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Review

Superior temporal gyrus volume change in schizophrenia: A review on Region of Interest volumetric studies☆

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ABSTRACT

Imaging studies of schizophrenia (SCZ) have repeatedly demonstrated volume differences in superior temporal gyrus (STG) and its subregions. Among them, some studies employed the Region of Interest (ROI) method. We carried out a systematic review of the published literature on STG volumetry MRI studies to examine the potential of ROI method for identifying specific structural differences and correlations with clinical variables including hallucinations and thought disorder symptoms in SCZ. Forty-six studies were identified as suitable for review and analysis including 1444 patients with SCZ and 1327 controls. Female and left-handed subjects are under-represented in the literature and insight from sex and handedness differences may be lost. Thirty-five studies reported significant differences in STG or subregional volumes including bilateral or unilateral ROI, and volume reduction was the most common change in SCZ. Thirty studies reported correlations between volume changes and clinical symptoms or syndromes and 18 found positive results. Among them, left STG or subregions appear to be more involved in the generation of hallucinations and thought disorder than right side. The majority of five follow-up studies found evidence of progressive changes in volumes. Clinical heterogeneity, MRI acquisition parameters, anatomical landmarks for ROI, and sample characteristics, are likely to be the main factors leading to heterogeneous results. Clearly this research links pathophysiological changes in the STG with the development of hallucinations and thought disorder in patients with SCZ, especially in the left side. There is a suggestion that these changes may be progressive but this requires more thorough and comprehensive assessment.

☆ Competing interests statement: The authors declare that they have no competing financial interests.

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Abbreviations: AH, auditory hallucination; BA, Brodman's areas; BPRS, Brief Psychiatric Rating Scale; DBM, deformation-based morphometry; DSM, Diagnostic and Statistical Manual of Mental Disorders; ERP, Evoked Response Potentials; GM, grey matter; GMV, grey matter volume; H, hallucination; HG, Heschl's gyrus; ICV, intracranial volume; ICC, intraclass correlation coefficients; MRI, magnetic resonance imaging; PT, Planum temporale; PP, Planum polare; ROI, Region of Interest; SCZ, schizophrenia; STS, superior temporal sulcus; STP, superior temporal plane; STG, Superior temporal gyrus; TD, thought disorder; TBV, total brain volume; TCV, total cerebral volume; VBM, voxel-based morphometry; WM, white matter; WMV, white matter volume

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Contents

1. Introduction

Structural brain differences in schizophrenia (SCZ) have been extensively investigated using magnetic resonance imaging (MRI). Many brain regions have been investigated including the temporal lobe structures (see reviews by Honea et al., 2005; Pearlson, 1997; Shenton et al., 2001; Wright et al., 2000). One of the most commonly implicated regions in these studies is the superior temporal gyrus (STG), usually in the left hemisphere (see reviews by Pearlson, 1997; Honea et al., 2005). The STG is a critically important brain region containing several important structures of the brain within an important network of connections to temporal limbic brain regions; which plays a major role in the production, interpretation and self-monitoring of language. Dysfunction of either the STG or its network of connections is pertinent to SCZ and closely linked to two key positive symptoms of the disorder, auditory hallucinations (AH) and thought disorder (TD) (see reviews by Allen et al., 2008; Pearlson, 1997; Shenton et al., 2001).

The superior temporal gyrus is one of three (sometimes two) gyri in the temporal lobe of the human brain. It is a long region located along the sylvian fissure dorsally and the superior temporal sulcus (STS) ventrally, and is subdivided into several regions both structurally and functionally. The most anterior portion of STG is temporal polar cortex (Brodmann area 38) (see a review by Pearlson, 1997). The dorsal surface of the STG is located within the sylvian fissure and is divided into Heschl's gyrus (HG), the planum temporale (PT), and the planum polare (PP) (Kim et al., 2003). STG contains several important structures of the brain, including primary auditory cortex (Brodman's areas [BA] 41/42) in HG and auditory association cortical areas (BA 22) in the anterior portion of PT that surrounds the HG (Kasai et al. 2003b; see a review by Pearlson, 1997; Shapleske et al., 1999). HG and PT have been thought of as candidates for the neural basis of language-related psychotic symptoms such as AH and TD in patients with SCZ (Yamasaki et al., 2007).

Structural imaging is widely used in the analysis of the volumes of the brains of people with medical and psychiatric conditions using MRI. Changes in brain volume or structure may be a direct marker of the involvement of a brain region in a pathological process. Barta et al. (1990) first reported a volume reduction of STG in patients with SCZ. Since then

there have been numerous studies on STG volumetry in subjects with SCZ which have reported volumetric deficits in the anterior, posterior, or total STG as well as subregions of the supratemporal plane such as HG or PT (Kim et al., 2003). When abnormalities have been found, they typically are reported on the left side. However, results are inconsistent and some studies have found no volumetric differences in the STG in SCZ when compared to healthy controls (e.g. Kulynych et al., 1996; Vita et al., 1995). The size of the STG has also been shown to relate to symptoms of SCZ, but with inconsistencies between reports. Barta et al. (1990) reported the volume of the left STG to be inversely correlated with AH and Shenton et al. (1992) reported the left posterior STG volume as negatively correlated with TD. Some studies reported reduced STG volume was correlated with delusions (e.g. Menon et al., 1995) and reduction in amplitude of the P300 Evoked Response Potentials (ERP) (McCarley et al., 1993). The later studies reported some positive results (see a review by Shenton et al., 2001). Still others have failed to find any relationship between the STG volumetric and clinical symptoms (e.g. Sanfilipo et al., 2000).

In the imaging literature as mentioned above, the most prominent method used to investigate STG structural differences is Region of Interest (ROI) analysis (see a review by Honea et al., 2005). ROI analyses, whereby the areas or volumes of a limited number of brain regions are estimated by manual delineation of their boundaries on a priori-defined ROI imaging data, have been the gold standard for structural MRI examinations although it is time-consuming. Their advantages include anatomical validity, definition of landmarks in native space and quantitative measures of the voxels in the regions under study (García-Martí et al., 2008). However, a limitation is that most ROI studies have included small numbers of patients because the method is labor-intensive and time-consuming, making it difficult to detect small effects and establish firm conclusions. It is therefore important that the results of all studies conducted be made available in a form that permits their combination and improves the estimation of the overall effect size.

Previous meta-analyses and reviews of brain structural differences in SCZ have been conducted (see reviews by McCarley et al., 1999; Wright et al., 2000) and also found regional deficits in the STG in SCZ patients compared with controls. Among them, Pearlson (1997) published a review on STG and PT in SCZ. The paper covered literature relating to STG structural and functional pathology and correlations with clinical symptoms derived from electrophysiology, structural and functional MRI studies. They found strong but not unanimous evidence of structural abnormalities of STG in SCZ, associated with AH and formal thought (language) disorder. However, more recent neuroimaging findings and the developments in brain imaging techniques and increasingly sophisticated analytical techniques, have led to clearer findings of STG structural abnormalities and correlations with some clinical variables in SCZ patients.

In this review we systematically reviewed the literature on the use of ROI analysis in SCZ structural MRI research focused on STG (including HG and PT) volume change and correlations between volume change and clinical symptoms including AH and TD in SCZ, compared with healthy subjects.

2. Methods

2.1. *Search strategy and inclusion/exclusion criteria*

A comprehensive search from a range of electronic databases, including EMBASE, PsycINFO, and PubMED was conducted up to July 2008. Key words used to identify the studies were: schizophrenia and magnetic resonance imaging and superior temporal gyrus, schizophrenia and MRI and superior temporal gyrus, schizophrenia and MRI and STG, schizophrenia and MRI and Heschl's gyrus, schizophrenia and MRI and planum temporale. The search was also complemented by manual and bibliographic cross-referencing.

Studies were considered for the review by using the following inclusion criteria: 1) they were published up until July 2008 as an article (rather than a letter or an abstract or a case report) in the journal in English; 2) they compared a group of subjects with SCZ (either first-episode patients or chronic patients) and a healthy comparison group; 3) all articles reporting data on the volume (either grey matter [GM] or white matter [WM] or both) of the STG as well as its subregions such as HG or PT using structural brain MRI techniques were included; 4) the studies used a ROI volumetric method for measuring brain regional volumes; 5) studies reporting results of SCZ but some patients had related diagnoses (e.g. schizoaffective disorder or schizophreniform disorder) were also included; 6) studies of early-onset SCZ such as child and adolescent patients were included; 7) studies of follow-up if a baseline information of STG or subregions volume was reported were included.

Studies were excluded if: 1) insufficient data were reported to extract the number of subjects in each group or the mean or the standard deviation of the volumes from MRI; 2) the structure measurement was an area (from a single slice rather than a volume; 3) the studies used the voxel-based morphometry (VBM), deformation-based morphometry (DBM) or tensor-based volumetric method for measuring brain regional volumes; 4) the study focused primarily upon relatives of patients with SCZ.

2.2. *Review process and data analysis*

Data extracted from the studies included the authors, year of publication, demographic variables (e.g. number, age, and gender), illness variables (e.g. diagnostic criteria and duration of illness), MRI variables (e.g. scanner, Tesla, and slice thickness), main volume change findings about STG or its subregions, and main findings about correlations between volume changes of STG or its subregions and clinical variables especially clinical symptoms. We calculated the rates of sex, handedness, and the total numbers of subjects according to the original studies. We also aimed to summarize similar results of different studies relating to volume changes in STG and their correlations with other clinical variables.

