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Effects of aging on the morphologies of Heschl's gyrus and the superior temporal gyrus in schizophrenia: A postmortem study

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ABSTRACT

The etiology of schizophrenia has been proposed to be neurodevelopmental based on neuroimaging and molecular biological studies. If there is neuronal vulnerability based on neurodevelopment failures in schizophrenic brains, then the impact of aging may have a greater effect on schizophrenic brains than on normal brains. To determine the impact of aging on schizophrenic brains, we investigated the age-related morphological changes of the cross-sectional area of the gray matter (GM) in the left Heschl's gyrus (HG) and the left superior gyrus (STG) in 22 schizophrenic and 24 age- and sex-matched normal control postmortem brains two-dimensionally. The subject groups were divided into younger groups (30–54 years of age) and older groups (65–84 years of age) on the basis of age at death. Both in schizophrenic and control subjects, the GM area in HG and the STG was significantly smaller in the older group than in the younger group, however, no significant differences were observed between the schizophrenic and control subjects. In the STG, the cross-sectional area of the white matter (WM) was also measured. In the older group, the ratio of the GM area to the WM area in the STG was significantly larger in schizophrenic subjects than controls, although there was no significant difference between the schizophrenic and control subjects in the younger group. These findings indicate that the impact of aging has a greater effect on the WM in the STG in schizophrenic subjects than in normal individuals, although the pathological basis is still unclear.

1. Introduction

A decreased cortical volume in schizophrenic brains has been repeatedly reported in cross-sectional imaging studies (Honea et al., 2005; Steen et al., 2006) and postmortem studies (Harrison, 1999; Iritani, 2007). It is understood that this morphological change occurs during the very early period of the formation of the central nervous system, because no gliosis has been found in the postmortem brains of schizophrenic patients (Arnold and Trojanowski, 1996). On the other hand, recent longitudinal imaging studies have also reproducibly reported a greater progressive loss of the cortical volume after disease onset (DeLisi et al., 1997; Kasai et al., 2003b; Nakamura et al., 2007). It is assumed that these phenomena depend on not only neuronal development (Thompson et al., 2001; Vidal et al., 2006) but also continued neuronal degeneration, the long-term use of antipsychotic drugs (Lieberman et al., 2005; Thompson et al., 2009) and unknown interactions between aging and schizophrenia (Harrison, 1999). However, the basis of the volumetric change after disease onset still remains unclear.

To investigate the impact of aging on schizophrenia, it is necessary to consider physiological atrophy and the concomitant presence of neurodegenerative disorders (e.g. Alzheimer-type dementia [ATD], frontotemporal lobar degeneration, etc.) separately. Most neuropathological studies have reported the frequency of Alzheimer-type neuropathological changes in schizophrenic brains to be equal to that in the general population (Powchik et al., 1998; Purohit et al., 1998; Jellinger and Gabriel, 1999), but it remains unclear how the physiological changes in the brain volume of schizophrenic patients occurs, compared to that of the normal brain. To investigate the impact of physiological atrophy, it is necessary to select elderly cases without significant neuropathological changes as study subjects. It is

Abbreviations: ATD, Alzheimer-type dementia; BA, Brodmann area; CPZ, chlorpromazine; CSI, circular sulcus of insula; DTI, diffusion tensor imaging; FTS, first transverse sulcus; GAF, Global Assessment of Functioning; GM, gray matter; HG, Heschl's gyrus; HS, Heschl's sulcus; PMI, postmortem interval; SI, sulcus intermedius; STG, superior temporal gyrus; STS, superior temporal sulcus; WM, white matter.

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impossible to detect neuropathological changes with the subtle and subclinical concomitant presence of neurodegenerative disorders or other organic factors, such as cerebrovascular changes, by neuroimaging investigations. A postmortem analysis has advantages in that it can determine subtle or subclinical neurodegenerative and organic changes which cannot be detected during the neuroimaging analysis of living subjects. In some cases, early onset frontotemporal dementia, organic psychotic disorders and so on are misdiagnosed as schizophrenia (Fujii et al., 2004; Velakoulis et al., 2009). Generally, schizophrenia is diagnosed based on the operational diagnostic criteria, such as the DSM IV-TR based on clinical symptoms, because so far no definite biological diagnostic tools have yet been established. In addition, neuropathological investigations of the schizophrenic brain are hardly ever performed posthumously in usual clinical settings. Therefore, it is important to perform postmortem neuropathological evaluations, even if the subjects are relatively young at the time of death.

Heschl's gyrus (HG) and its posterior region, the planum temporal (PT), are located on the dorsal surface of the superior temporal gyrus (STG). HG forms part of the primary auditory cortex (Brodmann area [BA] 41/42) and plays a crucial role in auditory perception, while the anterior portion of the PT, which surrounds HG, forms part of the unimodal auditory association cortex (part of BA22) and plays a critical role in language processing (Shapleske et al., 1999). In structural imaging studies, the gray matter (GM) in the STG and its sub-regions, such as HG or the PT, has been found to be smaller (McCarley et al., 2002; Takahashi et al., 2006) and even to decrease over time in schizophrenic patients (Kasai et al., 2003b; Salisbury et al., 2007). Moreover, their reduced size has been correlated with the degree of thought disorder (Shenton et al., 1992; Anderson et al., 2002) and auditory hallucinations (Barta et al., 1990; Onitsuka et al., 2004), especially when the difference is noted on the left side (Sun et al., 2009).

