Amygdala Subnucleus Volumes in Psychosis High-Risk State and First-Episode Psychosis

Short title: Amygdala subnuclei and psychosis

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ABSTRACT

Structural and functional abnormalities of the amygdala in schizophrenia have been well documented. Post-mortem studies suggest that the lateral nucleus is particularly affected in schizophrenia. It is not known whether the amygdala subnuclei are differently affected at the time of the first-episode psychosis or already at high-risk state.

75 first-episode psychosis patients (FEP), 45 clinical high-risk patients (CHR) and 76 population controls participated in this cross-sectional case-control study. Participants underwent T1-weighted 3T MRI scans, from which the amygdala was segmented using a newly developed automated algorithm. Because early adverse events increase risk for psychosis and affect the amygdala, we also tested whether experiences of childhood maltreatment associate with the putative amygdala subnuclei abnormalities.

Compared to the population controls, FEP had smaller volumes of the lateral, and basal nuclei. In CHR, only the lateral nucleus was significantly smaller compared to the control subjects. Experience of childhood maltreatment was inversely associated with lateral nucleus volumes in FEP but not in CHR.

These results show that the lateral and basal nuclei of the amygdala are already affected in FEP. These volumetric changes may reflect specific cellular abnormalities that have been observed in post-mortem studies in schizophrenia in the same subnuclei. Decreased volume of the lateral nucleus in CHR suggest that a smaller lateral nucleus could serve as a potential biomarker for psychosis risk. Finally, we found that the lateral nucleus volumes in FEP may be sensitive to the effects of childhood maltreatment.

Keywords: First-Episode Psychosis, Clinical High-Risk, Amygdala Subnuclei, MRI, Childhood Maltreatment

1. Introduction

Schizophrenia is associated with widespread abnormalities in brain morphology, in particular in the frontotemporal regions (Kelly et al., 2018; van Erp et al., 2018) including the amygdala (van Erp et al., 2016). Smaller amygdala volumes are also found in individuals with clinical high-risk for psychosis and may represent a component of the psychosis vulnerability network (Chan et al., 2011). The amygdala is involved in emotional and cognitive processes such as salience attribution, fear learning, and social cognition (Adolphs, 2010; LeDoux, 2007). Accordingly, schizophrenia patients show decreased amygdala activity in response to aversive emotional stimuli (Anticevic et al., 2010), and during a facial identification and evaluation tasks (Gur et al., 2007; Pinkham et al., 2008).

Prior research has not fully taken into account the fact that the amygdala is a complex structure comprised of 9 subnuclei visible in *ex-vivo* MRI (Saygin et al., 2017). These subnuclei have different cell populations, neurochemistry, connectivity patterns and functions (Janak and Tye, 2015; Pitkänen et al., 1997). How individual subnuclei are affected in first-episode psychosis (FEP) or clinical high-risk state (CHR) is currently unknown. A better understanding of the amygdala abnormalities at a subnucleus level may enable more accurate mechanistic theories of amygdala dysfunction in the development of psychosis.

The lateral nucleus is the main point of entry for sensory information to the amygdala (Pitkänen et al., 1997) that integrates this information before feeding it to other subnuclei. Prior evidence suggests that this nucleus is particularly affected in enduring schizophrenia. Post-mortem studies have shown decreased volumes (Kreczmanski et al., 2007), reduced number of neurons (Berretta et al., 2007; Kreczmanski et al., 2007), smaller nuclear volumes (Williams et al., 2016), and increased oligodendrocyte density (Williams et al., 2013) in the lateral or basolateral nucleus of schizophrenia patients. Also schizophrenia animal models have demonstrated increased firing

rates and disrupted connectivity of this nucleus (Chang and Grace, 2014; Du and Grace, 2016; Eom et al., 2017).

Two previous imaging studies analyzing the shape of the amygdala reported deformations in the basal nucleus region (Shenton et al., 2002), and the right basolateral nucleus (Mahon et al., 2015) in chronic schizophrenia. These imaging results are supported by findings in a post-mortem study (Kreczmanski et al., 2007). However, two other studies (Makowski et al., 2017; Qiu et al., 2013) investigating the shape of the amygdala in first-episode psychosis found no differences in the shape of the amygdala. To our knowledge, amygdala subnuclei volumes have not been studied in first-episode psychosis, or clinical high-risk states before.

Given the role of the amygdala in processing emotions and stress (Anticevic et al., 2010; Hall et al., 2008; Roozendaal et al., 2009), volumetric abnormalities in the amygdala may also reflect exposure to environmental stressors. Childhood maltreatment increases the risk of schizophrenia by an odds-ratio of 2.8 (Varese et al., 2012). The amygdala volume is altered by developmental stress (Teicher et al., 2016). In mice, early life stress increases the number of neurons in the amygdala (Cohen et al., 2013), which is reflected by some human volumetric imaging studies showing increased amygdala volumes after severe childhood neglect (Mehta et al., 2009; Tottenham et al., 2010). However, other studies have found smaller amygdala volumes in response to less severe childhood maltreatment (Edmiston et al., 2011; Hanson et al., 2015). These discrepancies may partially reflect the nonlinear development of the amygdala, differences in the type of maltreatment, and differences in imaging methodologies (Hanson et al., 2015). On the other hand, in individuals with a mental illness, childhood maltreatment has been consistently associated with smaller amygdala volumes (Kuo et al., 2012; Morey et al., 2016; Teicher and Samson, 2016). There is also some evidence that the lateral nucleus may be particularly vulnerable to stress during the development. Animal models suggest that prenatal stress leads to smaller lateral nucleus volumes and fewer numbers of neurons and glia cells (Charil et al., 2010;

