Morphological and functional abnormalities of salience network in the early-stage of paranoid schizophrenia

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A B S T R A C T

A salience network (SN), mainly composed of the anterior insula (AI) and anterior cingulate cortex (ACC), has been suggested to play an important role in salience attribution which has been proposed as central to the pathology of paranoid schizophrenia. The role of this SN in the pathophysiology of paranoid schizophrenia, however, still remains unclear. In the present study, voxel-based morphometry and resting-state functional connectivity analyses were combined to identify morphological and functional abnormalities in the proposed SN in the early-stage of paranoid schizophrenia (ESPS). Voxel-based morphometry and resting-state functional connectivity analyses were applied to 90 ESPS patients and 90 age- and sex-matched healthy controls (HC). Correlation analyses were performed to examine the relationships between various clinical variables and both gray matter morphology and functional connectivity within the SN in ESPS. Compared to the HC group, the ESPS group showed significantly reduced gray matter volume (GMV) in both bilateral AI and ACC. Moreover, significantly reduced functional connectivity within the SN sub-networks was identified in the ESPS group. These convergent morphological and functional deficits in SN were significantly associated with hallucinations. Additionally, illness duration correlated with reduced GMV in the left AI in ESPS. In conclusion, these findings provide convergent evidence for the morphological and functional abnormalities of the SN in ESPS. Moreover, the association of illness duration with the reduced GMV in the left AI suggests that the SN and the AI, in particular, may manifest progressive morphological changes that are especially important in the emergence of ESPS.

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1. Introduction

Paranoid schizophrenia is the most common subtype of schizophrenia, prominently characterized by delusions and hallucinations (DSM-IV). Traditionally, such patients are thought to demonstrate more stable clinical symptoms and higher cognitive and social functioning than others (First et al., 1995). Furthermore, it has been proposed that delusions and hallucinations may arise out of the aberrant attribution of salience to external and internal representations, in which delusions are implicated in individual’s effort to make sense of the aberrant salient experience, and hallucinations reflect aberrant salience on the internal representations (Kapur, 2003).

Recently, a salience network (SN) in the brain, identified by blood oxygenation level dependent (BOLD) data (Seeley et al., 2007), has been proposed as critical for detecting the salience of internal and external stimuli (Bressler and Menon, 2010). Interestingly, a recent review focusing on the SN demonstrated its critical role in psychosis, especially in delusions and hallucinations. Given that reality distortion is a cardinal psychopathological feature in paranoid schizophrenia, one may expect that SN deficits could be a prominent neurophysiological feature in this subtype schizophrenia. However, we know little about the role of the SN in the neuropathophysiology of paranoid schizophrenia. Exploration of this neural system may provide insight into the pathological mechanisms of paranoid schizophrenia.

It has been suggested that the SN principally consists of the bilateral anterior insula (AI) and anterior cingulate cortex (ACC) (Seeley et al., 2007; Bressler and Menon, 2010). Of the two nodes in the SN, the insula (Craig, 2002) has been shown to be involved in the subjective awareness of internal stimuli (e.g., disgust, anger, sexual arousal) and external stimuli (e.g., pain, taste, temperature), while the ACC has...
been considered to be part of an executive attention system related with internal affective response and monitoring (Pujol et al., 2002). Furthermore, it has been suggested that AI and ACC nodes of the SN respond to subjective salience across different tasks, whether cognitive, homeostatic, or emotional (Craig, 2002, 2009). In a recent fMRI study, by using Granger causality analysis, Sridharan et al. investigated the directional influence of the SN on other brain regions in responding to multimodal stimuli, and their findings demonstrated that AI played a critical causal role in activating the central executive network (CEN) and deactivating the default mode network (DMN) which are associated with task-processing and self-reference respectively (Sridharan et al., 2008). Taken together, these findings suggest that the SN may play an important role in the salience attribution and transmission of salience signals to other brain networks.

