Nonlinearity in the Somatosensory Cortex Response to Vibrotactile Stimulator in fMRI

Hyunsook Lee

Department of Oriental Biomedical Engineering, College of Health Sciences, SangJi University

The nonlinearity of hemodynamic response in the somatosensory cortex was investigated with vibrotactile stimulation. The stimuli consisted of a train of 25 Hz, each lasting five different duration periods, 2 s, 4 s, 8 s, 12 s, or 16 s with 20 sec periods of no vibration in a pseudo-random order. In order to understand the linearity on the change of stimulus duration for somatosensory cortex, two different tests- checking the linearity of system and finding the impulse response function from gamma-variate function were applied to analyze the hemodynamic response functions. They have produced nearly same results. The BOLD response in the somatosensory cortex is nonlinear for stimuli of less than 8 seconds, but nearly linear for stimuli greater than 8 seconds. The amplitude, area, TTP, and FWHM as functions of the stimulus duration were calculated and showed a significant downward trend with increasing stimulus duration for the amplitude and the area. It supports the ranges of nonlinearity are less than 8 seconds.

Key Words: BOLD fMRI, Vibrotactile device, Linearity, Somatosensory cortex, Brain activity

INTRODUCTION

Functional magnetic resonance imaging (fMRI) has recently emerged as a technique for mapping human brain function.[1-3] Blood oxygenation level-dependent (BOLD) contrast-based fMRI has been used as a noninvasive method to measure vascular oxygenation changes due to brain activity.[4,5] It has been known that the shape of the hemodynamic response in fMRI depends on the stimulus intensity, stimulus duration and interval, cerebral blood flow (CBF), etc.[6] Therefore, in designing activation experiments it is important to understand the effects of stimulus task parameters (e.g., rate, duration, amplitude) on the hemodynamic response.

Analysis method for fMRI experiments depend on a complete understanding of the BOLD response. Early fMRI experiments[7-9] reported a linear relationship between increasing parameters, such as duration, in the stimulus and the resulting hemodynamic response and used a linear system analysis for modeling the BOLD response.[10,11] But recent experiments[12-14] have shown an interesting amount of nonlinearity in the response. For the periodic stimulus, the BOLD response shows expected periodic one, but it is not easy to expect the BOLD response for the non-periodic case.

Understanding the nonlinearity of hemodynamic response with respect to stimulus duration will have an important impact on the analysis of fMRI experiments, where the stimulus prompts subjects for a response, for example, motor tasks,[15] language tasks in stroke patients[16] and complex reasoning tasks.[17]

It has been known that the nonlinearity of the BOLD response is caused by a combination of factors, such as neural adaptation, blood flow and oxygen extraction. But, it is not entirely clear if the BOLD response is always nonlinear or if there is a point at which it changes from nonlinear to linear. The relationship between task parameters and the magnitude of the hemodynamic response has not been investigated far in the somatosensory system.[18] Therefore this study was proposed to understand the linearity on the change of stimulus duration for somatosensory cortex in the design of fMRI experiment.

Submitted August 9, 2006, accepted September 25, 2006.
Corresponding Author : Hyunsook Lee, Department of Oriental Biomedical Engineering, College of Health Sciences, SangJi University, 660, Usan-dong, Wonju 220-702, Korea
Tel: 033)730-0416, Fax: 033)730-0403
E-mail: hslee@mail.sangji.ac.kr

The study for the effect of the rate of vibratory stimuli on the somatosensory cortex[19] demonstrated that there may be significant differences in the cortical representation of Meisser and Pacinian afferents. Such changes in anatomical activation patterns for somatosensory stimuli have been found by others[20] and they make rate-effect linearity studies of the somatosensory cortex difficult. Therefore, the present study will focus on the activation patterns elicited by a pneumatic vibrotactile stimulus in the range of flutter ($\leq$ 40 Hz) which is perceptive to Meissner corpuscles. The goal of the nonlinearity experiments is to examine the nonlinearity of the BOLD response across a range of duration periods.

