

When meaningless symbols become letters: Neural activity change in learning new phonograms

Akiko M. Callan,^{a,*} Daniel E. Callan,^b and Shinobu Masaki^a

^aBrain Activity Imaging Center, ATR International, 2-2-2 Hikaridai, Seika-cho, Soraku-gun, Kyoto 619-0288, Japan

^bComputational Neuroscience Laboratories, ATR International, Kyoto, Japan

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Left fusiform gyrus and left angular gyrus are considered to be respectively involved with visual form processing and associating visual and auditory (phonological) information in reading. However, there are a number of studies that fail to show the contribution of these regions in carrying out these aspects of reading. Considerable differences in the type of stimuli and tasks used in the various studies may account for the discrepancy in results. This functional magnetic resonance imaging (fMRI) study attempts to control aspects of experimental stimuli and tasks to specifically investigate brain regions involved with visual form processing and character-to-phonological (i.e., simple grapheme-to-phonological) conversion processing for single letters. Subjects performed a two-back identification task using known Japanese, and previously unknown Korean, and Thai phonograms before and after training on one of the unknown language orthographies. Japanese subjects learned either five Korean or five Thai phonograms. Brain regions related to visual form processing were assessed by comparing activity related to native (Japanese) phonograms with that of non-native (Korean and Thai) phonograms. There was no significant differential brain activity for visual form processing. Brain regions related to character-to-phonological conversion processing were assessed by comparing pre- and post-tests of trained non-native phonograms with that of native phonograms and non-trained non-native phonograms. Significant differential activation post-relative to pre-training exclusively for the trained non-native phonograms was found in left angular gyrus. In addition, psychophysiological interaction (PPI) analysis revealed greater integration of left angular gyrus with primary visual cortex as well as with superior temporal gyrus for the trained phonograms post-relative to pre-training. The results suggest that left angular gyrus is involved with character-to-phonological conversion in letter perception.

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Introduction

Letters (phonograms) are simple two-dimensional visual forms that have phonological information. For literates, reading letters is automatic and it is very difficult to prevent the process. The Stroop (1935) color-word test is a good example demonstrating the automaticity of the reading process. On the other hand, non-native letters for which pronunciation is unknown are just meaningless symbols. There is no automatic visual to phonological conversion when you see non-native letters. In order to determine brain regions involved with the process of visual to phonological conversion, one can investigate how neural activity for perceiving non-native letters changes as a result of learning the corresponding pronunciations.

There are quite a few functional imaging studies investigating neural processes underlying letter perception. Letter perception can be separated into two sub-processes: visual form processing and grapheme-to-phonological conversion processing. To extract letter-specific visual form processing, researchers compared letters with visual stimuli that belong to different categories. Letters were compared to faces (Allison et al., 1999; Tarkiainen et al., 2002; Puce et al., 1996), digits (Polk and Farah, 1998; Polk et al., 2002), checkerboards (Cohen et al., 2002), single geometric shapes (Tagamets et al., 2000), and objects (Joseph et al., 2003; Price and Friston, 1997; Sergent et al., 1992). Many of these studies reported that letters activated left fusiform gyrus (BA37) more than other categories (Cohen et al., 2002; Polk and Farah, 1998; Polk et al., 2002; Puce et al., 1996; Tagamets et al., 2000; Tarkiainen et al., 2002). The activation in left BA37 is often reported by functional neuroimaging experiments comparing reading words with the resting state (Beauregard et al., 1997; Brunswick et al., 1999; Fiez et al., 1999; Paulesu et al., 2000; Wagner et al., 1998). Cohen et al. (2000, 2002) studied hemifield-independent visual word form processing and labeled the middle portion of left fusiform gyrus as the visual word form area based on their findings and the clinical studies for patients with alexia. Since activation in this area is observed not only for visual word processing but also for other processing (e.g., object recognition, naming, auditory words processing), appropriateness of this labeling is still under debate

* Corresponding author. Fax: +81 774 95 1281.

E-mail address: acallan@atr.jp (A.M. Callan).

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(Cohen and Dehaene, 2004; Price and Devlin, 2003, 2004). Reported loci for letter string processing and for visual word processing are close to each other but Cohen et al. (2002) reported that left BA37 is activated more for words than for consonant strings.

Flowers et al. (2004) have reported that activation in left BA37 is not just activated by presence of letters but by attending to letters within a linguistic context. In their experiment, the same set of visual stimuli (single letters or symbols in either black or white color) was presented in separate sessions. For each session, subjects were told to respond to a specific target (either letter, symbol, or color) by pressing a button. According to their result, left BA37 is more activated when subjects responded to letters than to symbols or to colors even though subjects saw the same visual stimuli for all sessions. Furthermore, Joseph et al. (2003) suggest that processing in left BA37 is not category specific but is shared by both letters and objects. Results from the cognitive conjunction analysis also showed that left BA37 is conjointly activated when subjects named visually presented words, objects, letters, or colors (Price and Friston, 1997). Since reading is a postnatally acquired skill that has only gained widespread use since the 20th century, it is very unlikely that a certain cortical region evolved that is dedicated solely for reading alone. However, in non-human primates, the ventral visual pathway including the posterior inferior temporal–occipital region is activated by recognition of familiar objects (Ungerleider and Mishkin, 1982). Moreover, experience with visual stimuli has been found to lead to the development of neuronal assemblies in perirhinal cortex, a region in anterior medial inferior temporal cortex (Erickson et al., 2000). It is plausible to hypothesize that for humans, neuronal assemblies within BA37 (thought to be an auditory visual association area; Talairach and Tournoux, 1988) develop to preferentially respond to letters based on experience.

