Functional Anatomy of Musical Perception in Musicians

Takashi Ohnishi, Hiroshi Matsuda, Takashi Asada, Makoto Aruga[1], Makiko Hirakata[1], Masami Nishikawa, Asako Katoh and Etsuko Imabayashi

Department of Radiology and Psychiatry, National Center Hospital of Mental, Nervous and Muscular Disorders, National Center of Neurology and Psychiatry and [1]Department of Music, Tokyo National University of Fine Arts and Music, 4-1-1 Ogawa higashi, Kodaira City, Tokyo 187-8551, Japan

The present study used functional magnetic resonance to examine the cerebral activity pattern associated with musical perception in musicians and non-musicians. Musicians showed left dominant secondary auditory areas in the temporal cortex and the left posterior dorsolateral prefrontal cortex during a passive music listening task, whereas non-musicians demonstrated right dominant secondary auditory areas during the same task. A significant difference in the degree of activation between musicians and non-musicians was noted in the bilateral planum temporale and the left posterior dorsolateral prefrontal cortex. The degree of activation of the left planum temporale correlated well with the age at which the person had begun musical training. Furthermore, the degree of activation in the left posterior dorsolateral prefrontal cortex and the left planum temporale correlated significantly with absolute pitch ability. The results indicated distinct neural activity in the auditory association areas and the prefrontal cortex of trained musicians. We suggest that such activity is associated with absolute pitch ability and the use-dependent functional reorganization produced by the early commencement of long-term training.

Introduction

Musicians have special perceptuomotor skills, such as manual dexterity, sight-reading ability, ability to improvise and absolute pitch (AP) processing. Several studies have indicated that daily musical training, as used by professional musicians to increase and maintain their skill, can induce functional reorganization of the cerebral cortex (Elbert *et al.*, 1995; Schlaug *et al.*, 1995; Pantev *et al.*, 1998). For example, magnetic source imaging studies have revealed increased cortical representation of the somatosensory areas of the left-hand fingers in string players and auditory areas in skilled musicians (Elbert *et al.*, 1995; Pantev *et al.*, 1998). These data also indicated that the degree of use-dependent functional reorganization could depend on the age at which musical training began. It is also thought that musical training in childhood is important in the acquisition of AP — the ability to identify the frequency or musical name of a specific tone, or to identify a tone without comparing it with any objective reference tone (Marin and Perry, 1999). The difference in musical perception between musicians and non-musicians has been examined by mainly psychological and neurophysiological studies (Bever and Chiarello, 1974; Johnson, 1977; Mazzucchi *et al.*, 1981). Using a dichotic listening task involving violin melodies, Johnson reported that musicians demonstrated right ear superiority (left cerebral hemispheric dominance), while non-musicians showed a left ear advantage (right cerebral hemispheric dominance). Bever *et al.* reported similar results using a dichotic listening task. Neuroimaging and lesion studies have revealed that the right cerebral hemisphere is important for music processing (Zatorre *et al.*, 1994; Zatorre, 1998; Tervaniemi *et al.*, 2000). Although some reports have indicated that increasing musical sophistication causes a shift of musical processing from the right hemisphere to the left (Bever and Chiarello, 1974; Johnson, 1977; Mazzucchi *et al.*, 1981; Schlaug *et al.*, 1995), it remains a controversial issue. On the other hand, anatomical studies using magnetic resonance imaging (MRI) have indicated that AP may be associated with an anatomical difference in the left planum temporale (PT), a posterior part of the auditory cortex situated in the temporal lobe; however, its functional significance remains to be clarified (Schlaug *et al.*, 1995; Zatorre *et al.*, 1998). Here we present data from functional MRI (fMRI) that indicates that the cerebral activity pattern of trained musicians is different from that of controls.