3. Results

Forty-six studies were identified as suitable for review and analysis, having published ROI volumetric studies of the STG as well as its subregions using structural MRI techniques that contained sufficient data including volume means of SCZ patients and controls (Table 1). A total of 2771 subjects in the 46 studies were included, which comprised 1444 patients and 1327 controls. Five of these studies are follow-up studies which provided baseline data. Amongst the patient group the smallest size sample is 8 SCZ patients (Holinger et al., 1999),

Table 1 – Basic information and MRI methods employed in all reviewed ROI studies on STG or subregions volume measurement.

Study	N_0	Controls		Characteristics of SCZ patients						MRI variables	
		N_1	N_1'	N_2	N_2'	RM (%)	MA (Y)	ID (Y)	RRH (%)	Scanner	ST (mm)
Anderson et al. (2002)	31	15	15	16	16	100	42.5	19.69	100	GE 1.5 T	1.5
Barta et al. (1997a)	60	32	32	28	28	75	41.57	–	82	GE 1.5 T	1.5
Barta et al. (1997b)	29	18	18	11	11	–	72	–	–	GE 1.5 T	3
Barta et al. (1990)	30	15	15	15	15	100	30.6	–	87	GE 1.5 T	3
Bryant et al. (1999)	96	37	37	59	59	61	41	–	100	Sie. 2.0 T	3
Buchanan et al. (2004)	78	34	34	44	44	73	39	17.3	100	GE 1.5 T	1.5
Crespo-Facorro et al. (2004)	60	30	30	30	30	100	33.5	2.1	100	GE 1.5 T	1.5
DeLisi et al. (1994)	125	40	40	85	85	59	26.94	–	86	GE 1.5 T	5
DeLisi and Hoff (2005)	37	10	10	27	27	67	–	–	–	GE 1.5 T	5
Flaum et al. (1995)	189	87	87	102	102	69	31.8	9.7	92	GE 1.5 T	3
Gur et al. (2000)	210	110	110	100	100	51	29.2	6.5	100	GE 1.5 T	1
Havermans et al. (1999)	47	17	17	30	30	50	36.3	–	100	Phi. 1.5 T	3
Hirayasu et al. (2000)	42	22	4	20	3	80	27.3	–	100	GE 1.5 T	1.5
Hirayasu et al. (1998)	35	18	18	17	17	82	26.7	–	100	GE 1.5 T	1.5
Holinger et al. (1999)	18	10	10	8	8	100	38	–	0	GE 1.5 T	1.5
Jacobsen et al. (1998)	27	17	0	10	0	70	15.2	–	80	GE 1.5 T	1.5
Jacobsen et al. (1996)	62	41	41	21	21	62	14.6	–	71	GE 1.5 T	2
Kasai et al. (2003a)	27	14	14	13	13	77	27.2	–	100	GE 1.5 T	1.5
Kasai et al. (2003b)	35	22	8	13	0	77	27.2	–	100	GE 1.5 T	1.5
Keshavan et al. (1998)	34	17	17	17	17	71	25.41	3.13	71	GE 1.5 T	2.6
Kim et al. (2003)	50	25	25	25	25	100	25.4	–	80	GE 1.5 T	1.5
Kulynych et al. (1996)	24	12	12	12	12	100	29.5	–	100	GE 1.5 T	1.5
Kwon et al. (1999)	32	16	16	16	16	100	45.1	23.3	100	GE 1.5 T	1.5
Marsh et al. (1997)	108	52	52	56	56	100	35.9	19.3	84	GE 1.5 T	3
Matsumoto et al. (2001)	80	40	40	40	40	50	15.5	–	80	GE 1.5 T	1
McCarley et al. (2002)	33	18	3	15	0	80	27.6	0.44	100	GE 1.5 T	1.5
McCarley et al. (1993)	29	14	0	15	0	100	38	15.8	100	GE 1.5 T	1.5
Meisenzahl et al. (2004)	100	50	20	50	20	100	30	6.8	100	Sie. 1.5 T	1.5
Meisenzahl et al. (2002)	60	30	30	30	30	100	29.37	–	100	Sie. 1.5 T	1.5
Menon et al. (1995)	40	20	5	20	5	100	29.7	8	–	GE 1.5 T	3
Onitsuka et al. (2004)	51	28	28	23	23	100	42	19.1	100	GE 1.5 T	1.5
Pearlson et al. (1997)	106	60	60	46	46	70	31.8	–	83	GE 1.5 T	3
Rajarethinam et al. (2000)	40	20	20	20	20	100	22.9	10.35	85	GE 1.5 T	3
Sallet et al. (2003)	60	20	40	40	40	60	34	15.8	85	Phi. 1.5 T	1.2
Sanfilipo et al. (2000)	82	29	29	53	53	100	38.7	14.4	87	Vis. 1.5 T	2.8
Sanfilipo et al. (2002)	89	27	0	62	9	100	38.8	15.2	87	Vis. 1.5 T	2.8
Shenton et al. (1992)	30	15	15	15	15	100	37	15.8	100	GE 1.5 T	1.5
Sumich et al. (2002)	41	16	16	25	25	100	24	0.67	100	GE 1.5 T	1.5
Takahashi et al. (2006)	137	72	72	65	65	54	25.8	4	100	Sie. 1.5 T	1
Taylor et al. (2005)	34	16	16	18	18	–	11.8	–	–	GE 1.5 T	1.2
Tune et al. (1996)	29	15	15	14	14	50	39.22	–	–	GE 1.5 T	3
Vita et al. (1995)	34	15	15	19	19	63	25.6	1.6	100	GE 0.5 T	5
Woodruff et al. (1997)	85	43	43	42	42	100	32.4	11.1	100	Phi. 1.5 T	3
Yamasaki et al. (2007)	39	22	22	17	17	100	29.5	8.8	100	GE 1.5 T	1.5
Yamasue et al. (2004a)	54	27	25	27	25	74	30.4	9.81	100	GE 1.5 T	3
Yamasue et al. (2004b)	32	19	17	13	11	54	29.8	8.4	100	GE 1.5 T	1.5

GE = General Electric scanner; ID = means of illness duration (year, Y); MA = means of year at scan (year, Y); N_1 = numbers of controls; N_2 = numbers of patients; N_0 = numbers of total subjects in every study ($=N_1+N_2$); N_1' = numbers of new controls in study that were not included in previous studies we reviewed; N_2' = numbers of new patients in study that were not included in previous studies we reviewed; Phi. = Phillips scanner, R = right; RM = the rate of male patients (%); RRH = the rate of right-handed patients (%); SCZ = Schizophrenia; Sie. = Siemens scanner, ST = slice thickness (mm); Vis. = Vista HPQ Pickar; – = not available.

and the biggest size sample is 102 SCZ patients (Flaum et al., 1995). These studies were published from 1990 to 2007. From 46 studies identified we found some studies may have shared some common subjects such as some authors came from the same project group and the measurements may have contributed to another publication after the addition of new subjects. We tried to identify the information about the number of new subjects from the original studies. Where possible, we contacted the corresponding authors of some articles for complementary information. Finally we identified a total of 1193 unique patients and 1272 controls in the 46 studies. Table 1 summarized the information about demographic and general clinical variables and MRI method of the subjects in the 46 studies we reviewed.

3.1. *Demographic characteristics*

The age range of the SCZ group in the studies reviewed was 11.8 years to 72 years. Altogether four studies (Jacobsen et al., 1998; Jacobsen et al., 1996; Matsumoto et al., 2001; Taylor et al., 2005) comprised SCZ samples of a childhood-onset or early-onset form. The youngest patient sample was from childhood-onset SCZ patients (mean age=11.8, S.D.=3.2) (Taylor et al., 2005). The rest of the 42 studies were adult patient samples. The mean age in the youngest patient samples among adult studies was 22.9 years (S.D.=8.09) (Rajarethinam et al., 2000). The mean age of the oldest patient samples was 72 years (S.D.=10) (Barta et al., 1997b).

45.5% of studies (20 of 44 studies, 2 studies have no sex information) selected only male patients. In another 24 studies the rate of male patients was higher (50% to 87.5%). The number of male patients (n=1094) in the 44 studies was more three times that of female patients (n=321).

61% of studies (25 of 41 studies, 5 studies have no handedness information) selected full (100%) right-handed patients and only one article studied the full left-handed patients (Holinger et al., 1999). Rate of right-handed patients in another 16 studies occupied 71%–87%.

3.2. *General clinical information*

A number of inclusion criteria were used: 67.4% of studies (31 of the 46 studies) used the Diagnostic and Statistical Manual of Mental Disorders (DSM), Third Edition, Revised (DSM-III-R), 26.1% of studies (12 of 44 studies) used DSM, Fourth Edition (DSM-IV), one study used the International Statistical Classification of Diseases and Related Health Problems, Tenth Edition (ICD-10) Diagnostic Criteria for Research (Takahashi et al., 2006), one study used both DSM-III-R and DSM-IV (Buchanan et al., 2004), and one study used both ICD-10 and DSM-IV diagnostic criteria (Meisenzahl et al., 2004).

