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# Amygdala volume is reduced in early course schizophrenia

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ABSTRACT

Subcortical structural alterations have been implicated in the neuropathology of schizophrenia. Yet, the extent of anatomical alterations for subcortical structures across illness phases remains unknown. To assess this, magnetic resonance imaging (MRI) was used to examine volume differences of major subcortical structures: thalamus, nucleus accumbens, caudate, putamen, globus pallidus, amygdala and hippocampus. These differences were examined across four groups: (i) healthy comparison subjects (HCS, $n=96$); (ii) individuals at high risk (HR, $n=21$) for schizophrenia; (iii) early-course schizophrenia patients (EC-SCZ, $n=28$); and (iv) chronic schizophrenia patients (C-SCZ, $n=20$). Raw gray matter volumes and volumetric ratios (volume of specific structure/total gray matter volume) were extracted using automated segmentation tools. EC-SCZ group exhibited smaller bilateral amygdala volumetric ratios, compared to HCS and HR subjects. Findings did not change when corrected for age, level of education and medication use. Amygdala raw volumes did not differ among groups once adjusted for multiple comparisons, but the smaller amygdala volumetric ratio in EC-SCZ survived Bonferroni correction. Other structures were not different across the groups following Bonferroni correction. Smaller amygdala volumes during early illness course may reflect pathophysiologic changes specific to illness development, including disrupted salience processing and acute stress responses.



## 1. Introduction

Schizophrenia is a severe chronic illness associated with psychosis, thought disorganization and cognitive impairment (Tamminga, 2009). The significant functional decline of patients and 0.55% global lifetime prevalence (Saha et al., 2005) make understanding schizophrenia neurobiology important from both scientific and clinical perspectives. While cortical dysfunction, specifically in the prefrontal cortex (PFC) and the temporal cortex, is thought to be responsible for cognitive deficits and hallucinations (Barch et al., 2003; Deserno et al., 2012; Jardri et al., 2011; Tan et al., 2005), complementary studies have increasingly documented significant impairments in emotion processing, with nodes of dysfunction located in subcortical regions (Dowd and Barch, 2010; Nielsen et al., 2012; Pinkham et al., 2011; Schlagenhauf et al., 2014). For instance, abnormal amygdala function in response to emotional faces and decreased blood–oxygen level dependent (BOLD) activation in the ventral striatum during reward processing have been demonstrated in patients with schizophrenia compared to healthy controls (Anticevic et al., 2012b; Pinkham et al., 2011; Schlagenhauf et al., 2014). Such functional alterations are likely linked to structural abnormalities of subcortical nuclei, and these local changes in structure and function may ultimately be reflected in the disruption of large-scale neural networks in patients with schizophrenia (Anticevic et al., 2014a; Cole et al., 2011; Meda et al., 2009).

Schizophrenia symptoms are hypothesized to reflect dynamical

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changes in structure and function over the illness course (Douaud et al., 2009; Mane et al., 2009). Indeed, structural magnetic resonance imaging (MRI) studies in humans have revealed prefrontal and temporal cortical thinning among patients with schizophrenia compared to healthy controls (Nesvag et al., 2008; Voets et al., 2008; Yang et al., 2010), even at early stages of illness (Narr et al., 2005a,2005b). Examination of structural abnormalities of subcortical nuclei has yielded mixed findings. In general, meta-analyses of subcortical regions have suggested that patients with schizophrenia tend to have decreased gray matter volumes of subcortical regions, compared to healthy controls (Bora et al., 2011; Ellison-Wright et al., 2008; Haijma et al., 2013; Shepherd et al., 2012). Temporal lobe structures, including the amygdala and hippocampus, have been shown to be smaller in patients with schizophrenia compared to control subjects (Anderson et al., 2002; Gur et al., 2000; Marsh et al., 1994; Namiki et al., 2007; Wang et al., 2008) (though see: Killgore et al., 2009; Sanfilipo et al., 2000). Thalamic volumes have also been shown to be smaller in patients with schizophrenia, including at first-episode (Ananth et al., 2002; Andreasen et al., 2011; Kim et al., 2007; Staal et al., 2001). Striatal (caudate and/or putamen) findings have been mixed, with studies demonstrating increased, decreased, or similar volumes in patients with schizophrenia compared to control subjects (Glahn et al., 2008; Oertel-Knochel et al., 2012; Okugawa et al., 2007; Wang et al., 2008). Finally, inclusion of subcortical structural abnormalities in a statistical model of gray matter changes yielded accurate classification of subjects with or without schizophrenia, highlighting the importance of understanding subcortical structural changes in disease states (Kawasaki et al., 2007).