Kraszpulski et al., 2006). Moreover, repeated stress during the adolescence disrupts the GABAergic interneurons in the lateral nucleus (Zhang and Rosenkranz, 2016) and social isolation of juvenile rats results in dendritic abnormalities in the basolateral nucleus (Wang et al., 2012). FEP patients and individuals at familial high-risk for schizophrenia, who have experienced childhood maltreatment, have smaller amygdala volumes than patients and familial high-risk individuals without exposure to childhood maltreatment (Aas et al., 2012; Barker et al., 2016). However, it is currently unknown if the deleterious effects of childhood maltreatment in FEP or in CHR are specific to some of the amygdala subnuclei.

In the present study, we applied a newly developed segmentation algorithm (Saygin et al., 2017) to study amygdala subnuclei volumes in FEP patients and CHR individuals. These clinical groups were compared to age- and sex-matched population controls. Based on post-mortem studies in schizophrenia patients, we hypothesized that the lateral nucleus would be smaller in FEP relative to controls. Further, we wanted to test if this abnormality extends to CHR individuals. We had no specific hypotheses about the other subnuclei as prior post-mortem studies have not clearly demonstrated the involvement of those nuclei in psychotic illnesses. However, as no previous study has investigated this question *in vivo*, we decided to include all subnuclei in our primary analysis. We also hypothesized that childhood maltreatment associates inversely with the lateral nucleus volume. Finally, some (Killgore et al., 2009; Namiki et al., 2007; Watson et al., 2012) but not all studies (Joyal et al., 2003; Rich et al., 2016; Wang et al., 2008; Witthaus et al., 2009) have found correlations between clinical symptom severity or cognitive performance and volume of the whole amygdala. Therefore, we explored whether clinical symptom severity, duration of illness and exposure to antipsychotics were associated with reduced amygdala subnuclei volumes in this sample. As these analyses were exploratory, we did not have any specific hypotheses concerning the directionality or size of the effects.

2. Materials and methods

2.1 Participants

The intent-to-study groups consisted of 86 first-episode psychosis patients (FEP), 56 clinical high-risk patients (CHR) and 87 population controls between 18-50 years of age. FEP and CHR individuals were recruited from psychiatric services of the Hospital District of Southwest Finland. The study protocol was approved by the Ethics Committee of the Hospital District of Southwest Finland and the study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

DSM-IV Axis I diagnoses were confirmed using the Structured Clinical Interview for DSM-IV disorders (SCID-I/NP) (Supplementary Table 1 and Supplementary Table 2). Clinical high-risk status of all study subjects was assessed using the structured interview for prodromal syndromes (Miller et al., 1999). The subjects whose presence of psychotic syndrome criteria were not met were further assessed for fulfillment of criteria for either 1. brief intermittent psychotic symptom psychosis-risk syndrome, 2. attenuated psychotic symptom psychosis-risk syndrome, or 3. genetic risk and deterioration psychosis-risk syndrome as defined by the criteria for psychosis-risk syndromes in SIPS. Presence of any one of the three psychosis-risk syndromes indicated clinical high-risk group status. Population controls were excluded if they had past or present psychotic disorder or a first-degree relative with a psychotic disorder. Other psychiatric diagnoses were not excluded. Seven controls had a diagnosis of a non-psychotic axis-I DSM-IV disorder (Supplementary Table 3).

Subjects with a somatic or neurological illness possibly affecting brain structure or function, subjects with previous head injury with loss of consciousness for over five minutes, and subjects with alcohol or illicit drug dependence during the preceding 6 months were excluded. All MRI scans were examined by a neuroradiologist for coincidental findings. Then, all MRI scans and

segmentations were visually inspected for motion artifacts and tissue misclassifications in the amygdala by RLA. Three subjects were excluded due to incompatible MRI scan parameters, eight subjects due to coincidental MRI findings in clinical neuroradiological assessment (Supplementary Table 4) and one control subject was identified to be at familial high-risk for psychosis only after the scanning. Six subjects were excluded due to visible motion artifact in T1 scan and one patient due to lateral nucleus outlier volume (standard residual (SD) = 3.6 > ± 3.5 SD) and statistical influence (Cook's mean x 3 = 0.006 x 3 = 0.018; Cook's distance = 0.084 > 0.018). Visual inspection revealed failed amygdala segmentation in 14 subjects and those subjects were excluded. After exclusions, the final sample consisted of 75 first-episode psychosis patients, 45 clinical high-risk patients and 76 population controls (Table 1).