Ten studies recruited the samples of first-episode SCZ or related diagnosis (DeLisi and Hoff, 2005; DeLisi et al., 1994; Hirayasu et al., 2000; Hirayasu et al., 1998; Kasai et al., 2003a; Kasai et al., 2003b; Keshavan et al., 1998; Kim et al., 2003; McCarley et al., 2002; Sumich et al., 2002). One study collected data on patients with recent-onset SCZ (Matsumoto et al., 2001). One study used a later-life onset SCZ sample (Barta et al., 1997b). The other 34 studies used chronic SCZ samples and a few of studies included first-episode patients.

The mean illness duration for the SCZ patients group of these studies ranged from 0.44 years to 23.3 years, although we could not find this information in 45.5% of studies (20 studies).

Only two of 46 studies employed purely neuroleptic-naïve patients (Keshavan et al., 1998; Kim et al., 2003). One study employed 14 chronic patients including 9 neuroleptic-naïve and 5 neuroleptic-free patients (Tune et al., 1996). Eight studies have no detailed information about medication. Patients in the remaining 36 studies were receiving a form of neuroleptic treatment when MRI scanned. Among them, most patients received typical neuroleptic treatments. There are six studies which included a few neuroleptic-naïve or neuroleptic-free patients (Barta et al., 1997a; Hirayasu et al., 2000; McCarley et al., 2002; Sanfilipo et al., 2000; Taylor et al., 2005; Vita et al., 1995).

3.3. *MRI methods*

Acquired slice thickness for STG or subregions measurements in these studies ranged from 1 mm to 5 mm. Three studies acquired 1 mm slices (Gur et al., 2000; Matsumoto et al., 2001; Takahashi et al., 2006). Three studies acquired 5 mm slices (DeLisi and Hoff, 2005; DeLisi et al., 1994; Vita et al., 1995). Amongst 46 studies, 21 studies acquired 1.5 mm slices and 12 studies acquired 3 mm slices.

The vast majority (95.7%; 44 of 46 studies) used a GE 1.5 T scanner. One study used 0.5 T (Vita et al., 1995) and one study used 2 T (Bryant et al., 1999).

3.4. *Information about ROIs*

3.4.1. *Categories of ROIs or subregions of STG*

There are different ROIs according to the different partition methods the studies employed (see Table 2). Sixteen studies used the common partition method to trace left and right STG subregions to calculate the volumes. Thirteen studies further traced the anterior and posterior STG region besides measuring left and right STG volumes. Seven studies measured HG and PT volumes and further divided into left and right sides. The remaining eight studies divided the STG into the three subregions as anterior third, mid third and posterior third STG (Rajarethinam et al., 2000), or five subregions including HG, PT, PP, rostral and caudal STG (Takahashi et al., 2006). Several studies measured only anterior STG (Barta et al., 1997b) or middle and posterior STG (Menon et al., 1995), or PT (Meisenzahl et al., 2002; Sallet et al., 2003).

3.4.2. *Anatomical landmarks for ROI tracing*

According to the particular method employed, some studies selected the specific anatomic landmarks to define STG or subregions for tracing. These kinds of landmarks served as general guidelines to supplement the information derived from visual inspection of the MRI images and measurement rules. There were some studies that shared the same or almost the same method of anatomic landmarks of STG as well as subregions listed as below.

For example, there were 13 studies that completely employed or mainly employed the method of STG or subregional anatomic landmarks based upon Shenton et al. (1992)

(Anderson et al., 2002; Havermans et al., 1999; Hirayasu et al., 1998; Holinger et al., 1999; Jacobsen et al., 1998; Jacobsen et al., 1996; Kulynych et al., 1996, McCarley et al., 2002; McCarley et al., 1993; Meisenzahl et al., 2004; Sanfilipo et al., 2002; Sanfilipo et al., 2000; Yamasue et al., 2004a). The basic criteria of the anatomic landmark is: 1) for the anterior STG: from the first slice containing the white matter tract of the temporal stem to the last slice prior to the mamillary bodies; 2) for the posterior STG: from the first slice containing the mamillary bodies to the last appearance of the fibers of the crux of the fornix.

There were 4 studies that completely employed or mainly employed the method described by Barta et al. (1990) (Barta et al., 1997b; Barta et al., 1990; Flaum et al., 1995; Tune et al., 1996). The basic anatomic landmark for tracing is: cortex and white matter were assessed in three consecutive coronal levels. The STG was defined as bounded laterally by the superior temporal sulcus, medially by the lateral sulcus, and inferiorly by a line connecting the depth of the superior temporal sulcus and the circular sulcus of the insula.

Five studies completely employed or mainly employed the method described by Kim et al. (2000) (Crespo-Facorro et al., 2004; Kim et al., 2003; Onitsuka et al., 2004; Takahashi et al., 2006; Taylor et al., 2005). The general anatomic landmarks are defined as below: the superior border of STG was designated as the point of the lateral brain cortex on the same level with the most lateral point of the sylvian fossa. The border between the posterior and anterior STG was in the coronal plane, including the most anterior point of Heschl's sulcus or the sulcus intermedius if it existed. Tracing began on the coronal plane containing the posterior end of the posterior horizontal limb of the sylvian fissure. Tracing for the anterior STG ended on the plane including the anterior end of the sylvian fissure or temporofrontal junction. In almost all slices, tracing was performed along the lateral rim of the supratemporal plane dorsally and the deepest point of the superior temporal sulcus ventrally. Exceptionally, when the lateral rim of the PT did not reach the lateral surface, the superior border was the point of the lateral brain cortex of the same level with the most lateral point of the sylvian fossa. Corresponding portions in the slices containing Heschl's sulcus were included in the posterior STG, whereas portions adjacent to the planum polare in front of the anterior tip of HS were included in the anterior STG (Kim et al., 2003; Kim et al., 2000).

There were five studies (Hirayasu et al., 2000; Kasai et al., 2003b; Kwon et al., 1999; Yamasaki et al., 2007;Yamasue et al., 2004b) that completely employed or mainly employed the same method to define the anatomic landmarks for HG and PT for tracing, which is described in detail by Kasai et al. (2003b) and Hirayasu et al. (2000).

3.4.3. *Image planes tracing*

STG or subregions in most studies were traced on coronal planes and were checked on other image planes to confirm the accuracy of the ROI boundaries. However, HG in some studies (Barta et al., 1997a; Hirayasu et al., 2000; Kasai et al., 2003b; Kwon et al., 1999; Yamasue et al., 2004ab; Yamasaki et al. 2007) was identified firstly from the axial plane or manually outlined, and/or then traced proceeding from the most posterior coronal image with a mark to the most anterior. HG was then best visualized in reconstructed axial slices especially in cases where secondary transverse sulci could be seen. In addition, one study traced STG regions on the realigned sagittal series with the exception of the medial aspect of STG using the realigned coronal series (Gur et al., 2000).

3.4.4. *Volumetric correction*

STG or subregions volumetric analyses were corrected for variations in head size such as total brain volume (TBV) or total cerebral volume (TCV) or intracranial volume (contents) (ICV) (See Table 2). Some studies employed the relative volume (rate) method such as dividing by TBV or TCV or ICV (17 of 46 studies). There were 16 studies employing the method of relative volume dividing by ICV (100 × absolute ROI volumes/ICV). There were 2 studies employing the method of relative volume dividing by TBV (Barta et al., 1997b; Sallet et al., 2003).

Most studies employed the method to correct the head size by a covariate method. Amongst them, 9 studies analyzed the regional volume difference between groups by ICV as a covariate and one study employed ICV corrected z scores for the analyses (Marsh et al., 1997). 12 studies analyzed the regions volume by TBV or TCV as a covariate. There were 4 studies having the TBV and temporal lobe volume as the covariates (Barta et al., 1997a; Barta et al., 1990; Bryant et al., 1999; Pearlson et al., 1997).

Two studies used height as a covariate to control for differences in brain size (Havermans et al., 1999; Sumich et al., 2002) because one viewpoint thought that height could be used as a reasonable measure for premorbid brain volume (Arndt et al., 1991), as it is closely correlated to brain size in normal subjects and is unlikely to be influenced by pathological processes affecting the brain.

3.4.5. *Reliability of tracing ROI*

Imperfect inter-rater and intra-rater reliability (test–retest reliability) in MRI volumetrics is an important source of error and attention to this issue in itself is a reasonable index of study quality (see a review by Brierley et al., 2002). In the 46 studies reviewed the inter-rater intraclass correlation coefficients (ICC) values were from 0.70 to 0.99 according to the different studies and different subregions in these studies. The intra-rater ICC values of these studies were from 0.69 to 0.99. The ICC values in almost all studies were higher than 0.85 except that one study had a lower ICC value (Flaum et al., 1995). Table 2 lists the ICC values of these studies.

3.5. *Main findings in STG or its subregional volume changes when compared with controls*

Table 3 summarizes the main findings in STG volume change based on all of the 46 studies in this review when compared with controls.

About 24% of studies (eleven of the 46 studies) reported no significant difference in the volume of STG and/or its subregions between SCZ patients and controls (Barta et al., 1997a; Buchanan et al., 2004; DeLisi and Hoff, 2005; DeLisi et al., 1994; Havermans et al., 1999; Kulynych et al., 1996;

Table 2 – Information of ROI division, reliability of tracing ROI and volumetric correction for head size in reviewed studies reviewed on STG or subregions volume measurement.

