The Role of SMA for motor control in Patients with Cerebral palsy : A Functional MRI Study

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The Role of SMA for motor control in Patients with Cerebral palsy : A Functional MRI Study

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The Master's Thesis
Submitted to the Department of Medicial Science
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree of
Master of Medical Science

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June 2008

This certifies that the Mater's Thesis
of Seo Byung Sik was approved.

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June 2008

Acknowledgement

“우리가 알거니와 하나님을 사랑하는 자 곧 그의 뜻대로 부르심을 입은 자들에게는 모든 것이 합력하여 선을 이루느니라 (로마서 8:28)”

논문을 다 작성하고, 마지막 이 글을 쓸 때에, 제 머리 속에서 파노라마처럼 지난 2 년 반 동안의 시간에 대한 기억이 떠오릅니다. 학부 때 읽은 *Brave the Brain* 이란 책을 읽고서 신경영상을 공부하겠다고 다짐한 그 시절이 어느덧 지나 이제는 이 보잘것 없는 작은 열매를 가지고 나아가려고 하니 한편에서는 후련함이, 다른 한편에서는 아쉬움이 남습니다.

이 작은 결과를 위해 끊임없이 지지해주시고 지도해주신 박해정 교수님께 가슴깊은 감사를 드립니다. 처음 연세대 땅에 와서 많은 부분 헤메이고 부딪칠때에 끊임없는 인내로 지지해주셔서 이러한 결과를 낼 수 있었다고 생각합니다. 또한 이 논문을 위해 많은 부분을 지지해주신 이종두 교수님께도 감사를 드립니다. 뇌성마비라는 아직 완치가 불가능한 질환에 대해 끊임 없이 연구하시는 교수님의 모습에 저 또한 많은 부분에서 존경하지 않을 수 없었습니다. 후에 교수님의 연구가, 뇌성마비에 대한 새로운 지평을 열어가는 큰 발돋움이 되기를 소망합니다. 아울러 이 부족한 논문을 들고 찾아갔을 때 반겨주신 김흥동 교수님께도 감사드립니다. 이 세분의 교수님이 아니셨다면, 지금의 제 모습은 없었을 것이라고 생각합니다. 또한 많은 부분 강의를 통해 도움을 주신 해부학과 이종은 교수님과 약리학과 김동구, 김철훈교수님께도 감사를 드립니다.

또한 같이 2 년 반 동안 같이 생활한 MONET 연구실 동료 분들께도 깊은 감사를 드립니다. 특별히 영상에서부터 삶의 지혜까지 끊임없이 가르쳐주시고 저를 세워주신 오맹근 선생님께 먼저 감사드립니다. 선생님을 통해서 귀하고

값진 지혜와 영상에 대한 지식을 배우게 되어 큰 보람을 느낍니다. 그리고 쉼 없이 연구에 매진하시는 민병경, 김대진 박사님께도 두분의 연구에 큰 성과와 좋은 결과가 항상 함께하기를 소원합니다. 또한 같이 연구과정을 밟는 동안에 많이 도와준 우리 동료들 - 박범희, 전지원, 김중일, 이동하, 박성용 선생님들도 학위 과정 동안 큰 학문적 진전이 있기를 바랍니다. 그리고 지금은 이 자리에 없지만, 항상 인터넷과 기타 다른 부분으로 많이 도와준 저의 진실한 동료이자 친구인 임준혁, 이태선 선생님의 앞날에도 좋은 열매만 맺기를 소망합니다. 또한 이 결과를 내는데 너무나도 많은 부분 수고하시고 도와주신 영상의학과 MRI 파트 방사선사 선생님들과 핵의학과 선생님들께도 깊은 감사를 전합니다.

이 외에도 저의 2 년 반동안의 짧은 삶에서 깊은 영향을 주신 많은 분들이 계십니다. 특별히 저의 영적 안식처인 서울유니온 교회와 프린스찰스 목사님께 감사를 드립니다 (I express my gratitude to Seoul Union Church, my spiritual resting place and Rev. Prince Charles). 또한 지속적으로 저를 위해 기도해주시고 많은 부분 저를 도와주시는 신앙의 선배 박춘삼 목사님과 가족분들, 그리고 주섬김교회에도 깊은 감사를 드립니다. 또한 저의 모교인 서강대에서도 많은 부분 지혜와 도움을 주신 영문학과 이성범, 조숙환 교수님과 생명과학과 김정호 교수님, 심리학과 조긍호 교수님, 그리고 경영학과 전준수 교수님께도 깊은 감사의 뜻을 전해 드립니다. 또한 언제나 저를 웃게 해주고 삶의 많은 부분에서 즐거움과 기쁨을 누릴 수 있게 해준 서울유니온 교회친구들 - Autumn Hulke, Kimberly Scholma, Helen Kibby, Dolee Han, Seok Won Hyun, Hannah Kroon, Sarah Easton, Michael Clark, Jihye & Jisu Seo, Dustin & Rebecca Woodson (Dusty and Rebs ㅋ) - 에도 깊은 감사를 전합니다 (I'm thankful to all my friends in Seoul Church. You guys are my great happiness!). 또한, 삶의 나눔을 통해 서로를 지지하고 즐거움을 나눌 수 있게 해준

