Smaller amygdala subnuclei volume in schizophrenia patients with violent behaviors

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Abstract
To investigate the association between the volume of amygdala subnuclei and violent behaviors in patients with schizophrenia (SCZ). In the present study, we recruited 40 SCZ patients with violent behaviors (VS), 26 SCZ patients without violent behaviors (NVS), and 28 matched healthy controls (HC) who completed T1-weighted magnetic resonance imaging. Both the total amygdala and amygdala subnuclei volumes were estimated with FreeSurfer. When comparing the SCZ patients with HC, SCZ patients had a smaller volume of the left basal nucleus ($P < 0.05$, uncorrected). Further, the VS patients had a smaller volume of the left amygdala central nucleus than the NVS group ($P < 0.05$, Bonferroni corrected). Our study suggests that a smaller volume of the left amygdala basal nucleus may be a biomarker for SCZ and that a smaller volume of the left central nucleus may be relevant to violence risk in patients with schizophrenia.

Keywords Schizophrenia · Violence · Freesurfer · MRI · Amygdala subnuclei

Introduction
Epidemiology studies showed that patients with schizophrenia (SCZ) had a higher rate of violence convictions (Wallace et al., 2004). A meta-analysis reported that 9.9% of patients with schizophrenia exhibited violent behaviors while only 1.6% in the general population (Fazel et al., 2009; Wallace et al., 2004). It is important to identify the potential violence among patients with SCZ so that special management and interventions can be targeted.

There are some essential risk factors to predict violence in patients with SCZ (Dolan & Fullam, 2009). For example, insight deficits and positive symptoms were reported to be associated with violence in SCZ (Buckley et al., 2004). Emotional response, especially anger, was proven to mediate violence (Coid et al., 2013). Comorbidity of substance use contributed to a fourfold higher risk of violence in SCZ (Elbogen & Johnson, 2009; Fazel et al., 2009; Wallace et al., 2004). With the development of neuroimaging techniques, researchers began to explore the neural correlates of violent behaviors in SCZ, which might provide more reliable evidence to identify the potential risk of violent behaviors.

Magnetic Resonance Imaging (MRI) is a powerful non-invasive tool to examine cerebral structures. Previous studies have found that schizophrenia patients who committed murder had smaller hippocampal volumes than patients without a history of violence (Yang et al., 2010). The reduced amygdala, hippocampal, and total brain volumes were also reported in another study of schizophrenia patients with severe violence (Barkataki et al., 2006). Poor impulse control or enhanced hyper-arousal will increase the risks of committing violent behaviors (Haller, 2018; Struber et al., 2008), in which process the amygdala plays an essential role. Naudts’ meta-analysis reported that SCZ with a history of violence displayed a larger volume reduction of the amygdala compared to SCZ without violence (Naudts & Hodgins, 2005). However, Del’s study reported an opposite result, which suggested an association between increased volume of amygdala and violent behaviors.

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behaviors for SCZ (Bene et al., 2016). The inconsistent results may primarily be caused by the fact that the amygdala is a heterogeneous structure. According to the tissue type and connective pattern, the amygdala can be divided into central amygdala and basolateral amygdala (Hrybouski et al., 2016). The basolateral amygdala was shown to connect heavily with prefrontal regions and served as the gate that received afferent information from cortical and subcortical regions. Animal studies have shown that basolateral amygdala played an essential role in fear extinction (Uliana et al., 2018). The impaired ability of fear extinction may keep patients constantly in an unsafe situation, resulting in possible violent behaviors to defend themselves. A large sample study revealed a widespread volume reduction of amygdala subnuclei, including the lateral nucleus, in SCZ group (Barth et al., 2021). However, they didn’t investigate the association between these subregion volume and aggression. Zhang and colleagues’ study reported that decreased functional connectivity of basolateral nucleus was observed in first episode psychosis and correlated with positive symptoms (Zhang et al., 2020), which suggested basolateral nucleus might involve in regulation of aggressive behaviors.

