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Reproducibility Between two physicians of fMRI study on the Brain Activity Induced by Acupuncture (at BL62)

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Abstract

목적 : 신맥 혈위 자극이 뇌활성화 변화에 미치는 영향에 있어 자침 시술자간의 재현성을 fMRI 영상을 통해 평가하고자 하였다.

방법 : 본 연구는 건강한 성인 남자 15명을 대상으로 실시하였으며, 15명의 피험자 중 7명은 각각 2회 방문하였으며, 두 시술자에 의해 침을 맞고 총 4개의 데이터를 얻었다. 나머지 8명은 1회 방문하여 두 시술자에게 침을 맞아 2개씩의 데이터를 얻어 총 44개의 fMRI 데이터를 얻었다. 실험자간의 차이를 줄이기 위해 자침의 깊이와 회전, 강도 등을 동일하게 하였으며, 우측 신맥혈에 자침하였다. 침에 의해 활성화되는 영역을 확인하기 위해 블록디자인을 사용하여 fMRI를 촬영하였다.

결과 : 다른 날에 실시한 같은 시술자내의 재현성은 24 %, 같은 날 실시한 다른 시술자간의 재현성은 64 % 로, 다른 시술자간의 재현성이 서로 다른 날 실시한 같은 시술자내의 재현성보다 높게 나타났다.

결론 : 침을 이용한 fMRI의 실험에서 시술자에 의한 차이 외에도 실험하는 날짜의 차이, 피험자 인체의 생리적인 변화 등에 의한 차이가 크다는 것을 본 실험을 통하여 확인하였다. 그리고 자침의 깊이와 회전, 자극의강도 등을 동일하게 함으로써 다른 시술자간의 재현성을 높일 수 있다는 것을 확인했다. 추후 침실험에 있어서 여러 변수들에 의한 차이를 극복하고 재현성을 높일 수 있는 방법에 관한 더욱 심도 있는 연구가 필요하다.

Key words : fMRI, acupuncture, BL62, reproducibility.

Ⅰ. Introduction

Recently many people have became interested in acupuncture, and many studies using fMRI are being carried out to investigate its neurobiological mechanism and efficacy[2,4,5,7,11,13,15,19,23-27]. Some have reported that acupuncture can stimulate the central nervous system and have an effect on a specific area[22]. The fact that fMRIstudies have discovered that acupuncture induces the activity of specific area of the brain shows that acupuncture can modulate nerve function[1,6,14,20]. Even though these

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acupuncture studies using fMRI have lots of merits, the results have some problems about reproducibility and reliability. These studies are affected by physician, subjects, acupoint, kind of acupuncture, stimulus type and retention of acupuncture etc., so it is difficult to get a reproducible and reliable correlation between brain activity and specific acupoints. For example, Siedentopf et al.[17] reported that laser acupuncture activated the visual cortex of brain but Gareus et al.[3] could not confirm this finding. And Jian Kong et al.[8] reported that fMRI signal changes induced by electroacupuncture were more variable than those from the control finger tapping task. Through these studies we thought that reproducibility problem should be solved first.

So we investigated how to improve the reproducibility of acupuncture fMRI studies. Among the variable factors, we focused on physicians and scanning sessions.First, the interphysician reproducibility was measured using two physicians. In the test two physicians(P1, P2) performed acupuncture one after the other in the same fMRI scanningsession. In the Retest about 1 month later, the same physicians(P1, P2) administered acupuncture treatment and brain activities of test and retest of same physician (intraphysician) were also compared. For reducing variances between physicians, we set up a depth of insertion and rotation.

II. Materials and Method

1. Subject

This study was carried out on 15 healthy right-handed subjects. The subjects were all Korean men between the ages of 20 and 30. The local ethics committee of Kyung Hee University approved this study. All subjects met the guidelines for MRI imaging issued by Korean Advanced Institute of Science and Technology(KAIST). No subjects had head trauma, consciousness failure, or other illnesses. Some subjects were familiar with acupuncture.