In this study, to determine whether aging has a greater impact on schizophrenic brains than on normal brains, we investigated the age-related changes in the cross-sectional GM area in the left HG and the STG using post-mortem neuropathological slide specimens without significant neuropathological changes. In addition, we also investigated the age-related changes of the cross-sectional area of the white matter (WM) and the ratio of the GM area to the WM area in the left STG to identify differences due to aging in schizophrenic patients and normal subjects.

2. Experimental/Materials and methods

2.1. Subjects

Brain specimens obtained from 22 schizophrenic patients and 24 age- and sex-matched normal control brain specimens were obtained from autopsy cases at Tokyo Metropolitan Matsuzawa Hospital based on the following criterion: age at death≧30 years and ≦54 years for the younger groups (11 schizophrenic patients, 11 control subjects), and ≧65 years and ≦84 years for the older groups (11 schizophrenic patients, 13 control subjects). The demographic details of the subjects are summarized in Table 1.

We confirmed the diagnosis by reviewing the clinical records to verify that the cases satisfied the DSM-IV-TR criteria for schizophrenia, and that the control subjects had no evidence of psychiatric or neurological disorders.

We also excluded cases with significant neuropathological changes, such as neurodegenerative disorders (e.g. ATD, frontotemporal lobar degeneration, etc.), cerebrovascular diseases, brain invasion of tumors, severe malnutrition, metabolic encephalopathies, inflammatory or traumatic processes, and so on, based on the records of clinico-pathological conferences with several expert neuropathologists. We selected cases without any history of alcohol or substance abuse, convulsions or mental retardation based on the patient clinical records. We confirmed that all cases had sufficient social function before onset and had completed compulsory education.

Table 1
The basic demographic characteristics of the subjects.

	Control		Schizophrenia	
	Younger group	Older group	Younger group	Older group
Number	11	13	11	11
Sex (M/F)	6/5	8/5	7/4	5/6
Age at death (years) range (years)	45.0 ± 8.1 (31–54)	72.7 ± 4.4 (66–81)	44.4 ± 6.8 (33–54)	70.9 ± 5.1 (65–83)
Age at onset (years)	–	–	27.7 ± 13.6	29.7 ± 8.6
Duration of illness (years)	–	–	16.6 ± 10.7	41.2 ± 8.9
Subtype (Paranoid/ Disorganized/Catatonic/ Undifferentiated)	–	–	7/3/1/0	5/4/1/1
GAF scores	–	–	28 ± 4.3	24.3 ± 5.8
Mean daily antipsychotic dosage[d] (mg/day)	–	–	561.3 ± 216.0[a]	562.5 ± 459.6[a]
Lifetime daily antipsychotic dosage[d] (g)	–	–	3343.9 ± 1921.5[a]	8479.4 ± 6139.9[a]
Cause of death (Cardiac/ Respiratory/Other)	3/3/5	2/6/5	1/5/5	1/5/5
Cerebrum weight (kg)	1332.5 ± 165.9[b]	1310.8 ± 206.9	1360.0 ± 171.1	1265.9 ± 149.6
PMI (hours)	6.1 ± 5.4[c]	6.8 ± 4.9[c]	8.3 ± 13.6	10.9 ± 8.6[c]

GAF: Global Assessment of Functioning, PMI: postmortem interval.
There were no significant differences, except for in the age at death and duration of illness, between the younger and older groups ($p<0.01$, Mann–Whitney U test).
[a] Not known for 1 younger subject and 3 older subjects.
[b] Not known for 1 control subject.
[c] Not known for 2 younger control, 2 older control and 2 older schizophrenic subjects.
[d] Chlorpromazine milligram or gram equivalents.

We assessed the clinical severity in the predominant state using the Global Assessment of Functioning (GAF) scale (American Psychiatric Association, 2000), because this scale was easy to pick up retrospectively from the clinical records. It was impossible to evaluate the detailed degrees of symptoms in life retrospectively using the Brief Psychiatric Rating Scale or Positive and Negative Symptom Scale. We measured the sum of antipsychotic dosage taken throughout their lifetime (lifetime antipsychotic dosage) and the mean daily antipsychotic dosage (chlorpromazine [CPZ] milligram equivalents per day) by reviewing the clinical records.

This study was approved by the Nagoya University School of Medicine Ethical Review Board.

2.2. Brain tissue processing

In all cases, the cadavers were kept at 4°C before autopsies to prevent autolysis and tissue degeneration. All brains were extracted and fixed in 10% formalin within 48 h after death. After fixation, the brains were sectioned in the coronal plane. The brains were embedded in paraffin and cut at a thickness of about 10 μm. The sections were stained with hematoxylin-eosin and/or Klüver-Barrera.

2.3. Morphometric analysis

A morphometric analysis was performed by one of the coauthors blind to the diagnosis. In each subject, we used a neuropathological specimen slide from each left coronal slice at the level where HG, the hippocampus and the subthalamic nucleus appeared. Each slice was scanned into a computer as digital data (TIFF file) using an image scanner (CanoScan LiDE 500F; Canon Inc., Japan) at 600 dpi. The tracing and measurements of regions of interest were performed manually using the Adobe Photoshop 6.0 (Adobe Systems Inc., CA,