Materials and Methods

Subjects

Two groups, comprising right-handed subjects (Edinburgh handedness questionnaire) without history of neurological and psychiatric disorders and with normal audiological status, participated in the present study. The first group (n = 14) consisted of musical students (20–27 years old, two males and 12 females, with >12 years of 4–8 h of training per day) with AP (n = 10) or relative pitch (n = 4). Musicians were recruited from Tokyo National University of Fine Arts and Music. Before the experiment we interviewed musicians to collect information about the number of hours of practice, sight-reading ability, AP ability, the principal instrument and other instruments played, and the age at which musical training began. Absolute pitch ability was verified with an objective pitch identification test and a difficult solfeggio test consisting of atonal melodies and tension codes. The principal instruments of musicians were percussion (11 subjects) and piano (three subjects). All of them began musical training with the piano. Ten out of 12 musicians began their musical practice before 10 years old (mean age 6.2 ± 2.79 years old, range 3–16 years old). The age- and gender-matched control group (n = 14, 21–27 years, two males and 12 females) consisted of undergraduate and graduate students who had never played an instrument and had no formal musical education. Written informed consent was obtained from all subjects in accord with the ethical guidelines laid down by the local ethical committee.

Task

During fMRI, binaural presentation of an instrumental music stimulus (a part of Italian concert BMV 989 by J.S. Bach which was digitally recorded) in and 'on/off' paradigm with 24 s epochs was given. As far as we know, this piece have been never played vocally and all recorded versions were played by keyboard instruments, such as the piano or cembalo. The stimulus was presented by an air-conducting headphone. The same segment of music was played for 24 s at a comfortable listening level during each 'on' period. Subjects were asked to just passively listen to music. They were also asked not to accompany or sing with the listened music. During the 'off' period, no auditory stimulus were given and subjects were discouraged from thinking anything.

Post Hoc Questionnaire

We presented subjects with a *post hoc* questionnaire after fMRI measurements. The questionnaire was consisted of the following questions:

1. Do you know the title of the piece of music used as the stimulus?

Table 1
Regions exhibiting significant task-related activity

Region (Brodmann's area)	Tailrach coodinates			*t* value
	x (mm)	*y* (mm)	*z* (mm)	
Activated areas in musicians				
Left superior temporal gyrus (BA22)	–57	–38	9	10.99
Left middle temporal gyrus (BA21)	–55	–15	–1	8.95
Right superior temporal gyrus (BA22)	56	–19	4	8.08
Right middle temporal gyrus (BA22)	54	–3	–6	7.22
Left middle frontal gyrus (BA9)	–41	21	36	6.98
Activated areas in control				
Right superior temporal gyrus (BA22)	48	–15	–3	8.93
Right superior temporal gyrus (BA22)	59	–25	4	7.23
Left superior temporal gyrus (BA2 1)	–57	–19	2	6.93
Left middle temporal gyrus (BA2 1)	–57	–34	0	5.36
Areas more strongly activated in the musicians than in the control subjects				
Left superior temporal gyrus (BA22)	–57	–36	10	7.38
Right superior temporal gyrus (BA22)	52	–32	9	4.81
Left middle frontal gyrus (BA9)	–40	23	32	6.98
Correlation between the age of inception of musical training and the degree of activation				
Left superior temporal gyrus (BA22)	–55	–38	7	7.45
Correlation between absolute pitch ability and the degree of activation				
Left superior temporal gyrus (BA22)	–55	–36.8	12	7.24
Left middle frontal gyrus (BA9)	–42	24	34	5.55

2. Have you heard this piece of music before this experiment?
3. Have you played this piece of music? (musicians only).
4. Did you analyze or memorize the structure of the piece during scanning? (musicians only).
5. Did you imagine playing instruments with the stimulus during scanning? (musicians only).
6. Did you imagine the score of the piece of music during scanning? (musicians only).

The questionnaire revealed that 14 out of 17 musicians and all control subjects had never heard this particular piece. Two pianists and one composer played it, so we therefore eliminated these three musicians from the subjects for this study.

fMRI Procedure

Cerebral activation was measured with fMRI using blood oxygen level-dependent contrast (Ogawa *et al.*, 1990). After automatic shimming, a time course series of 75 volumes were obtained using single-shot gradient-refocused echo-planar imaging (T_R = 3000 ms, T_E = 60 ms, flip angle = 90°, in-plane resolution = 3.44 × 3.44 mm, FOV = 22 cm, contiguous 4 mm slices to cover the entire brain) with a 1.5 T MAGNETOM Vision plus MR scanner (Siemens, Erlangen, Germany) using a standard head coil. Head motion was minimized by placing tight but comfortable foam padding around the subject's head.

