<table>
<thead>
<tr>
<th>項目</th>
<th>内容</th>
</tr>
</thead>
<tbody>
<tr>
<td>書名</td>
<td>Pseudohypacusis in childhood and adolescence is associated with increased gray matter volume in the…</td>
</tr>
<tr>
<td>著者</td>
<td>Tomoda, Akemi; Kinoshita, Sumihito; Korenaga, Yuki; Mabe, Hiroyo</td>
</tr>
<tr>
<td>引用</td>
<td>Cortex, 48(4): 492-503</td>
</tr>
<tr>
<td>発行日</td>
<td>2012-04</td>
</tr>
<tr>
<td>テイプ</td>
<td>Journal Article</td>
</tr>
<tr>
<td>URL</td>
<td><a href="http://hdl.handle.net/2298/26062">http://hdl.handle.net/2298/26062</a></td>
</tr>
<tr>
<td>Copyright</td>
<td>© 2012 Elsevier</td>
</tr>
</tbody>
</table>
Pseudohypacusis in childhood and adolescence is associated with increased gray matter volume in the medial frontal gyrus and superior temporal gyrus

Akemi Tomoda\textsuperscript{a,*}, Sumihito Kinoshita\textsuperscript{a, b}, Yuki Korenaga\textsuperscript{a}, and Hiroyo Mabe\textsuperscript{a}

\textsuperscript{a}Department of Child Development, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan

\textsuperscript{b}Department of Otorhinolaryngology, Kumamoto City Hospital, Kumamoto, Japan

Abbreviated title: Pseudohypacusis and increased GMV

(Accepted on October 4, 2010)

*Corresponding author. Department of Child Development, Faculty of Life Sciences, Kumamoto University, 1-1-1 Honjo, Kumamoto, 860-8566, Japan

E-mail address: tomo@kumamoto-u.ac.jp (A. Tomoda)

Fax: +81-96-373-5200 Tel.: +81-96-373-5196
ABSTRACT

Pseudohypacusis is a somatoform disorder characterized by hearing loss with discrepancies between pure-tone audiometry and auditory brainstem response, but the underlying neuronal mechanisms remain unclear. Using voxel-based morphometry with magnetic resonance imaging for 14 unmedicated, right-handed patients and 35 healthy control subjects, we investigated whether functional hearing loss was associated with discernible changes of brain morphology. Group differences in gray matter volume (GMV) were assessed using high-resolution, T1-weighted, volumetric magnetic resonance imaging datasets (3T Trio scanner; Siemens AG) and analyzed with covariant factors of age, sex, socioeconomic status, and total GMV, which was increased by 27.9% in the left medial frontal gyrus (Brodmann area 10) ($p = .001$, corrected cluster level) and by 14.4% in the right superior temporal gyrus (STG) and the adjacent middle temporal gyrus (MTG) (BA42 to 21) ($p = .009$, corrected cluster level) in patients with pseudohypacusis. The GMV in the right STG (BA42) and verbal intelligence quotient were correlated significantly with the Wechsler Intelligence Scale for Children – Third Edition ($\beta = -.57$, $p < .0001$) and level of socioeconomic status ($\beta = -.55$, $p < .0001$). The present findings suggest that the development of the auditory association cortex involved in language processing is affected, causing insufficient pruning during brain development. We therefore assert that differences in the neuroanatomical substrate of pseudohypacusis subjects result from a developmental disorder in auditory processing.

Keywords: Pseudohypacusis; Somatoform disorder; Voxel-based morphometry; Medial frontal gyrus (Brodmann area 10); Superior temporal gyrus (Brodmann area 42)
1. Introduction

Pseudohypacusis is a somatoform disorder manifesting as hearing loss in the absence of organic disease; it is inconsistent with clinical or audiological evaluation (Austen and Lynch, 2004; Ban and Jin, 2006; {Lin, 2006 #2605}; Pracy et al., 1996). Pseudohypacusis is the most frequently reported etiology of sudden hearing loss in children (Psarommatis et al., 2009). The cause of pediatric hearing loss is not possible to determine in most cases: parents are usually unaware of any problem until notified by the child’s school because of the lack of consistency between observed social responses to sound (Rintelmann et al., 1991). Clinical discrepancies between behavior hearing thresholds and objective electrophysiological examinations, such as impedance audiometry, otoacoustic emissions, the Stenger test, and auditory brainstem response (ABR), will raise the suspicion of this disorder (Balatsouras et al., 2003; Durmaz et al., 2009; Musiek et al., 1995; Pracy and Bowdler, 1996; Qiu et al., 1998; Saravanappa et al., 2005). Pseudohypacusis is usually easier to diagnose in children than in adults because children are less likely to give consistently erroneous results on repeated testing. However, the diagnosis is often missed in children, probably because of a lack of awareness of this condition. Several recent studies have examined hearing function in relation to this disease using such techniques, but no investigation has assessed the possible neuroanatomic and structural abnormalities. Results of such investigations might help interpret the neurophysiology. Our clinical experience of patients with discrepancies between behavior and hearing thresholds suggests that some patients are not aware of hearing loss. Therefore, patients with pseudohypacusis might have uncertain stressors and experience changes in brain function, which induce cognitive dysfunction, engendering symptoms such as hearing loss.