On the other hand, the central amygdala acted as the core hub for sending out information to cortical and subcortical regions, among which it had a strong connection with the brainstem (Yoder et al., 2015) and was responsible for the fear-potentiated startle. Convergent evidence indicated central amygdala might act as essential hub for fear and anxiety (Shackman & Fox, 2016). Increased metabolism in central amygdala is usually associated with potentiated defensive responses (Feinstein et al., 2011). Researchers also suggested central amygdala played essential role in normal and abnormal aggression (Haller, 2018). A study conducted in nonforensic sample suggested association between abnormal functional connectivity of central amygdala and Fearless Dominance scores (Yoder et al., 2015). It is possible that subjects would commit violence against others due to the abnormal function or structure of central amygdala. However, to our knowledge, only one study reported the amygdala subnuclei features of SCZ with a history of severe violent behaviors and reported decreased volume of amygdala subnuclei (Tesli et al., 2020), providing limited evidence on this specific issue.

In this study, we aimed to investigate the volumetric differences of the amygdala at the subfield level in patients with or without violence. We hypothesized that patients with schizophrenia would have a smaller volume of the amygdala compared to HC and that the SCZ patients with violent behaviors (VS) would have more volumetric reductions in basolateral amygdala and central amygdala than the SCZ patients without violent behaviors (NVS). We also hypothesized that the volumetric reduction might correlate with violent behaviors.

**Material and methods**

**Participants**

A total of 66 SCZ patients were recruited from the inpatients in Shanghai Mental Health Center, meeting the diagnostic criteria for schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) by two senior attending psychiatrists. The psychotic symptoms were assessed by the Positive and Negative Symptom Scale (PANSS) (Peralta & Cuesta, 1994). Inclusion criteria included: (1) age between 18 and 45; (2) PANSS total score higher than 50; (3) year of education > 9 years; (4) no suicidal ideations or risk. Exclusion criteria included: (1) history of neurological illness; (2) with a diagnosis of other mental disorders than schizophrenia current or in the past history; (3) substance abuse or dependency within six months; (4) women who were pregnant; (5) pacemaker or mental implants or any other contradiction with MRI.

Modified Overt Aggression Scale (MOAS) was used to assess the frequency and severity of aggressive episodes with four sub-dimensions: verbal aggression, aggression against objects, aggression against self, and aggression against others (Alderman et al., 1997; Huang et al., 2009). The reliability and validity of the Chinese version of MOAS were reported by Huang’s team in 2009 (Huang et al., 2009). The MOAS was applied to assess the aggressive behaviors in the past six months. SCZ patients with MOAS scores ≥ 4 were defined as the violence group (VS, N = 40), and MOAS scores < 4 were defined as the non-violence group (NVS, N = 26). Daily defined dose (DDD) was quantified as olanzapine equivalent doses based on methods provided by Leucht (Leucht et al., 2016). Healthy controls were recruited from the community and their age, gender, and education were matched with the patients’ group. The study was approved by the Institutional Review Board of Shanghai Mental Health Center in accordance with the Declaration of Helsinki. Written informed consent was provided by all the participants.

**MRI acquisition**

MRI data were acquired at the radiology department of Shanghai Mental Health Center. T1-weighted images of all subjects were obtained with the high-resolution three-dimension magnetization-prepared rapid acquisition with gradient echo (MPRAGE) sequence (TR/TE = 2,530/2.34 ms, flip angle = 7°, field of view = 256 × 256 mm², 192 axial slices, voxel size = 1 × 1 mm³, no gaps). A professional radiologist
reviewed all acquired T1-weighted images to rule out potential subjects with morphological abnormalities, incomplete coverage of the whole brain, or severe artifacts by head movements.

Segmentation of amygdala and amygdala subregions

We applied Freesurfer (v7.1) to conduct brain segmentation and cortical surface reconstruction (https://surfer.nmr.mgh.harvard.edu/fswiki/FreeSurferWiki) (Dale et al., 1999; Fischl et al., 2002, 2004). The segmentation protocol of amygdala and amygdala subregions was implanted in the newest version of the Freesurfer pipeline (Saygin et al., 2017). By using the segmentation protocol, we divided the amygdala into nine subnuclei including the anterior amygdala area, cortico-amygdaloid transition area, lateral nucleus, basal nucleus, paralaminar nucleus, accessory basal nucleus, medial nucleus, central nucleus, and cortical nucleus, which was shown in Fig. 1. The volumes of the bilateral amygdala, bilateral amygdala subnuclei and intracranial volume (ICV) were obtained from each subject.

