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Differential Reorganization of Fusiform Gyrus in Two Types of Alexia after Stroke

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Lesions affecting the left fusiform gyrus (FG) commonly result in dyslexia and recovery largely depends on efficient reorganization of the reading network. We performed a follow-up fMRI study to elucidate the reorganization patterns of the FG according to the recovery of reading ability in two patients (MH with pure alexia and KM with alexia with agraphia) after stroke involving the left FG. Initially, MH was an effortful letter-by-letter (LBL) reader, and she improved to become a proficient LBL reader. The initial fMRI results showed scattered activation on occipital and ventral temporal cortex during reading, which was localized to right FG in the follow-up study. KM's severe alexia with agraphia did not improve, even after 6 months had passed since the onset of the alexia. The initial and follow-up fMRI results showed no significant activation in the bilateral FG or central higher language areas during word reading. Our results suggest that the reorganization of the FG is different according to the type of alexia and the amount of clinical recovery in each patient. Also, the successful reorganization of the visual component of reading in the right FG is responsible for the recovery of LBL reading in pure alexia.

Keywords: Pure alexia; Alexia with agraphia; Fusiform gyrus; Visual word form area; Functional MRI.

Introduction

The acquisition of literacy depends on the development of elaborate links between vision and language, between letter strings and sounds, and between letter strings and lexical entries in the memory system. To develop reading efficiency, a word-form recognition system must be used to allow for the rapid identification of visual words across a wide variety of irrelevant parameters, such as position, size, color, font or case. Such a word-form recognition system is called a visual word form (Warrington & Shallice 1980). Recent functional neuroimaging studies have provided considerable insight into the neural networks associated with written word processing. These studies were primarily focused on showing the patterns of activation in the left mid-fusiform gyrus that is associated with various reading paradigms. Cohen and colleagues (Cohen 2000; McCandliss, Cohen, & Dehaene 2003) proposed the visual word-form area (VWFA; Talairach coordinates,

 $x = -43$, $y = -54$, $z = -12$) which is located in Brodmann's cortical area 37 (BA 37) within the left occipitotemporal sulcus bordering the fusiform gyrus (FG). Meta-analysis (Bolger, Perfetti, & Schneider 2005) of the results of neuroimaging studies of word reading suggested that the writing systems utilize a common network of regions when processing words in English and other Western European languages, Chinese and Japanese Kana. The VWFA showed consistent localization in a variety of tasks and writing systems. However, few studies have reported the direct comparison of the patterns of activation when reading Hangul and Western languages. The alphabetic system of Hangul is quite different from that of Western and other East Asian languages. The arrangement of consonants and vowels is not linear, and their combination makes a syllable within the space of a square-like block that resembles the shape of Chinese characters. Thus, each character in Hangul can be regarded as a syllabogram. For example, ' \overrightarrow{e} ' $\overrightarrow{=}$ ' is a two-syllable Korean word that means

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'Korea', and can be decomposed into consonants and vowels, $\bar{\sigma}$ [h]+ $\bar{\sigma}$ [a]+ $\bar{\sigma}$ [n] $\bar{\sigma}$ [g]+ $\bar{\sigma}$ [u]+ $\bar{\sigma}$ [k]. An fMRI study suggested that reading Hangul appears to corroborate with that of alphabetic words at the general level (Yoon, Cho, Chung, & Park 2005).