Phonological processing in reading has been studied in various ways. Based on lesion studies, left angular gyrus has been considered a site associating visual and auditory (phonological) information in reading (Damasio and Damasio, 1983; Dejerine, 1891, 1892; Geschwind, 1965; Henderson, 1986). Geschwind (1965) hypothesized a neural route connecting the visual cortex and Wernicke's area through left angular gyrus in reading and this model is called "Wernicke–Geschwind model". Angular gyrus is located between occipital, temporal, and postcentral regions of the hemisphere. Visual, auditory, vestibular, cutaneous, and proprioceptive sensations overlap in this area (Luria, 1973). It is thought that angular gyrus has an important role for associating heard names and seen or felt objects (Geschwind, 1965). Therefore, it is plausible to hypothesize that angular gyrus is a site involved with associating visual and auditory (phonological) information in reading. However, many results from functional imaging studies do not agree with this theory. There are no specific cortical regions that are consistently reported by functional imaging studies, but there are several regions that are reported by multiple studies. They are left temporoparietal cortex including supramarginal gyrus and angular gyrus (Fujimaki et al., 1999; Kuriki et al., 1996; Law et al., 1991; Lee et al., 2003; Paulesu et al., 1993; Petersen et al., 1989), left superior temporal gyrus (Fujimaki et al., 1999; Kuriki et al., 1996; Paulesu et al., 1993; Pugh et al., 1996; Sergent et al., 1992;), and left inferior frontal lobe including Broca's area and insula (Fujimaki et al., 1999; Paulesu et al., 1993; Pugh et al., 1996; Sergent et al., 1992). Poeppel (1996) criticized the phonological processing studies' non-overlapping results and pointed out three

possible causes: (1) task decompositions were not sufficient; (2) distinct aspects of phonological processing were investigated; and (3) there are limitations in cognitive subtraction by PET. Specifically, the studies reviewed (Demonet et al., 1992; Paulesu et al., 1993; Petersen et al., 1989; Sergent et al., 1992; Zatorre et al., 1992) often subtracted activity from different types of tasks. Moreover, the influence of subtle variations of stimuli presentation and the uncontrollable automatic process of linguistic stimuli were also suggested to be the case for the inconsistency of results from various brain imaging studies (Indefrey et al., 1997; Price et al., 1994; Price, 2000; Sergent et al., 1992).

In addition to these causes, we suspect that the type of orthography might be related to the inconsistency in the results of brain imaging studies investigating phonological processing involved with reading. Many phonological processing studies use whole words as stimuli. Phonological processing of words is more complicated than of letters because it is not only a bottom-up (sublexical grapheme-to-phonological) process but also a top-down (lexical knowledge-to-phonological) process. This top-down influence on phonological processing is significant in a deep orthography such as English because grapheme-to-phonological conversion is not a one-to-one process (Wydel et al., 2003). Behavioral studies comparing effects of word length and word frequency have shown that word length has stronger influence on naming latency than word frequency in Dutch and Italian, in which grapheme-to-phoneme mappings is straightforward (shallow orthography). The results suggest that bottom-up processing has a stronger influence on reading in shallow orthographies than in deep orthographies (Hudson and Bergman, 1984; Bates et al., 2001). Paulesu et al. (2000), using positron emission tomography (PET), compared the Italian (shallow orthography) and English (deep orthography) students during reading words and non-words. They reported a language-related difference: left superior temporal regions were activated more for Italian readers and left posterior inferior temporal region and anterior inferior frontal gyrus were activated more for English readers. This indicates that the orthography type in a particular language environment has a substantial influence on neural processes in reading. One may assume that the top-down process can be avoided if single letters are used as stimuli. However, naming an English alphabet is not a simple grapheme-to-phonological conversion because the name is not the sound representation of the letter (e.g., [kei] is a name and /k/ is an associated phoneme of a letter 'k'). Therefore, if one wants to find out cortical areas that are responsible for a simple grapheme-to-phonological conversion, single letters from a shallow orthography have to be used as stimuli.

Japanese, Korean, and Thai use shallow orthographies. More precisely, Japanese and Korean use both shallow orthography (phonogram) and deep orthography (ideogram). In our experiment, phonograms of these three languages were used as visual stimuli. Japanese who could not read either Korean or Thai served as subjects. The differences of neural activity for native versus non-native orthographies and for pre- versus post-training were investigated. Two types of non-native orthographies (one trained and one not trained) were used in order to control for differential activity that might result from practice effects for the working memory task as well as varying physiological and neurological noise that may occur during the post-test session versus the pre-test session. Half of the subjects learned Korean and the other half learned Thai. The use of two orthographies that subjects were trained on instead of one allows greater generalizability of the results (data were analyzed based on trained or non-trained

condition irrespective to orthography type) helping to avoid confounds associated with identifying brain activity that may be specific to the processing of a certain writing system.