서강대학교 친구들, 그리고 연세대학교 죠이선교회 친구들 및 동문들께도 감사를 드립니다.

무엇보다도, 저의 연구에 대해 큰 도움을 주신 분들은 저의 가족들입니다. 어떠한 상황에서도 항상 지지해주신 가족들 앞에서는 너무나도 이 결과가 작아보입니다. 그래도 항상 저와 같이해준 가족들께 감사의 뜻을 전합니다.

마지막으로 이 논문을 통한 모든 영광을 하나님께 올립니다. 저의 모든 삶의 작은 부분까지 인도하시고 저의 방패와 구원자가 되셨습니다. 그리고 어떠한 어려움에서도 "내가 너와 함께하겠다" (이사야 41:10) 라는 말씀을 통해서 2 년 반의 기간을 잘 해내어 갈 수 있도록 해 주셨습니다. 수많은 말들과 언어를 이용한다고 해도 하나님에 대한 저의 감사는 표현할 수 없습니다. 다만 이 작은 문장으로서 저의 마음을 담아 표현합니다

"Soli Deo Gloria"

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Abstract

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Cerebral Palsy (CP) was one of the major neurological disorders in infants due to brain damage during the delivery. The damage results in movement disorder including spasticity and rigidity. Among the various regions for movement control, supplementary motor area (SMA) played an important role in movement inhibition. Using functional magnetic resonance imaging (fMRI), we studied the differences in the brain activation of SMA between the patients with CP and healthy controls. As a result, we found significant difference in activation on SMA (BA 6) and anterior cingulated cortex (ACC; BA 32). These areas also showed decreased percentage of signal change in patients with CP compared with healthy controls, since the activation of SMA was regarded to govern the error-related movement inhibition and error-related processing. In the CP, the decreased this activation on SMA may imply the deficit in motor function and movement disorder in CP.

Keywords: Cerebral Palsy, fMRI, SMA

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I. Introduction

Cerebral Palsy (CP) was the most common movement disorder in childhood. Steenbergen(2006) reported its prevalence of approximately 1.5-2.5/1000 live births(Lee et al., 2007). The definition of CP was focused on the behavioral aspect in which the region of paralysis was considered as an important factor. The cause of cerebral palsy was only focused on the brain damage and abnormality in brain development during the neonatal period (Kraegeloh-Mann, 2007). The disturbance of the brain generally occurred during the 3rd trimester by hypoxic/ischemic events, and generally resulted in periventricular leukomalacia (PVL), the abnormal dilation on the ventricular region due to vast neuronal cell death. Even the major cellular mechanism of CP was not known, but the patients of CP had shown major deficits in movement – rigidity, spasticity and inaccurate speech due to the problem in movement control on the facial nerve – and the relation between its pathological behaviors and brain function were under study.

With the rapid rising-up in neuroimaging techniques, it was getting popular to study structural, functional features of the brain in preterm infants. According to Nosarti's morphometric study with adolescents who were born in preterm, there were 6% decrease in total brain volume, 11.8% decrease of cortical gray matter, 15.6% in right and 12.1% in left hippocampus. Particularly, he noted that individuals with ventricular enlargement had twice the ventricular size compared with the brains of people without enlargement (Nosarti. 2002). The widened ventricle was highly correlated to the white matter reduction, which effected cognitive deficit. Especially, corpus callosum (CC) was one of the most vulnerable areas by abnormal ventricular enlargement. The lesion in this area was highly related with cognitive deficit in attention and other brain functions. Supported by previous reports, patients with severe Periventricular Leukomalacia showed learning disabilities and movement disorders on four limbs due to the lesion on the cortico-spinal tract (Staudt, et al., 2003).