Study	Subregion	GM–WM segmentation	Intra-class correlation coefficient (ICC) for tracing ROI		Volumetric correction method to control for variations in head size
			Inter-rater Reliability (*r*)	Intra-rater Reliability (*r*)	
Anderson et al. (2002)	A/P, L/R	GM	–	0.82	Relative volume (/ICV)
Barta et al. (1997a)	HG and PT, L/R	GM	–	0.92–0.99	TBV/temporal lobe as a covariate
Barta et al. (1997b)	A, L/R	Combined	$r>0.90$	$r>0.90$	Relative volume (/TBV)
Barta et al. (1990)	L/R	GM, WM	$r>0.86$	$r>0.86$	TBV or TLV as a covariate
Bryant et al. (1999)	L/R	GM, WM	$r>0.95$	–	TBV or TLV as a covariate
Buchanan et al. (2004)	L/R	GM, WM	0.89	–	No (no significant effect from TBV or ICV)
Crespo-Facorro et al. (2004)	HG, PT, PP	GM	0.93~0.98	–	ICV as a covariate
DeLisi et al. (1994)	STG and PT, L/R	–	–	$r>0.90$	TBV as a covariate
DeLisi and Hoff (2005)	L/R	Combined	–	0.95–0.99	TBV as a covariate
Flaum et al. (1995)	L/R	Combined	$r>0.70$	0.69–0.70	ICV as a covariate
Gur et al. (2000)	L/R	GM, WM	0.90–0.96	–	ICV as a covariate
Havermans et al. (1999)	L/R	Combined	–	0.85~0.98	height was used as a covariate
Hirayasu et al. (2000)	HG and PT, L/R	GM	0.882/0.881 (HG, L/R); 0.985/0.95 (PT, L/R)	–	Relative volume (/ICV)
Hirayasu et al. (1998)	A/P, L/R	GM	0.99	–	Relative volume (/ICV) and ICV also as a covariate
Holinger et al. (1999)	A/P, L/R	GM	The average ICC value is 0.85	–	dividing by ICV
Jacobsen et al. (1998)	A/P, L/R	Combined	0.92	0.97	TCV as a covariate
Jacobsen et al. (1996)	A/P, L/R	Combined	0.92	–	TCV as a covariate
Kasai et al. (2003a)	A/P, L/R	GM	0.99	–	Relative volume (/ICV)
Kasai et al. (2003b)	HG and PT, L/R	GM	0.95/0.96 (HG, L/R), 0.99 (PT)	0.95–0.99	Relative volume (/ICV)
Keshavan et al. (1998)	L/R	GM	0.97–0.99	0.94–0.97	ICV as a covariate
Kim et al. (2003)	A/P, L/R	GM	0.83–0.97	–	ICV as a covariate
Kulynych et al. (1996)	L/R	Combined	0.95	–	TBV/temporal lobe as a covariate
Kwon et al. (1999)	HG and PT, L/R	Combined	0.92/0.9 (HG, L/R); 0.93/0/91 (PT, L/R)	–	Relative volume (/ICV)
Marsh et al. (1997)	L/R	GM, WM	$r>0.85$ (even higher than 0.92) in most subregions while it is 0.83/0.81 in pSTG (L/R)	$r>0.92$ in most subregions while it is 0.88/0.85 in right aSTG (WM)/left total STG region	ICV as a covariate
Matsumoto et al. (2001)	L/R	GM, WM	$r>0.92$	$r>0.92$	TBV as a covariate

McCarley et al. (2002)	A/P, L/R	GM	0.99 (STG); 0.88 (HG); 0.95/0.98 (PT, L/R)	–	Relative volume (/ICV)
McCarley et al. (1993)	STG (A/P) HG and PT, L/R	GM	The average ICC value is 0.86	–	dividing by ICV
Meisenzahl et al. (2004)	A/P, L/R	GM	0.89–0.93	0.89–0.93	ICV as a covariate
Meisenzahl et al. (2002)	PT (A/P)	GM	0.88–0.93	0.92–0.96	Relative volume (/ICV)
Menon et al. (1995)	Middle and posterior	GM, WM	$r>0.98$ (L), $r>0.97$ (R)	0.92–0.96	ICV as a covariate
Onitsuka et al. (2004)	L/R	GM	0.99	–	Relative volume (/ICV)
Pearlson et al. (1997)	A/P, L/R	GM, WM	$r>0.98$ (L), $r>0.97$ (R)	0.92–0.96	TBV or TLV as a covariate
Rajarethinam et al. (2000)	A/P; anterior 1/3, mid 1/3, posterior 1/3	Combined	0.91	–	TBV and TCV as covariates
Sallet et al. (2003)	PT (A/P)	GM	0.91/0.84 (PT, L/R)	–	Relative volume (/TBV)
Sanfilipo et al. (2000)	L/R	GM, WM	–	0.92	ICV as a covariate
Sanfilipo et al. (2002)	L/R	GM, WM	–	0.92	ICV as a covariate
Shenton et al. (1992)	A/P, L/R	GM	The average ICC value is 0.86	–	dividing by ICV
Sumich et al. (2002)	HG and PT, L/R	–	0.90–0.95	–	height as a covariate
Takahashi et al. (2006)	HG, PT, PP, rostral, caudal STG	Combined	$r>0.88$	$r>0.88$	Relative volume (/ICV) and ICV also as a covariate
Taylor et al. (2005)	STG (A/P), HG, L/R	GM, WM	0.83 (aSTG); 0.88 (pSTG); 0.96 (HG)	COV in aSTG/pSTG/HG is 2.5%/3.2%/9.02%	TBV as a covariate
Tune et al. (1996)	L/R	Combined	$r>0.86$	$r>0.86$	No (no significant effect from TBV or ICV)
Vita et al. (1995)	L/R	Combined	–	0.88–0.96	Relative volume (/ICV)
Woodruff et al. (1997)	STG	Combined	0.89	$r>0.9$	Standardized effect sizes (adjusted for TBV)
Yamasaki et al. (2007)	HG and PT, L/R	GM	0.97/0.91 (HG, L/R); 0.91/0.92 (PT, L/R)	$r>0.97$	Relative volume (/ICV)
Yamasue et al. (2004a)	A/P, L/R	GM	0.87–0.99	0.92–0.99	Relative volume (/ICV)
Yamasue et al. (2004b)	HG and PT, L/R	GM	0.99/0.98 (HG, L/R); 0.99/0.99 (PT, L/R)	$r>0.99$	Relative volume (/ICV)

A = anterior; A/P = anterior/posterior; aSTG = anterior STG; COV = coefficient of variances; Combined = a volume combined GM and WM; GM = grey matter; ICC = intraclass correlation coefficients; ICV = intracranial (content) volume; L = left; L/R = left/right; P = posterior; pSTG = posterior STG; TLV = temporal lobe volume; TBV = total brain volume; TCV = total cerebral volume; R = right; rSTG = right STG; WM = white matter; – = not available.

Meisenzahl et al., 2004; Meisenzahl et al., 2002; Sallet et al., 2003; Vita et al., 1995; Woodruff et al., 1997; Table 3).

The remaining 76% of studies (thirty-five of the 46 studies) reported positive results. Among the positive results, about 43% of studies (fifteen of 35 studies) reported only unilateral effects in the STG or subregional volume change. The reduced volumes on the left side of STG and/or its subregions were more reported than on the right side. There were twelve of the 15 studies which reported reduced STG or subregions volume in the left side such as reduced in the left STG (Keshavan et al. 1998; Onitsuka et al., 2004; Shenton et al., 1992; Tune et al., 1996), left anterior STG (Pearlson et al., 1997), left anterior third and one half STG (Rajarethinam et al., 2000), left posterior STG (Hirayasu et al., 1998; Kasai et al., 2003a; McCarley et al., 1993), left PT (Kasai et al., 2003b; Kwon et al., 1999; McCarley et al., 1993; Sumich et al., 2002; Yamasue et al., 2004b) and left HG (Kasai et al., 2003b) according to the different partition methods used in different studies. However, only two studies reported unilateral volume reduction in the right side such as in the right posterior STG (Jacobsen et al., 1998), or right HG (Crespo-Facorro et al., 2004). The two studies had particular SCZ subjects such as childhood-onset SCZ patients (Jacobsen et al., 1998) or a mixed sample including six patients with first-episode, 11 patients with recent-onset (within five years) and 13 chronic inpatients (Crespo-Facorro et al., 2004).

About 37% of studies (thirteen of 35 studies) reported only bilateral reduction effect in STG or subregional volumes such as in the bilaterally anterior STG (Barta et al., 1997b), posterior STG (Menon et al., 1995; Yamasue et al., 2004a) or middle STG (Menon et al., 1995), PT (Yamasaki et al., 2007), HG (Takahashi et al., 2006) or bilaterally total STG (Anderson et al., 2002; Barta et al., 1990; Bryant et al., 1999; Flaum et al., 1995; Gur et al., 2000; Marsh et al., 1997; Sanfilipo et al., 2000; Sanfilipo et al., 2002). One study reported the increased effect in the bilateral STG and posterior segment volumes in adolescent inpatients (Jacobsen et al., 1996).