This experiment was designed to overcome some of the problems associated with experiments investigating phonological processing aspects of reading. First, simple grapheme-to-phonological conversion was investigated by using single phonograms from a shallow orthography as visual stimuli. This avoids potential top-down linguistic processing of the stimuli instead of bottom-up processing evoked by the stimulus. It may be more appropriate to call this process as character-to-phonological conversion because grapheme in many languages such as English can be a cluster of letters (e.g., -ough in cough or tough). Second, variance caused by different task demands was avoided by employing the same working memory task (two-back identification task) for pre- and post-tests. This avoids differences in brain activity caused by differential processing of the task rather than to the process under investigation. Although in principle, accomplishing the two-back identification task with letters or words does not necessitate reading processes, it has been claimed that when the task involves encoding of the stimuli it is difficult to ignore stimulus-specific properties (Tagamets et al., 2000). Tagamets et al. (2000) justified the use of a one-back test to investigate neural processes underlying reading by citing studies demonstrating that brain regions involved with processing stimulus-specific properties are enhanced when active encoding is required to accomplish the task (Baker et al., 1996; Corbetta et al., 1991; Courtney et al., 1996; Haxby et al., 1994, 1995). The Stroop (1935) effect attests to the difficulty in ignoring word information when the task is to name the color of the word. Third, variance caused by different visual features was eliminated because the same visual stimuli were used for both pre- and post-tests. This avoids differences in brain activity caused by subtle differences that may exist between stimuli. With the exception of physiological and neurological noise, the only difference between pre- and post-tests is expected to be caused by the acquired phonological knowledge associated with the newly learned non-native letters. Moreover, physiological and neurological noise were minimized by keeping the fMRI experiment time short. In general, learning experiments take a long time (i.e., weeks, months, or years) because it takes a long time for subjects to learn new knowledge completely. Since pre- and post-fMRI scans are obtained at very different times, their physiological and neurological noise levels are very different. In our experiment, subjects only learned five letters, so the whole experiment (pre-test, training phase, and post-test) took less than 1 h and all data were acquired without the subject leaving the MRI scanner. Because of the small number of letters and short duration of training, neural process of newly learned phonograms might be very different from native phonograms. We do not expect that this short experience leads to long-term organization of neuronal assemblies in BA37 but do expect existent neural processes involved with character-to-phonological mapping to be highly activated for newly learned phonograms.

Lee et al. (2003) performed a similar learning experiment using Korean and Japanese words to investigate “the changes in brain activation patterns associated with the learning of foreign words”. Based on the results of their study, they attributed left angular gyrus activation as reflecting newly acquired character-to-phonological conversion processing. Unlike Lee et al.’s (2003) study, the purpose for our study is more specified to identify brain regions involved with visual form processing and character-to-phonolog-

ical conversion processing in letter perception. Moreover, our study differs from theirs in many respects: (1) they used ‘words’ as stimuli instead of ‘letters’, so it was difficult for them to prevent top-down influence on phonological processing and to distinguish character-to-phonological association from written word-to-phonological or written word-to-semantic association; (2) the duration of their experiment was 16 days instead of 1 h, so direct comparisons between before and after learning was more difficult than our study, in fact, they did not report these comparisons in their paper; and (3) their task was different for the various visual stimuli (subjects were asked to read silently visual stimuli if they could and just looked at them if they could not read them); our study employed the same two-back task for the different visual stimuli. One potential limitation in the Lee et al. (2003) study that is avoided in our study is their use of different tasks for the various visual stimuli. As was discussed above, it may be somewhat difficult to discern brain activity underlying a certain process when different tasks are employed for the various conditions used to determine the process of interest. This may be the reason why Lee et al. (2003) did not find left angular gyrus activation in “silent reading” of Japanese words compared with “looking” at non-trained Korean words although they found the activation in “silent reading” of Japanese words compared with “silent reading” of trained Korean words during the first fMRI experiment on the second day of the learning phase.

Comparisons were planned to investigate brain activity underlying two different aspects of letter processing. The first is the comparison between native (Japanese) and non-native (Thai and Hangul) letter processing. This comparison was planned to assess the neural activity associated with letter-specific visual form processing. Because the non-native orthographies are meaningless symbols before training and subjects have much more experience with native orthographies, it is hypothesized that left fusiform gyrus (BA37) should show significant differential activity for this comparison if the area is functionally tuned for visual form processing of letters. The second is the comparison of post-relative to pre-tests for trained and non-trained phonograms. This comparison was planned to assess the change in neural activity in learning new phonograms and thus identify brain regions involved with character-to-phonological conversion. A further comparison of post- minus pre- for the trained non-native phonograms relative to the native and non-trained non-native phonograms controls for differential activity that may result from practice effects as well as varying physiological and neurological noise. It is hypothesized that the newly acquired character-to-phonological mappings cannot be ignored in carrying out the two-back task. In support of this hypothesis is the finding that stimulus-specific areas are activated when the task requires encoding of the stimulus (Tagamets et al., 2000). Therefore, it is expected that the brain regions involved with the character-to-phonological conversion processes (left angular gyrus) should show greater activity after relative to before learning.

Moreover, psychophysiological interaction (PPI: Gitelman et al., 2003; Friston et al., 1997) analysis was performed to assess the functional integration of left BA37 with other areas in relation to visual form processing of native letters. An additional PPI analysis was performed to assess the functional integration of left BA39 with other areas in relation to character-to-phonological processing of newly learned phonograms. For character-to-phonological processing, we were especially interested in the functional integration of left BA39 with primary visual cortex as well as

with superior temporal gyrus based on the Wernicke–Geschwind model (Geschwind, 1965).

Methods

Subjects

Eleven Japanese volunteers (ages 22–37 years, 8 males and 3 females), who had no previous knowledge of the Korean or Thai, participated in this study. All subjects were right-handed and scored above +80 on the Edinburgh Handedness Inventory (Oldfield, 1971). Subjects gave written informed consent for experimental procedures, approved by the ATR Human Subject Review Committee.

