Psychiatry Research: Neuroimaging 286 (2019) 69–75

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Subcortical structures and cognitive dysfunction in first episode schizophrenia

Fengmei Fan[a,b,1], Hong Xiang[c,1], Shuping Tan[a], Fude Yang[a], Hongzhen Fan[a], Hua Guo[d], Peter Kochunov[e], Zhiren Wang[a], L. Elliot Hong[e], Yunlong Tan[a,*]

[a] Beijing Huilongguan Hospital, Peking University Huilongguan Clinical Medical School, Beijing 100096, China
[b] State Key Laboratory of Cognitive Neuroscience and Learning & International Data Group/McGovern Institute for Brain Research, Center for Collaboration and Innovation in Brain and Learning Sciences, Beijing Normal University, Beijing 100875, China
[c] Chongqing Three Gorges Central Hospital, Chongqing 404000, China
[d] Zhumadian Psychiatry Hospital, Henan Province, China
[e] Maryland Psychiatric Research Center, Department of Psychiatry, University of Maryland School of Medicine, Baltimore, USA

ARTICLE INFO

Keywords:
Schizophrenia
First episode
Brain
Cognitive
Subcortical

ABSTRACT

Schizophrenia is associated with widespread cortical and subcortical abnormalities. Studies examining cognitive deficits in schizophrenia have historically focused on cortical deficits; however, many subcortical areas also support cognition. We sought to determine whether deficits in subcortical gray matter are linked to neurocognitive dysfunction in patients with first-episode schizophrenia. This study included 170 patients with first-episode schizophrenia and 88 healthy controls. Clinical symptoms, neurocognitive function, and structural images were assessed. Subcortical volumes were recorded. Patients had significant deficits in all cognitive domains, including processing speed, attention, memory, executive function and social cognition. Patients also demonstrated significantly smaller volumes in the amygdala, hippocampus, thalamus, and total cortical gray matter than did controls after Bonferroni correction for multiple comparisons. Reasoning/problem solving was significantly and positively correlated with the volume of the amygdala and nucleus accumbens in patients. Positive symptoms of psychosis were positively correlated with the volume of the amygdala and nucleus accumbens. In addition, the dose of antipsychotic medication was positively correlated with the volume of the amygdala, nucleus accumbens, caudate, putamen, and pallidum. In conclusion, schizophrenia is associated with profound cognitive deficits. Our findings suggest that subcortical structures contribute to specific domains of cognitive dysfunction in first-episode schizophrenia.

1. Introduction

Cognitive deficits in schizophrenia are a major contributor to poor functional outcomes (Arguello and Gogos, 2010; Fioravanti et al., 2012) and are an important clinical target for effective treatment development (Stip, 2006). Schizophrenia is linked to widespread deficits across multiple cognitive domains. In previous studies, cognitive deficits in schizophrenia were studied in the context of cortical abnormalities (Barch et al., 2003; Deserno et al., 2012; Jardri et al., 2011; Tan et al., 2005). Interestingly, a recent study by ENIGMA demonstrated widespread deficits in subcortical volumes in link with the genetic risk of schizophrenia (van Erp et al., 2016). Subcortical deficits, either directly or in conjunction with cortical areas, may underlie cognitive impairments in normal subjects and those with other disorders (Dowd and Barch, 2010; Juuhl-Langseth et al., 2015; Nielsen et al., 2012; Pinkham et al., 2011; Schlagenhauf et al., 2014). For instance, emotion-cognition regulation is associated with the amygdala (Janak and Tye, 2015; Quarto et al., 2018; Sah, 2017), impaired memory performance in schizophrenia is associated with the striatum and thalamus (Anticevic et al., 2011), and poor executive function in schizophrenia is in part attributed to dysfunction in the thalamus (Minzenberg et al., 2009). In the largest study of subcortical structures in schizophrenia patients, brain MRI scans showed smaller subcortical brain volumes in the hippocampus, amygdala, thalamus, accumbens, and intracranial volumes, as well as larger pallidum and lateral ventricle volumes in 2028 schizophrenia patients than in 2540 healthy controls (van Erp et al., 2016). Koshiyama et al. (2018) examined correlates between subcortical structures and cognitive and social function in

* Corresponding author.
E-mail addresses: fanfengmei@live.com (F. Fan), yltan21@126.com (Y. Tan).
[1] Contribute equally to this work.

https://doi.org/10.1016/j.pscychresns.2019.01.003
Received 9 October 2018; Received in revised form 9 January 2019; Accepted 11 January 2019
Available online 12 January 2019
0925-4927/

schizophrenic patients with a mean illness of 11 years; these results may be affected by medication and the duration of illness. We pursued the present study to determine whether subcortical structural deficits contribute to cognitive impairments in first-episode schizophrenia.

