Smaller Amygdala Subnuclei Volume in Schizophrenia Patients with Violent Behaviors

Hao Hu
Shanghai Mental Health Center
Fengju Liu
Shanghai Mental Health Center
Li Liu
Shanghai Mental Health Center
Yi Mei
Shanghai Mental Health Center
Bin Xie
Shanghai Mental Health Center
Yang Shao
Shanghai Mental Health Center
Yi Qiao (qiaoyi2004@msn.com)
Shanghai Mental Health Center https://orcid.org/0000-0002-8896-1003

Research Article

Keywords: schizophrenia, violence, Freesurfer, MRI, amygdala subnuclei

Posted Date: January 3rd, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1207078/v1

Abstract

Objective

To investigate the association between the volume of amygdala subnuclei and violent behaviors in patients with schizophrenia (SCZ).

Methods

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.

Results

When comparing the whole SCZ patients with HC, SCZ patients had smaller volume of the left amygdala and the left basal nucleus. Further, the VS patients had smaller volume of the amygdala central nucleus as compared to the NVS group.

Conclusions

Our findings suggested that a smaller volume of the amygdala central nucleus might be relevant to violence risk in SCZ patients.

1. Introduction

Epidemiology studies showed that patients with schizophrenia (SCZ) had a higher rate of violence conviction (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 and 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 and 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 and Hodgins, 2005). However, Del's study reported an opposite result, which suggested an association between increased volume of amygdala and violent behaviors for SCZ (Widmayer et al., 2018). 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. 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. To our knowledge, only one research reported the amygdala subnuclei features of SCZ with a history of severe violent behaviors and reported decreased volume of amygdala subnuclei (Tesli et al., 2020b), 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 in the amygdala compared to HC and that the SCZ patients with violent behaviors (VS) would have more volumetric reductions on the subfield level of the amygdala than the SCZ patients with violent behaviors (NVS). We also hypothesized that the volumetric reduction might correlate with violent behaviors.

2. Material And Methods

2.1 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 and 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 currently or in the past; (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. SCZ patients with MOAS scores ≥4 were defined as the violence group (VS, N=40), MOAS scores <4 were defined as 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). Heathly controls were recruited from the community and their age, sex and education were matched with 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 consents were provided by all the participants.

2.2 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 mm^2, 192 axial slices, voxel size=1×1mm^3, 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.

2.3 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; Fischl et al., 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 anterior amygdala area, cortico-amygdaloid transition area, lateral nucleus, basal nucleus, paralaminar nucleus, accessory basal nucleus, medial nucleus, central nucleus, and cortical nucleus. The volumes of the bilateral amygdala, bilateral amygdala subnuclei and intracranial volume (ICV) were obtained from each subjects.

2.4 Statistics

Continuous variables of demographic characteristics were statistically analyzed with students t-tests. Categorical data were analyzed with chi-square tests.

We applied repeated-measurement analysis of covariance (ANCOVA) to examine the volumes of amygdala and amygdala subfields with a within-group factor of hemisphere (left, right) and a between-group factor of group (VS, NVS and HC), controlling for age, intracranial volume, and selected clinical features showing a significant group difference. If the interaction effect of group and hemisphere was not significant on a particular subregion, we compared the average volume of bilateral subregions between groups. Otherwise, we compared the left and right subregions volume individually between groups. 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.

3. Results

3.1 Demographic and clinical characteristics

When comparing the whole SCZ group and HC, they had matched age and sex as shown in Table 1. The education level in SCZ was lower than HC. We summarized the demographic and clinical characteristics for VS and NVS groups in Table 2. VS and NVS subgroups had matched age, education level, and gender. 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 longer duration of illness than NVS subgroup. In additon, VS subgroup had higher MOAS total score, verbal aggression, aggression against objects, and aggression against others than the NVS group. There was no significant differences of "aggression against self" between VS and NVS subgroups.

Table 1
Demographic characteristics in SCZ and HC group

	SCZ (n=66)	HC (n=28)	Statistics
Age(years)	29.0±6.8	26.1±5.6	t=1.989, P=0.05
Sex(F/M)	27/39	9/19	χ^2 = 0.639, P=0.379
Education (years)	12.8±2.7	15.6±1.6	t=-6.113, P<0.001*
Note: *P < 0.05. Participants from SCZ with and without violent behaviors were treated as SCZ group.			