Overall experimental design

This study consists of three parts: pre-test, training phase, and post-test. The procedures for the pre- and post-tests were identical.

Pre- and post-tests

Subjects performed a two-back identification task during pre- and post-tests. Three types of letters were used as stimuli: Japanese, Thai, and Korean. Japanese was a native language and Thai and Korean were non-native languages for all subjects. All letters were phonograms, but subjects did not know how to pronounce either Thai or Korean phonograms. Five letters from each language (Fig. 1) were used and corresponded to five vowels (/i/, /e/, /a/, /o/, and /u/). Subjects learned either Thai or Korean letters during the training phase.

Trials were blocked by condition and there were three conditions: native (Japanese), trained non-native (Thai/Korean), and non-trained non-native (Korean/Thai). Each condition appeared four times in each session. Subjects did one session as a pre-test and one session as a post-test. Each task condition was alternated with a baseline condition in which just a fixation mark was presented. Each task condition lasted 24 s and the baseline condition lasted 9 s. The order of task conditions was randomized across sessions. In each block, letters were presented randomly twelve times at a rate of 1 every 2 s (1.5 s presentation of a letter followed by 0.5 s presentation of a fixation mark). Subjects responded to each stimulus presentation by pressing one of the two buttons on a response box held in their left hand. They were

instructed to press the left button when the letter was identical to the stimulus presented two times prior and to press the right button when it was not. Subjects only used their left thumb to press buttons. They did not have to respond for the first two stimuli, so the response started after the third stimulus presentation. To reduce brain activity caused by confusion to the task, subjects practiced the task until they could perform with over 70% accuracy prior to entering the MRI scanner. During the imaging session, stimuli were projected onto a screen at the head of the scanner bed via an LCD projector and subjects viewed the screen via a mirror attached to the head coil.

Training phase

Subjects learned either five Korean or five Thai phonograms during the training phase. The type of letter that they learned during the training phase was counterbalanced between subjects. Stimuli were native (Japanese) and one of the non-native languages that was the same used in pre- and post-tests. Trials were blocked by condition and there were three conditions: reading Japanese letters (RJL), learning non-native letters (LNL), and reading non-native letters (RNL). For both the reading conditions (RJL and RNL), a letter was presented above the fixation mark that was presented in the center of the screen for 1.5 s. Subsequently, a square box was presented under the fixation mark for 1.5 s. Subjects were instructed to read out the letter as soon as they saw the square box or guess and produce the sound of the letter if they did not know how to pronounce it. Letters were presented randomly 5 times at a rate of 1 every 4 s. For the training condition (LNL), a non-native letter was presented above the fixation mark, and 1.5 s later, a native letter that corresponded to pronunciation of the non-native letter was presented under the fixation mark for 1.5 s. For this condition, subjects were instructed to read out the native letter and try to associate the non-native letter with the speech sound. Letters were presented randomly 10 times at a rate of 1 every 4 s. Each letter was presented twice in each block. The order of the condition was always the same: RJL–LNL–RNL. This cycle was repeated four times in each session and subjects performed three sessions to learn non-native letters perfectly. Speech production responses were monitored by microphone attached to the head coil and recorded on a compact disc for later analysis.

MRI data acquisition and preprocessing

For structural and functional brain imaging, Shimadzu-Marconi's Magnex Eclipse 1.5 T PD250 was used at the ATR Brain Activity Imaging Center. Functional T2*-weighted images were acquired using a gradient echo planar imaging sequence (TR = 3000 ms, TE = 49 ms, flip angle = 90°, field of view = 192 × 192 mm, matrix size = 64 × 64 pixels). Thirty consecutive axial slices (thickness, 5 mm) covering the whole cortex and cerebellum were acquired. Before the acquisition of functional images, T2-weighted anatomical images were acquired in the same plane as the functional images (voxel size = 0.75 × 0.75 × 5 mm). T1-weighted anatomical images (voxel size 1 × 1 × 1 mm) were also acquired.

Images were preprocessed using programs within SPM2 (Wellcome Department of Cognitive Neurology, University College, London). Differences in acquisition time between slices were accounted for, movement artifact was removed, and images were spatially normalized (voxel size 2 × 2 × 4 mm) by using a

	/i/	/e/	/a/	/o/	/u/
Japanese	い	え	あ	お	う
Korean	이	에	아	오	우
Thai	อี	เอ	อา	โ	อุ

Fig. 1. Phonograms used as visual stimuli.

template defined by the Montreal Neurological Institute (MNI) and were smoothed using a 10-mm FWHM Gaussian kernel.

fMRI data analysis

Preprocessed MRI data were analyzed statistically on a voxel-by-voxel basis using SPM2. The time series for each voxel was high-pass filtered to 1/198 Hz, serial correlations were corrected by an autoregressive AR(1) model, and global signal changes were removed by scaling. The task-related neural activities were modeled with a box-car function convolved with the hemodynamic response function. For each subject, a native minus non-native contrast and post- minus pre-test contrasts (taking into account the baseline condition implicitly in the design) for each language were assessed. Then the subject-specific contrast images of parameter estimates were used as inputs for the second (random effect) level analysis. At the second level, one-sample *t* tests were conducted and a threshold of $P < 0.05$ (random field theory correction for multiple comparisons) was employed.

