Reproducibility of Hemispheric Language Dominance by Noun, Verb, Adjective and Adverb Generation Paradigms in Functional Magnetic Resonance Imaging of Normal Volunteers

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Purpose : We investigated the reproducibility of language lateralization by 4 different word generation paradigms or the rest contents in each paradigm using functional magnetic resonance imaging in normal volunteers

Materials and Methods : Nine normal volunteers with left-handedness (mean age: 25 yrs) were examined on a 1.5T MR unit using a single-shot gradient echo epibold sequence. Four different word generation paradigms of noun, verb, adjective and adverb were used in each normal volunteer for investigating language system. In each paradigm, two different rest contents consisted of only seeing the "+" symbol or reading the meaningless letters. Each task consisted of 96 phases including 3 activations and 6 rests of 2 different contents. Two activation maps in one task were obtained under two different rest contents using the correlation method. We evaluated the detection rates of Broca and Wernicke areas and the differences of language lateralization among four different word generation paradigms, or between the rest contents.

Results : The detection rates of Broca and Wernicke areas were over 67 % in 4 different language paradigms and there was no significant difference of them among language paradigms, or between two different rest contents. Language dominances, in all 4 different language paradigms, were shown to be consistent in 66 %, but were contrary with language paradigms in some subjects. The rest contents made no significant effect on dominant language dominance determination, but the success rates of the dominant language dominances determined from 4 language paradigms were higher in reading the meaningless letter (100 %, n=9) than in only seeing "+" on screen at the rest task (78 %, n=7).

Conclusion : High detection rates of Broca and Wernicke areas and high reproducibility of hemispheric language dominance in 4 different language paradigms showed functional MR imaging of our word generation paradigms was reliable and may be clinically useful. However, some inconsistency of hemispheric language dominance with language paradigms or the rest contents suggests that robust and reliable determination of language lateralization may need the performance of different paradigm types or the consideration of rest contents.

Index words: Functional magnetic resonance imaging, Language, Word generation paradigm, Hemispheric dominance

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Introduction

Many research groups have studied language system using functional MR imaging in neuroscience and neuroradiology (1-4). Especially, language lateralization determination using MR techniques has drawed the interest of many surgeons and radiologists in view of planning the neurosurgery treatment of the patients with epileptic foci or tumor to avoid the important cognitive areas related to motor or language system (5-7). Many literatures reported the successful results of functional MR imaging on language system and showed the possibility of its clinical usage (8-15). Functional MR imaging, however, was yet not used as a routine and clinical tool in broader medical fields and did not replace a conventional and invasive WADA test. That functional MR imaging of language system must be reliable and reproducible for determining hemispheric language dominance will be very critical to decide whether functional MR imaging can be used as a clinical routine tool.

MR system stability and task performance may be thought to be major factors to affect the reliability of Functional MR imaging. MR system stability is very important because very small signal intensity changes were induced temporally at the brain activation (16). The hardware-dependent system stability has been highly enhanced due to the development of modern electronic industry and had little technical problems in obtaining very stable images at many commercial MR systems. Therefore, task performance affected by relatively subjective factors such as the task contents and subjects' cognitive capabilities may be more important for the reliability of functional MR imaging. Because the subjects may have a variety of intellectual capabilities and can show different responses on the task due to different neurological behaviors with their physical or psychological conditions, their task performances can be different individually with task, especially for high order cognitive function such as language and memory. Task performance may determine whether functional map images are successful or not and change their patterns, from which hemispheric language dominance may be affected. Thus, if language dominance was determined from only one task, there may be much room for error in determining language dominance using functional MR imaging, which may be very large limitation for its clinical implementation. Currently, a variety of language paradigms such as word generation and word determination have been used and they activated Broca and Wernicke areas known as language center. However, few studies have been reported to compare a variety of paradigms in view of language lateralization and to evaluate its reproducibility (11-13, 15). In functional MR imaging, the regional difference of signal intensity between the rest and activation was used for map images, thus the rest contents can change the activation patterns and affect hemispheric language dominance in language tasks. Therefore, we investigated the detection efficiency of Broca and Wernicke areas with 4 different noun, verb, adjective and adverb word generation paradigms or rest contents in view of the clinical feasibility of our language paradigms and evaluated their reproducibility to test whether these word generation tasks or rest contents could show the same results in determining language lateralization by functional magnetic resonance imaging in normal volunteers.