Given that the SN may be critical for salience attribution, and that aberrant salience attribution may be involved in the pathophysiology of reality distortion (delusions and hallucinations), it is conceptually plausible that deficits in the SN leading to aberrant salience attributions may play an important role in the pathophysiology of paranoid schizophrenia. In the present study, we combined voxel-based morphometry (VBM) and resting-state functional connectivity assessments to the exploration of the morphological and functional characteristics of SN in patients with paranoid schizophrenia. We hypothesized that both morphological and functional abnormalities in the SN regions would be observed in patients with paranoid schizophrenia as compared to healthy controls; and that both the morphological and functional abnormalities in the SN regions would be mainly associated with reality distortion in the paranoid schizophrenia.

2.2. Image acquisition

All subjects underwent structural and functional MRI scanning using the same 1.5-T GE Signa Twinspeed MR scanner (General Electric Medical System, Milwaukee, USA). A standard head coil was used for radio frequency transmission and reception of the nuclear magnetic resonance signal. Foam pads and ear plugs were used to minimize head motion and scanner noise. All the subjects were instructed to keep their eyes closed, not to think about anything in particular and to move as little as possible. 3-D structural MRI images (T1-weighted) were acquired from the sagittal plane using spoiled gradient echo (SPGR) pulse sequence, scanning parameter: TR = 12 ms, TE = 4.2 ms, flip angle = 15°, 172 slices, matrix size = 256 × 256, and the field of view (FOV) = 24 × 24 cm². Slices were contiguous with slice thickness of 1.8 mm. Functional images were acquired by using a gradient-echo echoplanar imaging sequence sensitive to BOLD signal (TR/TE = 2000/40 ms, flip angle = 90°, FOV = 24 × 24 cm²). Whole-brain volumes were acquired with 20 contiguous 5 mm thick transverse slices with a 1 mm gap and 3.75 x 3.75 mm² in-plane resolution. For each subject, fMRI scanning lasted for 6 min and 180 volumes were obtained.

2.3. Structural MRI data processing and analysis

The structural images were processed with the VBMS toolbox (http://dbm.neuro.uni-jena.de/vbm), an extension of the SPM5 software package (Wellcome Department of Imaging Neuroscience, University College London, London, UK). The normalization, segmentation, and modulation were completed in one step, resulting in modulated GM. In the normalization, all images were spatially normalized to the T1-weighted template in the Montreal Neurological Institute (MNI) space, and were resampled into a final voxel size of 2 x 2 x 2 mm³. The modulated images were then smoothed with a full-width at half-maximum (FWHM) 8-mm Gaussian kernel for further analysis.

Voxel-based statistical analyses of modulated gray matter images were performed by SPM5 based on General Linear Model and Gaussian Random Field theory (Friston et al., 1995). The significance of GMV differences between the HC and ESPS groups was tested with analysis of covariance (ANCOVA) with years of education and total intracranial volume (TIV) as covariates. A height threshold was set at p < 0.001 and extent threshold was set at k > 25 voxels. We specifically focused on the SN mainly composed of AI and ACC, with further small volume correction (SVC) for multiple comparisons (p < 0.05, family-wise error (FWE) corrected) performed with WFU atlas software (Maldjian et al., 2003) to confirm the findings for the hypothesized regions. Because previous studies have suggested volume of the insula exacerbated following the illness duration (Chan et al., 2011), and the medication effects on the morphology of insula and ACC were conflicting (Palanuyappan and Liddle, 2012), we used further regression analysis within the ESPS group to examine the relationships of illness duration and medication dose with the gray matter volume of insula and ACC. The significance threshold was set at p < 0.001, with further small volume correction (SVC) for multiple comparisons (p < 0.05, FWE corrected). Moreover, since we hypothesized that SN deficits leading to aberrant salience attribution would result in delusions and hallucinations, we then extracted the volume value of the exact clusters with GM reduction in SN and performed a series of correlation analyses in SPSS to examine their relationships with delusions and hallucinations. The significant threshold was set at p < 0.05. In addition, correlation analyses were also performed to examine whether the gray matter...
deficits in SN were associated with PANSS total score, positive, negative and general psychiatric symptoms subscores.