For the computation of psychophysiological interaction (PPI) regressors representing the interaction of the psychological context with inputs from a specified region's activity, we used the process of signal deconvolution embedded in SPM2. The first eigenvariables were calculated for the voxels (sphere with 10 mm radius) of interests (left BA37 and left BA39). PPI regressors were calculated using a native minus non-native contrast for the pre-test for BA37 and using the trained non-native condition minus the baseline in pre- and post-tests for BA39. Those regressors were inserted as user-specified regressors in new session-specific design matrices and the contrast for the PPI was calculated for each subject. Then the subject-specific contrast images were used as inputs for the second level analysis. At the second level, one-sample *t* test was conducted for BA37 and paired *t* test with non-sphericity correction was conducted for BA39. A threshold of $P < 0.001$ (uncorrected) with a $P < 0.05$ (uncorrected) for cluster extent was employed. Additionally, small volume corrections ($P < 0.05$ corrected, sphere with a radius of 6 mm) were performed for the priori regions of interest in primary visual cortex and superior temporal gyrus.

Results

Behavioral performance

Button press responses during pre- and post-tests were analyzed using a 3 (language: native, trained non-native, and non-trained non-native) \times 2 (session: pre- and post-tests) within subjects analysis of variance (ANOVA). The mean percentages of correct responses and the mean reaction times (RTs) are plotted in Fig. 2. Because of a machine failure, one subject's data were lost. Subjects responded significantly more accurately ($F(1,9) = 13.04$; $P < 0.01$) and faster ($F(1,9) = 13.21$; $P < 0.01$) in the post-tests. There is no significant interaction for accuracy (i.e., improvements in accuracy were not significantly different for different language conditions), but there is a significant interaction for RT ($F(2,18) = 12.33$; $P < 0.01$) (i.e., improvements in RT were significantly different for different language conditions). The simple effects of session for RT were assessed for each language. RTs for native and non-trained non-native conditions were significantly reduced in the post-tests ($F(1,19) = 12.49$, $P < 0.01$ for native; and $F(1,19) = 53.23$, $P < 0.01$ for non-trained non-native). These analyses were also significant with the Geisser–Greenhouse correction, for which the critical $F(1,9) = 10.6$. On the other hand, there was no significant difference in RTs between pre- and post-tests for the trained non-native condition. In the post-tests, RTs were significantly shorter for the native condition relative to the trained non-native condition ($t(9) = 4.55$; $P < 0.002$), as well as for the non-trained non-native condition relative to the trained non-native condition ($t(9) = 4.31$; $P < 0.002$).

Brain imaging

Brain regions involved with letter-specific visual form processing were determined by comparison of native with non-native orthographies. The hypothesis tested is whether left BA37 is activated more for the native orthography (Japanese) than for the non-native orthographies (either Korean or Thai). Neither contrast revealed significant differential activity in left BA37 using random field theory correction or even a region of interest analysis without correction ($P > 0.05$ uncorrected). The region of interest analysis

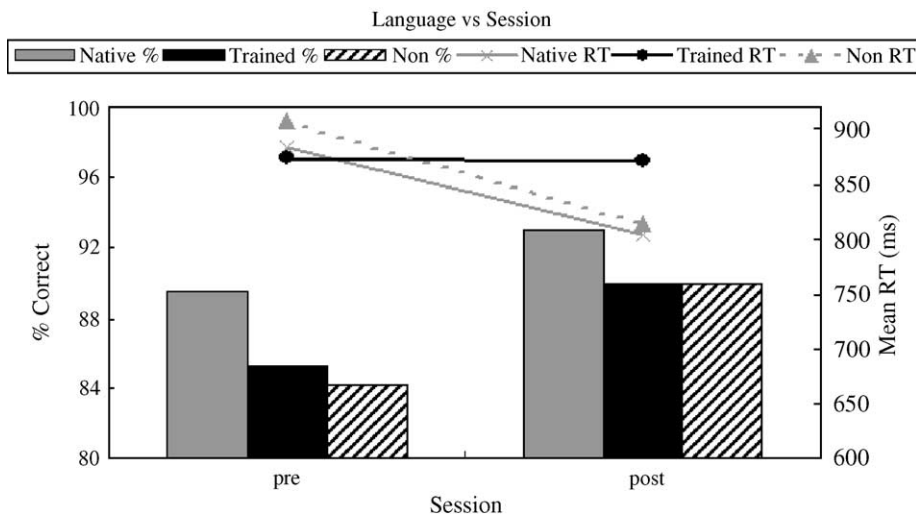


Fig. 2. The mean percentages of correct responses and the mean reaction times (RTs). Bar graphs indicate the mean percentages with the scale on the left. Line graphs indicate the RTs with the scale on the right. Native = native language (Japanese). Trained = trained nonnative language (Korean/Thai). Non = non-trained nonnative language (Thai/Korean).