Six studies reported mixed effects of volume changes including both bilateral and unilateral effects in the subregional volumes changes of some studies due to every change in different subregions according to the partition methods employed by different studies. These studies showed volume reduction in the total STG (Matsumoto et al., 2001; Takahashi et al., 2006), total posterior STG (Kim et al., 2003), bilateral posterior STG (Holinger et al., 1999), and total HG (Hirayasu et al., 2000; McCarley et al., 2002; Takahashi et al., 2006) and bilateral Caudal STG (Takahashi et al., 2006); and also showed volume reduction of unilateral effect such as in the left PT (Hirayasu et al., 2000; McCarley et al., 2002; Takahashi et al., 2006), left posterior STG (McCarley et al., 2002), right STG (Holinger et al., 1999; Matsumoto et al., 2001), and right posterior STG (Kim et al., 2003). One study reported the increased white matter volume (WMV) abnormalities in the right posterior STG (total and WMV enlargement), bilaterally posterior STG and right HG (Taylor et al., 2005).

From Table 3, we can find almost all studies reported the volume reduction whether in the bilateral or unilateral STG or its subregions. However, two studies reported increased effect regarding volume (Jacobsen et al., 1996; Taylor et al., 2005). Among them, one study reported bilateral STG and posterior segment volume enlargement in adolescent inpatients (Jacobsen et al., 1996). Another study reported increased effects in the WMV of STG (or subregion) (Taylor et al., 2005). The increased tendency in WMV of STG is not consistent with other of the 46 studies which reported the negative results (Marsh et al., 1997; Sanfilipo et al., 2002; Sanfilipo et al., 2000) or reduced effect (Matsumoto et al., 2001; Pearlson et al., 1997).

In 46 studies, there were 16 studies comparing only grey matter volume (GMV) of STG or subregions in patients with SCZ and controls. Twenty-five studies reported the change of the whole volume lumping GM and WM into their measurements or a few of them reported change of both GMV and WMV by itself of STG or subregions. However, in two studies we were unable to determine which kind of matter volume was measured (DeLisi et al., 1994; Sumich et al., 2002) (Table 3).

Some studies reported asymmetry of the STG or subregion volumes. 10 of 46 studies reported a significant difference in the laterality effect of volume in SCZ patients when compared with controls. However, 19 of 46 studies did not provide information about asymmetry of STG or subregions except that 17 of 46 studies reported negative results. Among 10 studies that reported positive results, 6 studies reported left-lateralized volume reduction in the total STG (Onitsuka et al., 2004), posterior STG (Hirayasu et al., 2000; Hirayasu et al., 1998), PT (Kwon et al., 1999), posterior STG and PT (McCarley et al., 2002) or anterior one-third STG (Rajarethinam et al., 2000). In the other 4 studies, Takahashi et al. (2006) reported SCZ patients were significantly less lateralized for the caudal STG volume than the control subjects. One study reported no left or right lateralization in PT in male patients although HG volume was preserved (Yamasaki et al., 2007). Two studies reported a different asymmetry pattern: reversed asymmetry (right-lateralized low volume) in the total STG in the left-handed patients (Holinger et al., 1999) or greater leftward laterality (right-lateralized low volume) in adolescent patients with recent-onset SCZ than in healthy volunteers (Matsumoto et al., 2001). Though no firm conclusion can be drawn from 10 studies, alterations in normal asymmetries, and a left-sided 'preference' of the pathology mainly in right-handed subjects, are findings that seem to be more common, except some studies coming from the left-handed subjects or adolescent patients with recent-onset. However, 17 of 46 studies reported no differences in volume asymmetry of STG or subregions including PT when compared with controls. Among them, one study reported there was no significant difference in the STG asymmetry between SCZ patients and controls (Meisenzahl et al., 2004). In addition, one study reported the reversal of the normal asymmetry for PT surface area in SCZ subjects although there was no significant difference in the GMV asymmetry of PT and HG in SCZ (Barta et al., 1997a).

3.6. *Main finding in correlation between STG and or its subregional volumes and syndrome and symptoms*

Sixteen of the 46 studies had no information, or did not investigate the correlation between STG or its subregional volumes and clinical symptoms. Eighteen of the other 30 studies reported positive findings while 12 of them had

negative findings. Some studies, which had no healthy controls but reported the correlation between symptoms in SCZ patients and STG or subregional volume, were not included in this review as per the inclusion criterion.

3.6.1. *Syndrome of symptoms*

Several studies reported correlations between STG or subregional volume changes and the clinical syndrome such as the syndrome of psychotic symptoms or positive symptoms. These studies found the syndrome of psychotic symptoms was negatively correlated with the left anterior STG volume (Kim et al., 2003), and the syndrome of positive symptoms was negatively correlated with PT GMV (Crespo-Facorro et al., 2004) or right PT volume (Yamasaki et al., 2007) or right posterior STG volume (Jacobsen et al., 1998) in the patients with SCZ.

3.6.2. *Hallucinations*

There were several studies reporting STG or its subregional volumes to be negatively correlated with hallucinations (especially AH) with the left STG (Barta et al., 1990; Onitsuka et al., 2004), left anterior third and one half STG (Rajarethinam et al., 2000), left PP (Takahashi et al., 2006), left PT (Sallet et al., 2003), and right STG (Matsumoto et al., 2001) volume.

3.6.3. *Thought disorder and delusions*

Some studies reported correlations between TD and STG or its subregional volumes such as in the left STG (Anderson et al., 2002; Barta et al., 1997a; Vita et al., 1995), left PT (Barta et al., 1997a), right STG (Matsumoto et al., 2001), or right anterior STG (Holinger et al., 1999).

There were several studies that particularly reported correlations between delusions and STG or its subregional volumes, such as left posterior STG total volume or GMV (Menon et al., 1995), left rostral STG volume (especially in the early-onset SCZ) and left PP volume (Takahashi et al., 2006).

Four studies reported that STG volume significantly correlated with subscale scores which might be linked with TD, such as correlations between left STG (and its posterior segment) and unusual thought content (Jacobsen et al., 1996); between left PT volume and stereotyped thinking (Sallet et al., 2003); between left PT volume and suspiciousness/Persecution subscale score of the Positive and Negative Syndrome Scale (PANSS) (Kwon et al., 1999); and between right PT volume and delusional behavior (Yamasaki et al., 2007).

3.6.4. *Other symptoms*

Right posterior STG GMV negatively correlated with the poor attention subscale of the PANSS (Anderson et al., 2002) while positively correlating with negative symptoms. There was no significant correlation between STG volume and disorganized symptoms (Kim et al., 2003).

3.7. *Main findings in correlations between STG and or subregional volumes and other variables*

Studies have reported conflicting findings in respect to the relationship between illness duration and STG volume. For example, studies have reported left STG volume to be negatively correlated with pre-treatment illness duration among male patients (Keshavan et al. 1998) and time in hospital (DeLisi and Hoff, 2005) and reduced HG volume to be correlated with greater illness duration (Crespo-Facorro et al., 2004). However, negative findings have also been reported (Gur et al., 2000). Similarly, bilateral STG volumes were positively correlated with the age at onset of psychosis in one study (Matsumoto et al., 2001) but not another (Marsh et al., 1997). In regards to medication, a study reported that elevated PP volume positively correlated with cumulative neuroleptic exposure (Crespo-Facorro et al., 2004).

However, several studies reported no significant correlation between STG volume and medication effects (Matsumoto et al., 2001), or between STG volume and age first medicated, duration of medication treatment, or medication dose (Kasai et al., 2003a).

One study reported left STG volume positively correlated with verbal fluency test performance (Vita et al., 1995) while another study reported no correlation between cognitive performance and HG or PT volume (Hirayasu et al., 2000).

There were several studies that reported positive results between P300 amplitude and STG or subregional volume. One study reported left hemisphere magnetic mismatch field which is a magnetic counterpart of mismatch negativity in response to change in speech sounds and showed a significant positive correlation with PT GMV (Yamasue et al., 2004b). Another study reported left posterior STG GMV reductions correlated with both P300 amplitude reduction and left<right topographic asymmetry (McCarley et al., 1993). One study reported left posterior STG and the left PT, but not other ROI, were positively correlated with left temporal P300 voltage (McCarley et al., 2002), while another study reported lower or no correlation (Havermans et al., 1999). One of the studies reviewed concluded that there is no association between the electrophysiological and structural measurements detected (Meisenzahl et al., 2004).

3.8. *Results from longitudinal studies*

Five follow-up studies were included in this review. One study was excluded as it had no baseline information about volume change although it reported bilateral posterior superior temporal GM to decline over time, and a relationship to greater Brief Psychiatric Rating Scale (BPRS) total and negative symptom scores in their group of chronic SCZ patients after a mean interscan interval of 3.6 years (Mathalon et al., 2001).