### 2.4. FMRI data processing and analysis

The SPMS software was used for fMRI image preprocessing. The first 10 volumes of each functional time series were discarded for signal equilibrium and participants’ adaptation to the scanning noise. The remaining 170 volumes were corrected for the acquisition delay between slices and for head motion. Participants who had head motion of more than 2.0 mm maximum displacement in any of the x, y, or z directions or 2.0° of any angular motion throughout the course of scan were excluded in the preprocessing procedures. Owing to excessive movement, only 77 patients and 68 controls could be included in this analysis. No differences of age (p > 0.05) or gender (p > 0.05) were found between the remaining patients and healthy controls. Further preprocessing procedures included spatial normalizing (resampling to 3×3×3 mm³) and spatial smoothing (full-width at half maximum = 4 mm). To further reduce the effects of confounders, six motion parameters, linear drift, and the mean time series of all voxels in the whole brain were regressed out after the images were smoothed. The fMRI data were then band-pass filtered (0.01–0.08 Hz) using REST software (http://restfmri.net/). Functional connectivity was examined using a method based on a seed region correlation approach (Horwitz et al., 1998). Since voxel-based morphometry analysis has shown morphological abnormalities in the SN sub-regions, including partial areas of bilateral AI and ACC regions, each of these exact clusters with reduced GMV was defined as a seed for functional connectivity analysis. Four correlation analyses were performed between the seed reference and the rest of the brain in a voxel-wise manner. Finally, the correlation coefficients in each voxel were transformed to z-values using the Fisher r-to-z transformation to improve normality.

Voxel-based comparison of z-value maps between HC and ESPS groups was performed using the two-sample t tests, with a significance threshold set at p < 0.001. Since this study specifically focused on the hypothesized SN regions, further small volume correction (SVC) for multiple comparisons (p < 0.05, FWE corrected) was performed like the VBM analyses. Furthermore, the relationships between clinical variables and functional connectivity within the SN sub-networks in the ESPS group were examined through correlation analyses.

Group differences on demographic and clinical factors were analyzed by t-test or Chi-square test using SPSS (SPSS, Chicago, IL, USA).

### 3. Results

The demographic and clinical data from the 90 patients and 90 healthy controls are shown in Table 1. There were no significant differences between the HC and ESPS groups in age (t = 1.18, p = 0.24) or gender (χ² = 1.90, p = 0.17), but there was a significant difference between the groups in years of the education (t = 2.50, p = 0.01).

#### 3.1. Morphometry analysis

Compared with the HC group (Fig. 1), the ESPS group demonstrated reduced GMV in bilateral AI and ACC (p < 0.001, uncorrected). Moreover, the finding of GMV loss in AI and ACC remained significant after small volume correction (p < 0.05, corrected by FWE). Regression analysis (Fig. 2A) showed that DoI was negatively correlated with GMV in the left AI (p < 0.001, uncorrected), and that medication dose was not significantly correlated with the GMV in bilateral AI and ACC. Moreover, the association between DoI and the reduced GMV in the left AI remained significant after small volume correction (p < 0.05, corrected by FWE). Furthermore, hallucinations were found to be significantly associated with gray matter loss in right AI in subsequent correlation analyses (r = −0.278, p = 0.04, Fig. 2C).

#### 3.2. Functional connectivity analysis

The exact clusters with reduced GMV in bilateral AI and ACC were selected as the seed regions for the functional connectivity analysis. When the seed was located in the left AI, significantly decreased functional connectivity of left AI with left ACC, right ACC and right AI (Fig. 3) was found in the ESPS group as compared to the HC group (p < 0.001, uncorrected). When the seed was located in the right AI, significantly decreased functional connectivity with left AI (Fig. 3) was only found in the ESPS group (p < 0.001, uncorrected). When the seed was located in the left ACC, significantly decreased functional connectivity with bilateral AI (Fig. 3) was found in the ESPS group (p < 0.001, uncorrected). When the seed was located in the right ACC, there was no significantly altered functional connectivity with this region. Moreover, the decreased functional connectivity within the salience sub-networks all remained significant after small volume correction (p < 0.05, corrected by FWE).