MATERIALS AND METHODS

1. Data acquisition and experimental protocol

Six normal right-handed male subjects (37$\pm$4.9 years old) participated in the study. In order to understand the nonlinearity between the duration of sensory stimuli and BOLD activation in the primary somatosensory cortex, a pneumatic vibrotactile device delivered a vibratory effect to a small rubber valve attached to the subject's right middle finger.[21] The frequency of stimulus was fixed to the 25 Hz because signal percentage change increases with increasing frequency.[22] Stimuli of 2 s, 4 s, 8 s, 12 s, or 16 s duration were presented in eight functional runs in a pseudo-random order alternating with 20 sec periods of no vibration. The acquisition began and ended with 20 sec without vibration. Total acquisition time was 5 min and 4 sec. Each stimulus was repeated two times for each run.

All of the imaging was acquired on a whole-body GE 3T LX scanner using a dome-shaped quadrature RF head coil. High resolution anatomic images were obtained using both a T1-weighted 3D-spoiled GRASS sequences (TR/TE/FA=23 ms/7 ms/25°, matrix size=256$\times$192, 1.3 mm thickness, 124 slices, FOV=240 mm) and a time-of-flight MR angiogram (TR/TE/FA=17 ms/4.9 ms/50°, matrix size=256$\times$128, FOV= 200 mm, 4 mm thickness) before the functional images. The functional data were acquired using a 1-shot spiral sequence (TR/TE/FA=1,000 ms/18 ms/60°) covering the supplementary motor area (SMA), the primary motor cortex and the somatosensory cortex with twenty contiguous coronal slices (slice thickness 4 mm, FOV=200 mm, matrix size=64$\times$64). Foam padding was used to minimize head motion. All experiments were undertaken with the informed consent of the volunteers, as approved by the Institutional Review Board for human studies.

2. Data analysis

The image processing and statistical analysis were performed with the use of AFNI software[23] and MATLAB (The Mathworks, Natick, MA). The reconstructed fMRI data were realigned with the use of 3-dimensional rigid-body registration method in order to minimize residual motion between images in the time series. After the linear trends of each time series were removed, eight fMRI runs containing randomized stimuli of the five different durations (2, 4, 8, 12, 16 sec) were concatenated and then sorted to create five separate runs, one for each duration. Five runs were obtained, each containing 16 trials for one specific duration. A cross correlation analysis using the gamma variate function was applied to the time course data of each duration (2, 4, 8, 12, 16 sec) and phase shifting was allowed to select the best reference waveform and then to localize activation in the somatosensory cortex. The hemodynamic responses for each duration were then averaged across all 16 trials. Maximum and minimum signal intensity was obtained from the curve and used to calculate the signal percentage change for each duration.

ROIs (Regions of Interest) were drawn in three slices showing sensorimotor cortex (S1) based on the activation map. The same ROIs were used for activation maps of 5 different durations. AlphSim was used to correct for multiple comparisons and to discriminate against false positive using a cluster size threshold approach. For a voxelwise p value of 10^{-5} and a cluster size of 160 μL (4 voxels), an alpla (false positive probability) <0.001 could be achieved.

The linearity of the hemodynamic response can be checked to obey two properties of additivity and scaling in the system. Given that $L(x_1)$ and $L(x_2)$ are the responses to an input x_1 and x_2, then the response to an input $x = a\ x_1 + b\ x_2$ is $L(x) = a\ L(x_1) + b\ L(x_2)$. In this experiment, we are concerned only duration of stimulus, not amplitude, for checking additivity. Changing the duration of the stimulus is changing the input from x to $x_1 + x_2$, where x_i represents the duration of the stimulus. If a result is linear, the BOLD response curve is expected to change from L(x) to $L(x_1)+L(x_2)$. Another test for linearity was applied to the HRF.[13] Gamma-variate function,

$$G(t) = a\, t^b \exp(-c \cdot t) \quad (1)$$

where the parameters a, b and c affect the amplitude, full width at half maximum (FWHM) and time to peak (TTP) of the response function was used to find the impulse response functions to the observed HRF's for each of five stimulus duration periods. Knowledge of the impulse function for different types of stimuli can increase understanding of the system's nonlinearity.