Table 1. Baseline characteristics and acupuncture response results of participants in this study

Subject	Sex	Age	Smoke	Test		Retest	
				Deqi	Pain	Deqi	Pain
S1	M	23	Y	Y	Y	N	Y
S2	M	29	N	N	Y	Y	Y
S3	M	24	N	N	Y(P1)		
S4	M	23	N	Y(P2)	Y(P1)		
S5	M	24	N	Y	Y(P1)	Y	Y
S6	M	32	N	N	Y	Y	Y
S7	M	23	N	Y(P2)	Y	N	Y
S8	M	25	N	N	Y(P2)	N	Y(P1)
S9	M	25	N	Y(P1)	Y(P2)	Y(P2)	Y(P1)
S10	M	26	N	Y	N		
S11	M	23	N	Y(P2)	Y(P1)		
S12	M	22	N	Y(P1)	Y		
S13	M	26	N	Y	N		
S14	M	20	N	N	Y		
S15	M	22	Y	Y(P1)	Y		

S : Subject. P : Physician. Smoke : history of experience, Y=yes, N=no

All subjects signed the informed consent. The subjects were instructed on the rules for fMRI imaging and on the experimental procedure, including acupuncture. They were also told that in three separate, randomly selected sessions, their brain would be scanned to measure the response to acupuncture stimulation.

2. Acupoint-BL62(Right)

The acupoint selected for the experiment wasright BL62. BL62 is located on the lateral aspect of foot, directly inferiorto the prominence of the lateral malleolus, in the depresstion between the inferior border of the lateral malleolus and the calcaneus. This is the starting point of the Yang heel meridian and is related to movement, sleep and arousal.

Fig. 1. The location of BL62

3. Needling and acupuncture

An acupuncture needle was inserted into the acupoint specified by a circle(2 ㎜ diameter) pre-marked on the skin of participants. Disposable needles were used(30 ㎜ long × 0.25 ㎜ diameter, needle grip 20 ㎜ long, stainless material, Dongbang Co, Seoul, Korea). On BL62 a needle was inserted to a depth of 10 ㎜ by two physicians. To reduce the physician variability, needle's depth and rotation were fixed using an acupuncture tube.

4. Design

We employed a block design method, with each session lasting total of 4min 12 seconds. Acupuncture was performed at BL62 on the right foot(red arrowhead). A dummy scan was carried out for 12 seconds before the experiment. After remaining at rest for 60 seconds, the acupuncture needle was inserted and rotated bidirectionally at the rate of 2 Hz for 30 seconds and then was removed immediately. After a rest period of 60 seconds, acupuncture manipulation was repeated in the same manner and another 60 second rest period followed. During the test, two physicians(P1,P2) performed acupuncture on each subject in the same scanning session, the order of physicians

was randomized. There was a 3-5minute intermission between each session. Through this we investigated theinterphysician reproducibility. Subjects did not know which doctor was performing acupuncture.

About one month later acupuncture administration was performed by the same physicians(P1,P2) and same manner, and brain activities were scanned to investigate the intraphysician's reproducibility. To reduce variances between physicians, we set up a depth of insertion, and rotation.

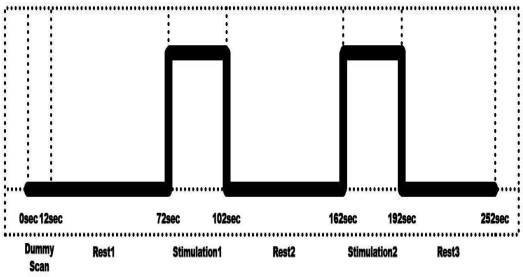


Fig. 2. Protocol of an acupuncture study and the location of BL62

- During 12sec: to MRI's signal stability dummy scan
- R1 : During 60sec, no acupuncture and carry out MRI scan
- S1 : During 30sec, BL62 needling, rotation 2Hz
- R2 : Pull out needle and MRI scan during 60 sec without stimulation
- S2 : During 30sec, same stimulation repeat
- R3 : Pull out needle and MRI scan during 60 sec without stimulation