2.2. MRI Acquisition and processing

All subjects were scanned with a Philips Ingenuity TF 3-Tesla PET/MR scanner using T1-weighted (Ultrafast Gradient Echo 3D, TR = 8.1 ms, TE-time = 3.7 ms, flip angle 7°, FOV = 256 x 256 x 176 mm^3 and voxel size 1 x 1 x 1 mm^3) sequence. The T1-weighted images were inspected for motion during the scan session and sequences were repeated when excessive motion was present. Amygdala subnuclei were segmented using a recently developed and validated algorithm (Saygin et al., 2017) (https://surfer.nmr.mgh.harvard.edu/fswiki/HippocampalSubfieldsAndNucleiOfAmygdala) in FreeSurfer development version (freesurfer-Darwin-OSX-ElCapitan-dev-20180207-e9879ec181) (Figure 1 and Figure 4). The algorithm uses Bayesian modeling to segment and estimate the volumes of nine subnuclei of the amygdala. The amygdala atlas was developed by manually segmenting amygdala in post-mortem samples using high resolution 7T MRI. More details about the algorithm can be found in previous publications (Iglesias et al., 2015; Saygin et al., 2017). The algorithm was initially validated by its ability to discriminate between healthy controls and Alzheimer's patients as well as healthy controls and autistic patients (Saygin et al., 2017). It has been recently used to study personality traits (Gray et al., 2018) and panic disorder (Asami et al.,

2018). To further assess the reliability of this method, we scanned 5 healthy participants twice during the same day. The scans were separated by approximately 5 hours. Each scan was segmented with the algorithm and test-retest metrics were calculated. The segmentation algorithm showed excellent rest-retest reliability, with the variability ranging from 1.1 to 5.5 % and intraclass correlation values from 0.83 to 0.99 (Supplementary table 5).

All nine subnuclei were included into the main analyses: the lateral nucleus, basal nucleus, accessory basal nucleus, cortico-amygdaloid transition area, central nucleus, medial nucleus, cortical nucleus, paralaminar nucleus and anterior amygdaloid area. It should be noted that this segmentation separates the lateral, basal, and accessory basal nuclei, which are often combined together as the basolateral nucleus (LeDoux, 2007).

2.3 Clinical measures

Experience of childhood maltreatment was studied using the self-report Trauma and Distress Scale (TADS) (Salokangas et al., 2016). TADS divides childhood maltreatment into 5 subscales using a total of 25 items rated on a 5-point Likert scale. The total scores range from 0 to 100. The subscales are: emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect. TADS measures distressing experiences during childhood and adolescence before the end of the compulsory education (In Finland, before the age of 16). The trauma ratings have shown good internal consistency, and to be reliable and valid in the Finnish general population (Salokangas et al., 2016). The items in TADS and in the childhood trauma questionnaire (CTQ) (Bernstein et al., 2003) have a good correspondence (Salokangas et al., 2018).

Psychosis symptom severity was assessed using the Brief Psychiatric Rating Scale (BPRS) (24 items, version 4.0) in 19 CHR and 39 FEP and with the Positive and Negative Syndrome Scale (SCI-PANSS)(Opler et al., 1999) in 24 CHR and 33 FEP. The scale was changed because during

the data collection phase, this study became a part of a multisite study. This merger did not result in any other changes in recruitment, assessment or data collection. PANSS total scores were converted to 18 item BPRS total scores, and correspondingly only 18 items of the BPRS were used for total scores (Leucht et al., 2013). Duration of illness was defined by the time period from the first appearance of positive symptoms until the scanning date. Antipsychotic medication use up to the scanning date were documented and verified against medical records. Cumulative antipsychotic exposure was calculated by multiplying the CPZ by the durations of corresponding drug treatment (Leucht et al., 2014). Wechsler Adult Intelligence Scale – III vocabulary scale (WAIS) (Wechsler, 1997) was used as an estimate of intelligence quotient (Ward, 1990).

2.4 Statistical analyses

2.4.1 Demographics

Age, WAIS scores, years of education, and TADS scores were compared between FEP, CHR and population controls using pair-wise t-tests. Sex differences between the groups were compared using chi-square tests.

2.4.2 Between group differences in the amygdala subnuclei

There were no significant differences in subnuclei volumes between the left and right hemispheres nor group by hemisphere by subnuclei interactions. Consequently, the subnuclei volumes were averaged over the left and right hemispheres in all further analyses to avoid unnecessary multiple comparisons. All volumes were normally distributed (Shapiro–Wilk's test $p > 0.05$). We first tested if there were overall group differences in the whole amygdala volume using an ANCOVA while covarying for age, sex, and total intracranial volume. We then conducted the following linear mixed effects analysis to test if there was a group by subnucleus interaction: volume ~ intercept + β_1 (group) + β_2 (subnucleus)+ β_3 (group by subnucleus) + β_4 (age) + β_5 (sex) + β_6 (total intracranial volume) + random (subject) + ε. In the analysis,

subnucleus was a within subject repeated measure. The volume was the dependent variable, and the group, subnucleus, interaction between group and subnucleus, age, sex, and total intracranial volume were independent variables. The analysis also includes a random intercept for each subject to account for subject specific effects. Although our main hypothesis only concerned the lateral nucleus, all other amygdala subnuclei were also included in the main model to comprehensively examine group differences in the amygdala.

Post-hoc pairwise between-group comparisons were then performed separately for each subnucleus using estimated marginal means. This resulted in 27 comparisons (3 groups, 9 subnuclei) that were corrected for multiple comparisons using false discovery rate.

2.4.3 Effect of childhood maltreatment on lateral nucleus

We tested if TADS total score was linearly associated with subnuclei volumes. Instead of modeling the effects of TADS total scores in all groups simultaneously, we chose to test our hypothesized effect of childhood maltreatment in FEP and CHR separately. The models were fit separately for each group and limited to the subnuclei that were smaller in either FEP or CHR. We used the following linear model fitted with robust regression using MM-estimation method: volume ~ intercept + β_1 (TADS total score) + β_2 (age) + β_3 (sex) + β_4 (total intracranial volume) + ε. β's represent the regression coefficients and ε the residual error. Finally, for the sake of completeness, we also fitted these models in the control group.