RESULTS AND DISCUSSION

The hemodynamic response function (HRF) in the somatosensory cortex averaged across repeated stimulus trials for each of five duration periods for each of the six subjects are shown in Fig. 1. These hemodynamic responses were then averaged across subjects to produce the group-averaged responses. As can be seen, HRF amplitudes increase in response to stimuli increasing from 2 to 8 seconds. Above 8 seconds of stimulus, the response amplitude stays relatively constant or, as oddly seen in the case of subjects 4 and 5, increases. The response to the 16-second stimulus has a noticeable double-peak in the case of subjects 2 and 3.

Shown in Fig. 2 are the results of additivity test for a group-averaged HRF's. The responses to shorter stimuli were used to predict the responses to longer stimuli. The 2-second response was shifted by 2 second and added to the 2-second response to predict the HRF to the 4-second stimulus. The HRF's for the 2-, 4-, and 8-second stimuli are used to predict the responses to 4-, 8-, 12-, and 16-second stimuli. Overpredictions were made in most cases. The prediction of 4-second response by the 2-second response is only slightly greater than the observed 4-second response, while the prediction of the

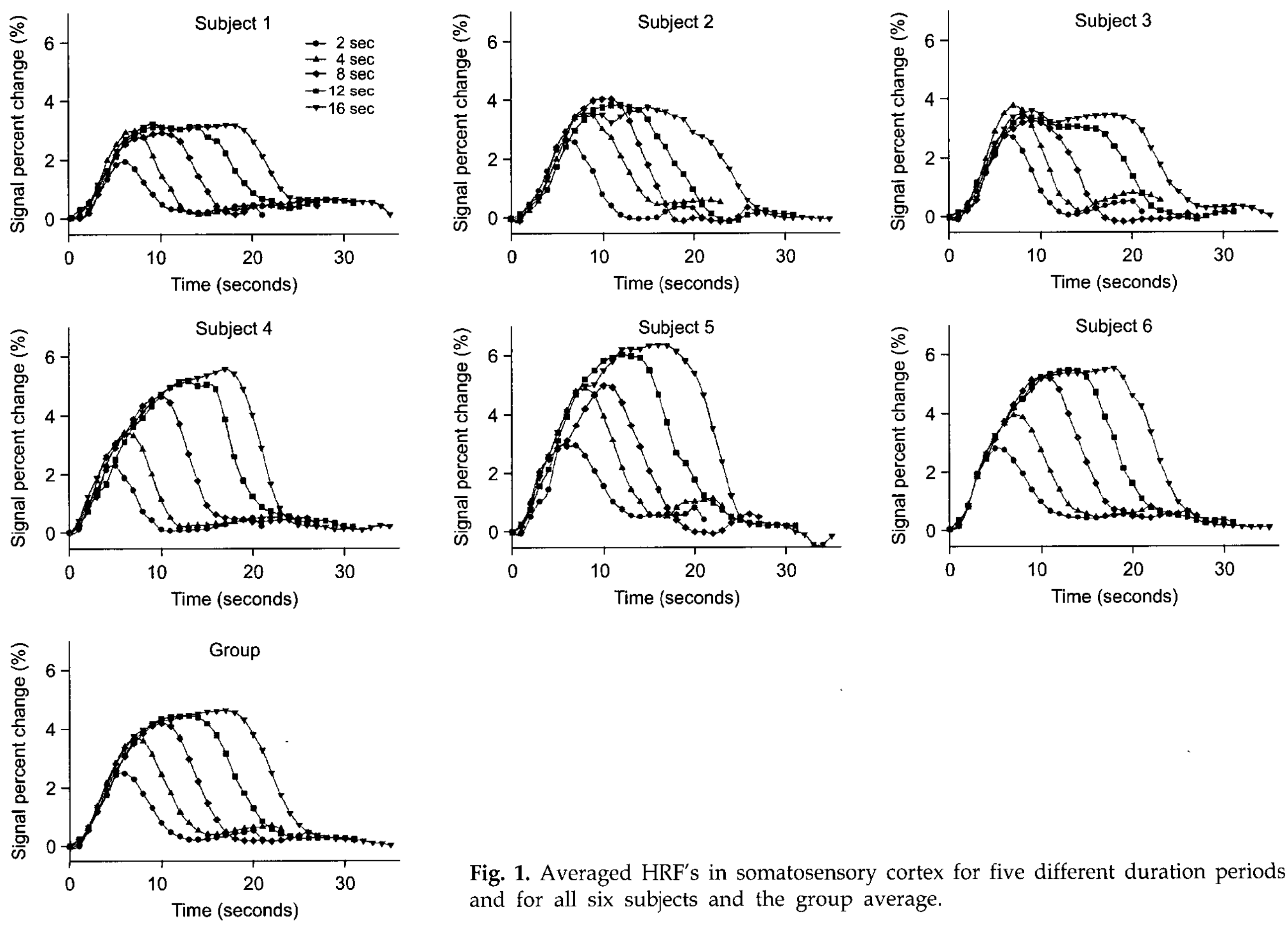

Fig. 1. Averaged HRF's in somatosensory cortex for five different duration periods and for all six subjects and the group average.

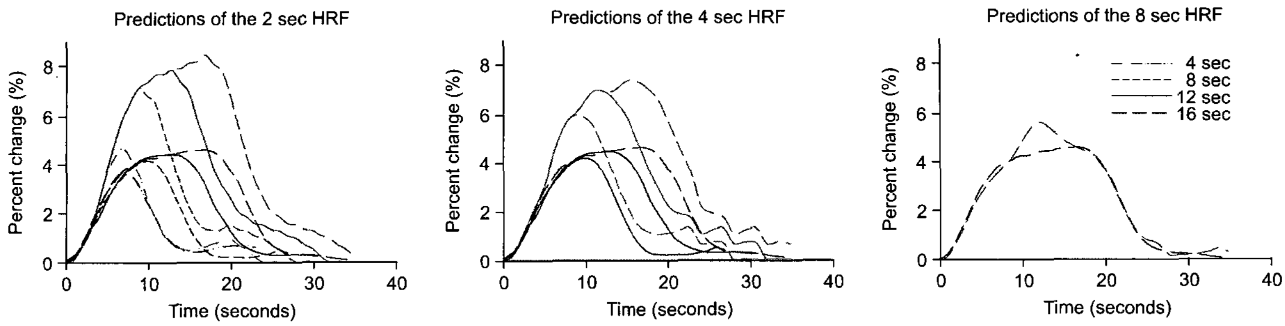

Fig. 2. The additivity test was used to assess the linearity of the BOLD response of the somatosensory cortex. Predictions (grey lines) from the 2-, 4-, 8-second stimuli are compared against the actual responses (black lines) from the 4-, 8-, 12-, 16-second stimuli. Overpredictions are seen in all cases except for the 16-second HRF prediction of the 8-second HRF.