Brain development is guided mostly by genetic factors, but the final form is sculpted by environmental factors and early experience. Exposure to emotionally traumatic events such as
childhood abuse and neglect are associated with alterations in the size and functional activity of various brain regions (Andersen et al., 2008; Bremner et al., 1997; De Bellis et al., 1999, 2002; De Bellis and Kuchibhatla, 2006; Richert et al., 2006; Teicher et al., 1997, 2004; Tomoda et al., 2009a). Attenuation of the N100 amplitude to the peculiar auditory perception associated with psychogenic hearing impairment has been reported in patients with pseudohypacusis (Schlauch et al., 1996), suggesting two possible mechanisms— inhibitory auditory processing and attention deficit— but the neural substrates of pseudohypacusis are not well understood.

To test our hypothesis that pseudohypacusis reflects an abnormal developmental trajectory of the brain regions involved in regulating emotion, aggression, attention, and cognition, this study investigated the gray matter volume (GMV) using an unbiased, whole-brain, voxel-by-voxel approach to examine control subjects and pediatric patients with pseudohypacusis, who were screened to exclude extraneous factors such as substance abuse, head injury, and fetal drug exposure, which might have influenced brain development. The study also assessed whether alterations in regional GMV are correlated with intellectual ability.

2. Subjects and methods

2.1. Subjects

The Committee of Life Ethics, Graduate School of Medicine, Kumamoto University approved the study protocol. Parents or guardians of all participants gave written informed consent.

This study examined 14 unmedicated patients with pseudohypacusis, 6 boys and 8 girls aged 8–16 years (mean age, 12.4 years; standard deviation [SD], 2.5 years), who were referred to our laboratory during 2006–2009 for examination of hearing loss detected by school screening tests (Table 1). All patients satisfied the diagnostic criteria for conversion disorder of the Diagnostic and
Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR® #300.11). To exclude other psychiatric diagnoses, the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) was administered by a licensed pediatric-psychiatric clinician.

To obtain data in normal age-matched subjects, 35 healthy school children aged 8–16 years were recruited as subjects from the community; school students were targeted. None had below-average intelligence, physical problems, or psychiatric psychopathology. The control group comprised 16 males and 19 females (mean age, 12.6 years; SD, 2.1 years).

Neither group’s subjects had a history of exposure to abuse, traumatic events, or head trauma. All participants were right-handed and unmedicated. Patients who had treatment with antidepressants or hypotension drugs, or who had diagnoses of neurological illness, migraine, obstructive sleep apnea, below average intelligence, or severe psychopathology were excluded from the study. Serious psychopathology was evaluated by referral to at least one pediatric psychiatrist if the patient presented indicative symptoms.

No patient or control subject had any history of DSM-IV-TR Axis I Disorder (based on SCID-I) including attention deficit hyperactivity disorder or psychological visual disturbance evaluated by an ophthalmologist, or any history of any form of abuse or drug abuse, head injury, or fetal drug exposure that might have influenced brain development. Table 1 presents the subjects’ physical characteristics.

2.2. Pure-tone audiometry and ABR test

Pure-tone audiometry was performed by audiologists in soundproof booths using standard TDH-39 earphones and Madsen ADS100 audiometers (Nagashima Corp., Tokyo, Japan), which were calibrated to Japanese standards regularly during the study period (Manwaring et al., 2007). The audiologists also examined the subjects’ ears for wax occlusion. The subject was asked to return for
assessment after treatment if necessary. Audiometric thresholds for air-conduction stimuli (in both ears) were established for frequencies at 125, 500, 1000, 2000, 4000, 6000, and 8000 Hz, with 3000 Hz if a 20-dB difference existed between the 2000-Hz and 4000-Hz thresholds. Bone conduction was evaluated whenever air-conduction thresholds were greater than the 15-dB hearing level (HL) for frequencies of 500, 1000, 2000, and 4000 Hz. Subjects were examined for any evidence of collapsed canals; if present, air-conduction thresholds at the higher frequencies were reassessed, taking care to reduce the pressure on the external ear.

