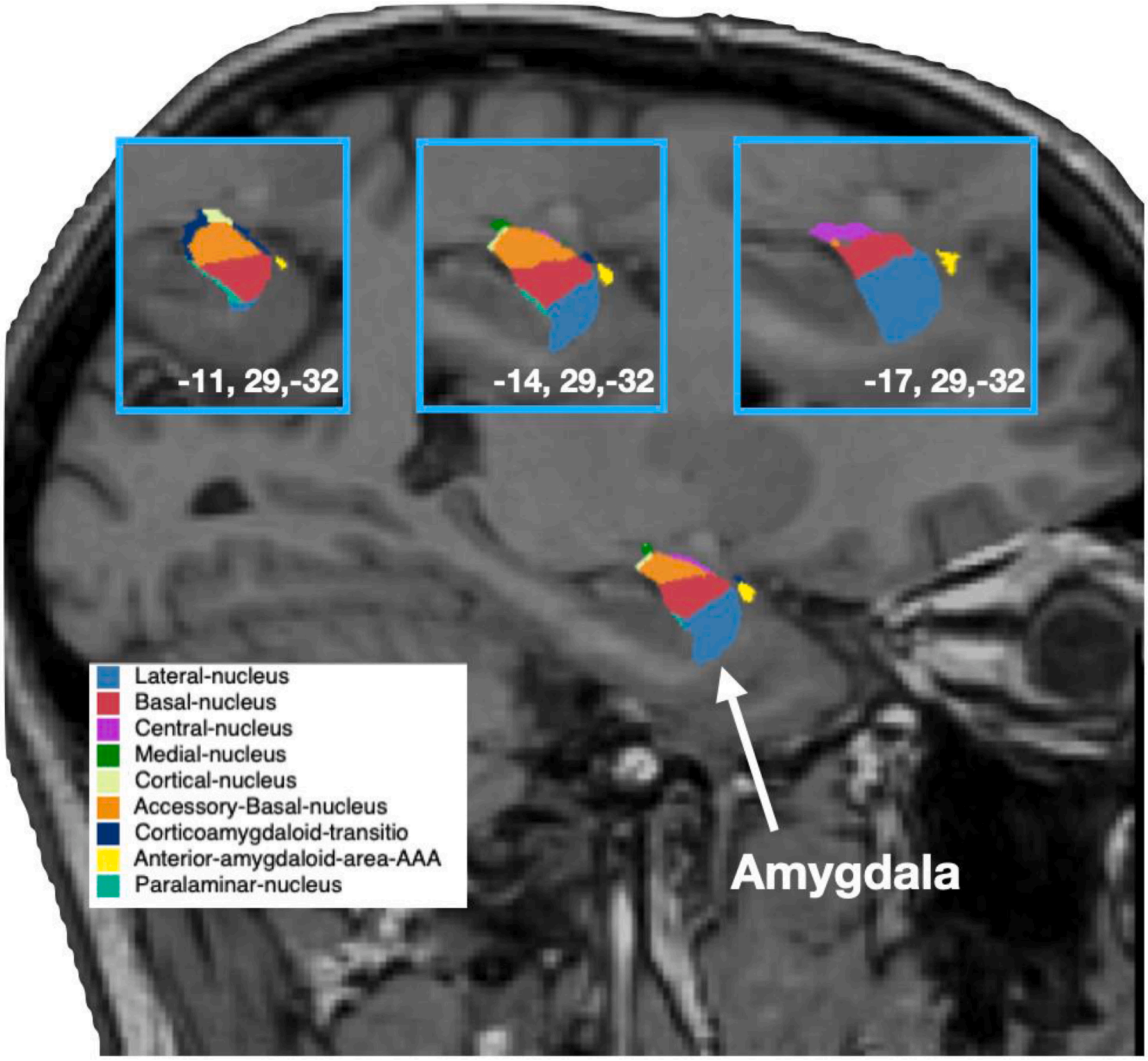

Fig. 1. Nuclei of the amygdala.