Data Analysis

Data were analyzed with Statistical Parametric Mapping software (SPM99, www.fil.ion.ucl.ac.uk/spm). The first five volumes of each fMRI scan were discarded because of the non-steady condition of magnetization, and the remaining 70 volumes were used for the analysis. Scans were realigned and spatially normalized to the standard stereotactic space of Talairach using an EPI template. The parameter for affine and quadratic transformation to the EPI template that was already fitted for Talairach space was estimated by least-squares means. Data were then smoothed in a spatial domain (full width at half-maxim = 8 × 8 × 8 mm) to improve the signal-to-noise ratio. After specifying the appropriate design matrix, delayed box-car function as a reference waveform, the condition, slow hemodynamic fluctuation unrelated to the task, and subject effects were estimated according to the general linear model and temporal smoothness into account. Global normalization was performed using proportional scaling. To test hypotheses about regionally specific condition effects, the estimates were compared by means of linear contrasts of each rest and task period. The resulting set of voxel values for each contrast constituted a statistical parametric map of the *t* statistic SPM{*t*}. Previous studies have indicated that the right superior temporal gyrus (STG) must be specialized for processing of music perception (Mazziotta *et al.*, 1982; Liegeois-Chauvel *et al.*, 1998; Zatorre, 1998; Tervaniemi *et al.*, 2000). Therefore, we determine lateralization of STG activation in each subject. The volume of activation in the STG of each hemisphere was determined as numbers of voxels exceeding a significance threshold of *a* = 0.005. A laterality index (LI) was calculated, corresponding to [left – right]/[left + right] × 100. This approach yields values ranging between +100 (strong left hemisphere dominance) and –100 (strong right hemisphere dominance). Furthermore, we applied a random effect model to generalize the inference drawn from multi-subject fMRI data (Friston *et al.*, 1999). Images of the estimated activation parameter *ai* were written out as an image. The inter-subject level of analysis proceeds using these subject images as raw data for a one-sample *t*-test (P = 0.001, uncorrected). The difference between musicians and controls were estimated using these subject images as raw data for a two-sample *t*-test (P = 0.001, uncorrected). A regression analysis was also done to find where the activation parameter *ai* responded linearly to the age at which musical training began and scores of the solfeggio test (P = 0.001, uncorrected).

Results

Post Hoc Questionnaire

None of the musicians employed as subjects could remember the precise title of the musical stimulus and had never played it; however, most musicians answered that it may have been composed by Bach or Handel. They also had not heard the stimulus before scanning. None of the control subjects had heard the musical stimulus before scanning. However, they recognized that it may be some kind of baroque music.

All musicians answered that they had just listened to the music and had not tred to analyze or memorize it. None of them tried to imagine the score of the presented music or to accompany it.