Using standard clinical ABR protocols, ABR data were recorded (SYNAX ER1100; NEC Corp., Tokyo, Japan) by pediatric audiologists (Yorgason et al., 2010). Equipment was electroacoustically calibrated annually and biologically checked daily. Click stimuli were of 100 sec duration, calibrated to normal HL. Tone burst stimuli used the Blackman gating function. The stimuli were detected using two surface electrodes placed on the forehead immediately above the intercilia; the other two surface electrodes were placed on the bilateral mastoid area of each patient. Stimuli were delivered through the headphone receivers. Times for test procedures were limited by constraints of the sound-proof room. Stimuli were delivered through ear insert receivers and probes in the external ear canal. Times for test procedures were limited by constraints of the operating room environment and the availability of previous test results. Noise in the operating room was considered not to affect the test results. The ABRs typically took 20 min per side. Audiologic testing was performed an average of five times.

2.3. Assessment measures

Low income and poverty might be important developmental risk factors related to psychopathology (Tomoda et al., 2009a). The parental socioeconomic status (SES) test was administered as a composite
measure of socioeconomic status (Hollingshead, 1965; Hollingshead and Redlich, 2007). The Wechsler Intelligence Scale for Children-Third Edition (WISC-III), an individually administered measure of intelligence intended for children aged 6 years to 16 years and 11 months, was administered to estimate their intellectual capacities (Wechsler, 1991). The severity of depressive symptoms was measured using the Zung self-rating depression scale (SDS), which is similar to the children’s depression inventory used in pediatric psychiatry {Zung, 1965 #2600}.

The validation and reliability of Japanese version of these scales have been confirmed. The version is applicable to Japanese children and adolescents (Fukuda & Kobayashi, 1973; Japanese WISC-III Publication Committee, 1998).

2.4. Brain imaging and analysis

High-resolution, sagittal T1-weighted and coronal Flair magnetic resonance (MR) imaging datasets were obtained using a Trio scanner (3T; Siemens Medical Solutions, Siemens AG, Erlangen, Germany) with an inversion-prepared three-dimensional multi-planar rapidly acquired gradient echo (MPRAGE) sequence and an eight-element phased-array RF reception coil (Siemens AG).

Generalized autocalibrating partially parallel acquisition (GRAPPA) and processing were used to reduce the scan time, with a GRAPPA factor of 2. Scan parameters were echo time/repetition time/inversion time/flip angle = 2.74 msec/2.1 sec/1.1 sec/12 deg; three-dimensional matrix 256 × 256 × 128 on 256 × 256 × 170 mm field of view; bandwidth 48.6 kHz; scan time 4:56. Licensed neuroradiologists conducted assessment of the Flair or T1-weighed images and completed their evaluations before our neuroimaging study began.

Voxel-based morphometry (VBM) is a fully automated whole-brain morphometric technique to detect regional structural differences between groups on a voxel-by-voxel basis (Good et al., 2001a,
The VBM was performed using Statistical Parametric Mapping 8 (SPM8) software (Wellcome Department of Imaging Neuroscience, University College London, London, UK; http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) for imaging processing (MATLAB 9.5; The MathWorks Inc., Natick, MA). Images were segmented coarsely into gray matter, white matter, cerebrospinal fluid, and skull/scalp compartments using tissue probability maps. The standard template that was used (Ashburner and Friston, 2000, 2005) conformed to the space defined by the International Consortium for Brain Mapping, National Institutes of Health P-20 project, and approximates the space described in the Talairach and Tournoux atlas (Talairach and Tournoux, 1988). The transform for this normalization was used to rewrite the original image into the standard space. Volume changes induced by normalization were adjusted via a modulation algorithm. Spatially normalized images were segmented into gray and white matter and then smoothed using a 12-mm full-width half-maximum isotropic Gaussian kernel. Regional differences in the GMV between groups were analyzed statistically using the general linear model. Potential confounding effects of age, sex, SES, and whole segment GMV were modeled, and the attributable variances were excluded (Tomoda et al., 2009a). The resulting set of voxel values was used to generate a statistical parametric map of $t$-statistics $\text{SPM}\{t\}$, which was transformed to a unit normal distribution ($\text{SPM}\{Z\}$) for comparison. The statistical threshold was set at $p < .05$, with correction for multiple comparisons at cluster level (height threshold of $Z > 3.09$) because of the increased sensitivity of clusters, to detect spatially extended signal changes (Hayasaka et al., 2004; Moorhead et al., 2005). Inference testing was based on the theory of Gaussian fields (Friston et al., 1996). Potential problems related to non-isotropic smoothness, which can invalidate cluster-level comparisons (Ashburner and Friston, 2000), were corrected by adjusting the cluster size from the resel per voxel image (Hayasaka et al., 2004; Worsley et al., 1999).
2.5. Statistical analyses

To identify regions that differed significantly between groups and to assess the association between alterations in GMV in the identified cluster and degree of hearing loss, SPM8 was used.