Differences in subcortical anatomical findings may reflect the heterogeneity of schizophrenia disease presentation. Illness duration in particular may be a factor that significantly moderates findings (Insel, 2010), and examining patients at different illness stages may lead to more specific information on changes in subcortical structures. We hypothesized that stages of illness may differentially affect subcortical regions. Specifically, we *a priori* hypothesized that the hippocampus, amygdala and nucleus accumbens, regions involved in sensory and emotion processing, may be altered in the early phase of illness when initial acutely psychotic symptoms are prominent. Those regions involved in motor processes, such as the globus pallidus, caudate nucleus and putamen, were hypothesized to be affected later in disease when negative symptoms dominate. Finally, a region such as the thalamus was hypothesized to be structurally abnormal across all phases of illness, as it is involved in an array of functions, including both sensory and motor processes. To test these hypotheses we employed a cross-sectional clinical design to quantify differences in subcortical gray matter volume across disease stages. Any other examinations of the effect of illness stage on subcortical regional volume were done in a post-hoc, exploratory analysis.

Total gray matter volume was controlled for to account for decreases in overall gray matter volume, a finding well-documented in both chronic and first-episode schizophrenia (Andreasen et al., 2011; Bose et al., 2009; Glahn et al., 2008; Gur et al., 1999; Hulshoff Pol et al., 2002; Vita et al., 2012). White matter changes have also been documented in schizophrenia (Bose et al., 2009; Ho et al., 2003; Hulshoff Pol et al., 2002; Pasternak et al., 2012), but only gray matter was corrected for because of the differential trajectories of progressive gray versus white matter changes, likely reflecting different pathophysiologic processes (Bose et al., 2009; Hulshoff Pol et al., 2002). Gray matter volumes of major subcortical structures were analyzed in healthy subjects (HCS), subjects at high-risk (HR) for schizophrenia, subjects in the early-course of schizophrenia (EC-SCZ), and subjects with chronic schizophrenia (C-SCZ). We specifically focused on the thalamus, caudate nucleus, putamen, globus pallidus (GP), nucleus accumbens (NAc), amygdala and hippocampus. Across all examined regions, results revealed a significant group effect only for amygdala volumetric ratios corrected for whole-brain gray matter differences, which were driven by a specific reduction in amygdala volumes in the early course of illness.

## 2. Methods

### 2.1. Participants

All participants were recruited from the clinics and community of China Medical University, Shengyang, China. The clinical samples (C-SCZ, $n=20$; EC-SCZ, $n=28$; HR, $n=21$) were recruited from outpatient clinics of the Department of Psychiatry, First Affiliated Hospital of China Medical University. All patients met DSM-IV criteria for schizophrenia, schizophreniform or brief psychotic disorder, exclusive of any other Axis I diagnosis. Two independent psychiatrists trained to use the Chinese translation of the Structured Clinical Interview (SCID) for DSM-IV (first, 2001; http://www.scid4.org/trans.html) assessed those patients older than 18 years of age. Those younger than 18 were assessed using the Schedule for the Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL Kaufman et al., 1997). Of the 48 patients with schizophrenia, 28 were within 1 year of their initial clinical presentation (defined as early course, EC-SCZ, mean=4.27 months of illness duration). This time frame was defined as the difference between the age of first evident symptoms (as reported by participants and confirmed with medical records and family) and the age at the time of scanning. EC-SCZ patients were then followed and confirmed to meet DSM-IV criteria for schizophrenia by trained clinicians. In contrast, C-SCZ patients met diagnostic criteria for at least 12 consecutive months (mean=64.45 months). While the distinction between EC-SCZ and C-SCZ is certainly arbitrary, we have employed this definition here for the purposes of a cross-sectional study, with additional analyses using duration of illness as a continuous measure. Of note, the EC-SCZ group does not necessarily encompass only those experiencing a first-episode. However, there is a large literature on neurobiological differences in first-episode schizophrenia, and the criteria for recruitment and average duration of illness for the EC-SCZ group in our study encompasses the time course of those recruited with first-episode in other studies (Gelber et al., 2004; Gupta et al., 1997; Lieberman et al., 2005; Nenadic et al., 2015; Rais et al., 2008; Wheeler et al., 2014). HR subjects were comprised of offspring of individuals with schizophrenia (at least one parent), and who were not past the age of peak illness risk ( $<30$ y/o) – these subjects therefore still had potential to develop illness. Of note, HR subjects were unrelated to any of the other clinical groups. Exclusion criteria for patients included current nicotine, alcohol or drug abuse/dependence, though subjects were allowed to have a history of nicotine and/or alcohol use. The Brief Psychiatric Rating Scale (BPRS (Overall and Gorham, 1962)) was used to evaluate patient symptoms. 95% of chronic patients and 43% of early course patients were taking antipsychotics at the time of data acquisition, and all medications and dosing were converted to chlorpromazine (CPZ) equivalents (Andreasen et al., 2010) (Table 1).

Healthy comparison subjects (HCS, $n=96$) were recruited at China Medical University through advertisement, and mean-matched to the clinical samples (HR, EC-SCZ, C-SCZ) by age, sex, ethnicity, handedness and parental socio-economic status (represented using parental education attainment) though not individual educational attainment. HCS also underwent a clinical evaluation with SCID or K-SADS-PLS by a trained psychiatrist to