2.4.4 Exploratory analyses

Firstly, we explored for possible linear associations of duration of illness, cumulative antipsychotic dose and clinical symptoms using a series of linear models in the FEP and CHR group separately. The models were fit using robust regression separately for each subnucleus and limited to the subnuclei that were smaller in either FEP or CHR to constrain the number of multiple comparisons. Secondly, we explored whether any of the amygdala subnuclei volumes

would differ between affective (n=21) and non-affective (n=54) or between smokers (n=36) and non-smokers (n=39) in FEP using a linear mixed effects model while controlling for age, sex, and total intracranial volume. Finally, we explored possible relationship between the TADS total score, clinical variables, years of education and WAIS vocabulary scores using Pearson correlation.

In all statistical analyses, p-values < 0.05 were considered statistically significant. Multiple comparisons were corrected using false discovery rate (FDR) correction at p-value < 0.05. All analyses were carried out with R version 3.5.2 (Eggshell Igloo)(R Core Team, 2017).

3. Results

3.1 Demographics

Table 1 shows that FEP, CHR and control groups did not significantly differ in term of age and sex. The age range for FEP was from 19.0 to 46.6, for CHR from 19.1 to 45.2, and for controls from 19.4 to 38.7. On average, the controls had attended school for 2 more years and had higher WAIS vocabulary scores than the FEP or CHR. FEP and CHR patients also reported more childhood maltreatment than the controls (Table 1).

3.2 Group by hemisphere differences in the amygdala

There was no asymmetry between the left and right amygdala subnuclei (hemisphere by group interaction $F_{2,3281} = 0.118$, $p = 0.8884$, and hemisphere by subnuclei by group interaction $F_{16,3281} = 0.171$, $p = 0.9999$). Therefore, for all subsequent analyses, volumes of the left and right amygdala subnuclei were averaged together.

3.3 Between group differences in the whole amygdala volume

The whole amygdala volume was different between the three groups ($F_{2,190} = 5.30$, $p = 0.0058$). Post-hoc tests revealed that the whole amygdala volume was smaller in FEP compared to controls (estimated marginal means ± standard error: 1902 ± 18.8 mm^3 versus 1988 ± 18.7 mm^3, $t_{190} = 3.239$, $p = 0.0014$), but not to CHR (estimated marginal means in CHR 1935 ± 24.3 mm^3, $t_{190} = 1.080$ $p = 0.2813$. The difference between CHR and the control group was not significant ($t_{190} = 1.713$, $p = 0.0883$).

3.4 Between group differences in the amygdala subnuclei

The linear mixed effects model including all three groups and nine subnuclei showed that there were subnucleus specific effects of groups (group by subnucleus interaction ($F_{16,1544} = 2.203$, $p =$

0.0040) while controlling for age, sex, total intracranial volume. Post-hoc pairwise comparison analysis (Table 2) revealed that the volume of the lateral nucleus was smaller in both the FEP (FDR p = 0.0001) and CHR (FDR p = 0.0006) compared to the control group. The lateral nucleus volumes did not significantly differ between the FEP and CHR (FDR p = 0.9504) (Figure 2). The basal nucleus was smaller in the FEP (FDR p = 0.0008) compared to the control group, but not in the CHR (FDR p = 0.5750) compared to the control group (Figure 2). The basal nucleus was also smaller in the FEP compared to the CHR group but this difference was not statistically significant after correcting for multiple comparisons (FDR p = 0.1718). The accessory basal nucleus, and cortico-amygdaloid transition area were non-significantly smaller in the FEP compared to the control group.

3.5 Effect of childhood maltreatment on lateral and basal nuclei

In the FEP group, we found a significant inverse association between the TADS total score and both lateral nucleus (β = -1.45, t_{62} = -2.852, p = 0.0059) and basal nucleus volume (β = -0.86, t_{62} = -2.350, p = 0.0220), while controlling for age, sex, and intracranial volume (Figure3). In contrast, there were no associations between the TADS total score and lateral (β = 0.36, t_{34} = 0.478, p = 0.6354) or basal nucleus (β = 0.16, t_{34} = 0.277, p = 0.7840) volumes in the CHR group. Similarly, the TADS total score was not associated with lateral (β = -0.67, t_{65} = -0.732, p = 0.4670, or basal nucleus (β = -0.59, t_{65} = -0.960, p = 0.3405) volumes in the control group. After FDR correction for 6 comparisons, only the association between the TADS total scores and lateral nucleus (FDR corrected p = 0.0354) in the FEP remained significant.

3.6 Exploratory analyses

Positive, negative or total symptom scores, cumulative antipsychotic exposure, or duration of illness, were not associated with lateral or basal nucleus volumes in FEP or CHR (Supplementary Table 6). The amygdala subnuclei volumes did not differ statistically significantly between affective and non-affective FEP (group by subnuclei interaction $F_{8,584}$ =

0.202, p = 0.9906, main effect of group $F_{1,70}$ = 2.517, p = 0.1171) or between smokers and non-smokers in the FEP (smoking by subnucleus interaction $F_{8,584}$ = 0.6196, p = 0.7617, main effect $F_{1,70}$ = 0.0135, p = 0.9079). Total TADS score did not correlate with duration of illness, antipsychotic use, clinical symptoms, WAIS vocabulary scores, or years of education (Supplementary Table 7).