Table 2
Demographic characteristics in NVS and VS group

	NVS (n=26)	VS (n=40)	Statistics
Age(years)	27.8±6.5	29.7±7.0	t=-1.126, P=0.264
Sex(F/M)	7/19	20/20	χ^2 = 3.471, P=0.062
Education (years)	13.0±2.8	12.7±2.6	t=0.479, P=0.634
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*
Aggression against self	0.0±0.0	0.6±2.1	t=-1.641, P=0.109
Aggression against others	0.0±0.0	6.7±5.4	t=-7.761, 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

Note: *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.

3.2 Amygdala subregions volume comparison between SCZ and HC groups

The SCZ group showed a reduced volume of left amygdala, compared with the HC group (F(1,89)=6.846, P=0.010*), adjusted for age, education, and ICV. The SCZ and HC groups showed no group differences in the volume of the right amygdala (F(1,89)=1.853, P=0.177).

There was a significant interaction between group and hemisphere for basal nucleus (F=7.278, P= 0.008) and corticoamygdaloid transition (F=4.412, P=0.039). For these two subregions, we separately compared group differences for left and right subregions. The volume of the left basal nucleus was significantly smaller in SCZ than HC (F(1,89)=5.453, P=0.022). We calculated the average volume for the amygdala subregions showing no significant interactions between group and hemisphere. There was no significant

differences of volumetric alteration in other amygdala subregions between the SCZ and HC groups (as shown in Table 3).

Table 3
Group comparisons of amygdala and subregions for SCZ and HC group

Brain regions	SCZ(n=66)	HC(n=28)	Statistics
Left amygdala	1712.6(216.6)	1895.1(199.1)	F(1,89)=6.846, P=0.010*
Right amygdala	1866.7(224.3)	1963.9(168.1)	F(1,89)=1.853, P=0.177
Lateral nucleus_aver	678.0(75.6)	712.8(73.4)	F(1,89)=1.111, P=0.295
Left basal nucleus	442.7(53.1)	482.1(57.6)	F(1,89)=5.453, P=0.022*
Right basal nucleus	466.5(49.9)	485.5(41.4)	F(1,89)=0.653, P=0.421
Accesory basal nucleus_mean	272.4(31.7)	288.2(30.5)	F(1,89)=0.741, P=0.392
Anterior amygdaloid area_mean	58.3(7.6)	60.4(6.1)	F(1,89)=0.005, P=0.945
Central nucleus_mean	44.6(7.8)	46.9(7.1)	F(1,89)=0.114, P=0.736
Medial nucleus_mean	20.1(4.5)	21.9(4.6)	F(1,89)=0.144, P=0.706
Cortical amygdala_mean	28.7(4.3)	29.8(2.5)	F(1,89)=0.002, P=0.969
Left_CA_trans	174.1(19.9)	188.7(21.7)	F(1,89)=3.753, P=0.056
Right_CA_trans	185.8(21.2)	193.5(16.7)	F(1,89)=0.066, P=0.798
Paralamina_nucleus_mean	50.7(5.7)	53.6(4.5)	F(1,89)=2.450, P=0.121

Note: *P<0.05. *_mean indicated the average volume of the left and right subregions. CA_trans, corticoamygdaloid transition.

3.3 Amygdala subregions volume comparison between VS and NVS groups

As shown in Table 4, significant interaction between group and hemisphere existed for the anterior amygdaloid area (F=4.089, P=0.048). Bilateral volumes of the anterior amygdaloid area were compared between VS and NVS groups. For the subnuclei exhibiting no interactions, we computed the average volume of left and right subnuclei individually. The central nucleus's average volume was smaller in the VS group than in the NVS groups (F=4.145, P=0.046), adjusting for age, duration of illness, and total intracranial volume. The other amygdala subregions didn't differ between groups.