Alexia is a syndrome characterized by a deficit in reading without deficits in spoken language or auditory comprehension. Patients with alexia can be classified as having peripheral or central alexia, depending on whether they are associated with a misperception of words or a disturbance of higher language processing (Warrington & Shallice 1980). The ability to read can be improved in patients with alexia. As it is associated with natural recovery, the application of dyslexia rehabilitation may facilitate the reorganization of reading networks during the recovery process (Adair et al. 2000; Beeson, Magloire, & Robey 2005; Maher et al. 1998). Since Dejerine described two distinct types of alexia: alexia with agraphia following a lesion in the left angular gyrus (AG) and pure alexia due to infarction of the occipital gyrus and splenium of the corpus callosum, recent neuroimaging studies provided converging evidence of the functional importance of the FG in various subtypes of pure alexia (Cohen et al. 2004a; Henry 2005; Marsh & Hillis 2005). Furthermore, the mechanisms of letter-by-letter (LBL) reading and its improvement are thought to result from the selective and successful shift of the visual component of reading to the right hemisphere, particularly to the homologue of the VWFA (Cohen et al. 2004a; Henry et al. 2005). One study (Adair et al. 2000) measured regional cerebral blood flow (CBF) before and after therapy in a patient with acquired phonologic dyslexia after infarction involving the temporal and inferior parietal lobe. After treatment, nonword reading led to increased CBF in the right posterior perisylvian cortices and bilateral Broca's area, and a modest increase in CBF was also detected in the posterior half of the right temporal lobe, including BA 37. The reorganization of the reading network after alexia is a dynamic process, and the patterns by which this occurs may be quite different depending on the lesion site, type of alexia and the clinical course of recovery. However, there is insufficient functional neuroimaging data in other types of alexia, and further research is needed in order to understand the role of the right FG in alexia with or without agraphia. In addition, functional neuroimaging studies on the processes involved in reading the Korean writing system, Hangul, are scarce, and alexia patients who were native Korean speakers have not been studied.

We designed this study in order to elucidate the differential reorganization patterns, especially in the fusiform gyrus (FG), in two patients with pure alexia and alexia with agraphia after stroke involving the left FG using a follow-up fMRI study.

Methods

We performed an fMRI study at 1 month after the onset of stroke in two patients and followed up 7 months (MH) and 5 months (KM) later. Informed consent to the procedures was obtained from each participant, and the Health Service Human Research Ethics Committee and the Committee on Experimental Procedures Involving Human Subjects of the Asan Medical Center approved this study.

Case MH

MH was a 56-year-old woman and she had been working as a dyer. Her native language was Korean and she did not know any other languages. She had received 12 total years of education and right hand laterality quotient examined by Edinburgh handedness inventory (EHI) (Oldfield 1971) was 100%. After an attack of spontaneous intracerebral hemorrhage in the temporoparietal area (Figure 1A), she could not discriminate between colors (achromatopsia) nor read any syllables or words. A visual field examination (HFA II, Humphrey®, Germany) revealed right homonymous hemianopsia. Her initial symptoms of global alexia

Fig. 1. (A) Brain CT of MH showing intracerebral hemorrhage in the left parietal and temporal region. (B) Diffusion-weighted brain MRI of KM shows extensive cerebral infarction involving the left ventral temporal cortex and parietal lobe.

gradually improved, and 1 month after the onset she was able to read Korean words laboriously through the LBL reading strategy. She participated in a daily class for an illiterate until the follow-up fMRI study.

Case KM

KM was a right-handed 59-year-old woman and she was a homemaker. She had received 12 total years of education and right hand laterality quotient was 100%. Her native language was Korean and she could not speak any other languages. She visited an emergency room (ER) due to severe headache and visual disturbance that had lasted for 2 days. Several hours after visiting the ER, she developed a language comprehension deficit without expressive difficulty, and she could not read any written words or numerals. There was no noticeable motor weakness in all four extremities. A visual field examination revealed right homonymous hemianopsia. After workup she was diagnosed as having an infarction in the left ventral temporal and parietal cortex due to Moyamoya disease, and the diamox SPECT revealed markedly decreased metabolism in the left occipito-temporo-parietal cortex (Figure 1B). She was discharged from the hospital 1 week later, but her symptoms of global alexia persisted throughout this study.

Language and behavioral test

We evaluated cognitive function with the Mini-Mental Status Examination (MMSE), and attention (auditory and visual continuous performance test) and memory (verbal and visual learning test) function were assessed with the computerized neuropsychological test (CNT, Max Medica, Seoul, South Korea). Language function including writing and reading ability was assessed with the Korean version of the Western Aphasia Battery (K-WAB) (Kertesz 1984). Also we examined four additional online tasks-same letter matching, picture naming, picture-word matching, and lexical decision tasks (LDT)-programmed in SuperLab 2.0 software (Cedrus, USA).