As the PVL was highly related with cerebral palsy, the ventricular lesion was suspected to be the major factor of the pathological movement in cerebral palsy. Due to their lesion, patients had deficits in skilled voluntary movement that was highly related with the patient's behavior abnormality including spasticity. To control movement, there were various cognitive processes and neuronal circuits required to govern the processes. Motor inhibition, one of the regulatory functions for accurate movement, was important in adjusting the behavior to the changing environment without making errors. The deficit of this inhibition in CP patients made their abnormal behaviors as pathological markers. Particularly, uncontrolled movements also made it difficult for the patients to perform minuscule movement operation using accurate motor control. Among the

regions involved for this cognitive function, supplementary motor area (SMA) was known to be engaged in selection and inhibition of motor function (Rubia et al., 2000; Picard et al., 1996). As a modulator of inhibitory motor function, the SMA received reciprocal input from prefrontal cortex and parietal cortex and commanded to the other motor areas (Faw, 2003).

Even though there were many cognitve task paradigms for knowing the role of SMA in movement inhibition, the Go-Nogo task was widely used for investigating movement inhibition (Durston, 2001; Blasi et al., 2006, Watanabe et al., 2002; Konish, 1999). This task was widely utilized to event-related fMRI (Konish, 1999). During the task, the participant should respond by pressing a button each time when “Go” signal was presented. However, if there was “No go” signal randomly presented to the participant, the participant should withdraw his or her response for a while. These two conditions (Go/No go) were mixed randomly with regard of HRF to make patients unable to expect which signal would be presented to the participants. The interested activation was during the inhibition of response by the “No go” signal, which involves inhibition. This activation should be separated from the activation evoked by the “Go” signal. For this scheme, we adopted event-related fMRI design than blocked-design because of its applicability to trial-by-trial analysis (Konish et al., 1999)

In this study, we would study the differences in activation on SMA using the Go/No go task between patients with cerebral palsy and healthy controls. This study would focus on the inhibition of movement, which could make participants adjust to abrupt changes

in response. We would also look for the relationship between the brain function and patients' pathological behavior from the difference of the response activation.

II. Materials and methods

1. Subject

Eight patients (two males and wix females, mean age: 17.8 ±8.4) with cerebral palsy and nine healthy volunteers (four males and five females, mean age: 21.7±1.2) participated as subjects. All healthy volunteers were right-handed, as measured by using the Annett handedness questionnaire translated into the Korean language (Anett, 1970). All healthy subjects were notified of the research and gave their written informed consent before participating in this study. The participants had no neurological or psychiatric history. The internal Review Board for clinical research involving human subjects in Severance hospital approved this study.

Patients were recommended from the residential doctors in severance hospital. After learning about the study and signing the informed consent, their personal information and basic clinical information including handedness was checked. There was only one left-handed patient and the other patients were right-handed. We did not include patients with attention deficit disorders due to the report that patients with attention deficit/hyper activity disorder (ADHD) showed poor performance in the Go-Nogo paradigm (A. B. Smith et al., 2006). All patients had a short training after the explanation of the paradigm.

2. Task

Each subject participated in one nine-minute functional imaging run during a single cognitive task session. The functional run consisted of an event-related task performed in response to auditory cues. The first cue, two seconds in duration, indicated the number of the button that the subject should press and the second auditory cue would show the “Go” or “Nogo” signal that signaled that the subject should press the button as fast as they could or not to press button. The ratio of “Go” and “Nogo” stimuli was 50% for each in the task. There was a two second gap between the first and the second signal in which subjects would prepare to press quickly. For confirming the activation in the specific brain area, we notified the subjects not to move any other parts of the body except the hand they would respond and banded their legs for restricting the patients’ pathological movement, which could affect the brain activity. The experimental paradigm was an event-related design with auditory stimulus and was applied using IFIS paradigm software (Invivo, USA). The design paradigm was launched on the stimulus system (Eloquence system, Invivo, USA) and stimulus was suggested to the participants when they were in the scanner with headset linked to a stimulus machine.

3. Image acquisition and data preprocessing

All scans were acquired using a Philips 3T scanner (IntraAchieva; Philips Medical System, Best, The Netherlands), which was equipped with shielded magnetic field gradients of 30 mT/m. A SENSivity Encoding (SENSE) head coil was used for radiofrequency transmission and reception of nuclear magnetic resonance signals. Head motion was minimized with restraining foam pads provided by the manufacturer. To minimize artifacts produced by head movement, structural T1s and fMRI images were sequentially acquired in a single scan time without a change in position. 277 contiguous 3.8-mm-thick axial slices covering the entire brain were collected using a single-shot, T2*-weighted echo planar imaging sequence depicting the blood-oxygenation-level-dependent (BOLD) signal (TE=30 ms; TR=2,000 ms; flip angle=90°; field of view=192 mm; and a matrix, 64 x 64). We used the first five volumes as dummy scans to allow for signal equilibration. High-resolution T1-weighted MR images (axial slices with 1.5-mm slice thickness; TE=4.6 ms; TR=9.5 ms; number of excitation=2; flip angle=8°; field of view=220 mm; and a matrix, 224 x 224) were collected before the functional data acquisition.