Linking subcortical and neurocognitive deficits in schizophrenia is challenging as subcortical structures are prone to changes in response to the dose and duration of treatment with antipsychotic medication (Belujon et al., 2014; Hartberg et al., 2011; Jorgensen et al., 2016; Rich et al., 2016) and the effects of chronic disease (Hartberg et al., 2011; Huhtaniska et al., 2017). For example, antipsychotic medication doses were associated with volumetric changes in subcortical structures in the Northern Finland Birth Cohort 1966 study (Huhtaniska et al., 2017). Animal studies have also shown that D2-receptor-blocking antipsychotic drugs may affect hippocampal-accumbens synaptic plasticity (Belujon et al., 2014). Such effects of antipsychotic medication, likely along with the chronic course of the illness, may confound the relationship between the subcortical brain structure and cognition. Testing in antipsychotic-naïve patients is an alternative approach although cognitive testing outcomes may be biased by the unstable psychotic state. We evaluated our hypothesis in first-episode patients with schizophrenia. The patients were without previous chronic antipsychotic medication exposure, and were recruited immediately after stabilization of psychosis symptoms after a sufficient but minimal duration of antipsychotic medications. We tested the full spectrum of cognitive domains and evaluated subcortical volumes measured by structural MRI within 2 weeks of the first hospitalization or first outpatient treatment in a large group of patients with schizophrenia.

2. Materials and methods

2.1. Participants

This study included a total of 170 patients with first-episode schizophrenia (88 males, 82 females, mean ± standard deviation [s.d.] age 24.6 ± 5.5 years, ranging from 15.5 to 43.8 years) and 88 healthy controls (38 males, 50 females, mean ± s.d. age 28.3 ± 6.7 years, ranging from 16.3 to 40.0 years). This study was conducted at two clinical sites both equipped with a 3 Tesla scanner and both sites followed the same recruitment criteria. Dataset 1 included ninety-five patients with first-episode schizophrenia (mean ± s.d. age 24.7 ± 6.1 years) and forty-nine healthy controls (mean ± s.d. age 25.4 ± 5.4 years) that were recruited from Chongqing Three Gorges Central Hospital in Chongqing, China. Dataset 2 included seventy-five patients with first-episode schizophrenia (mean ± s.d. age 24.4 ± 4.7 years) and thirty-nine healthy controls (mean ± s.d. age 31.9 ± 6.5 years) that were recruited from Zhumadian Psychiatry Hospital in Henan province, China. Typically, all patients had only initial visits to seek psychiatric care following the onset of psychosis and were immediately prescribed antipsychotic medication for symptom stabilization through inpatient or outpatient treatment at these two hospitals.

The inclusion criteria were as follows: (1) schizophrenia diagnosis according to DSM-IV (American Psychiatric Association, 1994) diagnostic criteria, (2) first outpatient treatment or less than 2 weeks since first hospitalization, (3) at least 6 years of education, (4) right-handed as confirmed by the short version of the Edinburgh Handedness Scale, and (5) male and female patients aged 16 years and above. Exclusion criteria included the following: (1) a history of head trauma, (2) concurrent or previous substance dependence or alcoholism besides smoking, (3) gross brain organic disease confirmed by T2 MRI, (4) Symptoms of significant involuntary movement, and (5) learning disability or mental retardation. Demographic data are provided in Table 1 (further details of the demographics for the two sites are in Table S1). All participants provided written informed consent and this study was approved by the Ethics Committee of the Beijing Huilongguan Hospital in Beijing, China, which was the coordinating site of the study.