4. Discussion

In the present study, we found subnucleus-specific volume reductions in FEP and CHR. In FEP both the lateral and basal nucleus were smaller compared to the control group, whereas in the CHR the volume deficit was limited to the lateral nucleus. Lateral nucleus volumes were on average equally decreased in the FEP and CHR. Decreased lateral nucleus volume in FEP is in agreement with prior evidence from post-mortem studies (Berretta et al., 2007; Kreczmanski et al., 2007; Williams et al., 2013; Williams et al., 2016) showing reduction in the lateral nucleus in schizophrenia patients. Our findings in CHR further suggest that a smaller lateral nucleus may be a biomarker for psychosis risk. The volumetric differences in the basal nucleus in FEP but not in CHR could be interpreted as a progressive morphology change in the amygdala during the conversion from clinical high-risk to psychosis. Alternatively, the basal nucleus may be smaller already prior to conversion, but is masked in this sample by the fact that only about a third of the CHR later convert to psychosis and thus represent true prodromal phase. Because of the cross-sectional nature of this study, we cannot differentiate between these two competing interpretations, and future studies using a longitudinal design are needed.

We also observed that childhood maltreatment was associated with smaller lateral nucleus volumes in the FEP patients. Finding from prior human studies on the effects of childhood maltreatment on the amygdala volume are mixed (Edmiston et al., 2011; Hanson et al., 2015; Mehta et al., 2009; Tottenham et al., 2010). In the light of these contradicting results, the negative finding in healthy controls is not surprising. Moreover, the control subjects reported much less childhood maltreatment compared to the FEP and CHR. In general, prior studies have observed negative association between severity of childhood maltreatment and total amygdala volumes in individuals with mental illness (Kuo et al., 2012; Morey et al., 2016) including schizophrenia (Aas et al., 2012). The current finding suggests further that the lateral nucleus may

be especially sensitive for deleterious effects of early life stress. Although the FEP and CHR groups had equally reduced lateral nucleus volumes and reported similar levels of exposure to early life stressors, there was no relationship between childhood maltreatment and amygdala subnuclei volumes in the CHR group. This finding is in contrast with an earlier study showing that individuals at high familial risk for schizophrenia, who have been exposed to childhood adversity, have smaller total amygdala volume compared to high familial risk individuals without childhood adversity (Barker et al., 2016). Reasons for the discrepancy are unknown, but differences in study population (clinical high-risk vs. familial high-risk), measure and severity of childhood maltreatment, and imaging methodologies may have contributed to the differing findings. In this study, we also had a fewer CHR compared to the FEP. Hence, more studies are needed to better understand the association of childhood maltreatment with the amygdala subnuclei volumes in CHR populations.

Exploratory analyses did not reveal associations between antipsychotic use, duration of illness or positive, negative or general symptom severity and the lateral or basal nucleus volumes. Interestingly, we observed that off-label use of antipsychotics was high in CHR. The amygdala contributes to many emotional and cognitive processes, such as memory formation, salience attribution and social cognition (Adolphs, 2010; LeDoux, 2007; Roozendaal et al., 2009). Accordingly, associations between smaller total amygdala volumes in schizophrenia and severity of general symptoms (Watson et al., 2012), lower face recognition ability (Namiki et al., 2007), and better verbal memory (Killgore et al., 2009) have been previously reported. However, to the best of our knowledge, none of these associations have been replicated in another sample, and several other studies have found no association of amygdala volume to any symptoms measure (Joyal et al., 2003; Rich et al., 2016; Wang et al., 2008; Witthaus et al., 2009). It is difficult to know exactly what functional and behavioral consequences these amygdala abnormalities have in FEP, because we did not find any correlations with symptoms.

Several other lines of investigation position the lateral and basal nuclei as putative key regions in the biological etiology of psychosis. The lateral nucleus is involved in reward processing, for instance lesion to lateral nucleus impairs amphetamine and cocaine produced place preference (Hiroi and White, 1991; Hsiang et al., 2014). The lateral nucleus is considered the main sensory input region to the amygdala (LeDoux, 2007), although many other regions also receive sensory afferents (Sah et al., 2003). Information about conditioned and unconditioned stimuli converge in the lateral nucleus and the conditioned signal is strengthened thorough Hebbian plasticity (Janak and Tye, 2015). The lateral nucleus is therefore a critical site for fear conditioning and fear extinction processes (Duvarci and Pare, 2014; Pape and Pare, 2010). Because the lateral nucleus participates in valuation of both negative and positive outcomes, it is considered broadly to be an important region for valence attribution (Janak and Tye, 2015). Within the amygdala, the information flows from the lateral to the basal nucleus, which further relays it to the hippocampus, nucleus accumbens, prefrontal cortex and other amygdala subnuclei (Roozendaal et al., 2009). The basal nucleus projections to the nucleus accumbens appear to be important for motivated behaviours, such as conditioned avoidance (Choi et al., 2010; Ramirez et al., 2015). More generally, distinct neuronal populations in the basal nucleus encode either a state of exploratory or defensive behavior (Gründemann et al., 2019). In animal models of schizophrenia, impaired fear extinction is related to abnormalities in connectivity between the basolateral nucleus and medial prefrontal cortex (Uliana et al., 2018). Human research has shown that fear extinction is impaired in patients with schizophrenia and this impairment is related to abnormal medial prefrontal cortex activation (Holt et al., 2012; Holt et al., 2009). The basal nucleus has the strongest reciprocal connections with the medial prefrontal cortex (Carmichael and Price, 1995; LeDoux, 2007). We found that the basal nucleus is diminished in size in FEP but not in CHR. Pertaining to these findings here, it is interesting that the functional connectivity between the amygdala and prefrontal cortex is reduced in early and chronic schizophrenia, but not in individuals at high-risk (Anticevic et al., 2013). Disruption of this connection has been shown to affect assessment of emotional stimuli (Mukherjee et al., 2016) in schizophrenia patients. Future

studies should test whether diminished basal nucleus volume associates with decreased connectivity between the amygdala and the prefrontal cortex.