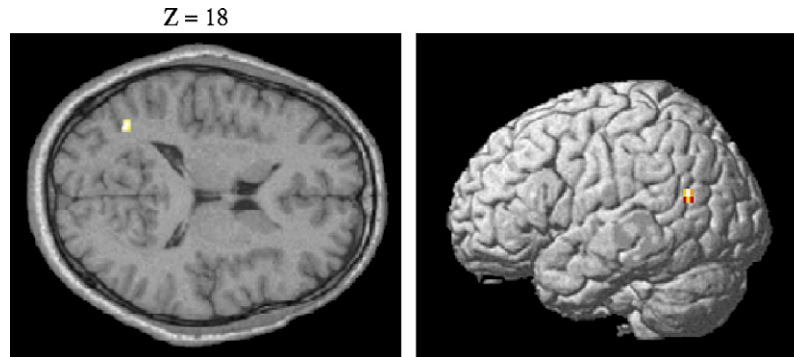


Fig. 3. A significant difference before and after learning phonograms. The left image shows the axial image ($Z = 18$) and the right one shows the rendering image on the lateral surface of the left hemisphere. Displayed voxels are associated with z -scores greater than 3.09 ($P < 0.05$ corrected).

was conducted in left fusiform gyrus BA37 (10 mm sphere at Talairach coordinates (TC: $-40, -59, -9$) (Talairach and Tournoux, 1988). This voxel was chosen because it locates center of the foci of left fusiform gyrus BA37 reported by numerous investigators [e.g., Cohen et al., 2000 ($-42, -57, -6$); Cohen et al., 2002 ($-39, -57, -9$); Flowers et al., 2004 ($-42, -71, -9$); Joseph et al., 2003 ($-41, -48, -6$); Polk et al., 2002 ($-37, -38, -7$); Price and Friston, 1997 ($-44, -62, -16$); Puce et al., 1996 ($-40, -66, -17$); Tarkiainen et al., 2002 ($-37, -70, -12$)]. Additional analyses were also conducted in which the non-native orthography conditions were combined for the pre-test, post-test, and the pre- and post-tests together. There were no significant differences for these contrasts assessed using the random field theory correction for multiple comparisons or the region of interest analyses ($P > 0.05$ uncorrected). It should be noted, however, that both the native and non-native conditions showed considerable activity in fusiform gyrus BA37 when compared to the baseline condition (peak at TC ($-40, -67, -13$), $z = 4.89$, $P < 0.05$ corrected, for the native condition, and peak at TC ($-44, -68, -10$), $z = 5.65$, $P < 0.05$ corrected, for the non-native condition).

Brain regions involved with automatically induced character-to-phonological (i.e., simple grapheme-to-phonological) conversion were determined by comparing the pre- and post-tests for each language condition separately. There were no significant differences between the pre- and post-tests for both the native and non-trained non-native conditions. For the trained non-native condition, there was a significant activation ($z = 5.30$, $P < 0.05$ corrected) in left BA39 (TC: $-40, -59, 18$) (Fig. 3). It is in a region identified by several studies as angular gyrus [e.g., Bookheimer et al., 1995 ($-44, -66, 32$); Demonet et al., 1992 ($-48, -52, 28$); Howard et al., 1992 ($-50, -48, 8$); Joubert et al., 2004 ($-40, -53, 32$); Lee et al., 2003 ($-56, -66, 22$); Price et al., 1994 ($-52, -38, 24$);

Small et al., 1996 ($-47, -58, 19$)]. An interaction analysis comparing post- minus pre- for the trained non-native condition relative to the native and non-trained non-native conditions showed significant differential activity for voxels identified in the above analysis within left angular gyrus ($z = 2.24$, $P < 0.05$ corrected).

Additionally, psychophysiological interaction (PPI: Gitelman et al., 2003; Friston et al., 1997) analyses were performed to assess the functional integration of left BA37 with other areas on visual form processing of native letters and one of left BA39 with other areas on character-to-phonological processing of newly learned phonograms. For the left BA37 PPI analysis, the peak voxel (TC: $-44, -68, -10$) in left BA37 during the two-back identification task (including both native and non-native language conditions) compared to baseline was used as the center voxel of interest. Regions more strongly connected to left BA37 in the native condition compared to the non-native conditions were right anterior cingulate (BA24) and right precentral gyrus (BA6) (Table 1). For the BA39 PPI analysis, the peak voxel (TC: $-40, -59, 18$) in the pre- and post-test comparison for the trained non-native condition was used. Table 2 shows the regions more strongly connected to left BA39 during processing non-native phonograms after training compared to before training. The results indicated that left BA39 was more strongly connected to primary visual cortex (BA18) and superior temporal cortex (BA22) in the trained non-native condition after training.

Table 1
Psychological interactions of BA37

A significant functional connectivity for native compared with non-native in pre-test			
Region	Coordinates x, y, z (mm)	Laterality	Activation maxima Z score
Anterior cingulate BA24	16, -9, 45	R	4.11
Precentral gyrus BA6	46, -8, 34	R	3.48

Brain activation for $P < 0.001$ (uncorrected) with a $P < 0.05$ (uncorrected) for cluster extent. R denotes right; L denotes left.

Table 2
Psychological interactions of BA39

A significant functional connectivity for trained non-native phonograms compared with ones before training			
Region	Coordinates x, y, z (mm)	Laterality	Activation maxima Z score
Caudate nucleus	-18, 25, -1	L	4.00
Anterior cingulate BA24	-14, 24, 14	L	3.92
Orbital gyrus BA11	-22, 36, -19	L	3.73
Superior temporal gyrus BA22	-42, -31, -5	L	3.73*
Occipital gyrus BA18	-12, 98, 12	L	3.13**

Brain activation for $P < 0.001$ (uncorrected) with a $P < 0.05$ (uncorrected) for cluster extent. R denotes right; L denotes left.

* Small volume corrected, $P = 0.006$.