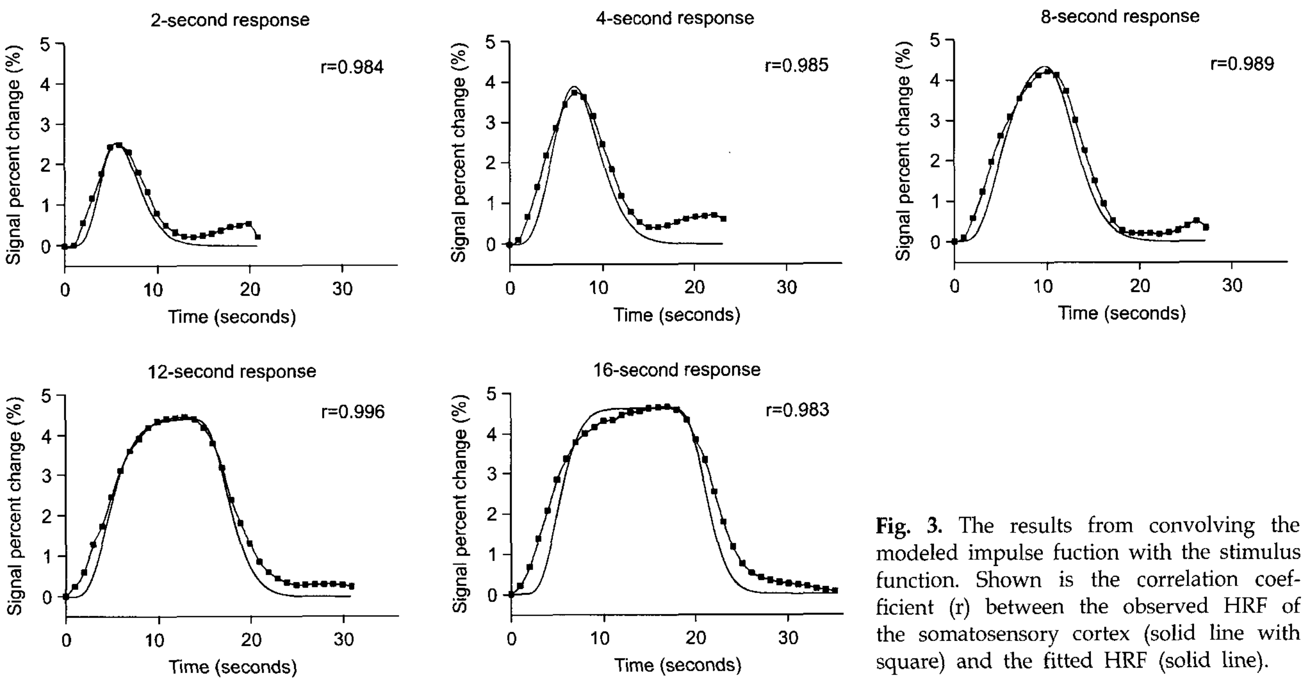

Fig. 3. The results from convolving the modeled impulse fuction with the stimulus function. Shown is the correlation coefficient (r) between the observed HRF of the somatosensory cortex (solid line with square) and the fitted HRF (solid line).

16-second response by the 8-second response is fairly consistent with the observed 16-second response. In this latter case, the amplitude is roughly even for both curves, although the predicted curve has a higher peak than the observed HRF. From this data, we can find that the BOLD response in the somatosensory cortex is nonlinear for stimuli of less than 8 seconds, but nearly linear for stimuli greater than 8 seconds.

The results from convolving the modeled impulse function with the stimulus function are shown along the observed HRF's for the group-averaged data in Fig. 3. The correlation coefficient (r) between the observed HRF and the fitted HRF was calculated. Although the fitted HRF fails to predict the tail end, it does fit the post-stimulus overshoot remarkably well.

In a linear system, the impulse function would be the same for any stimulus duration or intensity. Knowing how the shape of the impulse function changes as a stimulus parameter changes can help in better visualizing the point at which the system changes from nonlinear to linear. The impulse functions for each of the five stimuli durations for the individual subject data as well as for the group-averaged data are shown in Fig. 4. In most cases, there is a clear trend toward a