4.1 Limitations

The current study has several limitations. Firstly, parsing the amygdala based on MR images is difficult. There are currently no optimized MRI sequences for the amygdala segmentation and there have been several attempts to develop a segmentation algorithm for the amygdala. However, to our knowledge, the segmentation applied here is the first one that has been developed using an ex vivo sample (Saygin et al., 2017). Secondly, this is a cross-sectional study. Because only about a third of CHR patients develop psychosis (Fusar-Poli et al., 2012), the CHR group is inevitably heterogeneous. We were unable to test here if those who developed psychosis later had more widespread or severe volumetric reductions compared to those who did not. Thirdly, childhood maltreatment was documented retrospectively using a questionnaire, which may have led to lower rates of reported maltreatment (Goodman et al., 2003). Based on the TADS scores, the control group experienced very little childhood maltreatment making it difficult to investigate the interaction of childhood maltreatment and psychosis in the sample. Further, there are many confounds associated with developmental trauma including drug use, socio-economic deprivation and other factors related to the sequelae of trauma that our cross-sectional retrospective approach may have missed. We did not, for instance, specifically assess post-traumatic symptoms. Moreover, the TADS questionnaire does not differentiate the age at which maltreatment took place, which may be particularly important for amygdala function (Zhu et al., 2019). In future studies, the nonlinear development of the amygdala volume (Wierenga et al., 2014) and stress sensitive neurodevelopmental periods (Croft et al., 2018; Ogle et al., 2013) should be taken into account. Finally, the agreement between retrospectively reported and prospectively measured childhood maltreatment may be low (Baldwin et al., 2019).

4.2 Conclusions

In summary, the volume of the lateral nucleus of amygdala is affected in CHR and in FEP. In the early course of the psychotic illness we also observed a volumetric reduction of the basal nucleus. Finally, we show that among FEP patients, greater childhood maltreatment experience was associated with smaller lateral nucleus of amygdala supporting a role of environmental stressors in altered morphology during the development of psychosis.

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Contributions

R-L A., L.T. and H.L. had full access to all off the data, including imaging data. J.H. and R.K.R.S. took the responsibility for the integrity of the data and accuracy of the clinical data material and study protocols. J.H., R.K.R.S., and N.K. designed the study. R-L A. and L.T. took the responsibility of the accuracy of the imaging data, data analyses and statistical analyses. R-L A. and L.T. drafted the first version of the manuscript. R-L A. did most of the MRI scannings of the subjects, all of the data analyses, statistical analyses and the quality control of the data. L.T., H.L. and E.S. scanned some of the subjects. All authors critically revised the manuscript for important intellectual content. All authors approved the final version for publication.

Conflict of interest

None.

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Figure legends

Figure 1. Segmentation of the amygdala shown on a MNI152 template in **A)** axial, **B)** coronal, and **C)** sagittal orientations. **D)** A surface rendering of the subnuclei of the right amygdala viewed from the front (anterior view, left) and from the back (posterior view, right). Only 5 subnuclei are shown here for clarity. Surface rendering is based on a segmentation of the MNI152 template and is used for illustration only.

Figure 2. A) shows the lateral nucleus volumes and **B)** shows the basal nucleus volumes in control group (CTR), clinical high-risk (CHR) patients, and first-episode psychosis (FEP) patients. The volumes are adjusted for age, sex, and total intracranial volume. P-values are from an analysis of estimated marginal means and have been corrected for false discovery rate (FDR). Horizontal lines show the group mean and vertical line standard deviation.

Figure 3. Association between childhood maltreatment, **A)** the lateral nucleus volume (β = -1.45, t_{62} = -2.852, p = 0.0059) and **B)** the basal nucleus volume (β = -0.86, t_{62} = -2.350, p = 0.0220) in first-episode psychosis (FEP). The volumes are adjusted for age, sex and total intracranial volume. The line represents a robust fit between the adjusted volumes and TADS total score. Gray area shows 95 % confidence intervals.