2.2. Clinical procedures

Regardless of whether participants were treated on an inpatient or outpatient basis, they began antipsychotic medication treatment without delay. If patients met the above inclusion criteria, and the treating physician considered the patient to be stable enough to participate in a research MRI scan, patients were asked if they would participate in this study. After providing written informed consent, a case report form was completed, including demographic information, clinical symptoms, and cognitive function (details in the following paragraph). An MRI scan was then scheduled. All patients completed the MRI within 2 weeks of initiation of antipsychotic medication treatment. All patients were receiving atypical antipsychotics at the time of the scan: 41 patients were taking clozapine (commonly prescribed as the first choice in China), 55 were taking risperidone, 54 were taking olanzapine, 32 were taking quetiapine, 28 were taking aripiprazole, 10 were taking ziprasidone, 2 were taking paliperidone, 4 were taking perospirone, 3 were taking sulpiride and 1 was taking amisulpride. Some patients were taking two of the above antipsychotic medications. Three patients were also taking a typical antipsychotic drug, haloperidol. Two patients were taking antidepressants, one with paroxetine, and the other with mirtazapine. One patient also took alprazolam, an anxiolytic. In addition, 12 patients were receiving anticholinergic drug for side effects. And patients with clinically significant involuntary movements were excluded to reduce movement-induced artifacts in the scanner. The chlorpromazine-equivalent (CPZ) (Woods, 2003) was calculated for each patient.

2.3. Neurocognition and psychopathology assessment

Cognitive function was measured using the MATRICS Consensus Cognitive Battery (MCCB), validated Chinese versions (Kern et al., 2008; Nuechterlein et al., 2008; Zou et al., 2009). The MCCB includes seven cognitive domains: (1) processing speed: Trail Making Test, part A; Symbol Coding Subtest; Category Fluency Test, (2) attention and vigilance: Continuous Performance Test—Identical Pairs, (3) working memory: Wechsler Memory Scale, spatial span and digit sequencing test, (4) verbal learning: Hopkins Verbal Learning Test—Revised, (5) visual learning: Brief Visuos-patial Memory Test— Revised, (6) reasoning and problem solving: Neuropsychological Assessment Battery, mazes subtest, and (7) social cognition: Mayer-Salovey-Caruso Emotional Intelligence Test, managing emotions subtest. The MCCB required 1 to 1.5 hours for each subject. Raw scores were converted to Chinese-normalized T-scores (Kern et al., 2008; Nuechterlein et al., 2008; Zou et al., 2009). Seven domain T-scores and a composite T-score were computed. The clinical symptom assessment (Positive and Negative Syndrome Scale (PANSS)) was conducted by an attending psychiatrist from each site, who were trained to be reliable with intraclass correlation coefficient (ICC) above 0.80 before the trial.

2.4. MRI protocol

The MRI of dataset 1 was acquired using a Siemens 3T MRI scanner. Head motions were minimized by foam pads. The parameters for structural MRI were acquired by covering the whole brain with sagittal 3D-magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence: echo time (TE) = 2.98 ms, inversion time (TI) = 900 ms, repetition time (TR) = 2300 ms, flip angle (FA) = 9º, field of view (FOV) = 240 mm × 256 mm, matrix size = 256 × 240, thickness/gap = 1/0 mm. The MRI of dataset 2 was acquired using a GE 3T MRI scanner. T1-weighted images were acquired by covering the whole brain with sagittal 3D-MPRAGE sequence: echo time (TE) = 2.488 ms, inversion time (TI) =1100 ms, repetition time (TR) =6.77 ms, flip angle (FA) = 7º, field of view (FOV) = 256 mm × 256 mm, matrix size = 256 × 256, thickness/gap = 1/0 mm. Besides MPRAGE, participants also completed diffusion tensor imaging and those data were

Table 1
Demographics of participants.

Demographic information	Patient (n = 170)	Control (n = 88)	$\chi 2/t$	P
Gender M/F)	88/82	38/50	1.71	0.19
Age (year)	24.56 ± 5.49	28.26 ± 6.71	4.74	3.53×10^{-06}
Education (year)	9.91 ± 2.61	11.94 ± 3.63	5.19	4.90×10^{-07}
Illness duration (year)	0.99 ± 1.09			
Onset age (years)	23.65 ± 5.55			
Duration of untreated psychosis (year)	0.68 ± 1.04			
Symptoms				
PANSS positive	21.54 ± 6.66	-		
PANSS negative	18.10 ± 7.11	-		
PANSS general psychosis	38.22 ± 8.52	-		
PANSS total	77.86 ± 17.79	-		
Dose of antipsychotic medication (chlorpromazine- equivalent mg/day)	466.36 ± 315.56	-		

published as part of the ENIGMA consortium (Kelly et al., 2018). None of the subcortical structure data had been previously published.