5. Data acquirement

Images were acquired with a three-tesla MRI scanner(ISOL Tech, Kyunggido, Korea) that allows the researchers to perform echo planar imaging(EPI). BOLD functional imaging was obtained using a gradient echo T2 * weighted pulse sequence(TE = 25 ms, TR = 3000 ms, 180 images per slice, matrix = 64 × 64, field of view[FOV] = 220 ㎜, flip angle=90 degrees). The volume number was 30 and each slice was 4 ㎜ thick without a gap(voxel size 3.43 × 3.43 × 4 ㎜). Four dummy scans were collected to allow the equilibration of the MRI signal T1(TE = 16 ms, TR = 2800 ms, flip angle = 60 degrees, FOV = 192 ㎜, slice thickness = 5 ㎜) and 3D-T1(TE = 5.7 ms, TR = 10 ms, flip angle = 10 degrees)weighted images were also collected with high resolution.

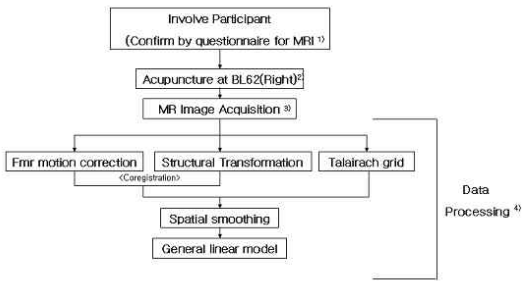


Fig. 3. The flow chart of the current study.

1. Questionnaire for MRI was the form from fMRI Laboratory of Brain Science Research Center, Korea Advanced Institute of Science and Technology.
2. Acupuncture at BL62(Right) was performed by a Korean medical doctor (the specialist on the department of meridian & acupoint with a 5-year career).
3. fMRI lab operator belonged to the fMRI Laboratory of Brain Science Research Center, Korea Advanced Institute of Science and Technology. MR image was acquired for one or two days.
4. Data processing was carried out by using BrainVoyager2000(R. Goeble and Max Planck Society, Brain Innovation B.V.).

6. Data analysis

The data analysis program used wasBrain Voyager 2000(R. Goeble and Max Planck Society, Brain Innovation B.V., Maastricht, Netherlands). To correct for the subject's motion, MR images were realigned using a 3-D motion correction program. Anthropotomy MR images wereconverted to normalized space coordinates. After coregistration of the anthropotomy MR images before normalization with functional MR image, functional MR images were converted to co-coordinates. The data form was 64 × 64 flat resolution and latticed 5mm thickness. Full Within Half Maximum(FWHM) value was converted to non-lattice through spatial smoothing, using a Gaussian filter. BOLD signal by GLM method sorting significantly active region was analyzed. The mean Image data was taken for group analysis and was analyzed by GLM method.

7. Reproducibility

The procedure[16] to measure reproducibility has been used to investigate reproducibility of fMRI. 15 test data results and 7 retest data results were analyzed with this method. The anterior ROI region which includes the frontal lobe activated from the test and the posterior ROI region which includes the parietal lobe and occipital lobe activated from the retest were analyzed. Comparison of the changing personal signal intensity ratios measures were assessed with Wilcoxon test, excluding those areas that exceeded the corrected p-value 0.005.

- $R^{ij}_{overlap} = 2 * V^{ij}_{overlap} / V^i + V^j$
- $R^{ij}_{size} = 2 * V_{smallest} / V^i + V^j$