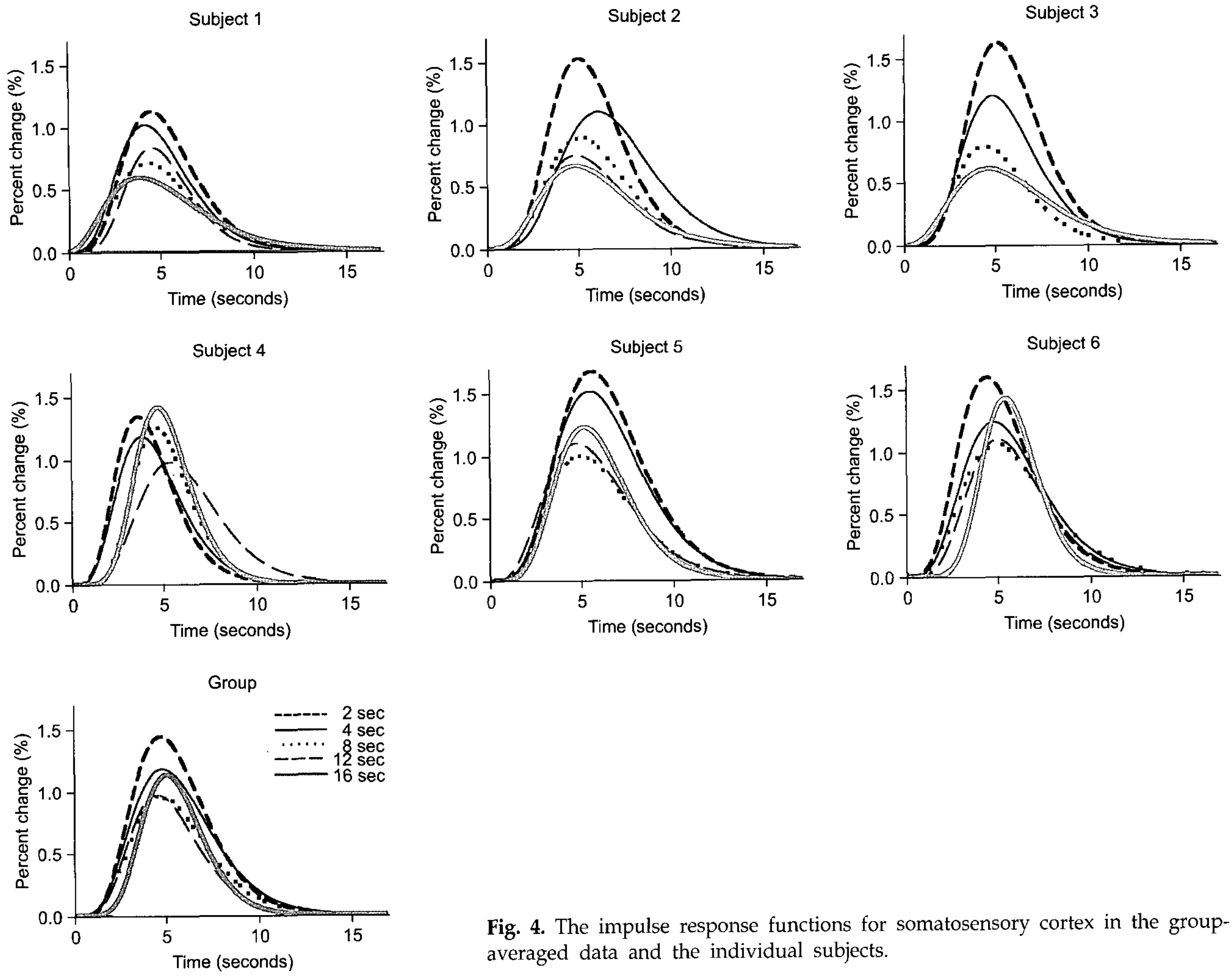

Fig. 4. The impulse response functions for somatosensory cortex in the group-averaged data and the individual subjects.

decrease in the amplitude of the impulse function as the stimulus duration increases. Subject 4 is anomalous in showing a 2-second impulse response function smaller than the 16-second impulse response function.