The clinical values were compared in both groups using Mann–Whitney’s U-test. Data are expressed as the mean ± SD. All statistical tests (ANOVA or ANCOVA and Fisher’s exact test for discrete variables) were two-sided; $P$ values less than .05 were inferred as statistically significant. Statistical analyses were performed using software (PASW Statistics 18; SPSS Inc., Chicago, IL). Exploratory correlation analyses were used to assess whether regional differences in GMV can account for a significant portion of the variance. Similarly, exploratory correlation analyses were performed to identify possible associations between GMV in identified regions and prespecified symptom ratings such as neuropsychological and audiometric variables. Multiple regression analysis was performed with age, sex, SES, SDS scores, pure-tone audiogram, verbal IQ scores, and total GMV as independent variables, and GMV in left MFG and right STG as dependent variables.

Further analyses were conducted to ascertain the degree to which GMV in the identified primary cluster was associated with levels of key covariates. The correlation coefficient was used to explore the relation between GMV in the identified cluster, neuropsychiatric measures, and depression scores, while controlling for age, sex, SES, and whole brain GMV. Data analyses for examining nonlinear regression lines between GMV in the identified cluster and age were conducted using R (R Development Core Team, R: A Language and Environment for Statistical Computing: http://www.R-project.org).

3. Results
Table 1 shows that the patient and control groups were well matched in terms of sex (Fisher exact, $p = .95$) and SES ($F = .012, p = .78$). A slight predominance of females was found in both groups along with a 'trend' of age difference ($F = 2.92, p = .09$). Patients and control subjects were predominantly middle class or higher, with similar measures of parental SES. In subsequent analyses, differences in the gender ratio, age, and parental SES were controlled for.

The most robust difference between the groups was in pure audiometry ($F = 58.63, p < .0001$). Patients and control subjects differed to a slightly significant degree in verbal intelligence quotient (IQ) ($F = 3.06, p = .09$) (Table 1), suggesting that the effect comes from their functional hearing loss as verbal IQ scores correlated strongly with the levels of pure-tone audiometry in pseudohypacusis subjects ($r = -.56, p < .0001$).

As expected, the patient group had significantly higher SDS scores ($F = 28.13, p < .0001$) with a mean of 44.8 ± 4.4, with 92% of patients showing predisposition for depression (40 points or more).

Hearing impairment was defined as the pure-tone average of audiometric hearing thresholds at 500, 1000, 2000, and 4000 Hz in the better of the two ears. No patient had abnormal ABR test results (Table 2). None of our patients exhibited evidence of focal structural abnormalities on Flair or T1-weighed MRI.

Two significant clusters of increased GMV were found in pseudohypacusis subjects (Fig. 1). The most prominent neural finding was the significant increase in GMV in the left medial frontal gyrus (MFG) in patients with pseudohypacusis (Brodmann area 10 [BA10]; Talairach’s coordinates $x = -30$ to -16, $y = 35$–49, $z = -4$ to 1, cluster size = 863, $p = .001$, $Z = 4.11$, corrected cluster level). The mean increase in GMV in this cluster was 27.9% in patients with pseudohypacusis. A slightly smaller cluster was apparent in the right superior temporal gyrus (STG) and the adjacent middle temporal gyrus (MTG) (BA42 to 21; Talairach’s coordinates $x = 51$–63, $y = -30$ to -18, $z = -9$ to 25, cluster size =
559, \( p = .009, Z = 3.79\), corrected cluster level). The mean increase in GMV in this cluster was 14.4%.

No other area of increased GMV was found with a corrected cluster probability value that approached significance.

As presented in Fig. 2, a significant correlation was found between the left MFG GMV and levels of pure-tone audiometry in the better of the two ears across all subjects (\( r = .508, p = .0002\), Fig. 2A), but none was apparent in pseudohypacusis (\( r = -.255, p = .46\)) or healthy control subjects (\( r = -.196, p = .25\)). The left MFG GMV correlated significantly with SDS scores across all subjects (\( r = .551, p < .0001\)) (Fig. 2A), but none was apparent in pseudohypacusis (\( r = .185, p = .60\)) or healthy control subjects (\( r = .102, p = .56\)). Similarly, a significant correlation was found between the right STG GMV and levels of pure-tone audiometry across all subjects (\( r = .384, p = .007\), Fig. 2B), but none was apparent in pseudohypacusis (\( r = -.285, p = .40\)) or healthy control subjects (\( r = -.131, p = .45\)). The right STG GMV correlated significantly with SDS scores across all subjects (\( r = .551, p < .0001\)) (Fig. 2B), but none was apparent in pseudohypacusis (\( r = .451, p = .17\)) or healthy control subjects (\( r = .15, p = .39\)).

Gender differences were found in pure-tone audiograms (Male: 22.1±27.1 dB, Female: 44.1 ±35.8 dB, \( p = .007\), Mann–Whitney’s U-test), verbal IQ scores (Male: 107.4±14.5, Female: 97.1 ±11.6, \( p = .01\), Mann–Whitney’s U-test), and total GMV (Male: .80±.05 liters, Female: .76 ±.05 liters, \( p = .01\), Mann–Whitney’s U-test). However, there were no gender differences in GMV in the left MFG or GMV in the right STG (MFG; \( p = .32\), STG; \( p = .48\), Mann–Whitney’s U-test).