Functional MRI

We used a block design, including picture naming, word reading and control trial blocks, over two sessions, to subtract the areas activated by simple visual input and oromotor movement from activation during picture naming and reading words. The first session consisted of 4 picture naming and 5 control blocks per session beginning with a control block (30 s per block, total 270 s). During the picture naming block, participants were instructed to report the name of a presented drawing of objects covertly and we made the black line drawings with shadings for this study (Figure 2A). The rate of stimulus presentation was one stimulus per every 3 s. We presented total number of 40 custom drawing of living and non-living objects as stimulus pictures and same images were used during initial and follow up fMRI studies. During the control block, the participants performed covert speech, saying a meaningless Korean phrase '무_무 (mu–mu)', when non-nameable custom drawing of geometrical figures were displayed (Figure 2B). Formation of second word reading session was similar to previous session and it consisted of 4 word reading and 5 control blocks. Participants were instructed to read presented Korean words covertly during the reading block (Figure 2C). We presented total number of 40 words, 2–4 syllables in length, and same number of high and low frequency words were included. In the control block, participants were instructed to say 'mu-mu' covertly when non-readable Arabic words were displayed (Figure 2D). Before the fMRI study, we trained two participants repeatedly to speak covertly using sample tasks of each session.

The blood-oxygenation-level-dependent (BOLD) fMRI measurement, which employs the echo planar imaging (EPI) technique, was performed using a 1.5T MR scanner (CV I, GE, USA) with a standard head coil. For the anatomic base images, 20 T1-weighted axial conventional spin echo images (5 mm thick) were obtained with a matrix size of 256×256 pixels and a field of view of 240 mm parallel to the anterior–posterior commissure. The EPI images were acquired over the same 20 slices for each epoch. The imaging parameters for each experiment were $TR/TE = 3$ s/30 ms, $FOV = 240$ mm,

Fig. 2. Examples of the task for fMRI study. Drawings in upper row are stimuli for picture naming session, picture naming (A), control task (B). Lower row is word stimuli for word reading session, Korean word (C) and control task written by Arabian (D). All the tasks were performed using covert speech.

matrix = 64×64 pixels, slice thickness = 5 mm, and flip angle $= 80^\circ$. The fMRI data were analyzed using SPM-II software (Wellcome Department of Cognitive Neurology, London, UK) implemented in the MATLAB program (Mathworks, Inc., Sherborn, MA, USA). The EPI images were spatially h, poroducing a toalt of 780 images for enique, was perforealigned to the first image for head motion, and the images were co-registered with the patient's structural T1 image. Afterward, the images were smoothed using an 8mm FWHM Gaussian kernel, and normalization was not performed. Statistical parametric maps were obtained, and voxels were considered significant at an uncorrected threshold of *p* < .0001.

The activation patterns of occipitotemporal cortex and FG were compared between initial and follow up studies using each patient's personal T2* weighted images. For each participant, a general linear test (GLT) contrasting activity associated with follow up study with that associated with initial was performed. All the voxels were considered in the subtraction and were identified as significantly activated if they passed a height threshold set at uncorrected $p < .0001$.

Results

Behavioral results

Case MH

At that time of initial study, her MMSE score was 18 out of 30 possible points and she scored below the 5th percentile on the auditory and visual attention and memory tests. Neuropsychological test revealed very low performance on the LDT. Seven months later, her MMSE improved to 25 points. The results of the attention tests were normal, but her performance remained low on the verbal learning test in the areas of registration and delayed recall. Her aphasia improved to the normal range, except for mild anomia, and she achieved proficiency in the LBL reading skill. Her performance on the other neuropsychological tests also improved to a near normal range (Table 1).