Spatial pre-processing and statistical analyses of the fMRI data were performed using SPM2 (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, London, UK). Preprocessing included slice time correction, realignment, spatial normalization, and spatial smoothing. Corrections for differences in slice acquisition time were performed for the interleaved sequence. Head motion was corrected by realignment, and then the corrected images were coregistered to the T1-

weighted image for each subject. The T1-weighted images were normalized to the standard T1 template, and the resulting transformation matrices were applied to the coregistered functional images. The functional data were smoothed with a Gaussian kernel of 8 mm full-width at half-maximum (FWHM).

4. Statistical analysis

Experimental trials for all three events were modeled separately using a canonical hemodynamic response function and its first-order temporal derivative. Each condition was made for contrast to see the specific brain activations during the test. We made statistical contrasts between stimuli for finding the brain area of activation in this task for each subject by defining 'Nogo vs. Go' contrast. The resulting set of voxel values for each contrast composes a statistical parametric map of the t-statistic (SPMt), and it was transformed to the unit normal distribution.

5. Group analysis

At a second level, random effects models were used for between-group differences of brain activations in each contrast. For each contrast, the contrast images from the first level were entered into a second level t-test, to create statistical parametric t-maps. We used a one-sample t-test for within-group analysis and a two-sample t-test for between-groups comparisons between patients and the healthy controls. A statistical threshold of $T=3.73(P<.001)$ was applied for two-sample t test and we accepted the number of

clusters at least 50 voxels. For each cluster, stereotactic coordinates (x, y, z in mm) refer to local maxima and t-max to the corresponding t-value. We also used Marsbar, a tool for SPM (http://marsbar.sourceforge.net/) to evaluate the percentage signal change on the activated regions.

III. Results

1. The pattern of intra-group brain activation in one-sample T test

During the one-sample t test, we could find broad activation over lateral and medial motor cortex in Go-Nogo contrast in both two groups ($P<.001$, $k>1500$). In this test, we could found bilateral activation over motor area in healthy controls. However we could also find weak left-dominant brain activation in patients with cerebral palsy compared with healthy controls. Also, there was no remarkable brain activation on motor area in Nogo-Go contrast.

2. Differences in brain activation and percentage of signal change during the comparison between two groups

In the two-sample t tests for the Nogo-Go contrast between control and CP patients, in comparing the healthy controls of patients, Anterior Cingulate Gyrus (ACC) and Paracentral lobule were activated on the left hemisphere. Also, precentral gyrus was activated contralaterally. In the differences of signal change in two groups, all activated regions in the healthy controls had a higher percentage of signal change. This

percentage was especially among the activated regions of the paracentral lobule and the precentral gyrus as corresponded to Brodmann Area 6.

When CP patients were compared with healthy controls, there was no activated region in this contrast.

Table 1. Differences in activation during Nogo-Go condition in healthy controls compared with CP patients

Anatomic location (BA): functional areas	Cluster	Z-score	Coordinate		
			x	y	Z
Healthy Control > CP Patient					
L Paracentral Lobule (6)	51	4.01	-4	-28	72
R Precentral Gyrus (6)	58	3.81	26	-16	52
L Anterior Cingulate Gyrus (32)	95	3.64	-18	38	2

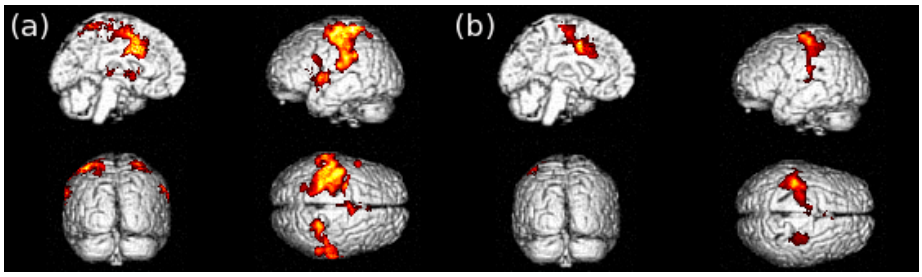

Figure 1 The brain activation on the motor area during one-sample t test in (a) healthy controls and (b) patients with cerebral palsy. It seems that there was more brain activation in control group

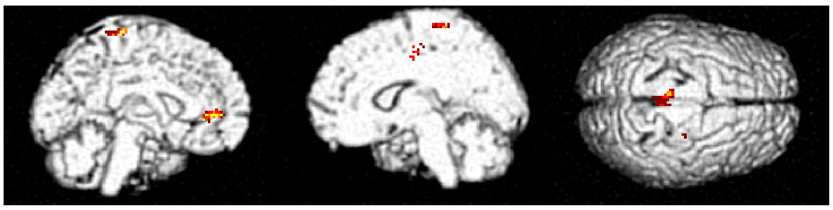

Figure 2. The difference in brain activation on Nogo-Go contrast between Healthy controls and patients with cerebral palsy. The activated regions were focused on SMA and ACC.