Multiple regression analysis, including that of hearing loss severity (levels of pure-tone audiometry in the better of the two ears) and the left MFG GMV, indicated that the left MFG GMV correlated significantly with the severity of hearing loss by pure-tone audiometry (\( \beta = .307, p = .04\)) in both group subjects (Table 3). However, GMV in the left MFG did not correlate significantly with the
severity of hearing loss in subjects of either group (patient group; $\beta = .028, p > .8$, control group; $\beta = -.277, p = .09$). Multiple regression analysis using the covariates included in the VBM analysis indicated that the GMV in the right STG showed high overall correlation ($r = .52, p < .0001$), with the major determinants being verbal IQ ($\beta = -.57, p < .0001$), total GMV ($\beta = .65, p < .0001$), and level of SES ($\beta = -.55, p < .0001$) (Table 4). In contrast, in the patient group and controls, total GMV (patients: $\beta = 1.02, p = .003$; controls: $\beta = .76, p < .0001$) and the level of SES (patients: $\beta = -.25, p = .044$; controls: $\beta = -.67, p = .024$) were significant independent variables, but the verbal IQ was not (Table 4). The right STG GMV correlated significantly with the hearing loss severity indicated by pure-tone audiometry ($\beta = .915, p = .04$) in the patient group. However, the right STG GMV did not significantly correlate with the severity of hearing loss in subjects of both group ($\beta = .183, p > .1$) or in subjects of control group ($\beta = -.192, p = .07$).

It is particularly interesting that the approximation curve in scatter plots shows the nonlinear relation between GMV in a point in the left MFG (BA10; Talairach’s coordinates $x= -20, y= 35, z= -3$) and age indicated delayed GMV reduction during brain development in the patient group, and a peak at the age of 12 years in the control group ($F = 9.29, df = 1, 47, p = .0038$) (Fig. 3A). Similarly, the approximation curve in scatter plots shows the nonlinear relation between the GMV in a point in the right STG (BA42; Talairach’s coordinates $x= 63, y= -30, z= -9$) and age indicated a delayed GMV reduction during brain development in the patient group, and a peak at the age of 12 years in the control group ($F = 20.06, df = 1,47, p < .0001$) (Fig. 3B).

No significant partial correlation was found between the GMV in the left MFG or right STG and measures of intelligence, or depression symptom ratings. Examination of voxels with reduced GMV in patients with pseudohypacusis revealed no significant corrected voxel level-cluster regions.
A VBM analysis of white matter volume (WMV) revealed a significant cluster of increased WMV in the right middle frontal gyrus in pseudohypacusis subjects (Talairach’s coordinates x = 24, y = -7, z = 48) (cluster size = 432, p = .006, Z = 4.86, corrected cluster level). However, examination of voxels with reduced WMV in patients with pseudohypacusis showed no significant corrected voxel level-cluster region.

4. Discussion

Childhood and adolescence are times of extreme physical and social change in humans, with important implications for both personality and brain development. Considerable progress has been made in the last few decades in elucidating the neurobiological aspects of brain development in human beings. Several VBM studies have provided an unbiased method of assessment of regional alterations in GMV. However, such studies present numerous limitations. Care must be taken to ensure that no issues exist in relation to alignment. Subjects in the two groups must be of virtually identical age and SES, which could affect growth and development, as well as a 'trend' towards difference in sex distribution, which can be statistically controlled for. This study provides preliminary evidence of increased GMV in the left MFG/BA10, right STG and the adjacent MTG/BA42 to 21 of children and adolescents with pseudohypacusis that were observed, respectively, with corrected p = .001 and .009 at the cluster level. Pseudohypacusis is common, occurring in about 2.5–3.0% of subjects in this age range (Ban and Jin, 2006; Berk and Feldman, 1958). This unexpected finding emerged from a global VBM analytical approach.

Curiously, a possible association between hearing loss and increased GMV in the MFG/BA10 was identified in a previous study of prelingually deaf subjects demonstrating significantly higher activation in the MFG as well as in the areas involved in the grapho-phonological route (Aparicio et
al., 2007). Other imaging studies of normal healthy subjects have shown that this region is involved in aspects of detecting and verbalizing specific words, and that it shows significant interactions between density and frequency of phonological-lexical competition and frequency of word recognition (Prabhakaran et al., 2006; Salvi et al., 2002). Functional MR imaging and positron emission tomography activation in the MFG might be related to the cognitive effort required by alternative strategies (compensation), which suggests activation of the neural mechanisms of linguistic, attentional, cognitive, working memory, and motor planning areas. Furthermore, the processing of emotional prosody involves bilateral networks encompassing the superior and medial temporal cortices, which suggests the value of research investigating the neuronal network that supports the processing of emotional information. This MFG region might provide the necessary computational resources for integrating frequency and density information to access a word (Prabhakaran et al., 2006).