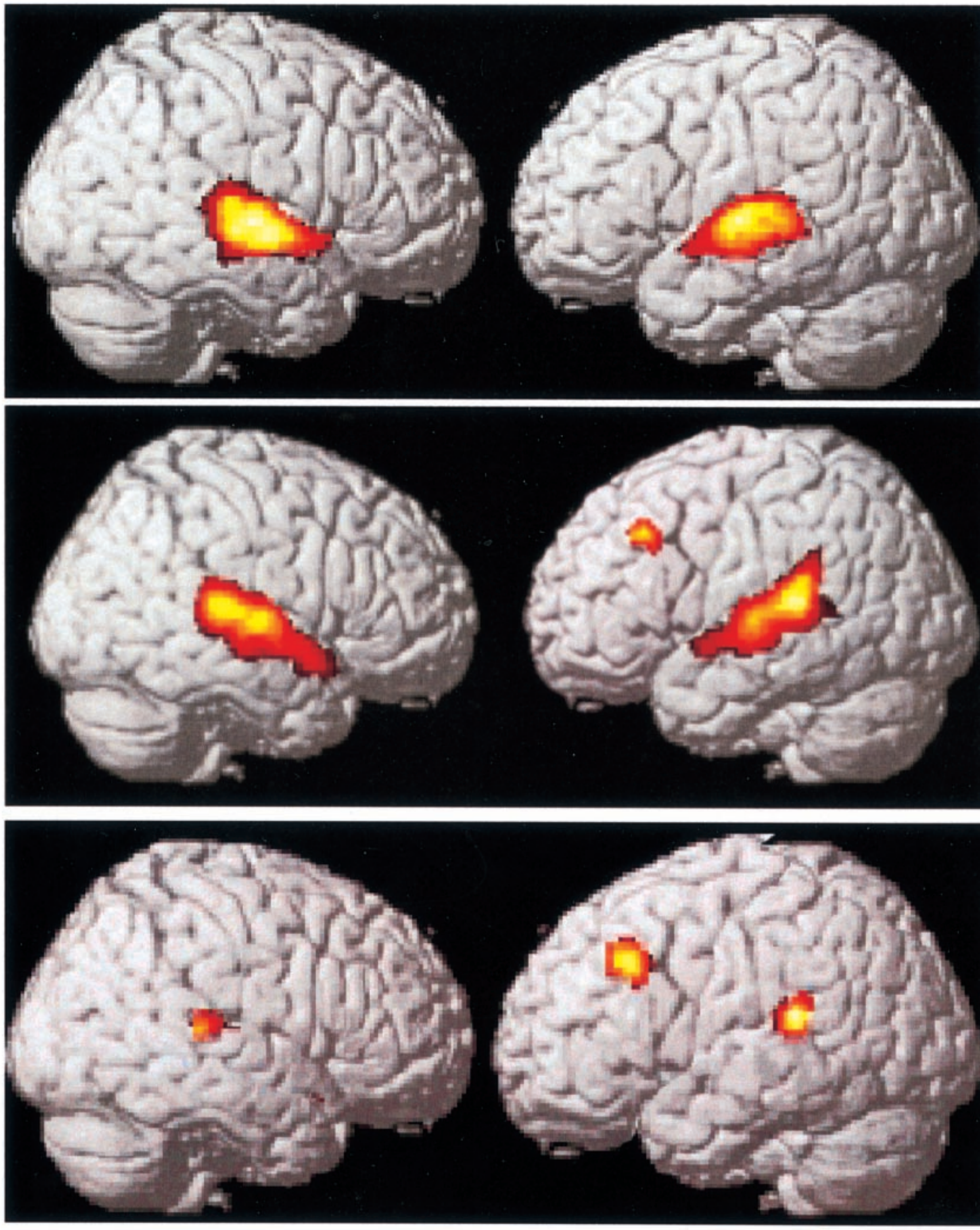


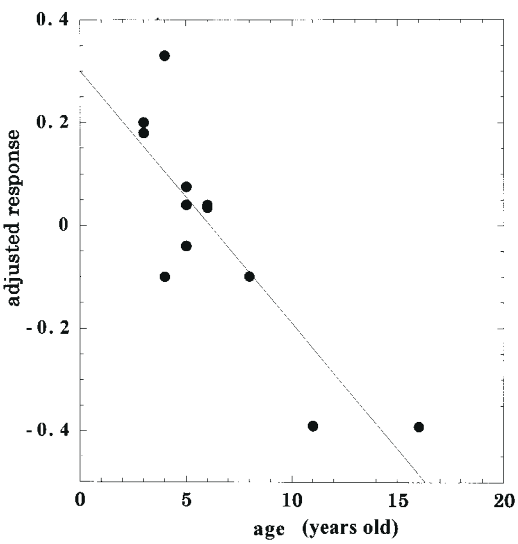
Figure 1. Brain surface projection of activated areas during passive music listening in control subjects and musicians. (*a*) The activation map of control group view from the right (right); the view from the left (left) shows right dominant activation in the temporal areas. (*b*) The activation map in the musicians group shows left dominant activation in the temporal areas. Activations in musicians are leftward and extend more posteriorly than those in the control group. An additional activation in the left posterior dorsolateral prefrontal cortex is noted. (*c*) A group difference map of the activation between musicians and control subjects shows stronger activations in musicians than in controls in the bilateral PT, especially in the left one and the left posterior dorsolateral prefrontal cortex.

Cerebral Activation during Passive Music Listening in Musicians and Controls

When compared with the resting baseline, the passive music listening produced significant activation in the bilateral superior and the middle temporal gyri [Brodmann's areas (BA) 21 and 22], known as the auditory association cortex, in both musicians and control subjects. The control subjects demonstrated right dominant temporal cortical activation (BA21 and BA22) during passive music listening (Fig. 1*a*, Table 1). Contrary to the control group, musicians showed left dominant temporal cortical activation (BA22, 21) during the same task (Fig. 1*b*, Table 1). *t*-values of temporal activations were greater on the left side for the musicians and greater on the right for the non-musicians. The laterality index in the STG of the musicians was significantly greater than that of the control group (two-sample *t*-test; $P < 0.01$, mean ± SD = 18.3 ± 14.8 in the musicians and –21.4 ± 5.35 in the control group).