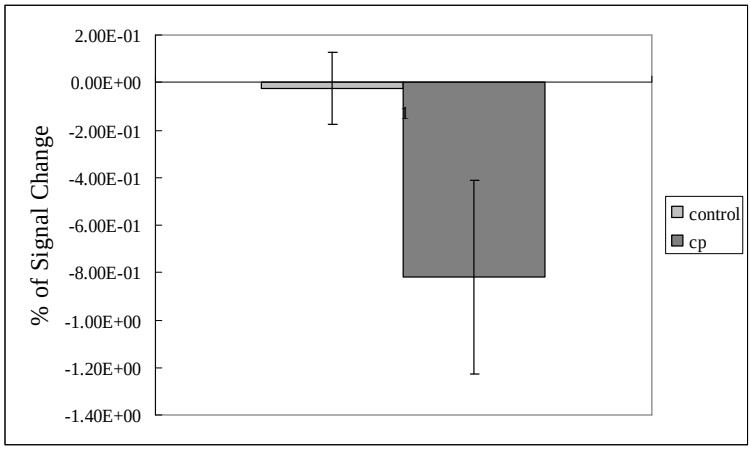

Figure 3. Percentage of signal change on left paracentral lobule. Even though both groups showed decreased change, there was bigger decrease in CP patients (mean -0.819 SD 0.409) than the control group (mean -0.0247 SD 0.15).

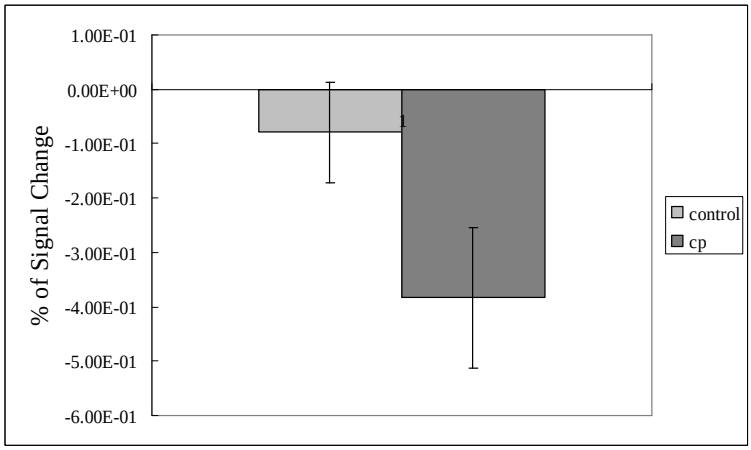

Figure 4. Percentage of signal change on right precentral gyrus. Even though both groups showed decreased change, there was bigger decrease in CP patients (mean -0.383 SD 0.129) than healthy controls (mean -0.0794 SD 0.093).

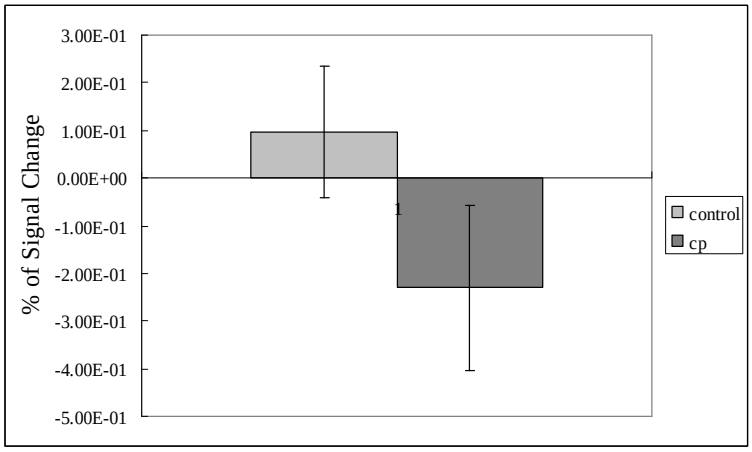

Figure 5. Percentage of signal change on left anterior cingulate cortex (ACC) between two groups. Healthy controls (mean 0.0975 SD 0.138) showed higher percentage than CP patients (mean -0.23 SD 0.173)

IV. Discussion

1. The brain activation of Nogo stimulis in the healthy control

This study focused on the question about the motor execution and inhibition in the CP patients compared to the healthy controls. Even though there were various areas engaged on the motor function, SMA was one of the keys to understanding the pathological phenomena in CP patients. During the response instigated by Nogo stimulus, there should be response inhibition and control. This inhibition and control invoked brain activations in the areas for these functions. If there was no damage in attention, SMA would play a major role in controlling the response after attentive processing.