Materials and Methods

Nine normal volunteers with left-handedness (man = 8, woman = 1, mean age = 25 years) were included in our experiments. Handedness was determined by Edinburgh handedness inventory. Consents of experiments from all volunteers were received. BOLD effect-based functional MR study was performed on a 1.5T MR unit (GE Horizon echospeed) using a single-shot gradient echo-epibold sequence (TR/TE/flip angle = 3000ms/50ms/90°, FOV = 240 mm, matrix = 64 × 64, slice thickness/gap = 6mm/0mm, 20 axial slices) provided by GE system. Whole brain was covered in our experiments. A flow-sensitive conventional gradient echo sequence (TR/TE/flip angle = 50ms/4ms/60°) was used for high-resolution anatomical images to cover the same brain region of epibold sequence. Additional 3D images were obtained using 3D gradient echo sequence (TR/TE/flip angle = 11ms/2ms/15°, FOV = 240 mm, matrix = 256 × 256, 124 slabs, nominal slice thickness = 1.5mm) for Talairach coordinate conversion. To minimize the gross head motion, neck-holders (MJ-200, USA) were used. The images were offline-reconstructed at workstation (SPARC 20, SUN Microsystems, Inc., USA) and transferred into Pentium III-PC. A series of MR images were obtained in axial planes. To exclude motion-

corrupted images, all MR images were surveyed in a movie procedure and evaluated using the estimation of center of mass of image signal intensities.

Four different word generation paradigms were used for each volunteer; noun, verb, adjective and adverb. Each volunteer was instructed to shout covertly the correspondent words such as noun, verb, adjective and adverb that could make incomplete and simple phrases or sentences meaningful. For example, in noun generation paradigm, if a phrase such as " red ( ) " was displayed on screen, volunteer covertly shouted a noun of "apple". Simple 8 phrases/sentences were presented at a rate of 1 per 3 seconds during each activation period of 24 seconds. Two different contents were applied for the rest in each language paradigm. One consisted of only seeing the "+" symbol (crosshairs rest) during 24 seconds and the other was to read the meaningless letters (pseudo-word rest) during the same duration. Each task consisted of 96 phases including 3 activations and 6 rests of two different rest contents (Fig. 1). All tasks were visual-guided by LCD projector (SHARP, Japan). Two activation map images were obtained with rest contents in each language paradigm by using the cross-correlation method (17). Reference data was defined as following our paradigm and processed with 4 seconds temporal delay and Gaussian convolution with a full width at half maximum of 4 seconds. For spatial normalization, Talairach coordinate conversion of map images along AC-PC line were performed (18). All mapping procedures were performed using homemade program on an IDL (Research Systems Inc., USA) platform. Language lateralization indices (LI) were defined as the ratio (L-R)/(L+R)*100, L being the number of activated pixels with p value under 0.000001 in the left hemisphere and R in the right hemisphere (9). Hemisphere contained all brain regions excluding cerebellum. We determined language dominance with the following levels; LI <-5 for right dominance, LI >5 for left dominance, $5>$LI>-5 for no dominance. Dominant language dominances were determined as being the largest dominance number from the results of 4 language paradigms in each subject. We evaluated the detection rates of Broca and Wernicke areas in our language paradigms and the differences of language lateralization among four different word generation paradigms, between the rest contents.

Results

The activation sites

All volunteers showed the EPI images free of the motion-artifact in both movie procedures and the evaluation of center of mass in signal intensity and provided successful functional map images. Most tasks activated Broca and temporal lobe including Wernicke area commonly, and the other activation sites of prefrontal lobe, premotor and motor areas, supplementary motor area, anterior cingulate, cerebellum, parietal lobe, and thalamus were found.