Furthermore, additional activation in the left posterior dorsolateral prefrontal cortex (DLPFC) (BA9) was noted. A significant difference between the musicians and the control group was

a



b

Figure 2. The area where activation responds linearly to the age at which musical training began. (*a*,*b*) There is a significant negative linear correlation between the age of inception of musical training and the degree of activation in the left PT.

noted in the bilateral PT, particularly in the left one and the left posterior DLPFC (BA9) (Fig. 1*c*, Table 1).

The Correlation between Cerebral Activation and the Age of Inception of Musical Training, Duration of Training and Absolute Pitch Ability

There was a significant negative linear correlation between the age of inception of musical training and the degree of activation in the left PT (BA22) ($y = 0.3 - 0.049x$, $r = 0.855$) (Fig. 2*a*,*b*, Table 1). However, no correlation between the duration of musical training and the degree of cerebral activation was seen in any region. There was a significant positive linear correlation between the AP ability determined by the solfeggio test and the degree of activation in the left posterior DLPFC (BA9) ($y = -0.84545 + 0.009471x$, $r = 0.78$) (Fig. 3*a*,*b*, Table 1) and the left PT (BA22) ($y = -2.06 + 0.0228x$, $r = 0.781$) (Fig. 3*a*,*c*, Table 1).

Discussion

Whether music is a right or left hemispheric function oversimplifies its neuroscience. Nevertheless, many neuroimaging and lesion studies have indicated that the right secondary auditory areas in the superior temporal gyrus surrounding the Heschl gyrus are important in the processing of melody and pitch perception, at least in musically naive subjects (Mazziotta *et al.*, 1982; Liegeois-Chauvel *et al.*, 1998; Zatorre, 1998; Tervaniemi *et al.*, 2000). Our finding of right dominant activation in the secondary auditory areas in the control group also indicates right hemispheric predominance for musical perception in musically naive subjects. Contrary to the control group, musicians showed left dominant temporal cortical activation (BA22, 21) during musical perception. A difference in familiarity with the musical stimulus between musicians and non-musicians was a possible confounding factor in this study; however, a *post hoc* questionnaire revealed that there was no such difference. Sergent *et al.* studied musical perception in professional pianists using PET (Sergent *et al.*, 1992). They reported that listening to a musical piece activated the right STG (BA22), which was not detected in a scale-listening task. The results suggested right hemispheric predominance for melody perception in musicians. Unlike the present study, they focused mainly on musical performance rather than perception. They did not mention the AP ability of their subjects. We assume that the discrepancy between Sergent *et al.*'s study and ours could be explained by the differences of subjects' characteristics.

The activation patterns in the musicians can be characterized as follows: (i) stronger activation in the PT than in non-musician controls; (ii) left dominant activation in the secondary auditory area, including the PT; and (iii) co-activation in the left posterior DLPFC (BA9). The results should be seen in the following contexts. First, neuroimaging studies have revealed that the posterior temporal area, including the PT, is involved in various aspects of pitch processing (Mazziotta *et al.*, 1982; Binder *et al.*, 1996; Griffiths *et al.*, 1998; Liegeois-Chauvel *et al.*, 1998; Zatorre, 1998). Secondly, earlier structural magnetic resonance morphometry has suggested that AP might be associated with