The SMA was separated into two distinct parts in general anatomy - preSMA and SMA proper (Rizzoratti et al., 1996). The activated area in this study corresponds to preSMA (BA 6) in this description. Many reports suggest the role of this area in motor function, which needed inhibition (Brandies et al., 1998; Natio and Matsamura, 1996; Rubia, 2000). PreSMA was also widely investigated and reported to be involved in decision-making and motor generation (Hamberstone et al, 1997; Rivkin et al., 2003).

According to Passingham (1996), the reciprocal input of preSMA comes from the dorsal part of the parietal area (Passingham, 1996, Faw 2003). This connection also includes dorso-lateral PFC (BA 9), and this reciprocal network ruled over the limb movements through brainsterm and spinal chord (Faw 2003). This network involves response inhibition and monitoring. In the Nogo condition, this circuit was used for top-

down cognitive controls of motor execution reflected by unexpected cues (Blasi et al., 2006, Corbetta & Shulman, 2002).

Our result also found that there was activation on the anterior cingulate cortex (ACC), which was known for involving in response conflict in healthy controls compared with patients with cerebral palsy. Many previous studies showed that the rostral ACC and SMA might be used for processing response conflict (Hester, et al., 2004). The ACC was reported to activate in relation to response conflict, rather than stimulus conflict (van Veen et al., 2001). The abrupt change of response in the Nogo condition brought the changes in response and the ACC would evaluate the conflict and indicate the control needs to be involved (van Veen et al., 2001)

Various studies reported the level of response conflict was significantly related with the degree of activation in ACC. These reports indicated the ACC monitors the conflict in responses, and modulated the behavioral schemes for more accurate actions (braver et al., 2001, Garavan et al., 2003). Even though the conflict hypothesis supposed the positive relationship between the degree of ACC activation and the frequency of responses, the pattern would be various for response conflict paradigm. However, Braver noted that the response inhibition task was rather 'special' for making high-level response conflict regardless of the frequency of Nogo stimuli (brave et al., 2001).

2. Differences in BOLD signal and its physiological implication

Even there were many reports on the negative BOLD signal, the specific reason of negative bold signal had not been found. However, negative BOLD response was

considered as a result of increased deoxyhemoglobin due to changes in cerebral blood flow (CBF) and brain volume (CBV) (Shmuel et al., 2002, Newton et al., 2005). We specifically found that negative BOLD was related with decreased CBF and CBV on the brain area (Newton et al, 2005).

From the study about the inhibitory mechanism on the ipsilateral M1 (Newton et al., 2005) movement inhibition was likely to involve GABA-ergic interneurons, which inhibits the excitation of pyramidal cells (Newton et al., 2005)

According to the study using [^{18}F]-FFMZ study on the patients with spastic diplegia, there was $GABA_A$ receptor binding on SMA bilaterally (Lee et al., 2007). Even though we did not know the etiological mechanisms of GABA on SMA, we could assume the binding of $GABA_A$ on the SMA was related to the negative BOLD response.

In addition, GABAergic modulators like lorazepam were also used in mediating inhibition on the medial prefrontal areas such as ACC (Northoff et al., 2007). During the study using fMRI and MRS, there was significant correlation between GABA concentration and negative BOLD response on ACC. Negative BOLD response was observed as a result of decreased neuronal activity and this decreased activity was modulated by increased GABA transmission (Northoff et al., 2007)

3. Role of SMA and its pathological meaning

Response inhibition in humans required complex interaction among various brain areas. To select the right alternatives, we used many brain functions from attention to modulation of our behavior for proper action. Response inhibition was used for

suppressing inappropriate responses when the context was changed. This function made the person inhibit what was wrong during the process.

Regions of brain for this function were interconnected for this function. From getting signal through inferior parietal area, various regions in prefrontal cortex were used to modulate error processing and inhibit final behavior. Along various studies with attention deficit-hyperactivity disorder (ADHD) patients, the role of anterior cingulate cortex was important for attention and cognitive control.

Various projections from PFC reached to the SMA via basal ganglia and the thalamus. Basal ganglia was known for its role in response inhibition by being modulated thorough excitatory thalamic transfer from the study with deep brain stimulation on subthalamic nucleus (STN) in patients with Parkinson's disease (van de Wiltenberg et al., 2006). This connection worked for selections of appropriate responses by modulating sensory inputs into adjusting motor function (Ridderinkhof et al., 2004).