The detection rate of Broca and Wernicke areas with paradigms

The detection rates of Broca (Brodmann 44 and 45) and Wernicke (Brodmann 21) areas, tabulated in Table 1, were very high and showed no significant difference among 4 different language paradigms irrespective of the rest contents. Also, there was no significant differ-

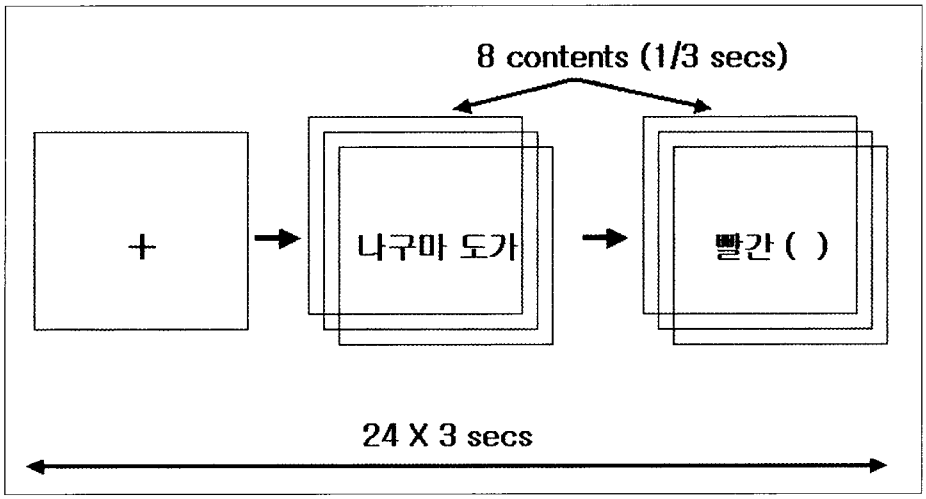

Fig. 1. Diagram of noun generation paradigm. Basic 3 conditions of the rest, the meaningless letter reading and noun generation were sequentially performed three times in one paradigm and each condition consists of 24 seconds. Eight different contents during each meaningless letter reading and noun generation period are shown at a rate of 1 per 3 seconds

ence in the detection rates of two sites between two different rest contents. In tasks of crosshairs rest, the detection rates of Broca and Wernicke areas ranged from 78% to 100%, and from 67% to 100%, respectively and, in tasks of pseudo-word rest, those of Broca and Wernicke areas were 89% and ranged from 67% to 100%, respectively. Through most language paradigms of two different rest contents, Broca and Wernicke areas were activated bilaterally than unilaterally and the detection rate of bilateral activation in Broca area decreased from crosshairs rest to pseudo-word rest. In Broca area, bilateral activation was 82% and 59% for

Table 1. The Detection Rates of Broca and Wernicke Areas in Word Generation Paradigms for Normal Volunteers (unit:%)

Broca	Language paradigm				Language paradigm			
	Crosshairs				Pseudo-word			
	noun	verb	adjective	adverb	noun	verb	adjective	adverb
bilateral	78 (n=7)	67 (n=6)	78 (n=7)	78 (n=7)	33 (n=3)	56 (n=5)	56 (n=5)	67 (n=6)
unilateral	22 (n=2)	11 (n=1)	11 (n=1)	22 (n=2)	56 (n=5)	33 (n=3)	33 (n=3)	22 (n=2)
no detection	0	22 (n=2)	11 (n=1)	0	11 (n=1)	11 (n=1)	11 (n=1)	11 (n=1)
Wernicke	Language paradigm				Language paradigm			
	Crosshairs				Pseudo-word			
	noun	verb	adjective	adverb	noun	verb	adjective	adverb
bilateral	45 (n=4)	56 (n=5)	56 (n=5)	67 (n=6)	45 (n=4)	45 (n=4)	67 (n=6)	56 (n=5)
unilateral	33 (n=3)	11 (n=1)	22 (n=2)	33 (n=3)	22 (n=2)	56 (n=5)	11 (n=1)	33 (n=3)
no detection	22 (n=2)	33 (n=3)	22 (n=2)	0	33 (n=3)	0	22 (n=2)	11 (n=1)

Crosshairs and pseudo-word denote the rest content is "+" and "to read the meaningless letters" respectively.