In the subsequent regression analyses in the ESPS group, when the RoI was set at the left ACC, the functional connectivity between left ACC and bilateral AI, which was identified reduced in the patients in functional connectivity analyses (Fig. 3), was found to be negatively associated with hallucinations (p < 0.001, uncorrected) (Fig. 2B). After small volume correction (p < 0.05, corrected by FWE), this association still remained significant. When the RoI was set at the right ACC, a significantly negative association between hallucinations and the functional connectivity from right ACC to left AI was identified (p < 0.001, uncorrected), but this association did not remain significant after small volume correction (p < 0.05, corrected by FWE). In addition, when the RoI was set at the right AI, the functional connectivity from right AI to right ACC was found to be positively associated with PANSS total score and general psychiatric subscore (p < 0.001, uncorrected), but these associations did not remain significant after small volume correction either (p < 0.05, corrected by FWE).

### 4. Discussion

Consistent with our hypothesis, ESPS participants showed significant gray matter reduction compared to the HC in SN regions, including both bilateral AI and ACC regions. Moreover, by using the SN regions with anatomical deficits as seed regions, functional connectivity analysis found abnormal functional integration within the SN sub-networks in ESPS patients. Subsequent correlation analyses revealed that both morphological and functional deficits in the SN were concurrently associated with hallucinations. In addition, the illness duration was significantly associated with gray matter loss in the left AI, and medication

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Note: PANSS, positive and negative syndrome scale; SD, standard deviation; P1, delusions; P3, hallucinations.
dosing had no significant correlation with the morphological and functional deficits within the SN in these patients.

Our systematic findings of morphological and functional deficits in the SN suggest that the cortical salience attribution may be dysfunctional in paranoid schizophrenia. Consistent with Kapur’s hypothesis (Kapur, 2003), which postulated that the inappropriate and excessive salience in the brain was responsible for the delusions and hallucinations in schizophrenia, our correlation analysis further identified significant association between hallucinations and both morphological and functional deficits in the SN. Since the SN has been demonstrated as critical for detecting the salience of internal and external stimuli (Bressler and Menon, 2010; Menon, 2011), it is possible that the morphological and functional abnormalities in the SN may give rise to the misattribution of the salience of internal experiences, which finally results in hallucinations in paranoid schizophrenic patients (Wylie and Tregellas, 2010).

Interestingly, our correlation analyses only found an association between SN deficits and hallucinations, but not delusions. What should be noted is that, delusion can be categorized as primary versus secondary phenomenon, in which primary delusions are mainly attributed to illogical justification, whereas secondary delusion may arise from hallucinations or other abnormal mental state (Palaniyappan and Liddle, 2012). Our findings suggest that SN deficits may directly lead to hallucinations, which may in turn give rise to secondary delusions in the paranoid schizophrenia. Conceptually, the illogical justification that may underlie primary delusions may require involvement of brain regions subserving higher-order cognitive processes, such as the prefrontal cortex; whereas deficits in the insula underlying homeostatic processes may directly lead to disrupted internal representations. Interestingly, evidence of the association between reality distortion and SN deficits is based mainly from findings of insular deficits with hallucinations (Shapleske et al., 2002; Gaser et al., 2004; Neckelmann et al., 2006; O’Daly et al., 2007; Garcia-Marti et al., 2008; Modinos et al., 2009; Nenadic et al., 2010). However, medication effects cannot be discounted in explaining the findings of this study, thus more studies exploring the relationship between SN deficits and delusions in drug-naïve patients are warranted.

In addition, we also found that a circuit from right AI to right ACC was significantly associated with PANSS total score and general psychiatric subscore, although these relationships did not remain survived after small volume correction ($p_{\text{FWEd}}<0.05$). Previous studies have found that insular deficits are associated with other aspects of

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**Fig. 1.** Gray matter volume comparisons between healthy controls and patients in the early-stage of paranoid schizophrenia. Panels A, B, C and D showed the gray matter volume reduction in the left anterior insula, right anterior insula, left anterior cingulate cortex and right anterior cingulate cortex respectively in schizophrenic patients; statistically significant differences in gray matter volume were defined as $p<0.001$, with a cluster size of 25 adjacent voxels. The color bar represents the range of T values.