2.5. Structural MRI data analysis

Subcortical volumes were obtained using FreeSurfer (Fischl, 2012; Fischl et al., 2002) (http://surfer.nmr.mgh.harvard.edu), including volumes of the left and right lateral ventricle, thalamus, caudate, putamen, pallidum, nucleus accumbens, hippocampus, and amygdala, as well as the total cortical gray matter volume and intracranial volume (ICV). The left and right lateral ventricle, thalamus, caudate, putamen, pallidum, accumbens, hippocampus, and amygdala were summed. These eight primary subcortical areas and the total cortical gray matter volume were the nine primary volumes of interest. The ICV was used as a covariate in all analyses to account for differences in head size. For quality control, we followed the ENIGMA pipeline (http://enigma.ini.usc.edu/): all regions of interest (ROIs) with a volume >1.5 or <1.5 times the interquartile range were identified and visually inspected by overlaying their segmentations on the subjects' anatomical images. Only ROI data for which segmentation was judged to be accurate upon visual inspection were subjected to statistical analyses.

2.6. Statistical analyses

We identified cognitive domains and subcortical structures that were significantly different between patients and controls, followed by correlation analyses of these measures. Each step was corrected for multiple comparisons. Specifically, group differences for each ROI were examined using univariate linear regression analysis, where each volume was the dependent variable and the diagnosis (patient, control), sex, age, education, ICV, and site were predictors, using a P value threshold of 0.0056 (i.e., 0.05/9) for Bonferroni correction for multiple comparisons. All cognitive variables were assessed for normal distribution using the Shapiro-Wilk test. Group differences for cognitive domains were examined using linear regression analysis including age, education, sex, and site as covariates with a P value threshold of 0.007 (i.e., 0.05/7). For brain structures and cognitive measures that both showed significant group differences, a partial correlation analysis was conducted in each group to examine their relationship after adjustment for age, sex, education, ICV, and site (the dose of antipsychotic medication in the patient group was also considered). In addition, we explored the correlation of all subcortical brain structures and all cognitive measures using the Bonferroni correction for multiple comparisons (7 cognitive parameters × 9 regions × 2 groups =126, $P < 0.05/126 = 0.0004$). We performed a correlation analysis between clinical symptoms and subcortical brain structures. In the correlation analysis, antipsychotic medication was included as a covariate.

3. Results

3.1. Demographic and clinical characteristics

The demographic and clinical characteristics of the participants are shown in Table 1. The age and education significantly differed among the groups. Age and education were used as covariates in all analyses. The age of onset for patients was 23.6 ± 5.6 (mean ± s.d.) years. The duration of untreated psychosis (DUP) was 0.68 ± 1.0 (mean ± s.d.) years, which is defined as the duration from onset of psychosis to first antipsychotic medication administration.

3.2. Cognitive functions

Compared to controls, all seven domains of cognitive function were significantly lower in patients with schizophrenia (all corrected $P < 0.05$, Fig. 1), in a covariance analysis adjustment for age, sex, education, and site. The DUP was inversely correlated with processing speed ($r = -0.18$, $P = 0.02$, Figure S1). The age of onset was inversely correlated with the total MCCB score ($r = -0.25$, $P = 0.002$) and verbal learning ($r = -0.25$, $P = 0.001$) and visual learning domains ($r = -0.25$, $P = 0.000006$, Figure S1). No significant correlation was found between cognition measures and PANSS or dose of antipsychotic medication.

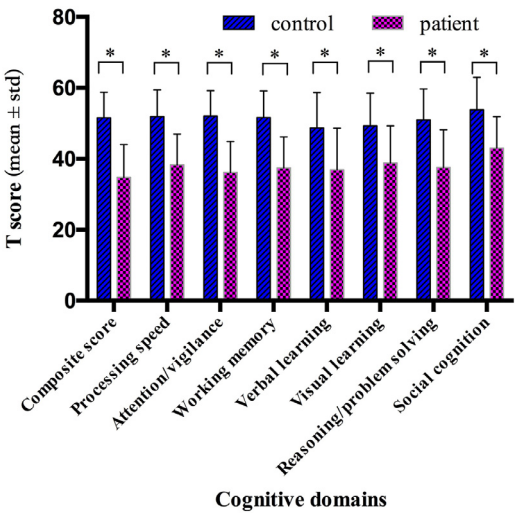

Fig. 1. Comparison of cognitive function between schizophrenic patients and normal controls. * represents Bonfferoni corrected $P < 0.05/7 = 0.007$.