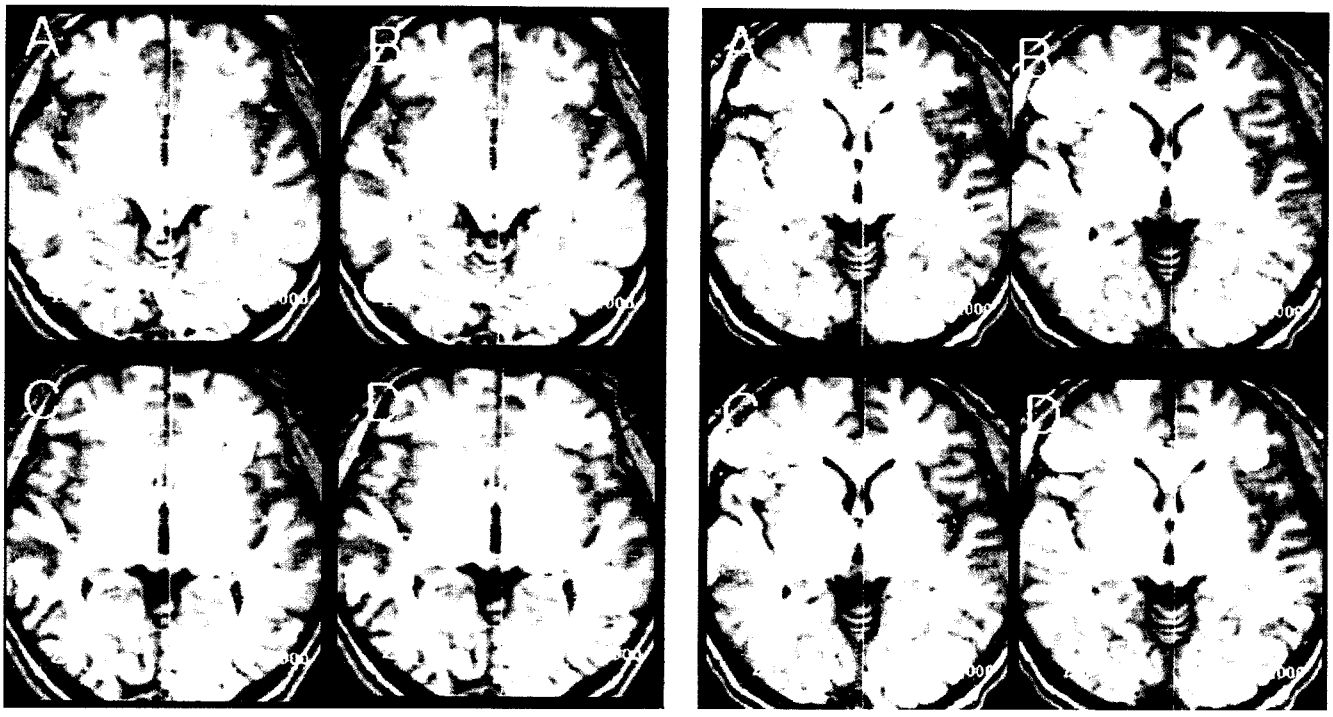

Fig. 2. Functional MR images of word generation paradigms in two normal volunteers with left-handed (A = noun, B = verb, C = adjective, D = adverb, $p < 0.000001$). Left: left Broca areas are dominantly activated in all language tasks and the activation of middle temporal lobes is bilaterally shown in noun, adjective and adverb generation tasks. Three language tasks except verb generation show left language dominance. Right: right Broca areas are dominantly activated in all language tasks, but left middle temporal lobe in only adverb generation task. All word generation tasks show the same right language lateralization.

crosshairs and pseudo-word rests, respectively. In Wernicke area, bilateral activation was 69% and 67% for crosshairs and pseudo-word rests, respectively. Only 4% of all 72 trials in all language tasks showed no detection of Broca and Wernicke areas.