**Fig. 2.** Associations of clinical variables with the morphological and functional deficits in salience network in the patient group. Panel A showed the significantly negative association between illness duration and gray matter volume in left anterior insula. Panel B(a) showed the negative association between hallucinations and the functional connectivity between left anterior cingulate cortex and left insula; B(b) showed the negative association between hallucinations and the functional connectivity between left anterior cingulated cortex and right insula. Panel C showed the negative association between hallucinations and gray matter volume in the right anterior insula.
Several fMRI studies have also suggested the involvement of SN functional abnormality in the neuropathology of schizophrenia, especially for hallucinations. Sommer et al. (2008) found that normal language production (silent word generation) activated bilateral insula and ACC, and language-related cortex, whereas spontaneous auditory hallucination activated bilateral insula and language-related cortex, but not the ACC. Interestingly, a recent fMRI study on the time course of hallucinations found that insula activation and ACC deactivation both preceded hallucinations onset (Hoffman et al., 2008). Both studies raised an intriguing speculation on which activation of insula and deactivation of ACC may be both involved in the processing of hallucinations in schizophrenia (Palaniyappan and Liddle, 2012). The reason for which, however, still remains unclear. According to the finding of Sridharan et al., anterior insula (fronto-insular cortex) had a significant causal effect on ACC activity (Sridharan et al., 2008). Notably, White et al. (2010), by using maximal-lagged correlation analysis, found that insular activity preceded ACC activation in healthy controls. These studies suggest that insula activity may exert a transient control signal on ACC activity. Hence, if the connection between insula and ACC was weakened in schizophrenia, this may explain why paralleling between insular activation and ACC deactivation would be observed in the processing of hallucinations. Our finding of weakened coupling between the insula and ACC, and its correlation with hallucinations, further support this speculation. Also, consistent with this, White et al. (2010) found reduced functional maximal-lagged correlation between insula and ACC in schizophrenia during information processing.

It is noteworthy that, our combined structural and functional imaging study differs from most previous multimodal imaging studies in schizophrenia (Calhoun et al., 2006; Pomarol-Clotet et al., 2010), in that we performed our functional connectivity analysis using the exact clusters within the brain regions where anatomic deficits were detected in the morphometry analysis as the seed regions. Our systematic findings thus provide more convergent evidence of both morphological and functional abnormalities in the SN in paranoid schizophrenia, although our research cannot establish the precise relationship between reduced gray matter volume and functional connectivity (Tregellas, 2009). Interestingly, a recent fMRI study focusing on the abnormalities of large-scale brain networks in a mixed schizophrenia and schizoaffective patients sample reported no functional alterations in the SN (Woodward et al., 2011). The discrepancy between this study and ours may be due to different methods of ROI definition or clinical heterogeneity. In this study, we examined only the paranoid subtype of schizophrenia. Additionally, it is more likely, conceptually speaking, that brain regions with morphological deficits will become abnormally coupled with other brain regions in schizophrenia.

Another important finding in the present study is the significant correlation between illness duration and gray matter morphological changes in the left AI. A series of studies focusing on the morphological alteration of the insular cortex conducted by Takahashi et al. has demonstrated progressive loss of gray matter in the bilateral insular cortex bilaterally (Borgwardt et al., 2010). Moreover, both Takahashi et al. and Chan et al. found decreased insular gray matter in populations at high-risk for developing schizophrenia (Takahashi et al., 2009; Chan et al., 2011). Post-mortem and proteomics studies have also found cellular and molecular abnormalities within the insular cortex in schizophrenia (Pennington et al., 2008a,b). With respect to the ACC, previous studies have reported significant gray matter reductions in the ACC in both patients with first-episode of illness and in individuals with prodromal symptoms who later develop frank psychosis (Borgwardt et al., 2008; Ellison-Wright et al., 2008).