MANCOVA was estimated with Box's test, while homogeneity of variances between diagnostic groups in the ANCOVA was tested with Levene's test, and the normality of the ANOVA residuals was assessed using the Shapiro-Wilk test. The volume estimates of the left and right hemisphere amygdala and nuclei were highly correlated and therefore summed together because of the lack of laterality hypotheses, thus minimizing the multiple testing burden and increasing statistical power.

9 participants (2 HC, 1 NPV, 1 PSY-NV, and 4 PSY-V) were excluded from analyses due to insufficient data quality, leaving a total sample $n = 204$. First, we flagged outliers deviating more than 4 times the mean of all the Cook's distances of residuals in our final model. For a participant to be removed from further analyses, we set up a cut-off of at least three nuclei marked as outliers. Additionally, in the subsequent pairwise analyses we removed all nuclei flagged as outliers for more stringent quality control.

To control for potential effects of medication, education, or substance abuse, we reran the analyses with the defined daily dosages (DDD) for antipsychotic medication, years of education, and DUDIT scores, which were added as covariates in separate models. Because IQ scores differed significantly between the groups, we reran the analyses in an IQ-matched sub-sample. To match IQ we used nearest neighbor matching with 1:1 ratio and logistic regression distance as implemented in the `matchIt` R package (Ho DE et al., 2007). Demographics for each group's comparison of IQ are listed in supplementary Table 1.

The effects of psychopathy traits on the amygdala nuclei volumes were tested in a subset of participants ($n = 34$) from the PSY-V and NPV groups. We tested using a linear model for whole amygdala volume and MANCOVA for the nine nuclei, keeping group (PSY-V and NPV) as an independent variable and controlling for PCL-R score, age, and ICV. The analyses were repeated for PCL-R factor 1 (affective/interpersonal traits) and factor 2 (antisocial traits) scores in separate models.

To account for multiple comparisons, we adjusted p-values using the false discovery rate (FDR) method for the number of nuclei and number of groups (Benjamini and Hochberg, 1995). Effect sizes were calculated with Cohen's d directly from the parameter estimate t-statistics (Nakagawa and Cuthill, 2007).

All statistical analyses were performed in R (version 4.1.0; www.R-project.org).

3. Results

3.1. Clinical and demographic characteristics

Clinical and demographic statistics are summarized in Table 1. There were significant differences between groups in age, illicit substance use, total years of education, and IQ, with higher age in the non-psychosis groups, and PSY-V having the highest substance abuse and lowest education and IQ. GAF-function was lower in PSY-V than PSY-NV and the NPV group scored lower than PSY-V and PSY-NV on the PANSS subscales. There were no other significant differences on a group level for

Table 1
Demographic and clinical characteristics. Abbreviations: HC, healthy controls; NPV, Non-psychotic violent offenders; PSY-V, violent offenders with psychosis; PSY-NV, non-violent patients with psychosis; SD, standard deviation; GAF, Global Assessment of Function scale, split version; PANSS, Positive and Negative Syndrome Scale; PCL-R Psychopathy Checklist-Revised; DDD, defined daily doses; AUDIT/DUDIT, Alcohol Disorders Identification Test/Drug Use Disorder Identification.

	PSY-NV $n = 67$		PSY-V $n = 29$		NPV $n = 19$		HC $n = 89$			
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	T, F	p-value
Age (years) at MR	30.57 (8.65)	19.04–54.48	34.37 (9.21)	21.45–57.56	42.4 (12.79)	24–65.9	37.48 (8.85)	19–56.4	$F = 11.29$	**<0,001**
Total Years of education	13.19 (2.5)	9–20	12.26 (2.9 g)	6–21	12.29 (3.53)	6–21	14.78 (2.18)	9–18	$F = 10.52$	**<0,001**
PCL-R ($n = 17/17$)			Median: 20	4–30	Median: 21	10–35			$U = 160$	0.6
Psych first admission	25.24 (6.27)	16–52	23.3 (6.36)	16–45					$T = 1.16$	0.25
GAF symptom	47.05 (12.2)	28–85	42.46 (10.02)	25–66					$T = 1.889$	0.063
GAF function	45.89 (11.63)	27–85	39.9 (9.13)						$T = 3.04$	**0.003**
PANSS positive	14.17 (4.94)	7–28	16.15 (7.36)	7–35	9 (3.82)	7–23			$F = 9.98$	**<0.001**
PANSS negative	17.39 (6.44)	7–32	17.78 (5.91)	9–31	8.84 (2.32)	7–14			$F = 17.46$	**<0.001**
PANSS general	32.79 (8.54)	17–54	30.93 (8.54)	18–54	21.89 (6.76)	16–39			$F = 12.84$	**<0.001**
Age at psychosis onset	23.06 (6.23)	14–52	23.43 (7.41)	14–43					T=−0.20	0.84
Audit score	6.04 (6.05)	0–22	4.74 (4.8)	0–16	7.14 (11.16)	0–39	6.15 (2.86)	0–13	$F = 0.74$	0.53
Dudit score	4.24 (6.44)	0–28	7.85 (9.29)	0–27	5.23 (11.1)	0–35	0.71 (2.09)	0–13	$F = 10.37$	**<0.001**
IQ	101.4 (15.03)	69–131	92 (14.7)	67–113	98.93 (11.28)	82–121	114.83 (8.63)	89–132	$F = 26.44$	**<0.001**
Antipsychotics DDD	1.41 (0.81)	0.25–3.58	2.34 (2.72)	0.63–15.08					T=-1.70	0.1