Language lateralization

Table 2 showed language lateralization indices of normal volunteers for 4 different word generation tasks. The language dominances in all 4 different language tasks were consistent in 66% (n = 6) for both crosshairs and pseudo-word rests; right dominance = 3, left dominance = 3 for crosshairs rest, and right dominance = 2, left dominance = 4 for pseudo-word rest. In these cases, the rest content showed no difference in dominant language dominance. Some subjects (11% (n = 1) for crosshairs rest and 22% (n = 2) for pseudo-word rest) had the same and left language dominances in 3 of 4 tasks and there was no difference of dominant language dominance between two different rest contents. For crosshairs rest, one subject showed the same language dominances in half of 4 tasks and the other had no lateralization in 3 tasks. In the meanwhile, for pseudo-word rest, one subject revealed right dominant language dominance from the fact that noun and verb generation tasks showed right dominance, adjective generation represented left dominance and adverb generation gave no dominance. Word generation paradigms showing different language dominance in each subject were as follows; noun (n = 2), verb (n = 2), adjective (n = 1) and adverb (n = 1) tasks for crosshairs rest, and noun (n = 1), verb (n = 1), adjective (n = 1) and adverb (n = 3) tasks for pseudo-word rest. The success rates of the dominant language dominances determined from 4 language paradigms were 100% (n = 9) and 78% (n = 7) for crosshairs and pseudo-word rests, respectively (Table 3) and in some with dominant language dominances, there were no difference of them between two different rest contents.

Discussion

Our language paradigms could detect Broca and temporal areas including Wernicke areas at very high rates

Table 3. Dominant Language Lateralization determined from 4 different word generation paradigms

	Dominant language lateralization	
Subject	Crosshairs	Pseudo-word
1	N	L
2	R	R
3	L	L
4	L	L
5	L	L
6	R	R
7	N	L
8	R	R
9	L	L

Crosshairs and pseudo-word denote the rest content is "+" and "to read the meaningless letters" respectively.
N:no lateralization, L:left dominance, R:right dominance

Table 2. Language Lateralization Indices of Word Generation Paradigms in Normal Volunteers (unit:%)

Subject	Language paradigm				Language paradigm			
	Crosshairs				Pseudo-word			
	noun	verb	adjective	adverb	noun	verb	adjective	adverb
1	-10.8	-1.76	0.13	1.39	36.5	6.57	12.9	16.9
2	-27.0	-30.1	-35.3	-12.3	-26.4	-31.2	-44.2	-31.6
3	49.9	33.9	13.0	46.9	17.9	29.5	25.3	22.3
4	17.3	-7.95	12.1	10.9	26.9	33.8	6.22	3.96
5	7.55	17.05	32.1	37.0	22.1	12.5	37.8	29.3
6	-31.6	-19.7	-20.9	-37.9	-5.2	-38.5	-18.2	-13.4
7	-11.3	-11.7	6.2	22.5	6.8	7.6	18.4	35.3
8	-24.1	-18.9	-13.2	-5.9	-15.7	-9.15	24.1	1.92
9	18.4	50.0	54.0	66.0	49.0	36.8	57.0	-2.69

Crosshairs and pseudo-word denote the rest content is "+" and "to read the meaningless letters" respectively.
Positive values means strong left dominance and negative values means strong right dominance.
Language lateralization indices (LI) were defined as the ratio (L-R)/(L+R)*100, L being the number of activated pixels with p value under 0.000001 in the left hemisphere and R in the right hemisphere.