Case KM

Her initial MMSE score was 19 points, and the auditory attention and verbal-learning test results were below the reference values. The results of the K-WAB showed good verbal language function, but she could not read any words or sentences, and she had difficulty writing (alexia with agraphia). In the neuropsychological online tests, she was able to match letters fairly well, but she could not discriminate between consonants and vowels. At the time of the follow-up evaluation, her K-WAB score showed improvement in the aphasia profiles. Her reading and writing inabilities persisted and she could hardly read single syllables, such as her last name. Other neuropsychological tests showed no remarkable improvement in comparison to the initial evaluations (Table 1).

fMRI results

Case MH

Activations in serial fMRI studies of two participants were summarized in Table 2. During picture naming, the initial fMRI showed activation in the right occipitotemporal junction and FG and the follow-up fMRI showed

Table 1. Results of neurobehavioral tests in cases MH and KM

		MН	KM		
Test	Initial	Follow-up	Initial	Follow-up	
MMSE(30)	18	25	15	19	
$K-WAB$ (AQ; 100)	68.8	91.2	58.0	81.8	
Spontaneous speech (20)	16	19	15	18	
Auditory comprehension (200)	123	197	57	145	
Repetition (100)	71	82	76	84	
Naming (100)	51	85	35	72	
Reading word or sentence (100)	27	74	6	24	
Writing (100)	76	81	18	23	
Neuropsychological language tests					
Same-letter matching (60)	58	60	51	58	
Picture naming (80)	36	64	25	40	
Picture–word matching (98)	85	93	65	68	
Lexical decision task (80)	29	—*	45	35	

Numbers in parenthesis are the highest score for each test.

MMSE, Mini-Mental Status Examination; K-WAB, Korean version of the Western Aphasia Battery; AQ, aphasia quotient. *MH did not complete the follow-up lexical decision task.

Initial study					Follow-up study						
			Coordinates					Coordinates			
Region	Cluster	\boldsymbol{x}	\mathcal{Y}	\boldsymbol{Z}	$\cal T$	Region	Cluster	\boldsymbol{x}	\mathcal{Y}	z	$\cal T$
Case MH											
Picture naming $>$ control											
L PCG	462	-42	-4	43	9.93	R OTG	129	27	-69	-24	7.86
R OG, FG	460	27	-71	-30	10.34	L PCG	33	-38	-9	42	7.10
R SMA	37	$\overline{7}$	11	32	4.71	R SMA	31	3	-1	47	5.88
R PCG	30	48	-8	29	5.71						
L OG	27	-19	-55	18	5.26						
L Thm	25	$\boldsymbol{0}$	$\boldsymbol{0}$	$\overline{2}$	4.40						
Word reading $>$ control											
L IFG	1038	-44	16	10	6.94	R MFG	328	36	54	11	7.29
L PCG	420	-38	-8	38	8.32	R FG	232	30	-61	-28	9.05
L OG	290	-12	-48	-34	6.54	L PCG	167	-38	-6	40	7.28
R IFG	119	56	15	-5	7.26	R IFG	149	51	42	-8	7.88
R MFG	91	41	46	τ	5.85	L IFG	125	-21	56	$-8\,$	7.93
R MTG	57	59	-1	-14	6.06	L STG	41	-26	-65	-7	7.70
RAG	44	22	-47	16	6.74	R SFG	40	6	19	28	5.13
L AG	25	-23	-58	27	5.23	R SMA	23	$\boldsymbol{0}$	-13	45	4.62
Case KM											
Picture naming $>$ control											
R OG	58	23	-45	-30	5.57	R OG	37	9	-46	-36	6.17
						R Cbll	28	13	-71	-19	4.04
Word reading > control											
R AG	70	26	-45	25	7.19	R MTG	64	40	14	-49	5.63
R STG	65	53	15	-20	6.41	R AG	54	27	-46	14	7.21
R MFG	32	41	45	15	7.88						
R Cbll	24	11	-38	-35	4.86						

Table 2. Results of activation in initial and follow-up fMRI in two patients with alexia

Uncorrected $p < .0001$, extent voxel > 20, AG, angular gyrus; Cbll, cerebellum; FG, fusiform gyrus; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; MTG, middle temporal gyrus; OG, occipital gyrus; PCG, precentral gyrus; SFG, superior frontal gyrus; SMA, supplementary motor area; SMG, supramarginal gyrus; STG, superior temporal gyrus; Thm, thalamus.

focalization in the right occipitotemporal junction. Subtraction between two fMRI studies showed activation in right occipitotemporal junction ($x = 24$, $y = -73$, $z = -15$; *Z =* 4.36) (Figure 3A, B).