Table 4
Group comparisons of amygdala and its subregions for VS and NVS group

Brain regions	NVS(n=26)	VS(n=40)	Statistics
Left amygdala	1656.0(191.5)	1800.0(227.4)	F(1,61)=3.741, P=0.058
Right amygda	1817.0(178.2)	1943.1(266.9)	F(1,61)=2.449, P=0.119
Lateral nucleus_mean	699.5(84.8)	664.0(66.4)	F(1,61)=1.016, P=0.318
Basal nucleus_mean	467.0(54.7)	446.5 (46.0)	F(1,61)=0.713, P=0.402
Accesory basal nucleus_mean	277.7(34.9)	269.1(29.3)	F(1,61)<0.001, P=0.998
Left anterior amygdaloid area	59.4(1.3)	58.26(1.1)	F(1,61)=0.137, P=0.872
Right anterior amygdaloid area	61.7(6.1)	60.9(10.0)	F(1,61)=0.346, P=0.558
Central nucleus_mean	46.9(1.3)	41.4(11)	F(1,61)=4.145, P=0.046*
Medial nucleus_mean	21.5(5.2)	19.2(3.8)	F(1,61)=2.354, P=0.130
Cortical amygdala_mean	27.8(4.3)	26.6(3.6)	F(1,61)=0.066, P=0.798
CA_trans_mean	180.8(18.6)	179.5(20.3)	F(1,61)=0.391, P=0.534
Paralamina_nucleus_mean	51.8(6.3)	50.0(5.3)	F(1,61)=0.362, P=0.550

Note: *P<0.05. *_mean indicated the average volume of the left and right subregions. CA_trans, corticoamygdaloid transition.

3.4 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 mean central nucleus volume□clinical features, and MOAS score (see Table 5).

Table 5
Correlation analysis between amygdala subregion volume and clinical features

	MOAS total	Panss-T	PANSS-P
Left basal nucleus	**-0.041**	**-0.058**	**0.087**
Central nucleus_mean	**-0.064**	**-0.063**	**0.205**

Note: Central nucleus_mean, the average volume of left and right central nucleus of amygdala.

4 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., 2018; Hoptman et al., 2010; Tesli et al., 2020a).

However, considering the heterogeneity of the amygdala's structure, it is rational to explore the subfields of the amygdala rather than take the amygdala as a whole. 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 to HC. Amygdala 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 (Onishi and 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. 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, 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., 2020b). 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.

In addition, the volume of the central nucleus was smaller in VS group compared to the NVS group, adjusted for age, duration of illness, and total intracranial volume. 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.

In summary, our study suggests that a smaller volume of left amygdala subnuclei might be relevant to violence risk in patients with schizophrenia.

Declarations

Acknowledgements

We thank Dr Yingying Tang who helped with the language revisions.

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.

Authors Contributions

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

Funding

This study is supported by grants from the Three-Year Action Plan for the Construction of Public Health System in Shanghai [grant number: GWIV-5, PI: Bin Xie]; the Science and Technology Commission of Shanghai Municipality [grant number 19411969400, PI: Xinyi Cao]; the National Natural Science Foundation of China[grant number 81302624, PI: Yi Qiao grant number 81873909 PI: Qiang Luo]; Quantitative evaluation based strategic research of interventions on relapse of schizophrenia [grant number 19411950800, PI: Bin Xie], Fund for Talents by Shanghai Mental Health Center [grant number 2018-FX-04, PI: Qian Guo], Qihang Foundation of Shanghai Mental Health Center [grant number 2019-QH-01, PI: Hao Hu]. The sponsor had no role in study design, in the collection, analysis, and interpretation of data, in the writing of the report, or in the decision to submit the paper for publication.

Competing Interests

None.