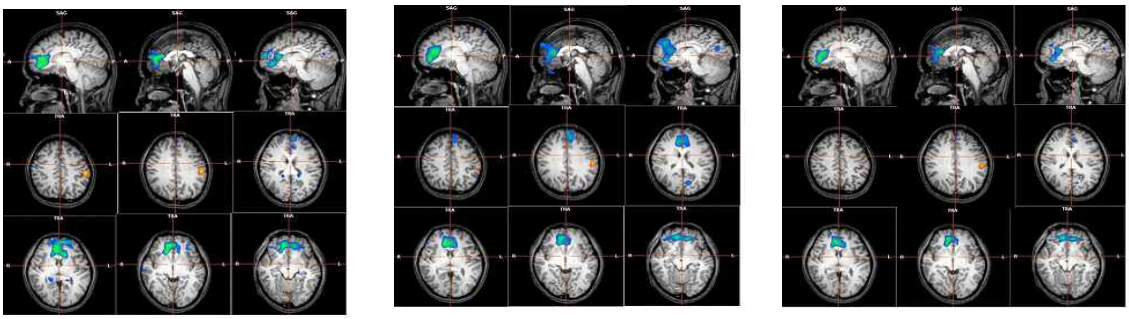
* V^i = activated region's volume at i

* V^j = activated region's volume at j

* $V^{ij}_{overlap}$ = activated region's initial volume

* $V_{smallest}$ = smaller volume between the two

III. Result



9 person's mean of P1 | 9 person's mean of P2 | Common region of P1, P2

Fig. 4. Averaged group activation and deactivation areas responding to acupuncture from fifteen subjects (Test)

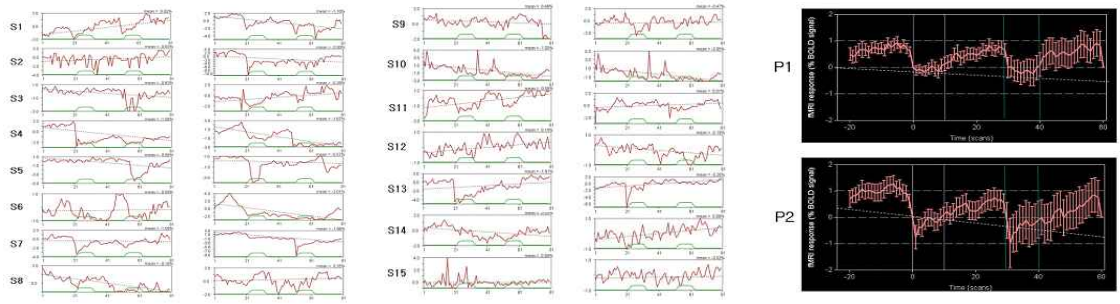
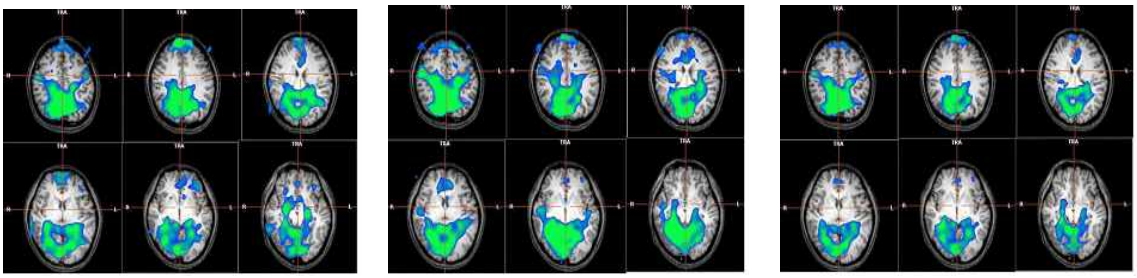


Fig. 5. Signal Intensity at anterior ROI (Test)

In the test, brain activity declined near the left gyrus frontalis superior(BA9), frontalis medialis(BA9), right frontalis medialis(BA10,11), and precentral gyrus(BA6) at the cerebral cortex frontal lobe. Brain activity also declined in Cuneus(BA18) at occipital lobe. However the brain was activated in the left parietal lobe postcentral gyrus(BA2).

At anterior ROI, the individual signal intensity means of the 15 subjects showed deactivation in response to acupuncture treatment.