other clinical and demographic variables (Table 1).

3.2. Amygdala and nuclei volumes

The descriptive statistics for nuclei and whole amygdala volumes (both hemispheres combined) are summarized in Table 2 and distributions are shown in supplementary figure 1.

The ANCOVA test on the whole amygdala volumes showed an overall difference between the four diagnostic groups F(3, 198) = 6.75, $p <$ 0.001. The Shapiro-Wilk test indicated normally distributed residuals, $W = 0.99$, $p = 0.30$, and Levene's test showed equally distributed variances $F = 1.72$, $p = 0.16$. None of the pairwise differences in whole amygdala volume reached significance after adjusting for multiple corrections (Table 3).

The MANCOVA of the nine amygdala nuclei volumes showed an overall significant difference in the multivariate statistics with Pillai's trace = 0.20, F(27) = 1.52, $p = 0.0472$, and Wilk's $\lambda = 0.81$, F(27) = 1.55, $p = 0.0384$, The Box test showed acceptable homogeneity of covariance (Box's $p = 0.147$).

In ANCOVA analyses (Table 4) we found significant between-subjects differences for the lateral nucleus F(3, 198) = 6.75, $p <$ 0.001), basal nucleus (F(3, 198) = 9.33, $p < 0.001$), the accessory basal nucleus (F(3, 198) = 7.66, $p < 0.001$), the anterior amygdaloid area (AAA) (F(3, 198)=4.66, $p = 0.00543$), cortico-amygdalar transition area (CATA) (F(3, 198) = 9.10, $p < 0.001$) and paralaminar nucleus (F (3, 198) = 6.59, $p < 0.001$)

Pairwise comparisons showed that PSY-V had smaller volumes of the basal nucleus (Cohen's d cD = 0.6, t = -2.8, $p = 0.0312$), CATA (cD = 0.7, t = -3.3, $p = 0.0203$), and AAA (cD = 0.6, t = -2.0, $p = 0.0312$) compared to HC. PSY-NV had smaller volumes of CATA (cD = 0.4, t = -2.8, $p = 0.0312$) compared to HC. (Table 5). There were no other significant results to report (Table 6). Distributions of amygdala nuclei volumes with significant findings are presented in Fig. 2.

Table 3
Multivariate Analysis of (Co)Variance results (MANCOVA), df – degrees of freedom, ICV – intracranial volume, Box's Homogeneity of Covariance Matrices Test $\chi^2 = 152.3$, df = 135, $p = 0.147$.