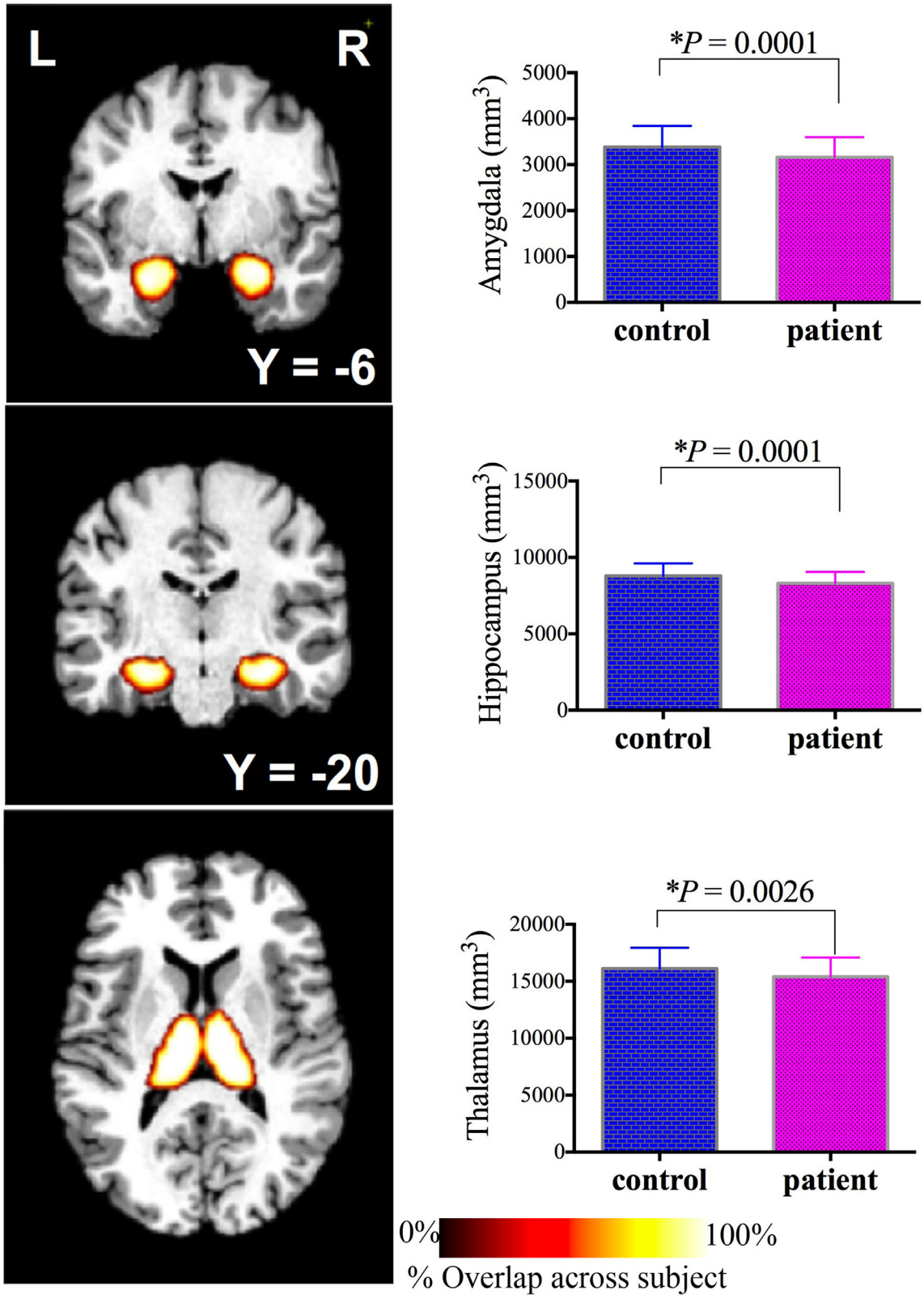

Fig. 2. Mean volumes of subcortical structures (mm^3).

3.3. Subcortical structure volumes

Patients showed significantly smaller brain region volumes in the amygdala, hippocampus, thalamus, and total cortical gray volume compared to controls (all P values <0.0056, Fig. 2), with age, sex, education, and site as covariates. Analyses of left and right hemisphere volumes separately showed similar findings and, therefore, left and right structures were averaged (Table S2).