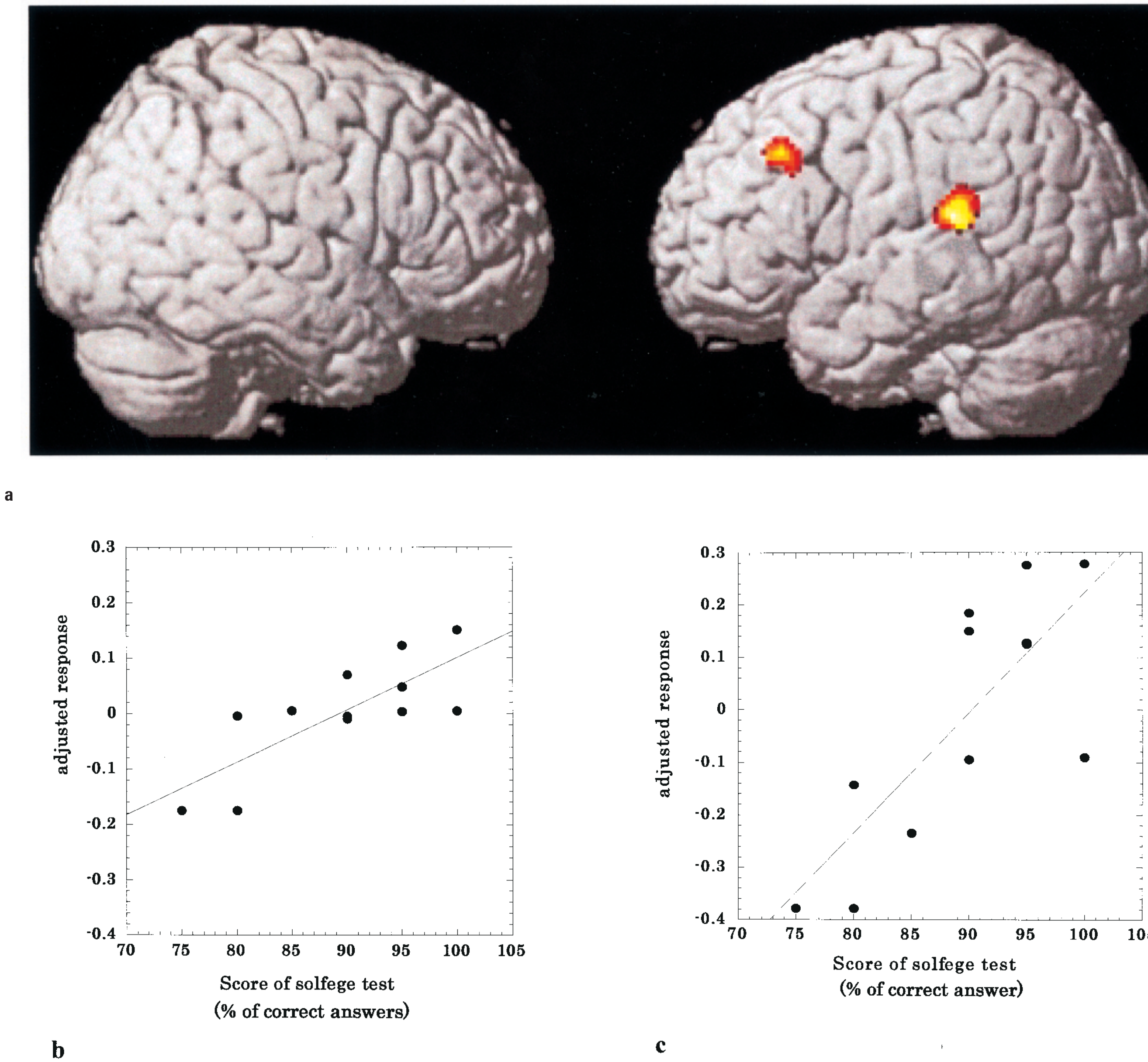


Figure 3. The area where activation responds linearly to AP ability. There is a significant postive linear correlation between the performance of the solfeggio test and the degree of activation in the left posterior dorsolateral prefrontal cortex (*a*,*b*) and the left planum temporale (*a*,*c*).

an anatomical difference in the left PT (Schlaug *et al.*, 1995; Zatorre *et al.*, 1998). Thirdly, a previous PET study indicated that activation in the left posterior DLPFC might represent part of the substrate for AP processing (Zatorre *et al.*, 1998). Fourthly, behavioral studies have demonstrated a difference in lateralization of musical processing between musicians and non-musicians, with more left-lateralized representation in musicians (Bever and Chiarello, 1974; Mazzucchi *et al.*, 1981). Finally, magnetic source imaging studies have revealed increased cortical representation of the somatosensory and auditory areas in skilled musicians (Elbert *et al.*, 1995; Pantev *et al.*, 1998). Therefore, our results may suggest that increasing musical sophistication should cause a shift of musical processing, or at least music perception, from the right to the left hemisphere and from the anterior portion of the superior temporal region to the posterior.