		value	F	df1	df2	p
Diagnosis	**Pillai's Trace**	**0,20**	**1,52**	**27**	**576**	**0,0,472,851**
	Wilks' Lambda	**0,81**	**1,55**	**27**	**556**	**0,0,384,775**
	Hotelling's Trace	**0,23**	**1,59**	**27**	**566**	**0,0,310,497**
	Roy's Largest Root	**0,18**	**3,80**	**9**	**192**	**0,0,001,969**
ICV	Pillai's Trace	0,38	12,95	9	190	<,0,000,001
	Wilks' Lambda	0,62	12,95	9	190	<,0,000,001
	Hotelling's Trace	0,61	12,95	9	190	<,0,000,001
	Roy's Largest Root	0,61	12,95	9	190	<,0,000,001
Age	Pillai's Trace	0,13	3,05	9	190	0,0,019,838
	Wilks' Lambda	0,87	3,05	9	190	0,0,019,838
	Hotelling's Trace	0,14	3,05	9	190	0,0,019,838
	Roy's Largest Root	0,14	3,05	9	190	0,0,019,838

IQ scores were available only for a subset of participants ($n = 16$ PSY-V/13 NPV/ 82 HC/62 PSY-NV), we repeated the pairwise analyses for IQ-matched subset of subjects. Only the results in the AAA (cD = 0.3, t = -3.0, $p = 0.0486$) between PSY-V and HC and CATA (cD = 0.5, t = -2.9, $p = 0.0486$) between PSY-NV and HC remained significant (supplementary Table 2). Among healthy controls, we found no correlation between IQ and amygdala volume (R = -0.022, $p = 0.84$).

Years of education ($n = 193$), DUDIT scores ($n = 174$) and DDD ($n = 81$) were available only for the subset of participants. Group differences in whole amygdala volumes remained significant ($p < 0.001$) when controlling for years of education and substance abuse, but there were no group differences ($p = 0.76621$) when controlling for antipsychotic

Table 2
Whole amygdala and amygdala nuclei volumes (sum of both hemispheres) in healthy controls (HC), non-psychotic violent offenders (NPV), psychotic patients with no history of violence (PSY-NV) and psychotic patients with history of violence PSY-V. Sd – standard deviation.

	HC		NPV		PSYNV		PSYV	
	mean	sd	mean	sd	mean	sd	mean	sd
Lateral.nucleus	1466.6	123.5	1411.6	109.4	1403.6	126.0	1385.6	107.0
Basal.nucleus	1019.9	95.2	946.3	65.1	972.1	96.5	952.0	84.6
Accessory.Basal.nucleus	601.4	60.9	560.6	45.9	568.5	58.5	563.0	52.7
Central.nucleus	106.2	14.4	102.0	9.4	101.7	14.6	100.2	11.5
Medial.nucleus	51.9	10.1	51.2	6.0	51.7	9.7	50.7	10.7
Cortical.nucleus	56.4	6.8	54.4	4.5	53.6	5.5	52.9	6.0
AAA	129.6	15.4	124.6	11.1	124.6	15.2	118.4	13.1
CATA	415.4	40.5	382.8	34.2	392.9	40.6	382.2	39.0
Paralaminar.nucleus	114.6	10.6	107.0	10.1	110.4	11.2	108.0	10.2
Whole_amygdala	3965.1	342.8	3751.2	262.8	3778.8	344.2	3734.8	327.4

Table 4
Group differences in amygdala nuclei volumes. Analysis of covariance results, homogeneity of variances between diagnostic groups was tested with Levene's test and normality of ANOVA residuals was estimated using Shapiro-Wilk test. To account for multiple comparisons, we adjusted p-values using false discovery rate (FDR) method for number of subfields (p_fdr). Significant results are marked in bold.

	F	Shapiro-W	Shapiro-p	Levene-stat	Levene-p	p	p_fdr
Lateral.nucleus	6.75	0.99	0.30	1.72	0.16	2.33E-04	**5.20E-04**
Basal.nucleus	9.33	0.99	0.58	2.05	0.11	8.51E-06	**5.11E-05**
Accessory.Basal.nucleus	7.66	1.00	0.76	0.94	0.42	7.18E-05	**2.15E-04**
AAA	4.66	0.99	0.08	0.95	0.42	3.62E-03	**5.43E-03**
Central.nucleus	1.37	0.99	0.42	1.71	0.17	2.53E-01	2.85E-01
Medial.nucleus	0.01	0.99	0.27	2.93	0.03	9.99E-01	9.99E-01
Cortical.nucleus	2.41	1.00	0.89	2.40	0.07	6.78E-02	8.71E-02
CATA	9.10	0.99	0.29	0.77	0.51	1.14E-05	**5.11E-05**
Paralaminar.nucleus	6.59	0.99	0.05	1.02	0.38	2.89E-04	**5.20E-04**

Table 5
Comparison of amygdala nuclei volumes between PSY-V, PSY-NV, NPV and HC. We adjusted p-values using false discovery rate (FDR) method for number of subfields and comparisons shown (p fdr). Significant results are marked in bold.