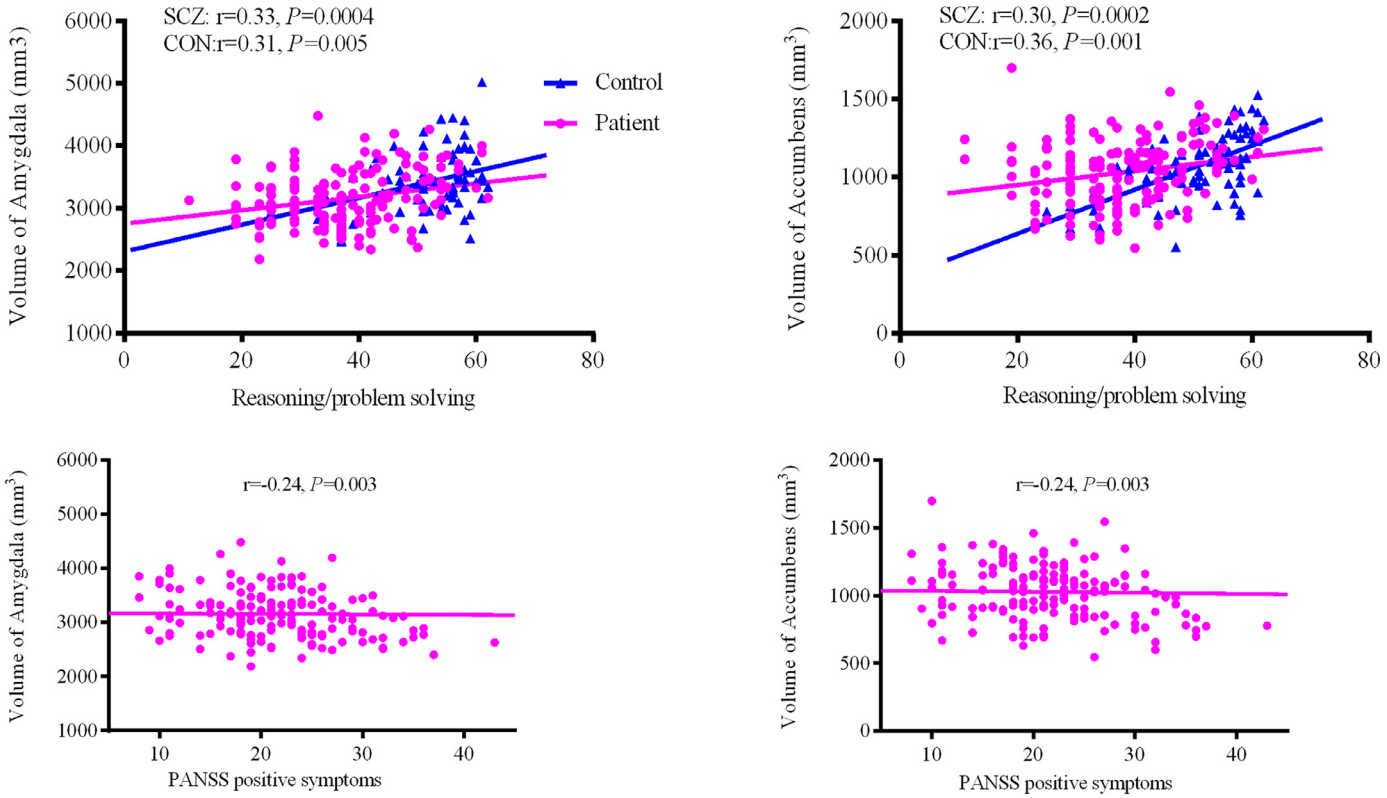

Fig. 3. Clinical and cognitive correlates with subcortical structure volumes.

3.4. Relationship between subcortical volumes and cognition

Between brain regions with significant patient-control differences, i.e., the amygdala, hippocampus, thalamus, total cortical gray matter volume, and the seven cognitive parameters, only the reasoning/problem solving function was significantly correlated with the volume of the amygdala in patients ($r = 0.33$, $P = 0.0004$) after Bonferroni correction for multiple comparisons ($P < 0.05/4$ regions $\times$ 7 cognitive domains = 0.0018) (Fig. 3).

In an exploratory analysis across all seven cognitive domains and nine brain volumes in each group, only reasoning/problem solving was significantly and positively correlated with the volume of the amygdala ($r = 0.33$, $P = 0.0004$) and nucleus accumbens ($r = 0.30$, $P = 0.0004$) in the patient group (significant after Bonferroni correction, Fig. 3). No significant correlation was found in the control group after Bonferroni correction. The complete results are shown in Table S4. Therefore, only the correlation between the amygdala and reasoning/problem solving was statistically significant in the patient group.