A further analysis of the functions is shown in Fig. 5, where the amplitude, area, TTP, and FWHM are plotted as functions of the stimulus duration. The dotted lines are the values of group data which extracted from the group-averaged data in Fig. 4 and the solid lines with error bars are the mean values of individual data. The values for the amplitude, area, TTP, and FWHM with increasing stimulus duration would be consistent when the BOLD response was linear. But a significant downward trend with increasing stimulus duration can be seen for the amplitude and the area. After 8 seconds of stimulus, the amplitude and area of the impulse function begin to level off. The downward curves for amplitude and area can be interpreted as being due to neural adaptation. Nangini et al[24] have assumed the input stimulus envelope is proportional to neural activity and neural activity exhibits both transient and steady-state components, consistent with extensive electrophysiological data. Their results have showed nonlinearity for shorter stimulus duration and overestimated BOLD signal with the time-shifted summation (TSS) procedure to assess linear time invariance (LTI). Therefore in order to further understand the nonlinearity, temporal characteristics of neural activity should be considered adequately. There are also slight trends seen for TTP, but not for FWHM. It has been known that the TTP of the BOLD response varies as a function of blood vessel diameter.[25,26] From the second linearity analysis, it appears that the BOLD response in the somatosensory cortex

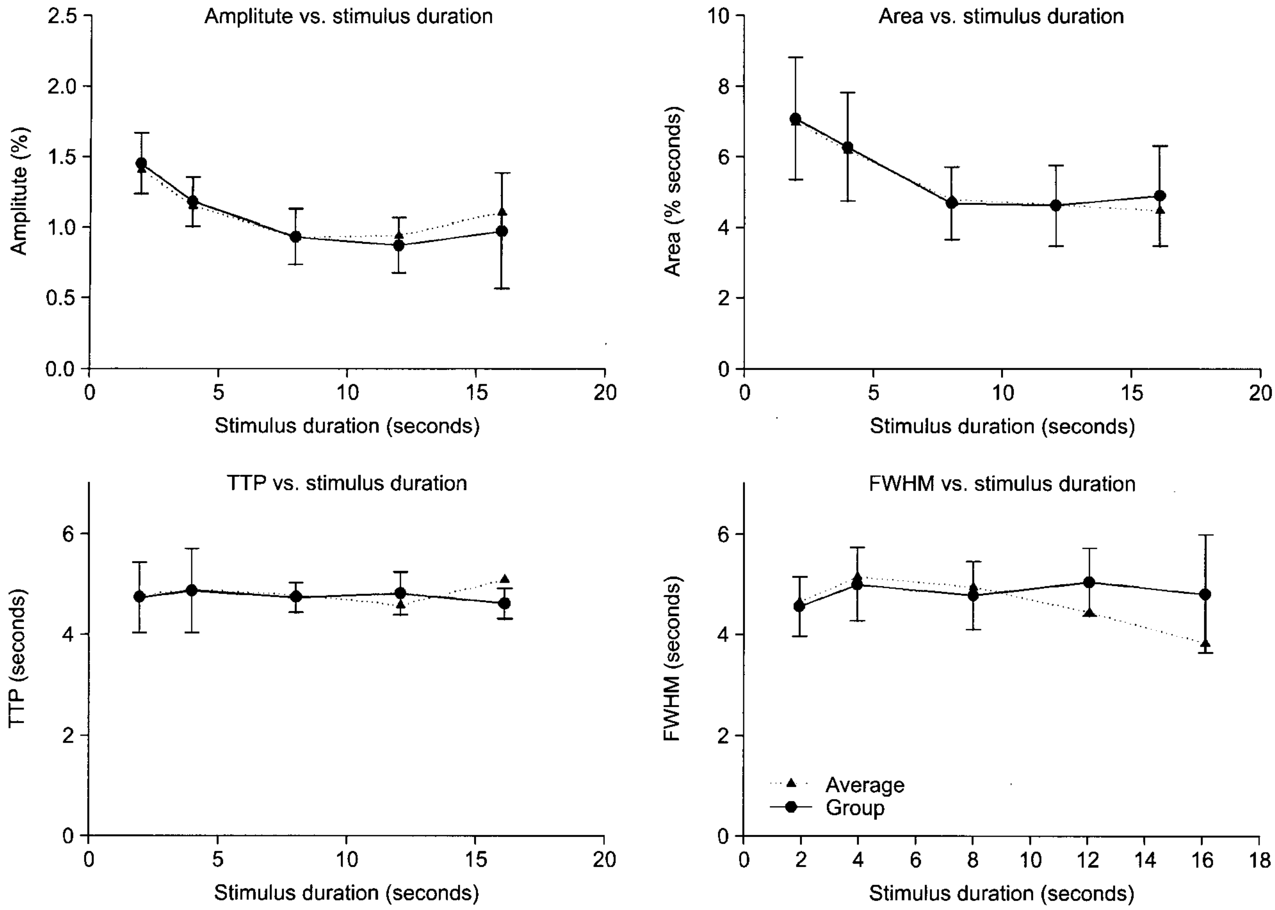

Fig. 5. The parameters of the impulse function for individuals and group data in the somatosensory cortex as functions of stimulus duration period.

is nonlinear for stimuli less than 8 seconds, but linear above this range.

CONCLUSION

This research on the linearity of the hemodynamic response in somatosensory cortex has found the ranges of nonlinearity are less than 8 seconds. The additivity test which used to check the linearity of the BOLD response and the other test which found the impulse functions for each HRF have produced nearly same results. The findings in this research may lead to new and interesting research ideas. Forming a