During word reading, the initial activation was observed at the left central reading network and its right homologous areas including bilateral inferior frontal gyrus (IFG), AG and precentral gyrus (PCG). Also, left occipital gyrus (OG), right middle frontal gyrus and right middle temporal gyrus was activated. The follow-up fMRI study showed similar activation in bilateral IFG and focalized activation in the right lateral FG within the ventral temporal cortex was detected. When comparing follow up with initial study activated consistently the FG homologous area to the VWFA ($x = 32$, $y = -56$, $z = -$ 25; *Z =* 7.72). And other areas including right superior temporal gyrus (STG; $x = 54$, $y = 20$, $z = -25$; $Z = 7.53$), left STG (*x =* −40, *y =* 35, *z =* −30; *Z =* 5.71) and left AG (*x =* − 22, *y =* − 56, *z =* − 35; *Z =* 4.75) were also activated (Figure 3C, D).

Case KM

The initial fMRI showed activation in the right occipitotemporal junction during the picture naming task and the follow-up results showed only focal activation of right OG. After subtraction of initial from follow up study activated left inferior temporal gyrus ($x = -22$, $y = -56$, *z =* − 35; *Z =* 4.75), left PCG (*x =* − 23, *y =* − 21, *z =* 45; $Z = 4.01$) and right OG ($x = 5$, $y = -43$, $z = -30$; $Z = 4.2$). But there is no activation in the right ventral occipitotemporal cortex which was activated in case MH (Figure 4A, B).

During word reading, right AG, STG and middle frontal gyrus were activated and right middle temporal gyrus and right AG showed activation in the follow up study.

Fig. 3. The results of fMRI study during picture naming (upper row) and word reading (lower row) in case MH with pure alexia. The displayed brain maps connected with lines were images of direct comparison between two longitudinal scans, follow up study minus initial study. Initial picture naming (A) activated right ventral occipitotemporal junction and the fusiform gyrus (arrow) and follow up study (B) activated occipitotemporal gyrus (arrow). Direct comparison from follow up to initial study showed activation in right occipitotemporal junction (thick arrow). During word reading, initial study (A) showed scattered activation in right middle temporal gyrus, and surrounding areas of lesion in left ventral temporal cortex and no remarkable activation was detected in right posterior fusiform gyrus (arrow). In follow up study (B) MH improved to be a proficient letter-by-letter reader and right fusiform gyrus (arrow) homologous to visual word form area (VWFA) was activated and right VWFA was consistently activated after subtraction from follow up study to initial study (thick arrow). To view this figure in colour, please visit the online version of this issue.

Fig. 4. The fMRI results during picture naming (upper row) and word reading (lower row) after subtraction of control task in case KM with global alexia with agraphia. The displayed brain maps connected with lines were images of direct comparison between two longitudinal scans, follow up study minus initial study. Initial (A) and follow up (B) picture naming task showed right occipital gyrus. Direct comparison between two studies activated left inferior temporal gyrus, left precentral gyrus and right occipital gyrus. Initial word reading task (C) activated anterior portion of right temporal lobe and follow up study (D) revealed no remarkable activation in bilateral fusiform gyri. Direct comparison of serial studies showed activation in right occipital gyrus, left middle frontal gyrus ($x = -47$, $y = -27$, $z = 25$; $Z = 7.53$) and left precentral gyrus. To view this figure in colour, please visit the online version of this issue.

There was no significant activation in the ventral temporal cortex or areas representing left language network. Subtraction from follow up to initial study showed activation in right OG (*x =* 22, *y =* − 53, *z =* 15; *Z =* 4.2), left middle frontal gyrus ($x = -47$, $y = -27$, $z = 25$; *Z =* 7.53) and left PCG (*x =* −23, *y =* − 36, *z =* − 40, *Z =* 4.23). There was no activation in right FG which was typically activated in case MH (Figure 4C, D).