Tables

Table 1. Demographic Characteristics of the Participants. Mean ± SD (n)

	FEP	CHR	Controls	FEP vs CTR[b]	CHR vs CTR[b]
Age, y	26.8 ± 6.0 (75)	25.8 ± 6.1 (45)	27.1 ± 4.9 (76)	0.678	0.182
Sex	34F / 41M (75)	20F / 25M (45)	43F / 33M (76)	0.167	0.197
Years of education	12.5 ± 2.0 (75)	12.1 ± 2.0 (45)	14.3 ± 1.7 (76)	< 0.001	< 0.001
WAIS Vocabulary standardized score (range 1–19)	9.9 ± 2.9 (70)	9.8 ± 2.4 (41)	11.6 ± 2.0 (74)	< 0.001	< 0.001
TADS Total score (range 0–100)	18.9 ± 13.4 (67)	18.6 ± 11.9 (39)	7.5 ± 7.9 (69)	< 0.001	0.005
TADS Emotional abuse (range 0–20)	5.6 ± 4.5 (67)	5.4 ± 4.4 (39)	1.8 ± 2.9 (69)	< 0.001	0.006
TADS Physical abuse (range 0–20)	2.0 ± 2.0 (67)	1.9 ± 2.6 (39)	0.7 ± 1.6 (69)	0.001	0.001
TADS Sexual abuse (range 0–20)	1.3 ± 2.9 (67)	0.5 ± 1.4 (39)	0.1 ± 0.3 (69)	< 0.001	< 0.001
TADS Emotional neglect (range 0–20)	6.6 ± 5.0 (67)	7.5 ± 4.4 (39)	3.0 ± 3.4 (69)	0.001	0.030
TADS Physical neglect (range 0–20)	3.4 ± 3.0 (67)	3.2 ± 3.2 (39)	1.9 ± 2.2 (69)	0.002	0.053
Duration of illness, years [a]	1.4 ± 2.7 (75)	-	-	-	-
Cumulative antipsychotic exposure[+]	21,857 ± 25,921 (75)	7613 ± 19,618 (45)	0	-	-
BPRS positive symptoms score (range 8–56)	16.7 ± 6.3 (72)	13.0 ± 3.8 (43)	-	-	-
BPRS negative symptoms score (range 5–35)	9.2 ± 3.7 (72)	9.2 ± 3.5 (43)	-	-	-
BPRS total symptoms score (range 18–126)	37.5 ± 12.2 (72)	35.8 ± 10.4 (43)	-	-	-
Estimated total intracranial volume (cm^3)	1466.0 ± 237.0 (75)	1451.0 ± 227.5 (45)	1448.3 ± 236.2 (76)	0.654	0.953

[+] Cumulative antipsychotic drug exposure up to the MR scanning day (in CPZ mg, based on CPZ equivalent conversion). [a] Time since appearance of positive symptoms [b] p-value of a chi square test (sex), or t-test (all other variables).

Table 2 shows results from post-hoc pairwise between-group comparison analysis including age, sex, and total intracranial volume as covariates.

Amygdala subnucleus	Contrast	Estimated difference (mm^3)	DF	t-ratio	p	FDR corrected p
Lateral nucleus	CTR - CHR	25.52	190	4.20	0.00004	0.0006
Lateral nucleus	CTR - FEP	24.84	190	4.73	<0.00001	0.0001
Lateral nucleus	CHR - FEP	-0.68	190	-0.11	0.91120	0.9504
Basal nucleus	CTR - CHR	8.36	190	1.38	0.17036	0.5750
Basal nucleus	CTR - FEP	21.03	190	4.01	0.00009	0.0008
Basal nucleus	CHR - FEP	12.67	190	2.09	0.03818	0.1718
AB	CTR - CHR	5.65	190	0.93	0.35376	0.8683
AB	CTR - FEP	11.88	190	2.26	0.02470	0.1334
AB	CHR - FEP	6.23	190	1.03	0.30607	0.8683
Central nucleus	CTR - CHR	2.36	190	0.39	0.69801	0.9504
Central nucleus	CTR - FEP	2.74	190	0.52	0.60228	0.9504
Central nucleus	CHR - FEP	0.38	190	0.06	0.95042	0.9504
CA	CTR - CHR	3.34	190	0.55	0.58338	0.9504
CA	CTR - FEP	12.15	190	2.32	0.02158	0.1334
CA	CHR - FEP	8.82	190	1.45	0.14813	0.5714
Medial nucleus	CTR - CHR	1.74	190	0.29	0.77480	0.9504
Medial nucleus	CTR - FEP	2.18	190	0.42	0.67851	0.9504
Medial nucleus	CHR - FEP	0.44	190	0.07	0.94263	0.9504
Cortical nucleus	CTR - CHR	1.66	190	0.27	0.78452	0.9504
Cortical nucleus	CTR - FEP	2.21	190	0.42	0.67352	0.9504
Cortical nucleus	CHR - FEP	0.55	190	0.09	0.92785	0.9504
AAA	CTR - CHR	2.97	190	0.49	0.62580	0.9504
AAA	CTR - FEP	5.14	190	0.98	0.32834	0.8683
AAA	CHR - FEP	2.17	190	0.36	0.72068	0.9504
PL	CTR - CHR	1.31	190	0.22	0.82981	0.9504
PL	CTR - FEP	3.87	190	0.74	0.46166	0.9504
PL	CHR - FEP	2.56	190	0.42	0.67351	0.9504

AB = Accessory basal nucleus, CA = Cortico-amygdaloid transition area, AAA = Anterior amygdaloid area. PL=Paralaminar nucleus, DF = degrees of freedom, FDR = false discovery rate.

Figures

Figure 1.