Statistics

Continuous variables of demographic characteristics were statistically analyzed with student’s t-tests or analysis of variance. Categorical data were analyzed with chi-square tests. For each of the regions of interest (basal nucleus, lateral nucleus, accessory basal nucleus, and central nucleus), we applied linear regression analysis and examined two orthogonal contrasts: “(VS + NVS)/2-HC” and “VS-NVS”, adjusting for age, intracranial volume and the education level. All continuous variables were z-scored before entering the model. Bonferroni correction was applied to control multiple comparison errors.

Pearson correlation analysis was applied to investigate the association between identified amygdala subregions volume and clinical features in VS group. The significant level was set to 0.05. All statistical procedures were conducted with SPSS v26.

Results

Demographic and clinical characteristics

The NVS, VS, and HC groups had matched age and gender as shown in Table 1. The education level in the three groups differed significantly (F(2,91) = 12.282, P < 0.001*). Regarding the clinical features, there were no significant differences in PANSS total score, negative subscale score, general psychopathology subscale score, DDD, and age of the first onset between VS and NVS subgroups. VS subgroup had higher PANSS positive subscale scores and a longer duration of illness than the NVS subgroup. In addition, the VS subgroup had a higher MOAS total score, verbal aggression score, aggression against objects score, and aggression against others score than the NVS group. There were no significant differences in the score of aggression against self between VS and NVS subgroups. The SCZ and HC group didn’t show any significant differences in age and gender but differed in education level (t = -6.113, P < 0.001).

Multivariate linear regression analysis for amygdala subregions volume

Table 2 presents the statistical results for the eight ROIs. The volume of the left basal nucleus showed significant differences between the schizophrenic patients and healthy controls (B = 8.837, t = 2.304, P = 0.024, uncorrected). The volume of the left central nucleus was significantly different between the NVS and VS patients (B = 2.678, t = 3.164, P = 0.002, survived Bonferroni’s correction), controlling for age, education, and TIV. No other amygdala subregions exhibited significant effects in both contrasts in the regression model.

Correlation between violence, symptoms, and amygdala subregions volume

For VS group, no significant correlation was found between left basal nucleus volume, clinical features, and MOAS score. There was no significant correlation between the left central nucleus volume, clinical features, and MOAS score (see Table 3).
Table 1  Demographic characteristics and clinical features in NVS, VS and HC group

|                          | NVS (n = 26) | VS (n = 40) | HC (n = 28) | Statistics |
|--------------------------|-------------|-------------|-------------|------------|
| Age(years)               | 27.8±6.5    | 29.7±7.0    | 26.1±5.6    | F(2,91)=2.639, P=0.077 |
| Sex(F/M)                 | 7/19        | 20/20       | 9/19        | χ²=4.190, P=0.123 |
| Education (years)        | 13.0±2.8    | 12.7±2.6    | 15.6±1.6    | F(2,91)=12.282, P<0.001* |
| PANSS-T                  | 84.2±9.4    | 87.9±16.0   | -           | t=-1.174, P=0.245 |
| PANSS-P                  | 21.5±4.3    | 26.5±5.9    | -           | t=-3.750, P<0.001* |
| PANSS-N                  | 20.0±5.3    | 18.5±7.3    | -           | t=0.902, P=0.371 |
| PANSS-G                  | 42.7±5.8    | 42.9±8.4    | -           | t=0.063, P=0.950 |
| MOAS total score         | 0.3±0.7     | 13.5±5.5    | -           | t=-15.051, P<0.001* |
| Verbal aggression        | 0.2±0.5     | 2.1±1.0     | -           | t=-9.839, P<0.001* |
| Aggression against objects | 0.04±0.2    | 3.7±2.5     | -           | t=-8.856, P<0.001* |
| Age of first episode (years) | 21.4±5.0    | 20.6±6.5    | -           | t=0.559, P=0.578 |
| Duration of illness (years) | 6.5±5.8     | 11.2±8.0    | -           | t=-2.784, P=0.007* |
| DDD (mg/d)               | 22.0±11.1   | 20.5±15.1   | -           | t=0.427, P=0.671 |