It is interesting that a PET study in normal subjects demonstrated that the right prefrontal cortex (BA10) also plays a role in language processing and serves as the neuroanatomical substrate of sound duration discrimination (Belin, 2002). Discrimination of sound intensity involves two cerebral networks: a supramodal right fronto-parietal cortical network responsible for allocation of sensory attentional resources, and a network of regions that include the right prefrontal cortex. This finding suggests that both the primary auditory cortex and the developmentally appropriate trajectory of cortical region are involved in the attention and discrimination of sound intensity. In this study, we evaluate the presupposition that developmental anomalies of BA10 in pseudohypacusis subjects do not allow them to pay attention. This impairment is compounded by a disturbance in cortical networking of the auditory area resulting from a lack of pruning during the appropriate period. The present findings suggest that development of the auditory association cortex involved in language processing might be
affected by stress that results in insufficient pruning during brain development. We therefore assert that differences in the neuroanatomical substrate of pseudohypacusis subjects are the result of a developmental disorder in the auditory process. The price of this ‘adaptation,’ however, might be reduced auditory function (Saravanappa et al., 2005), and an increased risk for other sensory deficits (Ban and Jin, 2006; Oakley, 1999; {Bowdler, 1989 #2637;Zhao, 2008 #2638}).

One identified region (STG/BA42) plays a critical role in processing of language and speech as an auditory association cortex that corresponds roughly to cytoarchitectonically identified Te2.2 to receive the core projection of the acoustic radiation {Morosan, 2005 #2632}. Previous studies of the morphology of organic hearing loss investigated the STG. A VBM study of prelingually deaf subjects found that posterior STG white matter was decreased on the left, corresponding to white matter that is inferior to the auditory cortex (Shibata, 2007). This result might represent hypoplasia of the auditory/speech-related tracts as a consequence of early deafness. Another VBM study in patients with congenital amusia (tone deafness) suggested impairment of the auditory-motor feedback loop and/or an auditory-motor mapping system (Mandell et al., 2007). It is particularly interesting that increased GMV in the STG was found in congenitally deaf subjects {Emmorey, 2003 #1671}, although no differences were found between the deaf and control groups in any auditory cortical region {Penhune, 2003 #2598}. Furthermore, our previous studies have demonstrated increased GMV in the STG and reduced fractional anisotropy in the arcuate fasciculus connecting Wernicke’s area and the frontal area in young adults exposed to childhood emotional stress because of parental verbal abuse (Choi et al., 2009; Tomoda et al., 2010). Nevertheless, nothing is known about the potential neurobiological abnormality of pseudohypacusis.

Traditionally, the arcuate fasciculus is known as the fiber tract connecting Wernicke’s area in the temporoparietal junction with Broca’s area in the inferior frontal gyrus. Results of recent anatomical
studies suggest that the arcuate fasciculus connects the caudal superior temporal area with frontal lobe areas and provides a pathway for the prefrontal cortex to receive and modulate auditory information {Makris, 2005 #2617}. Importantly, hemispheric asymmetry is a key feature of the language network {Catani, 2008 #2653}. That the left hemisphere is responsible for most language tasks is an extremely well-established fact about the brain; nevertheless when it comes to comprehending complex, natural language, the right hemisphere might play an important role in activities such as semantic processing {Jung-Beeman, 2005 #2664}. Speech comprehension has been shown to be a strikingly bilateral process, but the differential contributions of the subfields of left and right auditory cortices have remained elusive.

Previously, a DTI analysis of the degree of lateralization of three segments of the perisylvian language networks showed an extreme degree of leftward lateralization in more than half of the normal population {Catani, 2007 #2657}. An fMRI study showed complementary roles for the left and right superior temporal sulci in comprehending the speech signal {Obleser, 2008 #2636}. Similarly, a combined EEG and fMRI study explored stimulation-independent auditory networks and demonstrated a mild difference in “tuning functions” of the left and right Heschl’s gyrus (BA42) {Giraud, 2007 #2639}. In this study, the asymmetry of frontal and temporal results might represent current DTI tractography models of language pathways that project to STG, MTG, and the inferior parietal lobule (posterior segment of the arcuate fasciculus) {Catani, 2008 #2652}.

Exactly why hearing acuity is associated with increased right STG GMV in the patient group is unclear. They developed normally during their early childhood. Therefore, it is unlikely that the patients had more numerous axons. Hearing deprivation causing less careful attention, however, might affect activity-dependent changes in neural circuits and unmyelinated fibers that constitute a component of the pathway because these properties in the STG and inferior temporal gyrus are established later in
development; moreover, they appear to be susceptible to effects of experience during preadolescent and peripubertal periods {Gogtay, 2004 #2622; Grubb, 2010 #2621}. A report of a previous study described that STG and MTG show no distinct linear trajectory. They are thought to be a heteromodal association site (along with prefrontal and inferior parietal cortices) and are involved with integration of memory, audiovisual association, and object-recognition functions {Brauer, 2010 #2624}. Consequently, the temporal cortex continues to mature after other association areas, the functions of which it integrates, are developed.