HC	Group	Subfield	n(HC)	N(Group)	Cohen's d	CI 95% (lower, upper)		t value	p value	p fdr
HC	NPV	Lateral.nucleus	89	18	0.1	(-0.4	0.6)	-0.3	7.89E-01	7.89E-01
HC	NPV	Basal.nucleus	88	18	0.5	(0.0	1.0)	-2.1	4.24E-02	8.86E-02
HC	NPV	Accessory.Basal.nucleus	88	19	0.5	(0.0	1.0)	-2.0	5.18E-02	8.86E-02
HC	NPV	AAA	88	18	0.2	(-0.3	0.7)	-0.8	4.23E-01	4.48E-01
HC	NPV	CATA	89	19	0.5	(0.0	1.0)	-2.0	4.38E-02	8.86E-02
HC	NPV	Paralaminar.nucleus	88	17	0.3	(-0.2	0.8)	-1.2	2.24E-01	2.68E-01
HC	PSYV	Lateral.nucleus	89	28	0.4	(0.0	0.8)	-1.9	5.91E-02	8.86E-02
HC	**PSYV**	**Basal.nucleus**	**88**	**29**	**0.6**	**(0.1**	**1.0)**	**-2.8**	**6.92E-03**	**3.12E-02**
HC	PSYV	Accessory.Basal.nucleus	88	29	0.5	(0.1	0.9)	-2.3	2.20E-02	7.21E-02
HC	**PSYV**	**AAA**	**88**	**28**	**0.6**	**(0.2**	**1.0)**	**-2.9**	**4.98E-03**	**3.12E-02**
HC	**PSYV**	**CATA**	**89**	**28**	**0.7**	**(0.3**	**1.1)**	**-3.3**	**1.13E-03**	**2.03E-02**
HC	PSYV	Paralaminar.nucleus	88	29	0.5	(0.1	0.9)	-2.3	2.40E-02	7.21E-02
HC	PSYNV	Lateral.nucleus	89	67	0.2	(-0.1	0.6)	-1.5	1.23E-01	1.71E-01
HC	PSYNV	Basal.nucleus	88	67	0.3	(0.0	0.6)	-1.9	5.51E-02	8.86E-02
HC	PSYNV	Accessory.Basal.nucleus	88	66	0.3	(0.0	0.6)	-2.0	4.52E-02	8.86E-02
HC	PSYNV	AAA	88	67	0.2	(-0.2	0.5)	-1.1	2.73E-01	3.07E-01
HC	**PSYNV**	**CATA**	**89**	**67**	**0.4**	**(0.1**	**0.7)**	**-2.8**	**5.34E-03**	**3.12E-02**
HC	PSYNV	Paralaminar.nucleus	88	67	0.2	(-0.1	0.5)	-1.3	2.01E-01	2.58E-01

Table 6
Comparison of amygdala nuclei volumes between PSY-V, PSY-NV and NPV. We adjusted p-values using false discovery rate (FDR) method for number of subfields and comparisons shown (p fdr). No significant results were found.