We suggest that activations in the PT and left DLPFC should be associated with AP processing and use-dependent functional reorganization caused by early engagement of musical training. Before the fMRI experiment, musicians were interviewed to determine the age at which their musical training had begun and tested AP ability by using a difficult solfeggio test. There was a significant negative linear correlation between the age of inception of musical training and the degree of activation in the left PT (BA22). The data suggest that the degree of the use-dependent functional reorganization could depend on the age at which musical training began. This finding is similar to those reported in previous studies, which examined somatosensory representation of fingering digits in string players and cortical representation for piano tones in musicians (Elbert *et al.*, 1995; Pantev *et al.*, 1998). Although it is possible that such a functional reorganization could be dependent on the duration of training, we could not find any correlation between the duration of training and the degree of cerebral activation. In addition to the results of previous studies (Elbert *et al.*, 1995; Pantev *et al.*, 1998), our data suggest that functional reorganization of the left PT in musicians could be caused by the early commencement of training rather than long-term training. The left dominant PT activation for music perception that we observed in musicians corresponds to the result of an earlier MR study: a structural enlargement of the left PT in musicians (Schlaug *et al.*, 1995; Zatorre *et al.*, 1998). Our data therefore associate the use-dependent functional property with cortical architectonics and raise the possibility that musical experience during childhood may influence structural development of PT.

One possible alternative interpretation of the results here is that the different activation pattern only reflects a different strategy of musical perception that calls on the left hemispheric function (Mazziotta *et al.*, 1982). A previous PET study reported that left dominant temporo-parietal activation was found when subjects used 'highly organized' analytical approaches during a tonal memory task. In that study, greater activation of the right side than of the left auditory areas during the same task was found when subjects did not use a specific strategy (using visual imagery) (Mazziotta *et al.*, 1982). However, we asked our musicians to listen to the music passively. Indeed, the *post hoc* questionnaire revealed that they did not employ any specific analytic approach, especially visual imagery, during the fMRI measurements. Although they did not use any specific strategy consciously, it is still possible that the musicians have developed a different way of listening to music, which is inherently more analytical. There is a possibility that musical training not only changes the regions involved in musical perception, but may also change how the music is perceived.

The left PT is known as Wernicke's area, which is related to language comprehension. The human PT is a roughly triangular region of the superior temporal plane located posterior to the primary auditory field. It is, on average, larger in the left hemisphere, suggesting that it may play a specialized role in language and language lateralization (Steinmetz *et al.*, 1991). Why is the left PT involved in music perception in trained musicians? Do they employ a common strategy in music perception and language comprehension? We consider that the stronger PT activation in musicians than in controls could be related to AP processing. There was a significant positive linear correlation between the AP ability determined by the solfeggio test and the degree of activation in the left posterior DLPFC (BA9) and PT (BA22) (Fig. 3, Table 1). Because note labeling is obligatory for AP processors even when passively listening, these activations should represent part of the substrate for AP ability (Marin and Perry, 1999). Although a previous PET study indicated that the PT did not contribute to AP ability (Zatorre *et al.*, 1998), morphometric measures of the PT have suggested that AP may be associated with a structural difference in the left PT (Schlaug *et al.*, 1995; Zatorre *et al.*, 1998). Taken together, AP ability may arise from a qualitatively different neural process within the left PT. The left posterior DLPFC is also thought to be a part of the substrate for AP (Zatorre *et al.*, 1998). Our data also indicated that the left posterior DLPFC should be associated with AP ability. Functional neuroimaging studies of the human prefrontal cortex have revealed that it is associated with a broad range of different cognitive demands, such as perception, response selection, working memory and problem solving (Duncan and Owen, 2000). The posterior DLPFC has been shown to be important for conditional-associative learning of sensory stimuli (Petrides, 1985, 1990). Therefore, AP may be characterized as the ability to retrieve an association between a stimulus attribute (the pitch of sound) and a verbal label of the note name, such as A, D-flat, etc. Furthermore, the PT contains an auditory association area that projects directly to the most posterior portion of the DLPFC (Petrides and Pandya, 1988). We assume that AP ability may result from at least two neural mechanisms. One such possible mechanism is a form of conditional-associative learning (verbal–tonal association), which results from an interaction between computations in the PT and the left DLPFC. Another is the different initial stage of perceptual analysis processed in the left PT.