irrespective of the rest contents. Since Peterson (19) firstly reported the functional imaging of language system using word generation paradigm on PET system, many language paradigms has been designed and applied in neuroscience or clinical fields using imaging modalities of PET and MR units. A variety of word generation included noun and verb generation from incomplete sentence or phrases, verb generation associated with a specific noun, picture-naming, cued word generation, categorical word generation. From these paradigms, broader areas of frontal and temporal lobes including Broca and Wernicke areas has been reported to be involved with language system and many other activation sites like cerebellum, premotor cortex, supplementary motor area, anterior cingulate were found in many literatures (20-22). Many activation sites illustrated above were shown in our data. Because Broca and Wernicke areas have been historically known as language centers, high detection of Broca and Wernicke areas shows our language paradigms can be useful for studying language systems. Also, our study showed the rest contents made little effect on the detection rate of Broca and Wernicke areas. The meaningless letter reading is associated with both orthographical and phonological processes related to the identification of letters and their articulation. Therefore, our finding demonstrated orthographical and phonological processes might have little relationship with Broca and Wernicke areas. Our dominant bilateral activation in Broca and Wernicke areas represented both sides of them would share a portion of language processes although relatively dominant sides existed. In Broca area, decrease of bilateral activation from crosshairs to pseudo-word rests shows other language processes, related to Broca, but not orthographical and phonological processes, may have increased functional asymmetry.

The high consistency in language dominance between paradigms represents the high feasibility of functional MR imaging for reliable language dominance determination. The feasibility of functional MR imaging for determining language dominance and high correlation with WADA test was demonstrated in clinical studies (12-15). Although our data could not be compared with WADA test due to normal volunteers, high consistency of language dominance through 4 different word generation paradigms reveals there is the clinical potentiality of functional MR imaging for determining hemispheric language dominance. In fact, our word generation paradigms can be assumed to make nearly similar activation patterns due to similar sentence structures if it were not for specific language process related with word type of noun, verb, adjective and adverb. Therefore, high reproducibility of language dominance in 4 different language paradigms can be expected in our study if all experimental conditions were set to be good. Most subjects showed these assumptions came true in our results, but language paradigms in some subjects showed contradictory results for each other. Although the sources of these inconsistencies among language paradigms were unknown, our study showed different language dominances with language paradigms could exist, as shown in other literature. This finding suggests only one specific paradigm may make error in language dominance determination and several language paradigms are needed for its reliability and robustness. In addition, more evaluation on the precision of language dominance about each paradigm will be made through comparative study on patients with WADA test.

The different rest contents in the same activation paradigm can change the activation patterns because functional MR imaging used the difference of image intensities between the activation and rest periods. Less activation sites were detected in pseudo-word rest than in crosshairs rest for most subjects, which may be explained by the fact that orthographical components involved with the identification of letters could be eliminated in pseudo-word rest. Although our results showed the rest contents might make little effect on language dominance and the detection rates of Broca and Wernicke areas, pseudo-word rest was shown to induce the activation asymmetry of Broca and Wernicke areas, to say, from bilateral to unilateral. Also, the success rates of language dominance determination were a little higher in pseudo-word rest than in crosshairs rest. Because there was no gold standard for language lateralization in normal volunteers who did not undergo a WADA test, its accuracy with rest contents could not be known. However, the increase in the activation asymmetry of Broca and Wernicke areas, and higher success rates of language dominance determination in pseudo-word rest represented the usage of the meaningless letter reading as the rest content might provide larger possibility for a clinical tool as determining language lateralization.

Many reports (23-25) showed relationship of language system with handedness and different activation patterns or language lateralization for subjects with left-handedness from ones with right-handedness in functional MRI. Also, left-handedness was known to be more heterogeneous in language system compared with right-handedness. These facts may affect a variety of results shown in our word generation paradigms and induce lateralization inconsistency among word generation paradigms. Because our study examined only subjects with left-handedness, further study on right-handedness will be necessary.

We have some technical limitations in measuring lateralization indices. What the threshold of p value for the activation sites to be meaningful is and how we selected the region of interest where lateralization indices were measured may be the most critical. Currently, optimal thresholds of p value were not known for reflecting whole language systems precisely and they were used as determined by each research group. Although the threshold of p values could change the values of lateralization indices, these might make no effect on language dominance determination in our study. However, as their values were higher, it has been known that artifacts related to noises can be reduced and the possibility for measuring lateralization indices more precisely may be higher. Therefore, high thresholds in p value (=0.000001 in our study) were preferable for language lateralization determination. We used the hemispheric measurement in lateralization index. Although Broca and Wernicke areas has been known as language centers classically, recent researches showed many other important sites of frontal lobe, temporal lobe and cerebellum were involved with complex language networks (20-22). Therefore, hemispheric measurement including these sites will be thought to be reasonable and can reflect language system more exactly. However, Lehericy (26) reported functional MRI lateralization in the frontal but not in the temporal lobes were well correlated with the WADA test. More evaluation on the selection of the measurement areas for increasing the reliability and precision of language lateralization will be necessary.