Availability of data and materials

The data and materials can be provided upon reasonable requests**.**

References

1. Amano, T., Duvarci, S., Popa, D., & Pare, D. (2011). The fear circuit revisited: contributions of the basal amygdala nuclei to conditioned fear. *J Neurosci*, 31, 15481–15489
2. Bacq, A., Astori, S., Gebara, E., Tang, W., Silva, B. A., Sanchez-Mut, J. … Sandi, J. (2018). C., Amygdala GluN2B-NMDAR dysfunction is critical in abnormal aggression of neurodevelopmental origin induced by St8sia2 deficiency. Mol Psychiatry.
3. Barkataki, I., Kumari, V., Das, M., Taylor, P., & Sharma, T. (2006). Volumetric structural brain abnormalities in men with schizophrenia or antisocial personality disorder. *Behav Brain Res*, 169, 239–247
4. Buckley, P. F., Hrouda, D. R., Friedman, L., Noffsinger, S. G., Resnick, P. J., & Camlin-Shingler, K. (2004). Insight and its relationship to violent behavior in patients with schizophrenia. *Am J Psychiatry*, 161, 1712–1714
5. Coid, J. W., Ullrich, S., Kallis, C., Keers, R., Barker, D., Cowden, F., & Stamps, R. (2013). The relationship between delusions and violence: findings from the East London first-episode psychosis study. *JAMA Psychiatry*, 70, 465–471
6. Dale, A. M., Fischl, B., & Sereno, M. I. (1999). Cortical surface-based analysis. I. Segmentation and surface reconstruction. *Neuroimage*, 9, 179–194
7. Dolan, M. C., & Fullam, R. S. (2009). Psychopathy and functional magnetic resonance imaging blood oxygenation level-dependent responses to emotional faces in violent patients with schizophrenia. *Biol Psychiatry*, 66, 570–577
8. Elbogen, E. B., & Johnson, S. C. (2009). The intricate link between violence and mental disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Arch Gen Psychiatry*, 66, 152–161
9. Fazel, S., Gulati, G., Linsell, L., Geddes, J. R., & Grann, M. (2009). Schizophrenia and violence: systematic review and meta-analysis.PLoS Med6, e1000120
10. Fischl, B., Salat, D. H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C. … Dale, A. M. (2002). Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron*, 33, 341–355
11. Fischl, B., van der Kouwe, A., Destrieux, C., Halgren, E., Segonne, F., Salat, D. H. … Dale, A. M. (2004). Automatically parcellating the human cerebral cortex. *Cereb Cortex*, 14, 11–22
12. Gill, K. M., Miller, S. A., & Grace, A. A. (2018). Impaired contextual fear-conditioning in MAM rodent model of schizophrenia. *Schizophr Res*, 195, 343–352

13. Haller, J. (2018). The role of central and medial amygdala in normal and abnormal aggression: A review of classical approaches. *Neurosci Biobehav Rev*, 85, 34–43
14. Hoptman, M. J., D'Angelo, D., Catalano, D., Mauro, C. J., Shehzad, Z. E., Kelly, A. M. … Milham, M. P. (2010). Amygdalofrontal functional disconnectivity and aggression in schizophrenia. *Schizophr Bull*, 36, 1020–1028
15. Hrybouski, S., Aghamohammadi-Sereshki, A., Madan, C. R., Shafer, A. T., Baron, C. A., Seres, P. … Malykhin, N. V. (2016). Amygdala subnuclei response and connectivity during emotional processing. *Neuroimage*, 133, 98–110
16. Laszlo, K., Kovacs, A., Zagoracz, O., Ollmann, T., Peczely, L., Kertes, E. … Lenard, L. (2016). Positive reinforcing effect of oxytocin microinjection in the rat central nucleus of amygdala. *Behav Brain Res*, 296, 279–285
17. Leucht, S., Samara, M., Heres, S., & Davis, J. M. (2016). Dose Equivalents for Antipsychotic Drugs: The DDD Method. *Schizophr Bull*, 42(Suppl 1), S90–94
18. Naudts, K., & Hodgins, S. (2005). Neurobiological Correlates of Violent Behavior Among Persons With Schizophrenia. *Schizophrenia Bulletin*, 32, 562–572
19. Onishi, B. K. A., & Xavier, G. F. (2010). Contextual, but not auditory, fear conditioning is disrupted by neurotoxic selective lesion of the basal nucleus of amygdala in rats. *Neurobiology of Learning and Memory*, 93, 165–174
20. Patki, G., Atrooz, F., Alkadhi, I., Solanki, N., & Salim, S. (2015). High aggression in rats is associated with elevated stress, anxiety-like behavior, and altered catecholamine content in the brain. *Neurosci Lett*, 584, 308–313
21. Peralta, V., & Cuesta, M. J. (1994). Psychometric properties of the positive and negative syndrome scale (PANSS) in schizophrenia. *Psychiatry Res*, 53, 31–40
22. Saygin, Z. M., Kliemann, D., Iglesias, J. E., van der Kouwe, A. J. W., Boyd, E., Reuter, M. … Augustinack, J. C. (2017). Alzheimer's Disease Neuroimaging, I., High-resolution magnetic resonance imaging reveals nuclei of the human amygdala: manual segmentation to automatic atlas. Neuroimage 155, 370-382
23. Struber, D., Luck, M., & Roth, G. (2008). Sex, aggression and impulse control: an integrative account. *Neurocase*, 14, 93–121
24. Tani, H., Tada, M., Maeda, T., Konishi, M., Umeda, S., Terasawa, Y. … Uchida, H. (2019). Comparison of emotional processing assessed with fear conditioning by interpersonal conflicts in patients with depression and schizophrenia. *Psychiatry Clin Neurosci*, 73, 116–125
25. Tesli, N., van der Meer, D., Rokicki, J., Storvestre, G., Rosaeg, C., Jensen, A. … Haukvik, U. K. (2020a). *Hippocampal subfield and amygdala nuclei volumes in schizophrenia patients with a history of violence*. Eur Arch Psychiatry Clin Neurosci
26. Tesli, N., van der Meer, D., Rokicki, J., Storvestre, G., Rosaeg, C., Jensen, A. … Haukvik, U. K. (2020b). Hippocampal subfield and amygdala nuclei volumes in schizophrenia patients with a history of violence. *Eur Arch Psychiatry Clin Neurosci*, 270, 771–782