Among the five studies reviewed, the follow-up time interval was 1 year (Keshavan et al., 1998), 1.5 years (Kasai et al., 2003a; Kasai et al., 2003b), 2 years (Jacobsen et al., 1998), 5 years and 10 years (DeLisi and Hoff, 2005). One study which is the longest time follow-up study, examined the volume changes of the temporal lobe and the STG of 27 patients with SCZ and 10 controls (DeLisi and Hoff, 2005). The result showed no significant volume change over time in those structures. The other four studies found positive results. Keshavan et al. (1998) only followed-up a smaller subset of patients and reported STG volume reduction may

Table 3 – Main findings in STG or subregion volume in patients with SCZ and correlations with some clinical variables when compared with controls.

Study	Significant differences in STG or subregion volume in patients with SCZ when compared with controls	Significant correlations between STG or subregion volume and clinical variables including H and TD in patients with SCZ
Anderson et al. (2002)	Bilateral STG GMV reduced	Negative correlation between left STG and right pSTG absolute GMV and TD, Negative correlation between poor attention subscale of the PANSS and right pSTG absolute or relative GMV
Barta et al. (1997a)	No	Negative correlation between Left PT GMV and TD
Barta et al. (1997b)	Bilaterally anterior STG volume reduced	No correlation
Barta et al. (1990)	Left STG reduced ($P<0.01$), right STG reduced ($P<0.05$)	PC between reduced left STG volume and H especially AH
Bryant et al. (1999)	Bilateral STG volume reduced	–
Buchanan et al. (2004)	No	–
Crespo-Facorro et al. (2004)	Right HG GMV reduced	Negative correlation between PT GMV and positive symptoms, PC between elevated PP volume and cumulative neuroleptic exposure; negative correlation between HG volume and duration of illness
DeLisi et al. (1994)	No (only STG volume, no data of PT volume only PT area)	No correlation between STG volume and AH or TD
DeLisi and Hoff (2005)	No	Correlation between rSTG volume reduction; the number of total hospitalized, the greater the total time spent in hospital
Flaum et al. (1995)	Bilateral STG volume reduced	–
Gur et al. (2000)	Bilateral STG volume (specific to GM not WM) decrease which exceeded that of whole-brain (11.5%) only in men	STG GMV is not correlated with H, TD, neurocognitive parameters or illness duration
Havermans et al. (1999)	No	STG (including left aSTG) volume is not correlated with H, TD although left P300 amplitude reduced
Hirayasu et al. (2000)	Left PT and total HG GMV reduced	HG and PT volume is not correlated with H, TD or cognitive performances
Hirayasu et al. (1998)	Left pSTG volume reduced	–
Holinger et al. (1999)	The pSTG GMV bilaterally reduced; right side of the total STG GMV reduced	PC between right aSTG and TD, no correlation between H and STG volume
Jacobsen et al. (1998)	Right pSTG volume decreased	Correlation between decreases right pSTG volume and higher SAPS scores
Jacobsen et al. (1996)	Bilaterally larger STG and posterior segment	PC between left STG and pSTG volume and scores of BPRS subscales: conceptual disorganization and unusual thought content, no correlation between STG volume and antipsychotic exposure
Kasai et al. (2003a)	Left pSTG volume reduced	STG volume is not correlated with H, TD, age, age first medicated, duration of medication treatment, medication dose, or intracranial contents volume
Kasai et al. (2003b)	Left PT and left HG GMV reduced.	–
Keshavan et al. (1998)	Left STG volume decreased	Negative correlation between pre-treatment illness duration and left STG GMV in male patients
Kim et al. (2003)	Total pSTG and right pSTG GMV reduced	Negative correlation between left aSTG GMV and psychotic symptoms, right pSTG PC with negative symptoms but no correlation with disorganized symptoms.
Kulynych et al. (1996)	No	–
Kwon et al. (1999)	Left PT GMV reduced	Correlation between reduced left PT volume and the subscales scores of the PANSS: the suspiciousness or persecution subscale score
Marsh et al. (1997)	Bilaterally smaller STG GMV while WMV not	Smaller left pSTG GMV correlated with psychotic symptom sub-scores of the BPRS, which is not correlated with age at illness onset or the brain measurements
Matsumoto et al. (2001)	Total STG (GM+WM) and the right STG (GM) volume reduced	Negative correlation between right STG volume and TD or H; Bilateral STG volumes were PC with the age at onset of psychosis while no correlation with result from medication effects
McCarley et al. (2002)	Left posterior STG, left PT and total HG GMV reduced	Left pSTG and the left PT but not other regions of interest, were specifically PC with left temporal P300 voltage (abnormality)

Table 3 (*continued*)

Study	Significant differences in STG or subregion volume in patients with SCZ when compared with controls	Significant correlations between STG or subregion volume and clinical variables including H and TD in patients with SCZ
McCarley et al. (1993)	Left pSTG including HG and PT GMV reduced	Left pSTG GMV reductions correlated with both P300 amplitude reduction and left<right topographic asymmetry
Meisenzahl et al. (2004)	No	STG volume is not correlated with H, TD or electrophysiological measurements
Meisenzahl et al. (2002)	No	STG volume is not correlated with H, TD or P300 measurements
Menon et al. (1995)	Middle and pSTG GMV bilaterally reduced no difference in WMV	Negative correlation between left pSTG total volume or GMV and TD but no correlation between STG volume and H
Onitsuka et al. (2004)	Left STG GMV reduced	Negative correlation between left STG GMV and H but no correlation between STG GMV and TD
Pearlson et al. (1997)	Left aSTG GMV and WMV reduced	–
Rajarethinam et al. (2000)	Smaller left anterior 1/3 and one half STG	Negative correlation between left anterior third and one half STG volume and severity of H while not TD; left posterior STG volume negatively correlated with the severity of thought disorder.
Sallet et al. (2003)	No	PC between volume of left PT and the sub-items hallucinatory behavior, social withdrawal and stereotyped thinking (PANSS)
Sanfilipo et al. (2000)	Bilateral STG GMV reduced but not WMV	STG volume is not correlated with H, TD, or with negative symptoms
Sanfilipo et al. (2002)	Bilateral STG GMV reduced but not WMV	STG volume is not correlated with H, TD
Shenton et al. (1992)	Left STG GMV reduced	Negative correlation between left pSTG GMV and TD, no correlation between STG GMV and H
Sumich et al. (2002)	Left PT volume reduced while no significance in HG volume	–
Takahashi et al. (2006)	Bilateral STG and HG volume reduced, left PT volume reduced, bilateral caudal STG volume reduced	Left rostal STG volume negatively correlated with delusions especially in early SCZ, left PP volume negatively correlated with H and delusions
Taylor et al. (2005)	Right pSTG total volume and WMV enlargement, bilaterally pSTG (WMV increases), right HG (WMV increases)	–
Tune et al., (1996)	Left STG volume decreased while only reduced tendency in right STG volume	Negative correlation between STG volume (especially left side) and elevated striatal D2 receptor elevation, rSTG volume negatively correlated with age but not with duration of illness or premorbid social functioning, left STG volume negatively correlated with age and premorbid social functioning but not with duration of illness
Vita et al. (1995)	No	PC between left STG volume and verbal fluency test performance, STG laterality index was correlated with Thought, Language and Communication (TLC) scale total scores
Woodruff et al. (1997)	No	–
Yamasaki et al. (2007)	Significant reduction in bilateral PT GMV while no significant difference in HG GMV	Correlation between smaller right PT GMV and positive symptom and delusional behavior while no correlation between HG GMV and clinical symptoms
Yamasue et al. (2004a)	Bilateral pSTG GMV reduced	STG volume is not correlated with H or TD
Yamasue et al. (2004b)	Left PT GMV reduced while no significance in HG GMV	Left hemisphere magnetic mismatch field in response to change in speech sounds showed a significant PC with PT GMV

A = anterior; AH = Auditory Hallucination; aSTG = anterior STG; BPRS = the Brief Psychiatric Rating Scale; GM = grey matter; GMV = gray matter volume; H = Hallucination; P = posterior.; pSTG = posterior STG; PANSS = the Positive and Negative Syndrome Scale; PC = positive correlation (correlated); rSTG = right STG; SAPS = the Scale for the Assessment of Positive Symptoms; SCZ = schizophrenia; TD = Thought Disorder, WM = white matter; WMV = white matter volume; – = not available.

be reversed after a mean interval of 1 year (Keshavan et al., 1998). Kasai et al. (2003a; 2003b) found decreases in GMV over time in the left STG, more pronounced in the posterior portion than anterior portion; they also found greater decreases over time in the GMV of the left HG, and left PT after mean internal of 1.5 years. One study on childhood-

onset SCZ patients reported significantly greater decreases in bilateral STG and posterior STG, and right anterior STG during the 2-year follow-up interval (Jacobsen et al., 1998). Moreover, decline in right posterior STG was associated with high total scores on the Scale for the Assessment of Positive Symptoms at baseline and at follow-up. The limited studies may support the progressive change of STG (reduced volume) over time in SCZ patients, which is more pronounced in the left side.

4. Discussions

The possible role of STG in the pathology of SCZ has interested investigators for many years. Since Barta et al. (1990) conducted the first MRI study of STG volume in this patient group, the number of STG-focused MRI studies has increased substantially. Frequently used, the ROI method has much strength, namely anatomical validity. Although recently investigators have begun to employ the rapid voxel-based morphometry method, it is not a replacement for manual ROI-based analyses.