Conclusions

High detection rates of Broca and Wernicke areas shown in our study suggest noun, verb, adjective and adverb generation paradigms may be feasible for evaluating language system. In addition, although there were the intra-subject differences of lateralization indices among different language paradigms, the consistent determination of language dominance from 4 different language paradigms in most volunteers showed our word generation paradigms might be useful in clinical application. However, inconsistent language dominance among different paradigms or between the rest contents in some volunteers suggests that different paradigm types or the rest contents must be considered carefully for robust and reliable determination of language lateralization.

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정상성인의 뇌기능적 자기공명영상에서 명사, 동사, 형용사 그리고 부사 만들기 과제들에 대한 언어영역편재화의 재현성에 관한 연구

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송인찬[1,3] · 장기현[1,3] · 정천기[2] · 이상현[1] · 한문희[1,3]

목적: 본 연구는 정상 성인을 대상으로 기능적 자기공명기법을 사용하여 4개의 다른 언어생성과제들에 의한 언어영역 편재화의 재현성 여부와 각 언어생성과제에서의 휴지기의 내용이 미치는 언어영역편재화의 영향을 평가하고자 하였다.
방법 및 대상: 9명의 왼손잡이 정상 성인 (평균연령 25세)을 대상으로 gradient-echo epibold 기법을 사용하여 기능적 자기공명영상을 얻었다. 언어생성과제로서 명사, 동사, 형용사, 부사 만들기 과제를 사용하였다. 각 과제는 휴지기의 두가지의 내용 (화면상의 "+" 기호를 단지 응시하는 것과 의미 없는 문자를 읽는 것)을 포함한 6번의 휴지기와 3번의 활성기로 되어 있고 총 96 번의 반복 영상 촬영을 하였다. 한 과제 당 휴지기의 내용에 따른 두가지 기능적영상을 상관계수방법을 사용하여 얻었다. 언어생성과제 종류와 각 과제의 휴지기의 내용에 따른 Broca 와 Wernicke 영역의 관찰율과 언어영역의 편재화에 대한 영향을 평가하였다.
결과: 4가지의 언어생성과제들은 모두 높은 Broca 와 Wernicke 영역의 관찰율 (67% 이상)을 보였고 언어생성과제 종류와 휴지기의 내용에 따른 이들의 의미 있는 차이는 없었다. 4가지 언어생성과제에서 모두 일치된 언어영역 편재화 결과를 66% 의 피험자에서 보였지만 일부 피험자들은 일부 언어생성과제에서 상반된 언어영역 편재화 결과를 보여주었다. 4개의 언어생성과제로부터 결정된 주된 언어영역 편재화의 일치율은 휴지기 내용에 따라 의미 있는 차이가 없었다. 그러나, 휴지기의 내용 중 의미 없는 글자를 읽은 것 (100%, n=9)이 화면상 "+" 를 응시하는 것 (78%, n=7)에 비해 더 높은 언어영역 편재화 성공률을 보여 주었다.
결론: 높은 Broca 와 Wernicke 영역의 관찰율과 비교적 높은 언어생성과제간의 일치된 언어영역 편재화 결과들은 본 언어생성과제를 사용한 기능적영상기법이 임상적으로 유용할 수 있다는 것을 보여 주고 있다. 그러나, 일부의 언어생성과제간과 휴지기 내용에 따른 불일치된 언어영역 편재화는 견고하고 신뢰성 있는 결과를 위해서는 여러 언어생성과제의 수행과 휴지기 내용에 대한 고려 등이 필요하다고 생각된다.

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