In conclusion, there is a distinct cerebral activity pattern in the auditory association areas and prefrontal cortex of trained musicians. Such activity could be associated with AP ability and the use-dependent functional reorganization produced by long-term training.

Notes

This was supported by Health Science Research Grant (H12-005) from the Ministry of Health and Welfare.

Address correspondence to Takashi Ohnishi, Department of Radiology and Psychiatry, National Center Hospital of Mental, Nervous and Muscular Disorders, National Center of Neurology and Psychiatry, 4-1-1 Ogawa higashi, Kodaira City, Tokyo 187-8551, Japan. Email: tohnishi@hotmail.com.

References

Bever TG, Chiarello RJ (1974) Cerebral dominance in musicians and nonmusicians. Science 9:537–539.

Binder JR, Frost JA, Hammeke TA, Rao SM, Cox RW (1996) Function of the left planum temporale in auditory and linguistic processing. Brain 119:1239–1247.

Elbert T, Pantev C, Wienbruch C, Rockstroh B, Taub E. (1995) Increased cortical representation of the fingers of the left hand in string players. Science 13:305–307.

Duncan J, Owen AM (2000) Common regions of the human frontal lobe recruited by diverse cognitive demans. Trends Neurosci 23:475–483.

Friston KJ, Holmes AP, Price CJ, Buchel C, Worsley KJ (1999) Multisubject fMRI studies and conjunction analyses. NeuroImage 10:385–396.

Griffiths TD, Buchel C, Frackowiak RS, Patterson RD (1998) Analysis of temporal structure in sound by the human brain. Nature Neurosci 1:422–427.

Johnson PR (1977) Dichotically-stimulated ear differences in musicians and nonmusicians. Cortex 13:385–389.

Liegeois-Chauvel C, Peretz I, Babai M, Laguitton V, Chauvel P (1998) Contribution of different cortical areas in the temporal lobes to music processing. Brain 121:1853–1867.

Marin OSM, Perry DW (1999) The psychology of music, 2nd edn. Academic Press.

Mazziotta JC, Phelps ME, Carson RE, Kuhl DE (1982) Tomographic mapping of human cerebral metabolism: auditory stimulation. Neurology 32:921–937.

Mazzucchi A, Parma M, Cattelani R.(1981) Hemispheric dominance in the perception of tonal sequences in relation to sex, musical competence and handedness. Cortex 17:291–302.

Ogawa S, Lee TM, Kay AR, Tank DW (1990) Brain magnetic resonance imaging with contrast dependent on blood oxygenation. Proc Natl Acad Sci USA 87:9868–9672.

Pantev C, Oostenveld R, Engelien A, Ross B, Roberts LE, Hoke M (1998) Increased auditory cortical representation in musicians. Nature 23:811–814.

Petrides M (1985) Deficits on conditional associative-learning tasks after frontal- and temporal-lobe lesions in man. Neuropsychologia 23:601–614

Petrides M, Pandya DN (1988) Association fiber pathways to the frontal cortex from the superior temporal region in the rhesus monkey. J Comp Neurol 1:52–66.

Petrides M (1990) Nonspatial conditional learning impaired in patients with unilateral frontal but not unilateral temporal lobe excisions. Neuropsychologia 28:137–149.

Schlaug G, Jancke L, Huang Y, Steinmetz H (1995) *In vivo* evidence of structural brain asymmetry in musicians. Science 3:699–701.

Steinmetz H, Volkmann J, Jancke L, Freund HJ (1991) Anatomical left-right asymmetry of language-related temporal cortex is different in left- and right-handers. Ann Neurol 29:315–319.

Tervaniemi M, Medvedev SV, Alho K, Pakhomov SV, Roudas MS, Van Zuijen TL, Naatanen R (2000) Lateralized automatic auditory processing of phonetic versus musical information: a PET study. Hum Brain Mapp 10:74–79.

Zatorre RJ, Evans AC, Meyer E (1994) Neural mechanisms underlying melodic perception and memory for pitch. J Neurosci 14:1908–1919.

Zatorre RJ (1998) Functional specialization of human auditory cortex for musical processing. Brain 121:1817–1818.

Zatorre RJ, Perry DW, Beckett CA, Westbury CF, Evans AC (1998) Functional anatomy of musical processing in listeners with absolute pitch and relative pitch. Proc Natl Acad Sci USA 17:3172–3177.