Discussion

Cohen and colleagues (Cohen 2000; Dehaene, Le Clec, Poline, Le Bihan, & Cohen 2002) have labeled the most posterior part of BA 37 within the left OT sulcus bordering the FG as the VWFA. In their proposed visual processing model, during the early retinotopic processing of words the right and left hemispheric visual inputs processed hierarchically from V1 to V2 and V4 (Cohen et al. 2003). These visual inputs project to the VWFA in the left fusiform, and the right visual cortex conveys the inputs to the VWFA through the splenium of the corpus callosum. Many studies have supported the presence of a VWFA, but the existence and functional specialization of the VWFA is still under debate (Devlin, Jamison, Gonnerman, & Matthews 2006; Hillis et al. 2005; McCandliss et al. 2003; Price & Devlin 2003; Price, Winterburn, Giraud, Moore, & Noppeney 2003). Many neuroimaging results reported consistent activation of VWFA in response to reading words within and across writing systems and languages (Bolger et al. 2005). There are no known studies reporting the direct comparison of activation patterns between unique Korean writing system 'Hangul' and Western languages while reading. In an fMRI study (Yoon et al. 2005), Korean word reading activated bilateral FG, left middle frontal gyrus, left superior temporal gyrus, right mid temporal gyrus, precentral gyrus and insula and the results were similar to other writing systems.

Lesions affecting the ventral temporal cortex, including the FG, commonly result in selective reading impairment without difficulties in identifying single letters, which makes LBL reading possible. In our two cases of alexia, though they had a similar location of cortical damage in the left FG and parietal cortex, the type and degree of impairment in their reading abilities and their recovery courses were quite different. MH achieved a good level of LBL reading skill, but KM did not recover from severe alexia, even after 6 months had passed since the onset of alexia. Our fMRI results suggested that the two cases developed different courses of functional reorganization during reading. Compared to the picture naming task, MH's initial fMRI results during reading showed scattered activations of the bilateral lingual gyrus and left ventral temporal cortex. Seven months later, however, the

activations had transferred to the right posterior FG, including the so-called VWFA. These results support the results of previous reports (Cohen et al. 2004a, 2004b; Henry et al. 2005) that the clinical improvement from an initially poor LBL reader to a proficient reader was primarily related to a successful shift of the visual component of reading to the right hemisphere, especially to the right FG including the VWFA. The patient's continuous participation in a community based learning program for an illiterate might have facilitated the cortical networks in the right hemisphere during the reading process (Adair et al. 2000; Beeson et al. 2005). However, KM's clinical courses and reorganization patterns were quite different. During the follow-up fMRI studies, there were no remarkable activations in the bilateral FG or central language areas, which suggest a failure to successfully reorganize the damaged VWFA. Many researchers argued that global alexia was associated with damage to the ventral temporal cortex and left posterior interhemispheric callosal pathway, especially in the forceps major and splenium (Binder & Mohr 1992; Cohen et al. 2003; Sakurai et al. 2000; Silver et al. 1988; Usui et al. 2003). KM's MRI and diamox SPECT showed damage not only to the ventral temporal cortex, but also to the left interhemispheric callosal pathway and to the parietal cortex, including the AG and supramarginal gyrus (SMG). The AG is known as a multimodal integration area working as a semantic access node and a crucial transmodal interface between auditory system and knowledge. Also recent neuroimaging studies have indicated that the SMG is an area related to reading through the graphophonological conversion (GPC) route (Jobard, Crivello, & Tzourio-Mazoyer 2003; Mesulam 1998). Extensive damage to the inferior parietal lobule and the FG might interrupt the reorganization processes, and the top–down influences cannot reach the VWFA through the preserved long distance, U-shaped association fibers and activation by auditory words, whenever orthographic processing is required (Cohen et al. 2004a; O'Craven & Kanwisher 2000). In addition, she did not participate in any rehabilitation programs for alexia and agraphia, and therefore the chance for functional reorganization could be minimal.

In summary, our results of two patients with different types of alexia suggest that the recovery and improvement of the LBL reading skill in pure alexia after damage confined to the left ventral temporal cortex largely depends on the successful shift of the visual component of reading to the right homologue cortex and active participation in rehabilitation programs may facilitate the reorganization processes. However, extensive damage to the ventral temporal cortex together with the callosal reading pathways and higher reading center located in the inferior parietal lobule may lead to poor recovery from global alexia and the failure to reorganize the reading networks, including the FG.

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