9 person's mean of P1 | 9 person's mean of P2 | Common region of P1, P2

Fig. 6. Averaged group activation and deactivation areas responding to acupuncture from fifteen subjects (Retest)

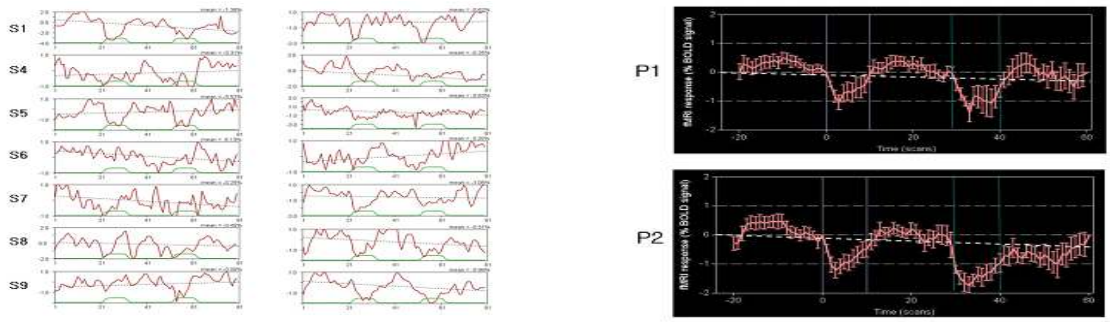


Fig. 7. Signal Intensity at posterior ROI (Retest)

In the retest, brain activity declined in both sides of the superior frontal gyrus(BA10), frontalis medialis(BA9), right superior frontal gyrus(BA6), middle frontal gyrus(BA6) at the cerebral cortex frontal lobe. Brain activity was also deactivated near theleft postcentral gyrus(BA3), precuneus(BA31) and superior temporal gyrus(BA22, 42) at the temporal lobe and toward the right in the superior frontal gyrus(BA8) at the parietal lobe. Brain activity was deactivated near both sides in the precuneus(BA31) and cuneus(BA18) at occipital lobe, As well as in the midbrain, pons at the brain stem. Brain activity also appeared towards both sides in declive, lingual, dentate and tonsil of cerebellum at cerebellum.

At posterior ROI, individual signal intensity means of the 7 out of 15 subjects showed deactivation in response to acupuncture treatment.

1) Reproducibility of Interphysicians

The 15 subjects' mean and signal change of anterior ROI Signal intensity from the test and the 7 subjects' mean and change of posterior ROI signal intensity from the retest are Table 2 and Table 3. Respectively there was not a significant intraphysician difference between signal changes ($p>0.05$). Using "$R^{ij}_{overlap} = 2 * V^{ij}_{overlap} / (V^i+V^j)$", the 7 subjects' test and retest results of interphysician reproducibility are 44.80% and 83.79% in Table 4. Interphysician reproducibility in the retest is higher than in the test. The mean is 64%.

Table 2. Singnal change and mean of signal intensity of Anterior region of interest(ROI) by acupuncture from fifteen subjects in Test

Physician	Subject	Signal change(%)	Mean	Physician	Subject	Singnal change(%)	Mean
	S1	0.03	4473		S1	-1.16	4178
	S2	-0.63	2059		S2	-3.93	1986
	S3	-0.63	4256		S3	-0.38	3947
	S4	-1.86	3909		S4	-1.67	3041
	S5	-0.95	4598		S5	-0.57	4684
	S6	-0.59	4497		S6	-2.01	4106
	S7	-1.09	2513		S7	-1.96	2676
P1	S8	-0.16	3947	P2	S8	0.35	4188
	S9	0.46	2658		S9	-0.47	2879
	S10	-1.00	3592		S10	-0.95	3667
	S11	-0.56	2518		S11	0.01	2423
	S12	0.14	3623		S12	-0.19	3444
	S13	-1.61	2543		S13	-0.26	2623
	S14	-0.50	3017		S14	0.08	3083
	S15	0.04	3764		S15	-0.02	3830

There was not significantly different between two physicians($p>0.05$).