G1	G2	Subfield	n(G1)	N(G2)	Cohen's d	CI 95% (lower, upper)		t value	p value	p fdr
PSYNV	NPV	Lateral.nucleus	67	18	0.2	-0.3	0.7	-0.9	3.86E-01	8.53E-01
PSYNV	NPV	Basal.nucleus	67	18	-0.1	-0.6	0.4	0.4	7.06E-01	8.53E-01
PSYNV	NPV	Accessory.Basal.nucleus	66	19	0.0	-0.5	0.5	-0.1	9.07E-01	9.07E-01
PSYNV	NPV	AAA	67	18	0.1	-0.4	0.6	-0.3	7.48E-01	8.53E-01
PSYNV	NPV	CATA	67	19	0.1	-0.4	0.6	-0.3	7.59E-01	8.53E-01
PSYNV	NPV	Paralaminar.nucleus	67	17	-0.1	-0.6	0.4	0.5	6.48E-01	8.53E-01
PSYNV	PSYV	Lateral.nucleus	67	28	0.2	-0.3	0.6	-0.7	4.91E-01	8.53E-01
PSYNV	PSYV	Basal.nucleus	67	29	0.3	-0.2	0.7	-1.2	2.27E-01	7.41E-01
PSYNV	PSYV	Accessory.Basal.nucleus	66	29	0.1	-0.3	0.6	-0.6	5.43E-01	8.53E-01
PSYNV	PSYV	AAA	67	28	0.5	0.0	0.9	-2.1	4.00E-02	3.80E-01
PSYNV	PSYV	CATA	67	28	0.3	-0.2	0.7	-1.2	2.47E-01	7.41E-01
PSYNV	PSYV	Paralaminar.nucleus	67	29	0.3	-0.1	0.7	-1.4	1.80E-01	7.41E-01
NPV	PSYV	Lateral.nucleus	18	28	0.4	-0.2	1.0	-1.5	1.43E-01	7.41E-01
NPV	PSYV	Basal.nucleus	18	29	0.1	-0.5	0.7	-0.4	6.67E-01	8.53E-01
NPV	PSYV	Accessory.Basal.nucleus	19	29	0.1	-0.5	0.7	-0.2	8.18E-01	8.66E-01
NPV	PSYV	AAA	18	28	0.6	0.0	1.2	-2.1	4.23E-02	3.80E-01
NPV	PSYV	CATA	19	28	0.3	-0.3	0.9	-1.0	3.12E-01	8.03E-01
NPV	PSYV	Paralaminar.nucleus	17	29	0.2	-0.5	0.8	-0.6	5.59E-01	8.53E-01

medication, where we used a linear model as medication was administered to two groups only: PSY-V and PSY-NV. Years of education ($F = 0.206$, $p = 0.650582$), substance abuse ($F = 2.486$, $p = 0.116742$) and antipsychotic medication ($t = 0.193$, $p = 0.84725$) did not show significant impact on whole amygdala volume. We found no significant volumetric differences for amygdala nuclei in any of three MANCOVA models, and none of antipsychotic medication (Pillai's trace=0.0869, F(9) = 0.719, $p = 0.689$), substance abuse (Pillai's trace = 0.078, F(9) = 1.512, $p = 0.148$), or years of education (Pillai's trace = 0.017, F(9) = 0.335, $p = 0.963$) had a significant effect on the volume of amygdala nuclei.

3.3. Psychopathy traits

PCL-R scores did not differ between PSY-V and NPV (total score PSY-V median = 20, NPV median = 21, $U = 160$, $p = 0.6$). There were no