3.5. Clinical correlations with subcortical volumes and cognition

Despite the short duration of medication exposure, we found that the dose of antipsychotic medication was positively correlated with the volume of the amygdala ($r = 0.52$ $P = 1.4 \times 10^{-12}$), caudate ($r = 0.21$, $P = 0.007$), putamen ($r = 0.41$, $P = 4.7 \times 10^{-8}$), pallidum ($r = 0.47$, $P = 2.1 \times 10^{-10}$), and nucleus accumbens ($r = 0.46$, $P = 8.3 \times 10^{-10}$). No significant correlation was found between the CPZ and ICV ($r = 0.09$, $P = 0.26$) and total gray matter volume ($r = 0.19$, $P = 0.02$), suggesting that the structure and short antipsychotic medication exposure relationship may be specific to certain subcortical areas. The age of onset was correlated with total gray matter volume ($r = -0.23$, $P = 0.004$, details in Figure S2). No correlation was found between subcortical structural volumes and the DUP (all $r < 0.09$, all $P > 0.17$). Finally, PANSS-positive symptoms showed a significant inverse correlation with the volume of the nucleus accumbens ($r = -0.24$, $P = 0.003$) and amygdala ($r = -0.24$, $P = 0.003$) in patients (significant after Bonferroni correlation of $P < 0.05/7$ regions = 0.007, Fig. 3).

4. Discussion

In the present study, we examined the relationship between cognition and subcortical structures in patients with first-episode schizophrenia. We found significantly smaller brain region volumes in the amygdala, hippocampus, thalamus, and total cortical gray mater volume, after an average of 8 months of untreated psychosis from disease onset, compared with age-matched controls. Schizophrenia patients showed reduced cognitive function in all seven domains of cognition as measured by MCCB. Between these significantly abnormal subcortical structures and cognitive domains, only reasoning/problem solving was significantly correlated with the volume of the amygdala in schizophrenia.

An extensive review of cognition supports generalized neurocognitive deficits in patients with schizophrenia (Moritz et al., 2017). In the present study, cognitive deficits were found in all MCCB domains in first-episode schizophrenia patients, consistent with previous reports (Gurovich et al., 2012; She et al., 2017). As expected, the overall cortical gray matter volume was significantly reduced in patients. While cortical abnormalities most likely contribute to cognitive deficit in schizophrenia (Barch et al., 2003; Deserno et al., 2012; Jardri et al., 2011; Tan et al., 2005), some subcortical structures are also known to play an important role in memory and emotion-cognition regulation tasks (Aleman and Kahn, 2005; Herbener, 2008; Nees and Pohlack, 2014). The smaller volumes of the amygdala, hippocampus, and thalamus were consistent with findings of previous studies (Koshiyama et al., 2018; van Erp et al., 2016), including the ENIGMA study, the largest subcortical structure study in schizophrenia (van Erp et al., 2016). Furthermore, Koshiyama found a significant correlation between

the right nucleus accumbens volume and memory in chronic schizophrenia (Koshiyama et al., 2018). Unlike the ENIGMA meta-analysis and the study by Koshiyama that included patients with chronic disease, our study examined younger patients with limited exposure to antipsychotics and still observed similar subcortical volume reductions. In particular, antipsychotics tended to be associated with greater subcortical volumes, suggesting that smaller volumes in the amygdala, hippocampus, and thalamus during the early course of schizophrenia are unlikely due to the use of antipsychotic medication.

When investigating the relationships between these subcortical structure abnormalities and cognition, reasoning/problem solving was associated with the volume of the amygdala and perhaps the nucleus accumbens in patients, demonstrating that the larger the amygdala and nucleus accumbens, the better the reasoning/problem solving function in first-episode patients. The same trends were also found in controls, indicating that this relationship may exist in the younger population in general and is not entirely a secondary effect due to an antipsychotic medication-induced improvement in cognition or subcortical structural changes. Human cognitive processes, including reasoning (Jung et al., 2014) and problem solving (Isen et al., 1987), are known to be affected by emotion. The amygdala is important for emotional processing (Adolphs et al., 1994; Anderson and Phelps, 2001; Janak and Tye, 2015) and learning-related plasticity (Johansen et al., 2011; Pape and Pare, 2010). Amygdala lesions in the human (Adolphs et al., 1994; Anderson and Phelps, 2001) or non-human (LeDoux et al., 1990) led to impaired emotional reactions to stimuli or an enhanced perception of emotionally salient events. Therefore, our findings indicate that a smaller amygdala volume, which plays an important role in emotion, is associated with poor reasoning and problem-solving functions in schizophrenia patients.