27. Wallace, C., Mullen, P. E., & Burgess, P. (2004). Criminal offending in schizophrenia over a 25-year period marked by deinstitutionalization and increasing prevalence of comorbid substance use disorders. *Am J Psychiatry*, 161, 716–727
28. Widmayer, S., Sowislo, J. F., Jungfer, H. A., Borgwardt, S., Lang, U. E., Stieglitz, R. D., & Huber, C. G. (2018). Structural Magnetic Resonance Imaging Correlates of Aggression in Psychosis: A Systematic Review and Effect Size Analysis. *Front Psychiatry*, 9, 217
29. Yang, Y., Raine, A., Han, C. B., Schug, R. A., Toga, A. W., & Narr, K. L. (2010). Reduced hippocampal and parahippocampal volumes in murderers with schizophrenia. *Psychiatry Res*, 182, 9–13
30. Yoder, K. J., Porges, E. C., & Decety, J. (2015). Amygdala subnuclei connectivity in response to violence reveals unique influences of individual differences in psychopathic traits in a nonforensic sample. *Hum Brain Mapp*, 36, 1417–1428
31. Zagrodzka, J., Hedberg, C. E., Mann, G. L., & Morrison, A. R. (1998). Contrasting expressions of aggressive behavior released by lesions of the central nucleus of the amygdala during wakefulness and rapid eye movement sleep without atonia in cats. *Behavioral Neuroscience*, 112, 589–602

Figures

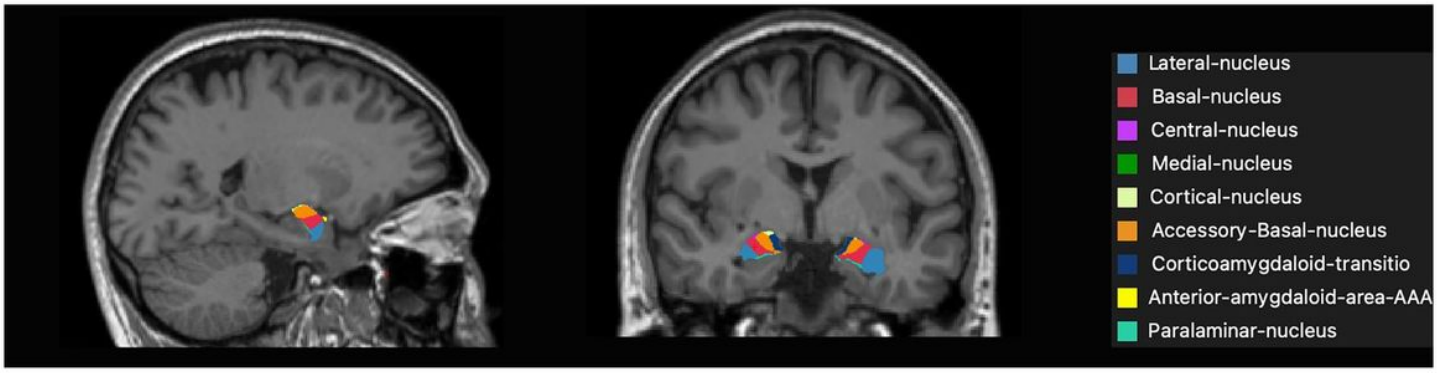

Figure 1

Amygdala subregions generated by freesurfer v7.1.1

Supplementary Files

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

- checklist.pdf