Table 3. Singnal change and mean of signal intensity of Posterior ROI by acupuncture from seven subjects in Retest

Physician	Subject	Signal change(%)	Mean	Physician	Subject	Singnal change(%)	Mean
	S1	-0.62	7140		S1	-1.38	6841
	S4	-0.31	7893		S4	-0.35	6744
	S5	-0.57	6480		S5	-0.63	5934
P1	S6	0.13	7495	P2	S6	0.20	6010
	S7	-0.25	6793		S7	-1.06	7369
	S8	-0.45	7500		S8	-0.51	7610
	S9	-0.09	6266		S9	-0.96	6853

There was not significantly different between two physicians($p>0.05$).

Table 4. Reproducibility of interphysicians and intraphysicians

	Reproducibility P1 and P2 in Test(%)[1]		Reproducibility P1 and P2 in Retest(%)[2]		Reproducibility Test and Retest in P1(%)		Reproducibility Test and Retest in P2(%)	
	R^{ab}_{size}	$R^{ab}_{overlap}$	R^{cd}_{size}	$R^{cd}_{overlap}$	R^{ac}_{size}	$R^{ac}_{overlap}$	R^{bd}_{size}	$R^{bd}_{overlap}$
Whole brain	58.19	44.80	91.73	83.79	20.91	17.99	58.68	31.49
Selected ROI	50.01	38.80	86.00	85.92				

a = P1_Test, b = P2_Test, c = P1_Retest, d = P2_Retest

1) ROI : Region of Anterior lobe

2) ROI : Region of Parietal lobe and Occipital lobe

2) Reproducibility of Intraphysician

Using "$R^{ij}_{overlap} = 2 * V^{ij}_{overlap} / (V^i+V^j)$", intraphysicianreproducibility compared with test and retest was examined. Intraphysician's reproducibility is in Table 4. P1 and P2 reproducibility are 17.99% and 31.49% respectively.

IV. Discussion

Machielsen[21] reported 61.7% reproducibility in the same scanning session and 50.7% reproducibility between several days of fMRI study using novel color pictures. Rombouts[16] reported 74% reproducibility between subjects of visual brain activation. Our study is not for a specific task, so it is more like the former. Therefore, interphysician reproducibility 64% is a considerable result. That the interphysician reproducibility is higher than the intraphysician reproducibility means that controlling the physician's variability can improve the interphysician reproducibility. However, the intraphysician reproducibility 24% was not very high. In the test, the two physicians deactivated the frontal lobe(Fig. 4.) and in the retest deactivated the parietal and occipital lobes (Fig. 5.). Because the measurement term of interphysician was just 3-5 minutes, but the measurement term between test and retest was 15-45 days. The longer interval may have allowed more changes to the subjects'physiological state, resulting in a lower reproducibility. Since Machielsen[21] reported a reproducibility of 50.7%, the intraphysician reproducibility can be improved from 24%. Jian Kong et al.[8] also reported that relatively large variability across different sessions within the same subjects, so multiple sessions should be used to accurately capture the activation. In acupuncture studies, the subject's physical state can affect the efficacy of acupuncture and alter the brain activity[9]. The subject's habituation of receiving the acupuncture can also influence the result[10]. Therefore, a physical baseline standard to control the subject's state is required, and research methodology for physicians is needed.

Reproducibility of acupuncture-induced brain activity in fMRI studies should be established and variable factors caused by physicians and subjects should be controlled during the experiment. A simple and reliable method of acupuncture administration also should be determined. To improve reliability and reproducibility, many acupuncture fMRI studies will be needed continuously.

V. Conclusion

1. The mean intra-physician reproducibility was 64%. When the right BL62 was stimulated by two physicians, the brain deactivation of the anterior lobe was significantly reproduced. On the retest of this BL62 stimulation, there was

a significant reproducibility of brain deactivation in the parietal lobe and the posterior lobe.

2. The low reproducibility deduced from the same physician was because the difficulty in controlling the variable produced by the subject. As the result of acupuncture is affected by the patient's condition, the subject's biological state also affects the brain activity. Therefore, for more in depth research using the fMRI, there is need to control the variation induced by the condition of the subject to enhance the reproducibility of the Test and Retest results from the same physician.

Acknowledgement

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