Current neuroimaging study for patient with a lesion on SMA – especially, preSMA – had revealed the deficit on inhibitory function by the lesion (Nachev, 2007). Along the result of the study, Nachev concluded the role of SMA in suppressing conflicting plans by switching from one conditioned action to another (Nachev. 2007). We consider that our results on CP patients were affected by the damages on the SMA, which played as a coordinator for executive motor function and motor inhibition. Due to this damage, we might consider the pathological behaviors were shown in CP patients.

V. Conclusion

We did the Go/Nogo test between patients with cerebral palsy and healthy controls. As a result, we found the difference in the activation on SMA and ACC between two groups. We also found a negative percentage of signal change in all brain regions, which showed decreased activation. These findings may imply that the decreased activation on SMA in CP should be considered in its relationship to the deficit in movement control and pathological behavior. Also we might consider that the GABA-ergic effect correlates with these areas and the decreased function in these areas for patients with CP for movement inhibition.

References

1. Lee JD, Park HJ, Park ES, Kim DG, Rha DW, Kim EY *et al.* Assessment of regional GABA(A) receptor binding using 18F-fluoroflumazenil positron emission tomography in spastic type cerebral palsy. *NeuroImage* 2007; **34**: 19-25.
2. Krageloh-Mann I, Horber V. The role of magnetic resonance imaging in elucidating the pathogenesis of cerebral palsy: a systematic review. *Dev Med Child Neurol* 2007; **49**: 144-51.
3. Nosarti C, Al-Asady MH, Frangou S, Stewart AL, Rifkin L, Murray RM. Adolescents who were born very preterm have decreased brain volumes. *Brain* 2002; **125**: 1616-23
4. Staudt M, Pavlova M, Bohm S, Grodd W, Krageloh-Mann I. Pyramidal tract damage correlates with motor dysfunction in bilateral periventricular leukomalacia (PVL). *Neuropediatrics* 2003; **34**: 182-88
5. Rubia K, Overmeyer S, Taylor E, Brammer M, Williams SC, Simmons A *et al.* Functional frontalisation with age: mapping neurodevelopmental trajectories with fMRI. *Neurosci Biobehav Rev* 2000; **24**: 13-19.
6. Picard N, Strick PL. Motor areas of the medial wall: a review of their location and functional activation. *Cereb Cortex* 1996; **6**: 342-53.
7. Faw B. Pre-frontal executive committee for perception, working memory, attention, long-term memory, motor control, and thinking: a tutorial review. *Consciousness and cognition* 2003; **12**: 83-139.

8. Durston S, Thomas KM, Worden MS, Yang Y, Casey BJ. The effect of preceding context on inhibition: an event-related fMRI study. *NeuroImage* 2002; **16**: 449-53.
9. Blasi G, Goldberg TE, Weickert T, Das S, Kohn P, Zoltick B *et al.* Brain regions underlying response inhibition and interference monitoring and suppression. *Eur J Neurosci* 2006; **23**: 1658-64.
10. Watanabe J, Sugiura M, Sato K, Sato Y, Maeda Y, Matsue Y *et al.* The human prefrontal and parietal association cortices were involved in NO-GO performances: an event-related fMRI study. *NeuroImage* 2002; **17**: 1207-16.
11. Konishi S, Nakajima K, Uchida I, Kikyo H, Kameyama M, Miyashita Y. Common inhibitory mechanism in human inferior prefrontal cortex revealed by event-related functional MRI. *Brain* 1999; **122 (Pt 5)**: 981-91.
12. Annett M. A classification of hand preference by association analysis. *Br J Psychol* 1970; **61**: 303-21.
13. Smith AB, Taylor E, Brammer M, Toone B, Rubia K. Task-specific hypoactivation in prefrontal and temporoparietal brain regions during motor inhibition and task switching in medication-naive children and adolescents with attention deficit hyperactivity disorder. *Am J Psychiatry* 2006; **163**: 1044-51.
14. Rizzolatti G, Luppino G, Matelli M. The classic supplementary motor area was formed by two independent areas. *Advances in neurology* 1996; **70**: 45-56.
15. Brandeis D, van Leeuwen TH, Rubia K, Vitacco D, Steger J, Pascual-Marqui RD *et al.* Neuroelectric mapping reveals precursor of stop failures in children with attention deficits. *Behav Brain Res* 1998; **94**: 111-25.