*P<0.05; PANSS Positive and negative symptom scale; PANSS-T PANSS total score; PANSS-P PANSS positive score; PANSS-N PANSS negative score; PANSS-G General psychopathology score; MOAS Modified overt aggression scale; DDD Defined daily doses. VS, schizophrenia with violent behaviors. NVS, schizophrenia without violent behaviors. HC, healthy control

Table 2  Multiple variate linear regression analysis for the volume of the eight amygdala subregions

| Region                        | HC-(VS+NVS)/2   | NVS-VS | Age       | Edu       | TIV |
|-------------------------------|-----------------|--------|-----------|-----------|-----|
| Left basal nucleus            | t = 2.304       | t = 1.245 | t = 1.272 | t = -0.289 | t = 7.138 |
|                               | P = 0.024*      | P = 0.216 | P = 0.207 | P = 0.774 | P < 0.001 |
| Left central nucleus          | t = 0.990       | t = 3.164 | t = 0.867 | t = 0.169 | t = 5.782 |
|                               | P = 0.325       | P = 0.002** | P = 0.388 | P = 0.866 | P < 0.001 |
| Right basal nucleus           | t = 0.776       | t = 0.808 | t = 1.415 | t = -0.160 | t = 7.141 |
|                               | P = 0.440       | P = 0.421 | P = 0.161 | P = 0.874 | P < 0.001 |
| Right central nucleus         | t = -0.453      | t = 1.210 | t = 1.541 | t = 0.061 | t = 5.234 |
|                               | P = 0.652       | P = 0.230 | P = 0.127 | P = 0.952 | P < 0.001 |
| left lateral nucleus          | t = 0.794       | t = 1.340 | t = 1.055 | t = 0.028 | t = 7.539 |
|                               | P = 0.429       | P = 0.184 | P = 0.294 | P = 0.978 | P < 0.001 |
| Right lateral nucleus         | t = 1.141       | t = 1.214 | t = 0.902 | t = -0.639 | t = 6.479 |
|                               | P = 0.257       | P = 0.228 | P = 0.370 | P = 0.525 | P < 0.001 |
| Left Accessory Basal nucleus  | t = 1.453       | t = 1.024 | t = 1.455 | t = 0.774 | t = 8.400 |
|                               | P = 0.150       | P = 0.309 | P = 0.149 | P = 0.441 | P < 0.001 |
| Right Accessory Basal nucleus | t = 0.166       | t = -0.425 | t = 1.112 | t = 0.548 | t = 6.801 |
|                               | P = 0.868       | P = 0.672 | P = 0.269 | P = 0.585 | P < 0.001 |

*P<0.05(uncorrected), **P<0.05(Bonferroni corrected). VS, schizophrenia with violent behaviors. NVS, schizophrenia without violent behaviors. HC, healthy control. TIV, total intracranial volume

Table 3  Correlation analysis between amygdala subregion volume and clinical feature

|                  | MOAS-T | PANSS-T | PANSS-P |
|------------------|--------|---------|---------|
| Left basal nucleus | -0.041 | -0.058  | 0.087   |
| Left central nucleus | 0.025 | -0.067  | 0.124   |

Note: *P<0.05. The table showed the correlation coefficient for the selected correlation analysis