More severe positive symptoms were associated with smaller amygdala and nucleus accumbens volumes. After exploring specific symptom items in PANSS, the suspicion items showed the most robust inverse correlation with the volumes of the amygdala ($r = -0.29$, $P = 0.0004$) and nucleus accumbens ($r = -0.29$, $P = 0.0004$), suggesting an association between suspicion and the volume of the amygdala and nucleus accumbens, which may warrant additional confirmatory investigation.

Cognitive function was also related to the age of onset (Figure S1), although the effect was likely secondary to the effect of age on cognition as the correlation was no longer significant once age was included as a covariate. A negative correlation was found between DUP and processing speed, suggesting the earlier patients received treatment, the better their cognitive processing speed performance.

We observed a significant positive correlation between antipsychotic medication dosages and several subcortical volumes, including the amygdala, putamen, caudate, pallidum, and nucleus accumbens, despite the short exposure to antipsychotic medications. In animal studies, treatment with intraperitoneal injections of olanzapine for 28 days had effects on amygdalar and hippocampal neuronal populations which were thought to be caused by a change in neuropeptide activity in rats (Palasz et al., 2016). Acute one hour and chronic 14 days treatment with quetiapine increased the mitochondrial respiratory chain complex activity in the rat hippocampus, amygdala, and nucleus accumbens (Ignacio et al., 2015). To our knowledge, it has not been reported whether these changes were related to increased subcortical volumes in animal studies. Our data suggest that 2 weeks of antipsychotic medication is sufficient to alter subcortical structure volumes, a novel observation. We should emphasize that our findings are based on cross-sectional data; therefore, a causal interpretation is not possible. Additional longitudinal human or animal studies are needed to confirm the minimal duration of exposure necessary to alter brain volumes in these subcortical structures.

The two-site study data have several other limitations. Participants from site 2 were not fully matched in age and education. We repeated the analysis in each site and found that the main results were similar in each site (Table S3). The scanners at the two sites were different types of 3T scanners, which may have induced some additional noise. We adjusted this difference to a certain extent by considering the two sites as covariates.

5. Conclusion

Young schizophrenia patients already showed a smaller amygdala, hippocampus, thalamus, and total cortical gray volume early in the disease course with minimal antipsychotic medication exposure. Among them, a smaller subcortical volume of the amygdala and perhaps the nucleus accumbens were significantly associated with poorer cognitive function in the reasoning/problem-solving domain. Although the amygdala is traditionally perceived as an emotion regulation center, our findings suggest that in the early stage of psychosis, the amygdala significantly contributes to the difficulty in problem solving in patients, which may have implications for identifying early intervention strategy to improve cognitive deficits in schizophrenia.

Author contribution

Conceived and designed the study: Yunlong Tan, Shuping Tan, Zhiren Wang, Fude Yang.

Collected the data: Yunlong Tan, Hong Xiang, Shuping Tan, Zhiren Wang, Hua Guo, Hongzhen Fan.

Analyzed the data: Fengmei Fan, Hongzhen Fan, Shuping Tan, Peter Kochunov, L.Elliot Hong.

Wrote the paper: Fengmei Fan, L.Elliot Hong, Yunlong Tan, Shuping Tan.

Acknowledgments

We thank Shiyou Tang from Chongqing Three Gorges Central Hospital, Ping Wang and Dong Wei from Zhumadian Psychiatry Hospital for their assistance in collecting data, Yong He from Beijing Normal University and MeKenzie Ritter from National Institute of Mental Health for their comments in this manuscript. Funding was received from National Natural Science Foundation of China (No. 81761128021, 81401115, 31671145Please check funding information and confirm its correctness.), National Institute of Health grant (R01MH112180), Beijing Municipal Administration of Hospitals' Youth Programme (QML20172001), and Beijing Municipal Administration of HospitalsClinical Medicine Development Special Fund (XMLX201513, XMLX201609). Funders have no role in data analysis, interpretation, or publication.

Data access and responsibility

The principal investigator, Yunlong Tan, has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicting interest

All authors have declared no conflicting interests.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2019.01.003.

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