Postmortem studies in schizophrenia have also found decreased populations of neuronal and glial cells in the ACC (Benes, 1993). It is noteworthy that, our combined structural and functional imaging study differs from most previous multimodal imaging studies in schizophrenia (Calhoun et al., 2006; Pomarol-Clotet et al., 2010), in that we performed our functional connectivity analysis using the exact clusters within the brain regions where anatomic deficits were detected in the morphometry analysis as the seed regions. Our systematic findings thus provide more convergent evidence of both morphological and functional abnormalities in the SN in paranoid schizophrenia, although our research cannot establish the precise relationship between reduced gray matter volume and functional connectivity (Tregellas, 2009). Interestingly, a recent fMRI study focusing on the abnormalities of large-scale brain networks in a mixed schizophrenia and schizoaffective patients sample reported no functional alterations in the SN (Woodward et al., 2011). The discrepancy between this study and ours may be due to different methods of ROI definition or clinical heterogeneity. In this study, we examined only the paranoid subtype of schizophrenia. Additionally, it is more likely, conceptually speaking, that brain regions with morphological deficits will become abnormally coupled with other brain regions in schizophrenia.
cortices in schizophrenia (Takahashi et al., 2004, 2009). A recent likelihood estimation meta-analysis found that gray matter reduction in the insula is associated with a predisposition to schizophrenia as well as with progression of schizophrenia (Chan et al., 2011). Taken in combination with our finding that medication dosing was not associated with reduced gray matter volume in the left AI, it may be inferred that the gray matter deficits of AI are more likely related to the illness itself and to the deterioration associated with illness progression. Unlike the AI, the ACC, another core region of the SN, did not show significant correlation with DL. Previous studies on the relationship of the ACC and DL have been inconsistent. Wang et al. found a significant correlation between the thinning of the ACC and longer duration of illness (Wang et al., 2007), but Whitford et al. found no progressive gray matter reduction in the ACC in the first 2–3 years following the onset of schizophrenia (Whitford et al., 2006). The differences in findings between these studies, however, may be an artifact of differences in medication effects (Chan et al., 2011). In addition, the progression of brain morphological alterations may differ across different subtypes of schizophrenia. Further studies conducted on drug-naive patients with different subtypes of schizophrenia may clarify these differences. Nevertheless, our findings of a correlation between reduced gray matter in the left AI and DL supports that notion that the AI progressively changes with the progression of ESPS.

The neurobiological mechanism whereby aberrant attribution of salience in the SN leads to schizophrenia symptomatology remains unclear. One possibility involves a special class of large bipolar spindle cells called Von Economo neurons (VEN). These neurons are mainly distributed in the AI (or in the fronto-insular cortex) and in the ACC (Watson et al., 2006), and are exclusively present in humans and great apes (i.e., they are absent in lesser apes) (42). Reduced VEN density in the ACC has been reported in early-onset schizophrenic patients (Brüne et al., 2010). Another possibility for the neurobiological mechanism of aberrant salience attribution in the SN is concerns dopaminergic dysfunction. Dopaminergic dysfunction is thought to result in disrupted attribution of salience and to lead to the emergence of psychopathological symptoms like delusions, especially in the early stage of psychotic disorders (Heinz and Schlagenhaus, 2010).

In conclusion, the convergent evidence of morphological and functional abnormalities within the SN, combined with their associations with hallucinations in the present study, suggests a potentially important role for the SN in the neuropathophysiology of paranoid schizophrenia. Furthermore, the significant correlation of DL with reduced gray matter in the left AI suggests that the SN and the AI, in particular, may be the key brain regions in which progressive abnormal changes in the early stages of paranoid schizophrenia lead to deepening psychopathology.

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Contributors

ZNL, WDP, LL and HEZ designed the study and wrote the protocol; XOH, HHL collected the imaging data and clinical information; LLJ, HBT and KK managed the reference search and analysis; WDP, LL, FW and BCS undertook the statistical analysis, and WDP wrote the first draft of the manuscript.

Conflicts of interest

None.

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