Discussion

Aggression and violence are correlated with disturbed impulse control, fear regulation, and threat processing, which supports the potential role of the amygdala in SCZ with violent behaviors, as evidenced by previous studies (Bacq et al., 2020; Hoptman et al., 2010; Tesli et al., 2020).
However, considering the heterogeneity of the amygdala, it is rational to explore the subfields of the amygdala. In accordance with previous studies, the present study revealed that the volumes of amygdala subnuclei were decreased in patients with SCZ compared to healthy control. Specifically, the volume of the left basal nucleus was significantly smaller in the SCZ group compared with the HC group. The t result for the left basal nucleus couldn't be corrected by the Bonferroni method, which might be largely caused by the small sample size. However, this result might also provide valuable evidence on the biomarker for SCZ. The basal nucleus is a hub for relaying information from the lateral amygdala to the central amygdala nucleus, which elicits fear-potentiated reactions (Amano et al., 2011). Accumulating evidence has proven that the amygdala basal nucleus is involved in the process of contextual fear conditioning (Amano et al., 2011; Onishi & Xavier, 2010). Impaired contextual fear-conditioning was associated with SCZ, as evidenced by animal and human research (Gill et al., 2018; Tani et al., 2019). Decreased volume of the basal nucleus may be related to impaired fear conditioning, which was supported by previous studies (Anglada-Figueroa & Quirk, 2005; Koo et al., 2004). Anglada and colleagues' study provide evidence that rats with basal nucleus lesioned after conditioned fear training wouldn't express the behaviors of conditioned fear, suggesting that the basal nucleus played an essential role in plasticity in fear conditioning (Anglada-Figueroa & Quirk, 2005). Another animal study also showed that conditioned fear responses were significantly impaired in BLA-lesioned animals (Koo et al., 2004). We speculate that schizophrenia patients (including patients with violent behavior) might have a weak ability to associate the cues of violent acts with moral shames and social punishment. In the present study, compared with HC group, the volume of the left basal nucleus was smaller in the SCZ group. However, basal nucleus volume was not significantly different for VS and NVS groups. We propose that decreased volume of the left basal nucleus may be a biomarker for SCZ rather than SCZ with violent behaviors. To our knowledge, only one research has reported the volume alteration of amygdala subregions in SCZ with a history of violent behaviors (Tesli et al., 2020). In line with that study, our study found the volumetric reduction of the left amygdala basal nucleus in the SCZ group. However, no differences in amygdala nuclei volumes were found between VS and NVS groups in that study.

The multivariate regression analysis showed that the volume of the left central nucleus was significantly smaller in VS group compared with the NVS group, which could be corrected by the Bonferroni method. Amygdala central nucleus is the primary region for sending neural signals from the amygdala to the cerebral cortex and brainstem and is responsible for the emotion-induced elevated sympathetic nervous reaction. In accordance with our hypothesis, animal study reveals that aggressive behaviors are related to the damage of the amygdala central nucleus (Zagrodzka et al., 1998). In addition, oxytocin can modulate anxiety behaviors via oxytocin receptors within the amygdala central nucleus (Laszlo et al., 2016). Elevated anxiety behaviors in rats are proven to be associated with high aggressions (Patki et al., 2015). We speculate that reduced volume of the amygdala central nucleus might correlate with decreased number of the oxytocin receptor, which may reduce the modulation function of oxytocin and thus increase aggression behaviors.

However, our study has several limitations. Firstly, the sample size was relatively small. Secondly, our study was cross-sectional in nature, which limited the power to predict future violence. Thirdly, the duration of illness in VS group was significantly longer than that in the NVS group, which might influence the result. This issue was addressed by considering the duration of illness as covariates. Fourthly, we haven’t collected fMRI and structural MRI data, so it was hard to do multimodal MRI analysis, which might be more powerful. In future research, we will collect multimodal MRI data and predict violence in a prospective study. Lastly, the diagnoses were not confirmed by a structured clinical interview tool, which was a weakness of the current study. The diagnoses were made based on the criteria of DSM-IV by senior attending psychiatrists’ clinical interviews, which made the diagnoses clinically reliable.

In summary, our study suggests that a smaller volume of left amygdala basal nucleus may be a biomarker for SCZ, and that a smaller volume of left central nucleus might be relevant to violence risk in patients with schizophrenia.

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Authors contributions Yang Shao, and Bin Xie designed the study protocol and supervised the administration of the study. Yi Qiao collected the MRI data. Hao Hu did the analysis and wrote the primary manuscript. Fengjiu Liu, Li Liu and Yi Mei collected the clinical data.

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Data availability The data and materials can be provided upon reasonable requests.
Declarations

Ethical approval All study procedures were approved by the Institutional Review Board of Shanghai Mental Health Center, which was in accordance with the Declaration of Helsinki.

Consent to participate Written informed consents were provided by all the participants.

Consent to publish All authors consented this paper to be published in Brain imaging and behaviors.

Competing interests None.

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