16. Naito E, Matsumura M. Movement-related potentials associated with motor inhibition under different preparatory states during performance of two visual stop signal paradigms in humans. *Neuropsychologia* 1996; **34**: 565-73.
17. Humberstone M, Sawle GV, Clare S, Hykin J, Coxon R, Bowtell R *et al.* Functional magnetic resonance imaging of single motor events reveals human presupplementary motor area. *Annals of neurology* 1997; **42**: 632-37.
18. Rivkin MJ, Vajapeyam S, Hutton C, Weiler ML, Hall EK, Wolraich DA *et al.* A functional magnetic resonance imaging study of paced finger tapping in children. *Pediatr Neurol* 2003; **28**: 89-95.
19. Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. *Nature reviews* 2002; **3**: 201-15.
20. Hester R, Fassbender C, Garavan H. Individual differences in error processing: a review and reanalysis of three event-related fMRI studies using the GO/NOGO task. *Cereb Cortex* 2004; **14**: 986-94
21. van Veen V, Cohen JD, Botvinick MM, Stenger VA, Carter CS. Anterior cingulate cortex, conflict monitoring, and levels of processing. *NeuroImage* 2001; **14**: 1302-08
22. Braver TS, Barch DM, Gray JR, Molfese DL, Snyder A. Anterior cingulate cortex and response conflict: effects of frequency, inhibition and errors. *Cereb Cortex* 2001; **11**: 825-36.
23. Garavan H, Ross TJ, Murphy K, Roche RA, Stein EA. Dissociable executive functions in the dynamic control of behavior: inhibition, error detection, and correction. *NeuroImage* 2002; **17**: 1820-29.

24. Shmuel A, Yacoub E, Pfeuffer J, Van de Moortele PF, Adriany G, Hu X *et al.* Sustained negative BOLD, blood flow and oxygen consumption response and its coupling to the positive response in the human brain. *Neuron* 2002; **36**: 1195-10.
25. Newton JM, Sunderland A, Gowland PA. fMRI signal decreases in ipsilateral primary motor cortex during unilateral hand movements were related to duration and side of movement. *NeuroImage* 2005; **24**: 1080-87.
26. Northoff G, Walter M, Schulte RF, Beck J, Dydak U, Henning A *et al.* GABA concentrations in the human anterior cingulate cortex predict negative BOLD responses in fMRI. *Nat Neurosci* 2007; **10**: 1515-17.
27. van den Wildenberg WP, van Boxtel GJ, van der Molen MW, Bosch DA, Speelman JD, Brunia CH. Stimulation of the subthalamic region facilitates the selection and inhibition of motor responses in Parkinson's disease. *J Cogn Neurosci* 2006; **18**: 626-36.
28. Ridderinkhof KR, van den Wildenberg WP, Segalowitz SJ, Carter CS. Neurocognitive mechanisms of cognitive control: the role of prefrontal cortex in action selection, response inhibition, performance monitoring, and reward-based learning. *Brain and cognition* 2004; **56**: 129-40.
29. Nachev P, Wydell H, O'Neill K, Husain M, Kennard C. The role of the pre-supplementary motor area in the control of action. *NeuroImage* 2007; **36 Suppl 2**: 155-63.

Abstract (in korean)

뇌성마비 환자의 보완운동역의 역할에 대한 기능 자기 공명 영상 연구

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서 병 식

뇌성마비는 신생아의 출산 전, 후의 뇌 손상을 통한 신경학적 장애이다. 이 기간에 나타나는 장애를 통해 강직성 운동장애, 경직 등이 일어나게 된다. 인간의 운동기능에 대해 관여하는 여러 뇌 영역 중에, 보완운동영역은 운동의 억제와 관련하여 중요한 역할을 하고 있다. 기능 자기공명영상을 이용하여, 우리는 뇌성마비 환자와 건강한 일반인 간의 보완운동영역에 대한 활성화를 연구하였다. 고해상도 자기공명영상 스캐너를 이용하여 뇌 영상을 획득하였고, 분석은 SPM2 분석도구를 이용하여 뇌 활성화의 차이와 신호 변화의 퍼센트를 확인하였다. 결과로서 우리는 보완운동영역과 전방대상피질에서 활성화의 차이를 확인 할 수 있었고, 각 영역에 대한 신화변화 퍼센트에서도 차이를 확인 할 수 있었다. 이로서 우리는 보완운동영역이 오류에 관련한 운동억제에 기능을 하는 것으로 예상하였다. 또한, 이 결과는 뇌성마비 환자군에서 이 영역의 낮은 활성화가 환자의 뇌 기능상 문제와 병적 행동과 관련이 있는 것으로 추정된다.

핵심되는 말: 뇌성마비, 기능자기공명영상, 보완운동영역