Brief report

Structural abnormalities of the right inferior colliculus in schizophrenia

Do-Hyung Kang\textsuperscript{a}, Ki Won Kwon\textsuperscript{b}, Bon-Mi Gu\textsuperscript{b}, Jung-Seok Choi\textsuperscript{a}, Joon Hwan Jang\textsuperscript{a}, Jun Soo Kwon\textsuperscript{a,c,}\textsuperscript{*}

\textsuperscript{a}Department of Psychiatry, Seoul National University College of Medicine, Seoul, Republic of Korea
\textsuperscript{b}Interdisciplinary Program in Brain Science, Seoul National University, Seoul, Republic of Korea
\textsuperscript{c}Clinical Cognitive Neuroscience Institute, SNU-MRC, Seoul, Republic of Korea

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Abstract

Although structural and functional neuroimaging studies of schizophrenia have suggested that impaired connectivity in the extensive network of cortical and subcortical areas is involved in its pathophysiology, there were no studies have investigated the structural integrity of the lower sensory brain areas including the inferior (IC) and the superior (SC) colliculus. The IC plays an important role in mediating auditory gating processes and inhibitory neural transmission, while the SC is a key structure in a distributed network mediating saccadic eye movements and shifts of attention, both of which have been linked to the pathophysiology of schizophrenia. We compared the morphologies of the IC and SC, which are involved in the early stage processing of visual and auditory stimuli, in patients with schizophrenia (\(N=28\)) and healthy controls (\(N=34\)) using high-resolution magnetic resonance imaging. Subjects with schizophrenia had a significantly smaller right IC, compared with controls. The reduced IC volume suggests that a structural abnormality of the IC in patients with schizophrenia may be involved in the auditory cognitive dysfunction of schizophrenia.

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1. Introduction

Schizophrenia is a complex neuropsychiatric disorder, and abnormalities in brain development may play important roles in its pathophysiology (Arnold et al., 2005; Gottesman and Gould, 2003). Recently, structural and functional neuroimaging studies of schizophrenia have provided evidence that an impairment in the connectivity of distributed neural networks is involved in its pathophysiology (Meyer-Lindenberg et al., 2002; Burns et al., 2003; Highley et al., 2003; Foucher et al., 2005; Kubicki et al., 2005; Whalley et al., 2005). The extensive reciprocal connections from cortical to subcortical brain areas suggest that lower sensory brain areas are influenced by the integrity of higher cortical networks. Additionally, deficits in early sensory processing have been consistently reported in both the
auditory (Rabinowicz et al., 2000) and visual (Butler and Javitt, 2005; Uhlhaas et al., 2005) domains, and they are correlated with the severity of schizophrenia (Rojas et al., 2002; Uhlhaas and Silverstein, 2005). Furthermore, convergent lines of evidence report progressive changes in the functional (Umbricht et al., 2006) and structural (Kasai et al., 2003) indices of early auditory processing in schizophrenia. Taken together, previous findings suggest that the structural integrity of early sensory areas in schizophrenia should be investigated.

The dorsal midbrain consists of the superior (SC) and the inferior (IC) colliculus, which modulate visual and auditory stimuli, respectively (Zervas et al., 2005). The IC, the major structure of the auditory midbrain, plays an important role in mediating auditory gating processes and inhibitory neural transmission (Li and Yue, 2002; Pollak et al., 2002), while the SC is a key structure in a distributed network involving areas that mediate saccadic eye movements and shifts of attention (Li and Basso, 2005; Lynch and Tian, 2005).

As no previous study has investigated the morphology of the SC and the IC in patients with schizophrenia, we evaluated the volumes of these dorsal midbrain structures in patients using high-resolution magnetic resonance imaging (MRI), and investigated their relationships with clinical parameters.

2. Methods

2.1. Subjects

Twenty-eight schizophrenic patients (14 males, 14 females) and 34 healthy comparison subjects (16 males, 18 males) participated. All of the patients met DSM-IV criteria for schizophrenia based on the Structured Clinical Interview for DSM-IV (SCID-IV) (First et al., 1996), and were recruited from the outpatient clinic at Seoul National University Hospital. Healthy comparison subjects were recruited through newspaper advertisements. They had no history of any psychiatric or medical illness. The demographic characteristics of the patients and healthy controls are summarized in Table 1. All the patients with schizophrenia and the comparison subjects were righthanded (Annett, 1970), and free from any hearing problem. The duration of illness in patients with schizophrenia was assessed by both chart review and direct interviews probing when the patients first revealed their psychotic symptoms. The patients were receiving atypical antipsychotic medications at the time of participation. Clinical symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), and the mean PANSS total score was 52.4 (S.D. = 12.0). This study was approved by the local institutional review board, and written informed consent was obtained from all subjects after the procedures had been explained fully.