It is particularly interesting that recent studies in typically developing children {Lu, 2009 #2626} showed an alternative connection to the temporal lobe (Wernicke’s area) via the ventrally projecting extreme capsule fiber system, suggesting a role for experience in mediating brain structure – activation relations and the brain’s plasticity to adjust its function to available structural prerequisites in childhood and certain relations between language development and brain maturation {Brauer, 2010 #2624}. Activity-dependent changes in neural circuits are crucial for brain development and memory formation. For example, hearing deprivation increased the total sodium currents in the axons. Those neurons can regulate the position of an entire subcellular structure according to their ongoing levels and patterns of electrical activity. This novel form of activity-dependent plasticity might fine-tune neuronal excitability during development {Grubb, 2010 #2621}.

The most unexpected finding obtained during this study was that the GMV in the STG was higher in subjects with lower verbal IQ scores: The relation was direct, continuous, and clear. We had predicted that the GMV would be reduced in this region. Nevertheless, in retrospect, the present finding makes sense. Results of recent studies indicate that this region continues to mature into late adolescence and early adulthood with a progressive decline in the regional cerebral blood flow, presumably associated with dendritic pruning (Devous et al., 2006). Therefore, a low GMV in subjects within this
age range might be indicative of typically healthy development. Our finding of an inverse relation between GMV in the right STG/BA42 and level of SES is also consistent. One potential explanation is that parents with higher levels of education and financial status tend to provide their children with richer verbal stimulation; this might be reflected in a developmental trajectory that emphasizes both a high degree of overproduction prior to puberty and by extensive pruning during adolescence, as occurs in subjects with superior IQs (Shaw et al., 2006). A possible alternative explanation for increased GMV in the identified regions is that children with pseudohypacusis are at increased risk, which would depend on the nature of the uncertain emotional stress to substantiate it.

Results of MR imaging of human brain maturation during childhood have consistently shown subtle increases in GMV and increases in all white matter volume, as well as subtle increases in all brain volume along with regionally variable patterns of reductions in GMV and increases in all white matter volume during adolescent years (Giedd et al., 1996, 1999; Sowell et al., 2003). A significant, nonlinear decline occurred in gray matter density with age, most rapidly between 7 and about 60 years, over the dorsal frontal and parietal association cortices on both the lateral and interhemispheric surfaces (Sowell et al., 2003). Age effects were inverted in the left posterior temporal region, where the gray matter density gain continued up to age 30 and then declined rapidly. The trajectory of maturational and aging effects varied considerably over the cortex. Visual, auditory, and limbic cortices, which are known to myelinate early, showed more linear patterns of aging than the frontal and parietal neocortices, which continued myelination into adulthood. Our findings also reflect that the posterior temporal cortices, which typically support language functions, have a more protracted course of maturation than any other cortical region has. The spatial and temporal distributions of tissue density changes have also been mapped (Sowell et al., 1999a, 1999b), revealing a pattern of maturational changes that are consistent with that expected based on postmortem studies of
myelination (Benes et al., 1994) and synaptic pruning (Huttenlocher, 1979; Huttenlocher and de Courten, 1987). Specifically, reduction in cortical gray matter density occurs primarily in the dorsal parietal and some frontal regions between childhood and adolescence (Sowell et al., 1999a).

Cross-sectional data show that the GMV of the identified regions decreases at a much more rapid rate from age 12 in control subjects with normal hearing acuity than patients with pseudohypacusis. However, this decrease might not result in an end point of developing process relative to early childhood because this area appears to continue to mature throughout late adolescence/early adulthood (Devous et al., 2006; Gogtay et al., 2004). Our results in healthy control subjects suggest that progressive cellular maturational events such as increased myelination might be equally as important during the postadolescent years as regressive events such as synaptic pruning in determining the ultimate density of mature frontal lobe cortical gray matter (Sowell et al., 2003). Such studies have also revealed that the synapses in the cerebral cortex are reduced progressively throughout childhood and adolescence, with parallel reductions in cerebral metabolism (Giedd et al., 1996, 1999; Sowell et al., 2001). Recent in vivo structural imaging reports have described spatial and temporal patterns of brain maturation between childhood, adolescence, and young adulthood that are generally consistent with postmortem studies of cellular maturational events such as increased myelination and synaptic pruning.