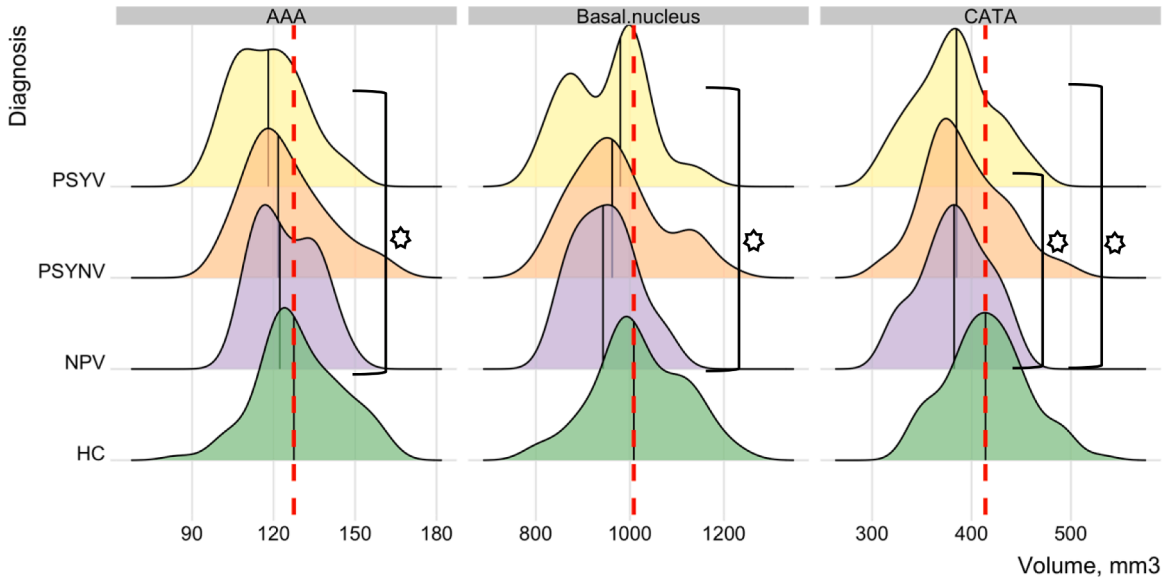

Fig. 2. Distribution of amygdala nuclei volumes. Medians of each distribution are shown, additionally mean of HC is shown in dashed red line. Significant results are marked by asterisks (all p_fdr < 0.05). We adjusted p-values using false discovery rate (FDR) method for number of subfields and number of groups.

significant differences between groups, nor effects of PCL-R scores for whole amygdala: t(29) = -0.21, p = 0.833 or amygdala nuclei Pillai's trace = 0.305, F = 1.025, p = 0.452 for the multivariate nuclei analysis). There were no significant associations between factor 1 and whole amygdala volume: t(29) = -0.42, p = 0.677) or factor 2 and whole amygdala volume: t(29) = 0.331, p = 0.742) or amygdala nuclei volumes (Pillai's trace = 0.489, F = 2.129, p = 0.076 for factor 1 and Pillai's trace = 0.385, F = 1.460, p = 0.226 for factor 2).

4. Discussion

We found smaller amygdala nuclei volumes in patients with psychosis (with and without a history of violence) compared to healthy controls, but no significant volumetric differences associated with non-psychotic violence or differences between psychotic and non-psychotic violent offenders or violent and non-violent psychosis patients. Contrary to our expectations, psychopathy traits were not associated with any of the amygdala nuclei volumes.

The amygdala nuclei volume reductions associated with psychotic violence are in line with our previous study among schizophrenia patients with a history of violence (Tesli et al., 2020). More specifically, we found smaller volumes of the basal nucleus, AAA, and CATA in violent individuals with psychosis compared to HC. The basal nucleus is part of the basolateral complex which is important for cognition and emotion (Asami et al., 2018), fear memory, and modulation of stress-induced emotional responses (Martijena and Molina, 2012). In dangerous situations, the basal nucleus activates the central nucleus, which is important for freezing, arousal, and the autonomic nervous system (Fudge and Tucker, 2009). The AAA is located anterior to the central nucleus, (Sims and Williams, 1990), extends to the periamygdaloid area/cortex (Garcia-Amado and Prensa, 2017), and has connections to the olfactory system (Cádiz-Moretti et al., 2016). AAA is involved in sustaining attention and memory, which is occupied by magnocellular cholinergic neurons that secrete acetylcholine (Zheng et al., 2019; Sims and Williams, 1990). The CATA has been suggested to have a vital role in social communication (Bzdok et al., 2013) as well as in evaluation of negative emotions (Kilts et al., 2003). In non-violent patients, we only found smaller volumes in CATA compared to HC.

We did not find any significant associations between psychopathy and amygdala nuclei volumes, with the PCL scores as a continuous variable (reflecting a quantitative trait), or with the subdomains of interpersonal (factor 1) or anti-social (factor 2) traits (Walters et al., 2015).

However, as the PSY-V and NPV did not differ in PCL-total scores (i.e. psychopathy traits) it may reflect the well-documented co-morbidity between schizophrenia and psychopathy in forensic populations (Fullam and Dolan, 2006). The lack of associations between psychopathy and amygdala nuclei volumes is in line with some earlier studies (Pujol et al., 2019), although reduced amygdala volumes in psychopathy or anti-social behavior have been more widely reported (Johanson et al., 2019).