4.1. *ROI volumes change in SCZ patients*

A perusal of Table 3 indicates that the significantly different STG and/or subregional volume in patients with SCZ (when compared to normal, healthy control subjects) is in at least one STG subregion and not confined to the left STG as reported by Barta et al. (1990). For example, some studies especially on childhood-onset or adolescent patients or only left-handed patients (Holinger et al., 1999) showed there were volume changes in the bilateral STG or subregions and/or in the right side. The volume changes in STG or subregions were reported in several kinds of samples including the first-episode SCZ patients or related diagnosis (Hirayasu et al., 2000; Hirayasu et al., 1998; Kasai et al., 2003a; Kasai et al., 2003b; Keshavan et al., 1998; McCarley et al., 2002), chronic SCZ patients (e.g. Anderson et al., 2002; Bryant et al., 1999; Shenton et al., 1992), adult-onset patients or childhood-onset patients (Jacobsen et al., 1998; Jacobsen et al., 1996; Matsumoto et al., 2001; Taylor et al., 2005) and the late-life onset SCZ patients (Barta et al., 1997b).

In total 35 studies reported the positive results. Amongst them, most showed the reduced effect in STG or several subregional volumes, which is consistent with the results of some VBM studies. For instance, some VBM studies found there were reduced STG or subregional volume changes such as in the left STG (Bonilha et al., 2008; Jayakumar et al., 2005) and bilateral STG (Chua et al., 2007; Tregellas et al., 2007). The significant volume change is more reported. However, a question regarding whether STG or subregion volume changes are static or progressive or reversible is currently a controversial topic and has remained elusive (see reviews by DeLisi, 1999 and Harrison, 1999). Four follow-up studies showed significant progression of STG including HG and PT volume changes over time at least among subgroups of people with SCZ, which were also supported by some studies including VBM studies (e.g. van Haren et al., 2007; Meisenzahl et al., 2008). There is a suggestion that STG volume changes may be progressive, which conflicts with the neurodevelopmental model of SCZ (e.g. Bloom 1993), and one study we reviewed that did not find the progressive change over time (e.g. DeLisi and Hoff, 2005). Hence, this requires more thorough and comprehensive assessment. In addition, we found the volume reduction of STG was often reported to be a specific abnormality in SCZ. For example, two studies compared the volume change between SCZ patients and bipolar manic psychosis and found low volume of the left posterior STG or left PT and total HG grey matter is specific to SCZ (Hirayasu et al., 1998; Hirayasu et al.; 2000, also see a review by Hirayasu, 2007). Likewise, another study found left anterior STG reduced and an alteration of normal posterior STG asymmetry was specific to SCZ not bipolar disorder (Pearlson et al., 1997). One study reported bilaterally smaller anterior STG is specific to later-life onset SCZ while not in Alzheimer's disease (Barta et al., 1997b). Certainly, it needs more studies to further replicate this specific volume change for SCZ patients.

Amongst the 35 studies that reported positive results, about 43% of these studies (fifteen of 35 studies) reported a unilateral effect of reduction where that is most pronounced on the left side. These studies reported significantly reduced volume in the left STG including anterior, anterior third, posterior STG, left PT and left HG (see Table 3). The left STG is of particular interest to SCZ which is a cortical area thought to be a substrate of auditory and language processing (Galaburda et al., 1978) and may be related to the common symptoms including AH and TD. Crow et al. (1989) postulated the left hemisphere may be more vulnerable to insult or damage because it develops later than the right hemisphere. Particularly, PT, as a portion of the surface of the posterior STG, is important as a candidate for the neural basis of SCZ, as it is related to disturbances in language and thought in SCZ and it evinces the most prominent left-right asymmetry (see reviews by Pearlson, 1997; Shapleske et al., 1999).The PT is larger on the left than the right in the normal controls, whilst in the SCZ patients reversed asymmetry of the PT was reported because left PT volume reduced and some studies also showed right PT was larger than the left in SCZ compared with normal controls (see a review by Shapleske et al., 1999). In the studies we reviewed, twelve studies particularly measured PT volume and eight of 12 studies showed volume reduced in the left PT which is consistent with most previous studies.

Except the unilateral effect, in our review there were about 37% of studies (thirteen of 35 studies) that reported bilaterally reduced STG or subregional volumes and 17% of studies (six of 35 studies) reported the mixed effect of volume changes of STG or its subregions including unilateral and bilateral effects in different subregions. This effect of volume change is in contrast with the effect reported by a review (Honea et al., 2005). The review included 15 VBM studies and we found that bilateral STG reductions were the most frequent finding. Among them, 57% of studies found this deficit in the left hemisphere, and 50% found it in the right hemisphere. The complicated volume changes in these studies we reviewed may suggest the variety of STG morphological abnormalities in patients with SCZ which may not be confined to a simply unilateral effect or bilateral effect. The reduced or increased effect on STG or subregional

volumes change when there are different kinds of partition methods employed by these studies, while reduced effect of volume was the most common change in SCZ.

Although volume change of the STG (or subregion) in SCZ has been fairly well demonstrated, it is a fact that there are still about 24% of studies which reported negative results about STG volume change, which also can be found in some VBM studies. For example, Honea et al. (2005) reported 6 of 15 VBM studies had no difference in STG volume in SCZ patients when compared with controls. One recent VBM study (Wolf et al., 2008) also showed a negative result about STG volume alteration in patients with SCZ. One of the explanations for this discrepancy about positive and negative results is difference in the methodology, i.e. the type of image sequence, MRI slice thickness selected; neuroanatomic definition of STG, method used to trace the STG (GM versus GM and WM) and sample selection. In 46 studies we reviewed, three of 11 studies which reported negative results acquired 5 mm thick MRI slices which may be too gross to allow for the detection of subtle volume changes (DeLisi and Hoff, 2005; DeLisi et al., 1994; Vita et al., 1995).

4.2. *Correlations between ROI volume changes and common symptoms*

The STG MRI volume abnormalities have been a rich source of correlations with SCZ clinical data (McCarley et al., 1999) although the brain structural correlates of specific symptoms, such as AHs, are not clearly defined. The STG includes the primary and association auditory cortices and has been strongly implicated in the experience of auditory hallucinations (O'Daly et al., 2007). Previous research has reported the complex AHs only in the vicinity of the STG when electrically stimulated multiple cortical and subcortical areas in bilateral hemisphere of epileptic patients (Penfield and Perot, 1963). The result from functional magnetic resonance imaging studies also showed SCZ patients with AH had increased functional activation in this area (Shergill et al., 2000).

Among 30 studies including the correlation analysis with symptoms, 60% of studies (18 studies) reported positive results about the correlations between STG or subregional volume and clinical symptoms or syndrome. Amongst 18 studies, Barta et al. (1990) was the first to report a negative correlation between left STG volume and AH. Later studies also found several STG subregions to be correlated with hallucinations (especially AH). These regions are mostly in the left side: left STG, left PT, left PP. Only one study reported severity of hallucinations as inversely related to right STG volume, in an adolescent SCZ sample (Jacobsen et al., 1998). The result of this review suggests that left STG or subregions appear to be more involved in the generation of AH than right side. It is not consistent with a recent VBM study which reported that right STG GMV loss was correlated with severity of AHs (O'Daly et al., 2007). Up to 70% of SCZ patients suffer from AH (Nayani and David, 1996). AHs remain one of the most intriguing phenomena in psychopathology although some hypotheses have formed evidence including that from imaging studies. The findings in our review support STG or its subregions may be the common candidate region related with the production of hallucinations. It is certain that there are other brain structural abnormalities associated with AH in SCZ such as in the left insula, middle temporal gyrus besides STG, which can compose a network of brain areas and their respective contributions to the hallucinatory experience (see a review by Allen et al., 2008).

TD is a hallmark symptom and it is a primary feature of SCZ. As early as 1911, Bleuler predicted that TD would ultimately be linked to a brain abnormality. Shenton et al. (1992) observed that left posterior STG volume was associated with TD. In the current review there were a number of studies reporting a significant correlation between TD and STG or subregional volume. These ROIs are left STG, left posterior STG, left rostral STG, right STG, right anterior STG, left PT, and left PP in several studies. The different ROIs correlated with TD may be due to the differences between different samples, the diversity of TD symptomatology when scanned, and partition methodology.

These findings (the correlations between clinical symptoms including H and TD, and STG or subregional volume) lend support to the contention that STG or subregional volume change especially in the left side may result in clinical manifestations that form the core of the SCZ psychopathology. However, we also noted that not all studies showed the significant correlations between clinical symptoms and STG or subregions volume changes.

4.3. *Confounding factors and methodological considerations*

There are a number of confounding factors and methodological issues in brain structure studies, which may lead to the inconsistencies among some studies we reviewed. They included medication effects, different sample sizes, over-representation of men, sampling from a chronically ill population, variability in the size of brain structures in the general population, problems in measurement procedures (thickness and spacing of slices), differences in measurement procedures among different research centers (use of different ROI boundary definitions), and failure or different methods to control for head size, age, and hand preference (see a review by Leung and Chue, 2000).