2.2. MR acquisition and processing

MR images were acquired on a 1.5 T scanner (Philips Intera, Philips Medical System, Best, The Netherlands) using a T1-weighted 3D-spoiled gradient recalled echo pulse sequence with the following imaging parameters: acquisition matrix = 512 × 512, voxel size = 0.45 × 0.45 × 1 mm; axial slices = 170 axial slices, field of view = 230-mm, repetition time = 25 ms, echo time = 4.6 ms, flip angle = 30°, slice gap = 0 mm. The MR images were processed using an image-processing software package (ANALYZE version 5.0, Mayo Foundation, Rochester, MN, USA). The images were resampled to 1.0 mm³ voxels, reoriented and spatially realigned to the conventional position. The data sets were then filtered using anisotropic diffusion methods (Perona and Malik, 1990) to improve the signal-to-noise ratio. To extract images of the brain, tissues exterior to the brain were removed using the semi-automated region growing method. Using the fuzzy C-means algorithm, the extracted brain images were segmented into gray matter, white matter and cerebrospinal fluid. The intracranial volume was calculated by summing up the subtotal volumes of these three components (Bensaid et al., 1996; Cannon et al., 1986).

2.3. Volume measurements

The neuroanatomical regions of interest (ROIs) focused on the SC and IC (both right and left) and were traced on sagittal slices using ROI module in the ANALYZE program. The ROIs were drawn by tracing the projecting parts on all coronal slices of a 3D T1 image.
The right boundary of the left colliculus was defined as the first projecting part on the border between the midbrain and third ventricle, passing to the left at the midline of the brain. Where the projecting parts disappeared, the left boundary of the left colliculus was drawn. The upper and lower boundaries were traced on the sagittal plane in the right middle of the left and right borders. The upper and lower boundaries were defined as the first projecting part of the SC and IC, respectively, on the border between the midbrain and the third ventricle. The line connecting the upper and lower boundaries was set as the bottom of both the SC and the IC (see Fig. 1). To separate the SC and the IC, we drew a line between the SC and the IC in the sagittal plane that discriminate the two structures most efficiently (see Fig. 1). The methods used to trace the right SC and IC were the same as for the left SC and IC except they were to the right of the midline of the brain. Volumes of the colliculi were calculated by counting the number of gray matter voxels in the ROI. Usually 20–30 slices were obtained along sagittal axis for each ROI. The inter-rater reliability was assessed using two independent raters (K. W.K. and B.M.G.) who were blind to all information. The estimated intra-class correlation coefficients (ICC) were 0.917 (left SC), 0.711 (left IC), 0.896 (right SC), and 0.831(right IC).

2.4. Statistical analyses

We used t tests to examine group differences in the demographic and clinical variables. All measures of the IC and SC volumes were subjected to analysis of covariance (ANCOVA), with diagnosis as a between-group factor and intracranial volume (ICV) as a covariate. The relationships between the volumes of each ROI and subject characteristics (age, age of onset, duration, and PANSS score) were investigated using Pearson’s correlation coefficients. All statistical analyses were two-tailed, and P<0.05 was used as the level of significance. All statistical analyses were conducted using SPSS for Windows software, version 11.0 (SPSS, Chicago, IL, USA).

3. Results

The mean ICV was 1064.70±97.90 ml for the schizophrenia group, and 1103.65±166.36 ml for the normal comparison group (t=1.09, df=60, P=0.28). Table 2 shows volumes of each ROI subregion and the results of the ANCOVA, taking ICV as a covariate and diagnosis as a grouping variable. As shown in Table 2, the right IC volume was significantly smaller in patients with schizophrenia (F=5.95, df=1, 60, P=0.018). We found no significant relationship between the volumes of each colliculus and age, age of onset, duration, and subscale and total score of the PANNS subscale and total scores for the patients with schizophrenia.

4. Discussion

To our knowledge, this is the first study to investigate the structure of the dorsal midbrain using MRI in patients with schizophrenia. Although Nopoulos et al. reported a reduced midbrain volume in patients with schizophrenia compared with normal controls, the volumes of the SC and the IC were not included in their study (Nopoulos et al., 2001). Descending projections from the auditory cortex, which is located in the superior temporal gyrus, to the thalamus and IC are thought to contribute to optimal sensory signal extraction and may be involved in long-term, use-dependent plasticity (Bajo and Moore, 2005; Senatorov and Hu,

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**Table 2**

Absolute volumes (mm³) of the superior colliculus and the inferior colliculus of the patients with schizophrenia and controls

<table>
<thead>
<tr>
<th>Region</th>
<th>Schizophrenia (n=28)</th>
<th>Controls (n=34)</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior colliculus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>153.85 (28.71)</td>
<td>164.79 (24.64)</td>
<td>1.83</td>
<td>0.18</td>
</tr>
<tr>
<td>Right</td>
<td>150.39 (26.83)</td>
<td>159.21 (30.71)</td>
<td>0.88</td>
<td>0.35</td>
</tr>
<tr>
<td>Inferior colliculus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>126.56 (20.55)</td>
<td>134.79 (16.02)</td>
<td>2.44</td>
<td>0.12</td>
</tr>
<tr>
<td>Right</td>
<td>113.18 (14.82)†</td>
<td>123.60 (16.23)</td>
<td>5.95</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Data are given as mean (S.D.).