Generally, there is a tendency that smaller gray matter volumes in the brain indicate dysfunction (Mercadante et al., 2021). For schizophrenia, changes in the limbic system volume in patients may serve as an early indication for the impending development of the disease (Zheng et al., 2019; Li et al., 2015), and volume changes are further related to the course of schizophrenia (Zheng et al., 2019). Psychopathy is associated with a basic failure in emotional reactivity and associative learning, and this can, at least partly, be driven by dysfunctional affective-motivational systems reliant on the amygdala and interconnected structures (Vieira et al., 2015; Blair, 2013).

Reduced volume in the frontal-temporal-parietal-subcortical circuit has been closely related to violent behaviors in male adolescents (Zhang et al., 2019), but in our study, we did not find reduced amygdala volume in NPV, contrary to our expectations.

Volume reduction, and supposedly dysfunction, in the basal nucleus, which is involved in emotion, cognition, and modulation of stress, make aggressive behavior more likely. The AAA is involved in sustaining attention and memory (Zheng et al., 2019), and we may speculate that it plays a role in aggression and violence. A study of incarcerated youth in a maximum-security juvenile facility found that fearlessness correlated negatively with gray matter volume in the amygdala (Walters and Kiehl, 2015). The lower volumes in the amygdala nuclei in PSY-V patients could be involved in violence due to increased fearlessness. While patients with psychosis usually perceive excessive fear due to their persecutory delusions (Ullrich et al., 2014), PSY-V patients may perceive less fear because of co-morbid psychopathy (Fullam and Dolan, 2006). Fearlessness is associated with low arousal in emotional situations and also with low responsiveness to threats, and this may lead to risky and antisocial behavior (Thomson et al., 2019).

Moreover, a reduction in somatostatin-immunoreactive (SST-IR) neurons in the amygdala have been reported in patients with

schizophrenia, which may indicate that amygdala change might disrupt anxiety regulation and responses to fear in schizophrenia (Pantazopoulos et al., 2017). Such a disruption or increase in anxiety could also possibly make these patients more violence-prone.

The major limitation of this study is the small subject sample which reflects the difficulties of recruiting participants with concurrent severe mental illness and violent offending, related to safety, severe psychopathology, and ability to consent. The subject sample was still in a similar range as previous studies of MRI-derived brain volumes in violent offenders with psychotic disorders (Fjellvang et al., 2018). Despite the adjustment for multiple comparisons, the relatively large number of tests (9 amygdala nuclei, four subject groups) increases the risk for false positive results, warranting replication in independent samples. The study only included males, which reflects the populations in the security hospital wards and prisons, as well as the higher prevalence of violence among males (Staniloiu and M.H., 2012). However, the findings may be sex-specific, as supported by a recent report of sex-specific brain volumetric characteristics (including the medial temporal lobe) in a forensic sample (Anderson et al., 2019). The use of PCL-R to assess and score psychopathy in violent patients with schizophrenia may be confounded by the presence of concurrent psychotic symptoms (Moran and Hodgins, 2004). However, the majority of patients were in a stable phase of their illness during study procedures, i.e. they were on medication, and for most of the time during the examinations/interviews, they presented with low to moderate psychotic symptoms. The PCL-R covers lifetime behavior and traits, i.e., the score also depends on their history from before the onset of psychosis. We only had PCL scores for a subsample of participants.

The strengths of the study include a thorough clinical characterization of all participants, with validated scoring instruments. The PCL-R score was split into factors 1 and 2 to assess different subdomains of the psychopathy construct (Hare, 2003). All subjects were scanned on the same scanner with no major upgrades during the study period. All scans were visually inspected, and we used the validated FreeSurfer software for automated MRI-processing and amygdala segmentation and automated MRI quality control based on machine learning.

To conclude, we report smaller specific amygdala nuclei volumes in psychosis patients with and without a history of violence (compared to healthy controls), but no association between psychopathy traits and amygdala nuclei volumes. The results need replication and should be further investigated in larger subject samples. A possible association between psychosis and psychopathy traits in violent offending should be accounted for in future studies searching for the neurobiological signature of psychotic violence.

Disclosures

All authors report no conflicts of interest.

Declaration of Competing Interest

All authors of the manuscript titled: "Associations between amygdala nuclei volumes, psychosis, psychopathy, and violent offending" certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2021.111416.

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