A major confounding factor in neuroimaging studies in general and in studies investigating brain volume change of SCZ patients in particular, is the (cumulative) intake of antipsychotic medication (see a review by van Haren et al., 2008). It is also a confounding factor when interpreting the STG volume (change). The best way to control the confounding factor is to recruit the neuroleptic medication naïve or free patients. It is acknowledged that recruiting adequate numbers of this cohort for this type of study could be difficult. Amongst 46 studies reviewed, only two of the 46 studies included purely neuroleptic-naïve SCZ patients (Keshavan et al., 1998, Kim et al., 2003). One study employed the neuroleptic-naïve and neuroleptic-free patients (Tune et al., 1996). There are six studies which included a few neuroleptic-naïve or neuroleptic-free patients not, entire samples. Most of the patients in 36 studies were receiving some kind of neuroleptic treatments when scanned by MRI except the information about history of medication in 8 studies is not available. Some studies found that STG or PP volume change was correlated with medication effects

(Crespo-Facorro et al., 2004; Tune et al., 1996) while two studies found no correlation between STG volume change and medication effect (Kasai et al., 2003a; Matsumoto et al., 2001). It is therefore useful to study the early phase of the illness (such as first-episode patients) in order to exclude the confounding effects of illness chronicity and long-term medication (van Haren et al., 2008). Eight of the 46 studies collected data of first-episode patients. Among them, six studies reported positive results although having different partition methods, such as reduced left STG (Keshavan et al., 1998), reduced left posterior STG (Hirayasu et al., 1998; Kasai et al., 2003a; McCarley et al., 2002), reduced left PT and total HG (Hirayasu et al., 2000; Kasai et al., 2003b; McCarley et al., 2002). Two of the 8 studies did not find the significant difference in STG or subregional volume in patients with SCZ (DeLisi et al., 1994; DeLisi and Hoff, 2005), but it may be assumed that relatively thick slices (5 mm) through the STG will not detect the subtle changes occurring in SCZ and may account for the negative findings (DeLisi et al., 1994).

One of the major factors affecting the variance of general and regional cerebral volume is sex (Nopoulos et al., 1997). There are a number of evidences from port-mortem studies (e.g. Vogeley et al., 1998) and MRI studies on gender specific STG volumetric difference in SCZ (see a review by Leung and Chue, 2000). In these ROI studies we reviewed, it is a pervasive phenomenon that near 50% of studies selected only male subjects. Female subjects are under-represented in the literature and insight from sex differences may be lost. It is necessary to include both male and female subjects to reflect accordingly the morbidity rate as a function of gender and investigate sex differences in STG volume or correlation with some clinical variables, in our opinion.

MRI slice thickness is another factor to potentially affect the results, and this is directly related to the visual resolution of the image. Partial volume artifact (the averaging of signal intensities across all tissue within the slice) increases with slice thickness and results in a blurring of anatomical boundaries. Further, for any given slice thickness, partial volume artifact introduces more error as the volume of a given Region of Interest decreases and as the surface area to volume ratio increases (Flaum et al., 1995). Slice thickness of the studies in the current review ranged from 1 mm to 5 mm. Only three of the 46 studies used 1 mm and three studies used 5 mm, but the majority used 1.5 mm (21 of 46 studies) and 3 mm (12 of 46 studies). When reviewing STG or subregional volume change, there was no significant difference in all of the three studies which acquired 5 mm thick slices. It may be that the slices scanned were too thick to detect the subtle changes in STG or subregional volume change occurring in SCZ (DeLisi et al., 1994). Only three studies (Gur et al., 2000; Matsumoto et al., 2001; Takahashi et al., 2006) using 1 mm slice thicknesses of MRI scans reported bilaterally reduced STG volume, and among them one study reported that STG volume decrease up to 11.5% exceeded that of whole brain but only in male patients (Gur et al., 2000). MRI technology has advanced considerably over the past decade to a point where the acquisition of 1 mm slices is a virtual routine. Future studies will undoubtedly take advantage of more advanced techniques to further control bias and enhance precision, allowing a more accurate and detailed assessment STG or subregional volume anomalies.

The grey–white matter differentiation is important for SCZ volumetric studies. It has been reported that GM deficits in the STG are more pronounced than WM deficits in SCZ (e.g. Gur et al., 2000; Marsh et al., 1997). Measuring GM volume separately may be more sensitive than measuring of the volume grey and white matter combined (Shenton et al., 1997). However, about 12 of 46 studies reported a volume lumped GM and WM. Those studies had combined GM with WM taken into account in volumetric analyses, which is a fact that could have obscured differences of only one of these two components and also makes it difficult to assess whether group differences were related to alterations in grey matter volume, white matter volume, or both. It may contribute to the inconsistent findings of 46 studies. As previous review suggested (see a review by McCarley et al., 1999), it also often renders comparison between studies problematic.

There were other confounding factors or methodological issues including clinical heterogeneity and differences of definition of ROI landmarks. STG neuroimaging results are not always replicated, which also probably reflects lack of homogeneity of the study samples. The diversity of the symptomatology in SCZ, unstable symptoms at different stages of illness, and variation in sample sizes may lead to different results of imaging studies. The kinds of ROI anatomical definitions or landmarks may lead to bias although one study did not find the significant differences of PT asymmetry in patients with SCZ using three definitions of PT borders (Meisenzahl et al., 2002). In addition, the difference of MRI acquisition parameters besides slice thickness, partition methods of ROI, the methods of volumetric correction, sample size and other factors may also lead to different results.

4.4. *Limitations of the review*

There were some limitations of the review study. First, we chose to only analyze ROI measurements of STG or subregional volume. This inevitably neglects potentially important differences in other brain regions. However, we focused on the STG because it is one of the most commonly implicated regions of brain structure abnormalities in SCZ and closely linked to H and TD (see reviews by Allen et al., 2008; Pearlson, 1997; Shenton et al., 2001). Second, the ROI method has been the gold standard for structural brain MRI examinations, namely anatomical validity. However, ROI-based volumetric analysis also has some limitations including but not limited to the time-consuming nature of manual ROI drawings, both in delineating a priori-defined regions and in the rigorous training needed to ensure rater reliability (Kubicki et al., 2002). In our reviewed literature, there was relatively high rater reliability in the measurement of STG or subregion volume in almost all studies, which suggests that the reliability, the potential limitation, was not a major concern. The ROI method needs the large time investment, which often limits tracing studies to the examination of a small number of regions of interest, neglecting potentially important differences in other brain regions (Tregellas et al., 2007). However,

even a rapid and fully automated whole-brain measurement technique, VBM method, is not a replacement for manual ROI-based analyses (Giuliani et al., 2005). The ROI method still has many strengths. Third, our review focused on only MRI studies, by definition not including other approaches such as post mortem studies. Postmortem studies of the brains of SCZ patients have been conducted for over a century. However, neuropathological changes from postmortem are subtle and no pathognomonic "lesions" have been reported (Keshavan et al., 2008). Postmortem studies have been limited by the problems of postmortem tissue being compromised by the difficulties in making ante-mortem diagnoses, long postmortem intervals, variable treatment of the specimens after death, shrinkage or expansion during preservation, variable tissue quality, typically small sample sizes and the difficulty in finding appropriate controls (Allen et al., 2002; Lewis, 2002; Keshavan et al., 2008). These limitations made us prefer selection of only MRI studies. Particularly, the brain changes at the time of symptom onset are only observable by imaging technology. Although data from postmortem studies are still useful, at present MRI is the most commonly used method to study brain size and macrostructure, supplanting postmortem surveys and measures of brain size based on the external size of the skull (Peters et al., 1998). The main advantages of in vivo MRI over postmortem studies include much greater control over subject selection and the ability to digitally manipulate brain images, allowing parcellation and measurement of a variety of brain subregions and structures (Allen et al., 2002). Moreover, there are only a small number of postmortem studies focusing on STG or subregions and most of them are postmortem microscopic studies (e.g. Bowden et al., 2008). There are only four studies focused on STG volume change. Among them, 3 of four studies reported positive results, which found the volume reduction in the left STG (Highley et al., 1999), left PT (Falkai et al., 1995), or middle compartment of STG (reaching from the mamillary body to the lateral geniculate body) (Vogeley et al., 1998) when compared with controls. One study found no significant difference in the volume of the left or right STG in SCZ patients (Hobson et al., 1995). The results from postmortem studies are similar to the results of MRI studies: the varieties of volume change and left-sided reduction are more prominent.

5. Conclusions

We reviewed 46 studies that used ROI volumetry to identify STG or its subregions volume changes in the brains of patients with SCZ. Female and left-handed subjects are under-represented in the literature and insight from sex and handedness differences may be lost. Of the 46 studies, 35 reported a significant difference in STG or subregional volume including bilateral or unilateral ROI and volume reduction was the common change in patients with schizophrenia. There were 30 studies reporting correlations between STG or its subregional volume changes and clinical symptoms or syndrome and 18 of them found positive results. Among them, left STG or subregions appear to be more involved in the generation of H and TD than right side. These findings lend support to the contention that STG or subregional volume change may result in the clinical manifestations that form the core of the SCZ psychopathology. Clinical heterogeneity, MRI acquisition parameters, anatomical landmarks for ROI and demographic characteristics of subjects are probably main factors that lead to different results. Thus, it is likely that more consistent structural differences in SCZ would be reported if ROI volumetry was applied to clearly defined patient groups characterized by symptom profile, age, sex, handedness, and disease duration using the same or similar MRI acquisition parameters and standard anatomical landmarks for ROI definition.

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