** Small volume corrected, $P = 0.027$.

Discussion

Neural activity associated with letter perception was investigated in this study. Japanese subjects who did not have any knowledge about Thai and Korean phonograms were trained on the phonograms of one of the non-native languages. Neural activity during a two-back identification task pre- and post-training was recorded. Our main interest was determining brain regions involved with visual form processing and brain regions involved with character-to-phonological conversion processing for letter perception. Letter-specific visual form processing was assessed by comparing native (Japanese) with non-native (Thai and Korean) conditions. The comparison did not reveal any significant differential brain activity. Left fusiform gyrus (BA37) failed to show differential brain activity between native and non-native conditions even when using the region of interest analyses without correction ($P > 0.05$ uncorrected). These results do not support the hypothesis that left fusiform gyrus is functionally tuned for visual form processing of letters. The result of the PPI analysis indicated that left fusiform gyrus is more strongly connected to right anterior cingulate (BA24) and right precentral gyrus (BA6) for the native condition compared to non-native condition. In general, those areas are not considered as functional foci for the language processing. The anterior cingulate is often reported for the working memory task and the BA6 is known to be involved in motor functions. Subjects used their left hands for the button responses and right BA6 has an important role for controlling their left hands. Therefore, the enhanced functional connectivity in right BA6 may be related to the button press responses rather than visual form processing of native letters.

Character-to-phonological conversion processing was assessed by comparing post- with pre-tests for each language condition. After training the pronunciation of non-native phonograms, left angular gyrus (BA39) was activated more during the two-back identification task. This neural change was not due to practice effects because the same change was not observed in native nor non-trained non-native conditions. It is also unlikely that the change in activity is a result of greater visual familiarity with the letters due to greater exposure as a result of training because no difference in activity was found between the very familiar native letters and the non-familiar non-native letters before training. The result of the PPI analysis indicated that left angular gyrus is more strongly connected to left caudate nucleus, left anterior cingulate (BA24), left orbital gyrus (BA11), left superior temporal gyrus, and left primary visual cortex (BA18). The enhanced integration of left angular gyrus with primary visual cortex and with superior temporal cortex supported the Wernicke–Geschwind model (Geschwind, 1965) for reading.

Letter-specific visual form processing

Although many previous functional imaging studies reported that letter-specific visual form processing is located in left fusiform gyrus (BA37) (Cohen et al., 2000, 2002; Polk and Farah, 1998; Polk et al., 2002; Puce et al., 1996; Tarkiainen et al., 2002), it was not observed in this study. These results are consistent with those of Joseph et al. (2003) and Price and Friston (1997) suggesting that both letters as well as objects (in this case meaningless symbols) can activate left fusiform gyrus. In our study, left fusiform gyrus was activated by both the native and non-native languages with no significant difference with respect to the degree between them. The results of our study, however, are in contrast to those of Flowers et al. (2004) in which fusiform gyrus showed greater activity to the

same stimuli when they were attended to as letters than as symbols or colors. As Flowers et al. (2004) stated; the enhanced activity in left fusiform gyrus may be caused by attending to linguistic aspects of stimuli (single letters), but not by merely perceiving the letter-specific visual form. The tactile activation of left fusiform gyrus by Braille reading in blind subjects also indicates that the activity is not specific to a visual input but more likely reflects processes involved with associating a sensory input (can be visual or tactile) with linguistic knowledge (Büchel et al., 1998). Many studies reported left fusiform gyrus using passive viewing tasks (e.g., passive viewing of letter strings versus face). Passive viewing has less control over the subjects mental processing during the task, so subjects probably were doing more linguistically oriented processing in their minds while they were viewing letter strings than in other conditions. It is possible that the n -back task used in our study did not require sufficient linguistic associative processing to differentially activate left fusiform gyrus. Consistent with this hypothesis differential activity in left fusiform gyrus for letters and non-letter shapes was not reported in other fMRI studies using n -back tasks (Nystrom et al., 2000; Tagamets et al., 2000).

Character-to-phonological conversion processing

The results of our study indicate that left angular gyrus is activated more in the post-test than the pre-test for the trained non-native condition but not for the native and the non-trained non-native conditions (Fig. 3). The tasks and the visual stimuli were identical in both pre- and post-tests. The only difference we assumed was the newly acquired phonological knowledge of the letters. All the subjects learned the character-to-phonological mapping for the five non-native letters they were trained on within the short training period. The durability of these mappings in the long-term was not investigated. The issue under study here is determining the effect the newly acquired character-to-phonological mapping has on brain processes involved with the two-back task. Because the same change was not observed in the other conditions post-relative to pre-training (native and non-trained non-native), we concluded that the change in neural activity was caused by character-to-phonological conversion processing for the newly learned phonograms. The results of the interaction analysis showing greater post- minus pre-activity for the trained non-native condition relative to the native and non-trained non-native conditions further suggest that the results are due to character-to-phonological conversion rather than from practice effects or varying physiological and neurological noise.

The PPI results showed enhanced functional connectivity with left BA39 in left caudate nucleus, left anterior cingulate, left orbital gyrus, left superior temporal gyrus (BA22), and left occipital gyrus (BA18). The activation in the caudate nucleus is reported for reading and hearing (Buchsbaum et al., 2005; Vorobyev et al., 2004). The caudate nucleus is hypothesized to have a critical role in category learning (Ashby et al., 1998). There are a few functional imaging studies support this hypothesis (Filoteo et al., 2005; Monchi et al., 2001). The enhanced connectivity with the caudate may reflect the learning of the new non-native phonogram category. The most interesting finding in the PPI analysis was the enhanced coupling of left BA22 and that of left BA18 to left BA39. This indicated that the functional connection corresponding to the Wernicke–Geschwind model (Geschwind, 1965) for reading was used more for perceiving non-native phonograms after training than before training.