This study revealed a strong association between verbal IQ scores and increased GMV in the right STG/BA42, but this correlation does not prove any causative relation between low verbal performance and increased GMV. Various alternative explanations can be advanced, such as the possibility that individuals with increased GMV in the STG are prone to over-interpret verbal communications as stressful. How these alterations might affect function is unclear. We suspect that the potential effects are much more subtle and that they might influence the subject’s response to
emotionally laden content or to highly personal communications. Prospective longitudinal studies might help to clarify any causal relation.

The main limitation of this study is the small patient group. For that reason, we used a less strict approach (false discovery rate) rather than family wise error to detect differences between the groups. Although the size of this group was adequate to reveal differences from control subjects, the method and group provided insufficient statistical power to detect small potential differences between patients with different stressful events.

Furthermore, although VBM studies are rapidly increasing our understanding of the effects of disease processes on GMV, caution is necessary for interpretation of volume changes in GM density. The significance of the group differences and the strength and propriety of the anatomical–functional correlations suggest that GMV differences in these regions represent areas of insufficient pruning during proper brain development. Further confirmation must occur through replication in larger samples and through refinements in resolution {Pereira, 2008 #2618}.

Our findings should generalize well to subjects with pseudohypacusis but no psychological visual disturbance because we selected subjects without regard to visual disturbances such as spiral and tubular visual fields. It remains to be seen whether the same findings emerge in subjects with pseudohypacusis together with other forms of psychological visual disturbance. Although this is a preliminary study of modest size, we characterized children and adolescents who, to the best of our knowledge, suffered only from functional hearing loss. The present findings might also be useful for the development of therapeutic strategies for treating pseudohypacusis. Most forms of psychotherapy necessitate that patients process the feedback verbally and follow guidance that is given by the therapist; patients therefore rely on language to communicate their experiences and emotional states. However, if speech processing and language comprehension abilities are altered because of past
stressors, then novel treatment methodologies might be necessary to cope effectively with such neurobiological differences on the developing brain.

**Acknowledgments**

Drs. Tomoda and Kinoshita contributed equally to the present paper as first authors. We thank Tomoko Yamaguchi, BA for assistance in subject recruitment and Dr. Martin H. Teicher for his helpful comments with this manuscript and our anonymous reviewers for their insightful comments.

**Financial Disclosures**

This study was performed with the support of Special Coordination Funds for Promoting Science and Technology from the Japanese Ministry of Education, Culture, Sports, Science, and Technology, and Grant-in-Aid for Scientific Research from Japan-U.S. Brain Research Cooperation Program which had no other involvement in the study. There are no conflicts of interest including any financial, personal, or other relationships with persons or organizations for any author related to the work described in this article.
FIGURE LEGENDS

Fig. 1 - Portrayal of the locations of significant differences between pseudohypacusis subjects and control subjects in regional gray matter volume as revealed by voxel-based morphometry. Significantly higher gray matter densities in pseudohypacusis subjects were measured in the left medial frontal gyrus (Brodmann area 10) and in the right superior temporal gyrus and the adjacent middle temporal gyrus (Brodmann areas 42 to 21). Color scale: 0–6 represents t-values.

Fig. 2 - (A) Scatter plots portraying the relation between gray matter volume in the left medial frontal gyrus (Brodmann area 10; Talairach’s coordinates $x= -20, y= 35, z= -3$) and levels of pure-tone audiogram (left graph) and SDS scores (right graph). (B) Scatter plots portraying the relation between gray matter volume in the right superior temporal gyrus (Brodmann area 42; Talairach’s coordinates $x= 63, y= -30, z= -9$) and levels of pure-tone audiogram (left graph) and SDS scores (right graph).

Fig. 3 - (A) Scatter plots and the approximation curve showing a nonlinear relation between age and gray matter volume in the left medial frontal gyrus (Brodmann area 10; Talairach’s coordinates $x= -20, y= 35, z= -3$) in the patient (red dot and line) and control groups (blue dot and line). Each line and confidence limits fit by regional tricubic least-squares with smoothing (loess function in R). (B) Scatter plots and the approximation curve showing the nonlinear relation between age and gray matter volume in the right superior temporal gyrus (Brodmann area 42; Talairach’s coordinates $x= 63, y= -30, z= -9$) in the patient (red dot and line) and control groups (blue dot and line). Each line and confidence limits fit by regional tricubic least-squares with smoothing (loess function in R).
REFERENCES


Oakley DA. Hypnosis and conversion hysteria: a unifying model. *Cogn Neuropsychiatry*, 4: 243-265,


Salvi RJ, Lockwood AH, Frisina RD, Coad ML, Wack DS, and Frisina DR. PET imaging of the
normal human auditory system: responses to speech in quiet and in background noise.


Saravanappa N, Mepham GA, and Bowdler DA. Diagnostic tools in pseudohypacusis in children.


Talairach J and Tournoux P. *Co-planar Stereotaxic Atlas of the Human Brain: 3-dimensional*