† df=1, 60, P<0.05 compared with controls.
mediated by a distributed network of cortical and subcortical regions (Shergill et al., 2000) reported that auditory verbal hallucinations in patients with schizophrenia may be handled by the cortico-collicular circuitry. Furthermore, converging evidence suggests that the auditory cortex plays a critical role in experience-dependent auditory plasticity through inhibitory influences via GABAergic collicular interneurons (Mitani et al., 1983). 

In particular, Sweet et al. suggested that impairments of auditory corticocortical feedforward projection neurons underlie the deficits in auditory processing seen in patients with schizophrenia (Sweet et al., 2003; Thoma et al., 2004). In addition, Shergill et al. (2000) reported that auditory verbal hallucinations in patients with schizophrenia may be mediated by a distributed network of cortical and subcortical areas including the right IC.

The cortico-collicular projections appear to be glutamatergic (Brandao et al., 2005; Moncoutiet et al., 2006; Saldana et al., 1996), providing direct excitatory influences to ascending collicular neurons and indirect inhibitory influences via GABAergic collicular interneurons (Mitani et al., 1983). Furthermore, converging evidence suggests that the auditory cortex plays a critical role in experience-dependent auditory plasticity through descending projections to the IC (Xiao and Suga, 2005; Zhang et al., 2005). Taken together, our finding of a reduced IC volume suggests that the deficits in auditory processing observed in patients with schizophrenia are mediated not only by the corticocortical circuitry, but also by the cortico-collicular circuitry.

In addition to auditory processing, the functional connection of the IC with the amygdala is an important filter for sensorial information of an aversive nature, which plays an important role in the expression of defensive behavior (Brando et al., 1999; McIntosh and Gonzalez-Lima, 1998; Nobre et al., 2004). Furthermore, it has been suggested that unconditioned defensive responses in the IC are mediated by an \( N\)-methyl D-aspartate (NMDA) mechanism, the dysfunction of which is consistently implicated in the pathophysiology of schizophrenia (Goff and Wine, 1997). Combined, structural abnormalities of the IC in patients with schizophrenia may be related to the disrupted fear conditioning and anxiety-like symptom observed in these patients.

In this study, we observed a significant structural difference only in the right IC. This finding may seem surprising considering the left preference in structural abnormalities reported in the investigation of schizophrenia. From the standpoint of functional connectivity with the superior temporal cortex, however, O’Daly et al. (2007) demonstrated the prominent volume decrease of the right superior temporal gyrus in schizophrenia patients with persistent auditory hallucination. Furthermore, prominent activation of the right hemisphere, including the right IC during auditory hallucinations, was also evident in a functional neuroimaging study (Shergill et al., 2000). Taken together, these reports and our findings of a volume decrease in the right IC suggest that the right hemisphere may preferentially mediate the auditory cognitive dysfunction of schizophrenia.

In addition, we found no significant volume differences in the SC between groups. Considering the extensive mutual networks between the IC and SC, and their intimate developmental origin (Zervas et al., 2005), our findings are intriguing. Nevertheless, Dagnino-Subiabre et al. (2005) suggested that chronic stress has more deleterious effects in the subcortical auditory system than in the visual system. They found that stress induced dendritic atrophy in the IC neurons and did not affect neuronal morphology in the SC. Furthermore, it has been suggested that the auditory P3 component of the event-related potential is often selectively or more severely impaired relative to the visual P3 component in schizophrenia, and as compared with the visual P3, the auditory P3 seems relatively independent of medication and clinical symptom profile (Mathalon et al., 2000; Pfefferbaum et al., 1989; van der Stelt et al., 2004). From this perspective, our findings of a reduced volume of the IC and a normal volume of the SC partially concur with previous reports and present additional structural evidence that the disturbance in auditory processing is a more prominent and enduring phenomenon in the pathophysiology of schizophrenia.

We acknowledge several limitations in our study. First, the validity of the ROI method used could not be verified because no previous studies of the IC and SC have been conducted. However, the relatively high ICC between raters, suggests that our method is an effective way of measuring the IC and SC morphology using MRI. Second, all the patients with schizophrenia who participated in this study were taking antipsychotic medication. Therefore, we could not exclude the possibility of that the medications affected the dorsal midbrain volumes, although no significant correlations were observed between the IC and SC volumes and the current antipsychotic dose and duration of illness. Finally, we found no significant correlation between the IC volume decrease and clinical symptom severity in patients with schizophrenia in the current study. However, from the point of view of brain network systems, structural abnormalities may lead to alterations of interactions between brain regions, resulting in cognitive dysfunction and symptomatic expressions of schizophrenia. A longitudinal investigation of first-episode or drug-naive
patients with schizophrenia is needed to extend our findings. In conclusion, our results suggest the possibility that a structural abnormality of the IC in patients with schizophrenia might be involved in both the auditory cognitive dysfunction and symptomatic expression characteristic of schizophrenia.

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References