The behavioral results also indicate this added new process in the post-tests. Because of practice effects, the reaction times (RTs) in the post-tests for the native and the non-trained non-native conditions were reduced significantly, but the RTs for the non-native trained condition were not reduced. This interaction was not observed in the accuracy measurement because it may be not as sensitive as the reaction times. We maintain that the RTs were not reduced because of the learned character-to-phonological mapping (that cannot be ignored when carrying out the two-back task) added extra processing time.

Consistent with our results, Lee et al. (2003) reported left angular gyrus activation in learning of Korean words by Japanese. They acquired fMRI data on the 2nd day and the 16th day of the learning. After 15 days of learning Korean words, left angular gyrus was more activated for Korean words that subjects did not learn (i.e., they did not know the meaning of the words nor the pronunciation of the words as a whole) but did know the pronunciation of some of the phonograms of the words because the same phonograms were used in Korean words that they learned. Therefore, they concluded that left angular gyrus activation was due to newly acquired character-to-phonological conversion process for the non-native phonograms.

Our findings support the classical neurological model for reading. Since Dejerine (1891, 1892) reported left angular gyrus lesion in a man who suddenly became unable to write and read (alexia with agraphia), left angular gyrus has been considered as an important site for written language processing. Based on the lesion studies, Geschwind (1965) proposed that left angular gyrus was an area associating visual and auditory information in reading. In his model, reading is processed by the route connecting, primary visual cortex, angular gyrus, and Wernicke's area.

There are numerous reasons why many functional imaging studies do not find angular gyrus activation: The use of words instead of letters may result in lexical-to-phonological (top-down) processing that requires less grapheme-to-phonological (bottom-up) processing; the use of orthographies with ambiguous phonological mappings may not optimally activate stimulus-driven grapheme-to-phonological conversion processing. Subtraction methodology may be sensitive to differences in task and/or stimulus features between conditions that may obscure activity reflecting grapheme-to-phonological conversion processing in angular gyrus. Although many functional imaging studies using subtraction methodology did not find left angular gyrus activity, ones using functional connectivity analysis (in agreement with our results) reported that there is a strong functional connection between left angular gyrus and occipital and temporal regions in non-impaired readers and that this strong functional connection in the left hemisphere is absent in dyslexic readers (Horwitz et al., 1998; Pugh et al., 2000).

We tried to overcome some of the problems associated with experiments investigating phonological aspects of letter perception but there are several issues that have to be kept in mind when interpreting our results. (1) Newly learned non-native letters may not be processed in the same manner as well-experienced native letters. As can be seen in our behavioral results, character-to-phonology association training induced extra processing time in the two-back identification task. This suggests that the character-to-phonological conversion process for newly learned phonograms is not as automatic as the one for native phonograms. (2) It is unclear whether subjects retained long-term establishment of character-to-phonological mappings for the items

that they learned during the study. Learning phonograms under the experimental conditions of this study may be very different from learning phonograms in relation to acquiring a foreign language. Subjects only learned five phonograms and all subjects could pronounce them correctly by the end of the first session out of three training sessions. The learning of the phonograms in this study may not be long-term but should nonetheless have a strong influence on neural processes involved with character-to-phonological conversion during the post-test two-back task that took place right after the training session. (3) It is possible that the enhanced activity in left angular gyrus may not reflect the character-to-phonological conversion process but rather "extra work load" caused by newly acquired knowledge. Indeed posterior parietal (including angular gyrus) activity has been found for verbal working memory encoding tasks (Jonides et al., 1998). Because we did not include a condition to control this possibility, we cannot exclude this hypothesis. However, we believe this hypothesis is unlikely because the reported regions associated with increasing task difficulty (occipitoparietal cortices, anterior cingulate, cerebellum, right dorsolateral prefrontal, left inferior frontal gyrus, and right posterior parietal cortex) do not include left angular gyrus (Gould et al., 2003; Dräger et al., 2004). Furthermore, other brain regions besides angular gyrus that are involved with working memory (Broca's area, premotor area, supplementary motor area, dorsolateral prefrontal cortex, supramarginal gyrus, anterior cingulate, and the cerebellum; Smith and Jonides, 1998; Jonides et al., 1998; Tsukiura et al., 2001) are not differentially activated post-relative to pre-training for the learned stimuli as one would expect if the results were due only to an "extra work load".

Conclusions

This experiment investigated brain regions involved with visual form processing and character-to-phonological (i.e., simple grapheme-to-phonological) conversion processing for letter perception. The results of this experiment do not support the hypothesis that left fusiform gyrus (BA37) is functionally tuned for visual form processing of letters. However, consistent with the results of clinical lesion studies as well as imaging studies investigating functional connectivity, the results of this experiment strongly support the involvement of left angular gyrus (BA39) for associating visual and auditory phonological information in letter perception. The lack of left angular gyrus activation in letter or word perception for some functional imaging studies may be due to mediation by top-down processes as well as by the nature of the orthographic system of the language under study. This study attempts to control for these possible confounds by utilizing presentation of single letters from orthographic systems that are composed of phonograms with completely regular pronunciation as well as by using a methodology employing the same task and stimuli (attempting to avoid some of the problems associated with subtraction based analysis) in which differences in neural processing can be attributed predominantly to the acquisition of character-phonology association. Given the strict criteria used to assess significance in this study it is likely that some brain activity was missed in other brain regions. However, the presence of activity in left angular gyrus strongly suggests that this region is involved with character-to-phonological conversion processing in letter perception.

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