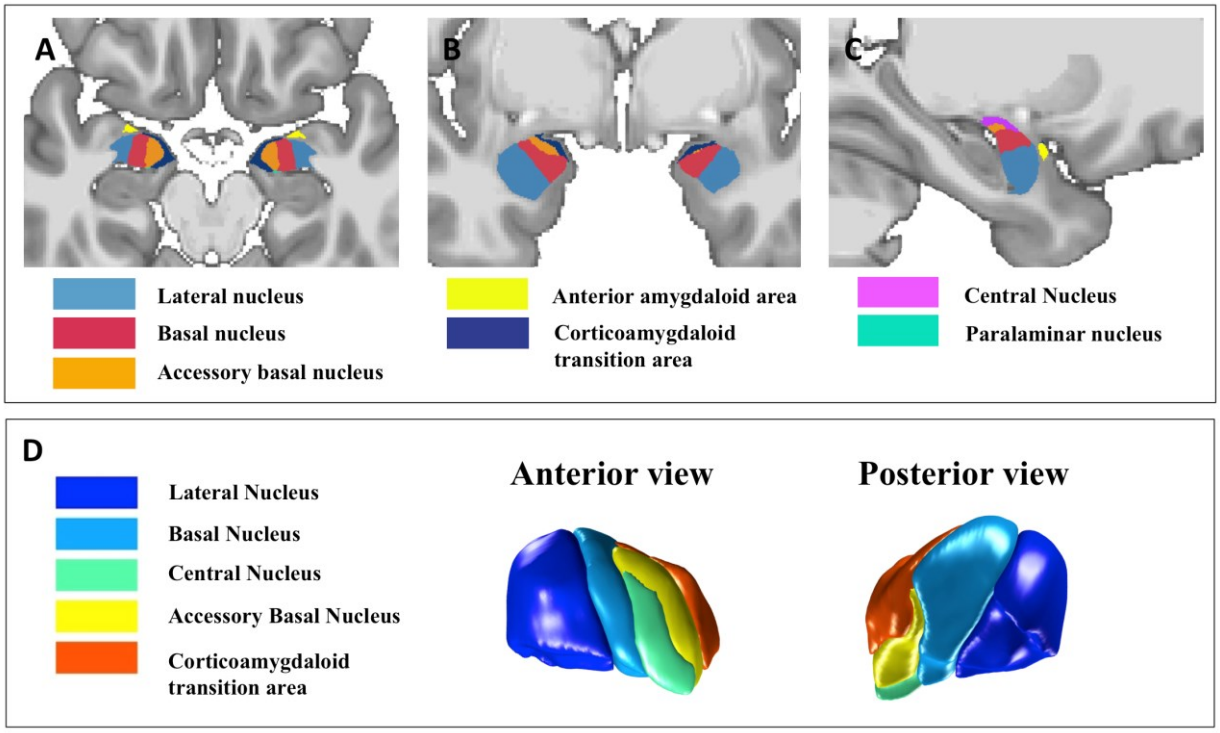

Figure 2.

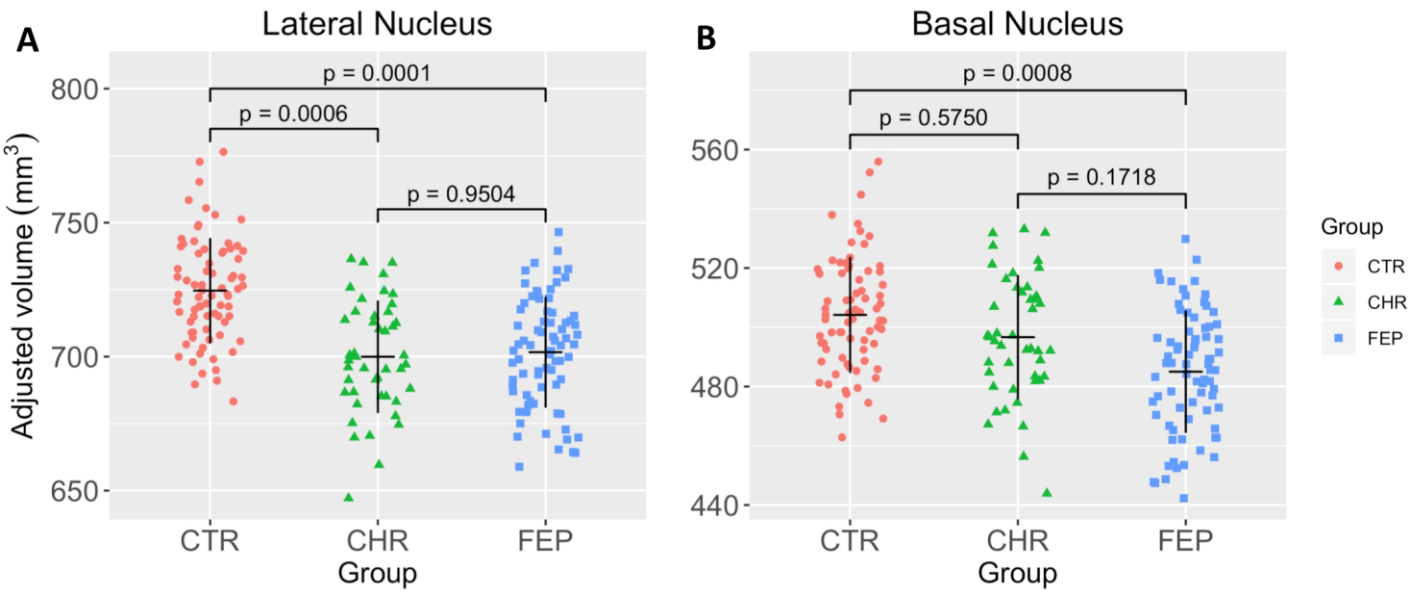

Figure 3.