mathematical model of nonlinearity would be useful to interpreting fMRI results where the duration of brain activity is not constant. This includes language tasks on stroke patients or memory experiments on Alzheimer's patients. Variations in nonlinearity can also occur during different steps of neural processing throughout the brain. By understanding the differences between brain activation at different levels of cortical processing, we can better improve fMRI results of complex mental tasks. Such research ideas must await a more thorough understanding of the nonlinear response of BOLD signals throughout the brain.

ACKNOWLEDGMENTS

This research was supported by Sangji University Research Fund, 2004. Use of resources and facilities at the Gainesville, Florida VA medical Center is gratefully acknowledged. Thanks to Drs. K. Peck, R. Briggs, and D. Soltysik for helpful discussions.

REFERENCES

1. **Sanders JA, Orrison WW**: Functional magnetic resonance imaging. Orrison WW, Lewine JD, Sanders JA, Hartshorne MF: *Functional Brain Imaging*. Mosby, St. Louis, MO (1995), pp. 239-326
2. **DeYoe EA, Bandettini P, Neitz J, Miller D, Winans P**: Functional magnetic resonance imaging (FMRI) of human brain. J Neurosci Methods 54:171-187 (1994)
3. **Binder JR, Rao SM**: Human brain mapping with functional magnetic resonance imaging. Kertesz A: *Localization and Neuro-imaging in Neuropsychology*. Academic Press, Orlando, FL (1994), pp. 185-212
4. **Ogawa S, Tank DW, Menon R, et al**: Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. Proc Natl Acad Sci USA 89: 5951-5955 (1992)
5. **Kwong KK, Belliveau JW, Chesler DA, et al**: Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. Proc Natl Acad Sci USA 89:5675-5679 (1992)
6. **Boynton GM, Engel SA, Glover GH, Heeger DJ**: Linear systems analysis of functional magnetic resonance imaging in human V1. J of Neuroscience 16:4207-4221 (1996)
7. **Buxton RB, Wong EC, Frank LR**: Dynamics of blood flow and oxygenation changes during brain activation: the balloon model. Mag Reson Med 39:855-864 (1998)
8. **Schlaug G, Sanes JN, Thangaraj V, et al**: Cerebral activation covaries with movement. NeuroReport 7:879-883 (1996)
9. **Rao SM, Bandettini PA, Binder JR, et al**: Relationship between finger movement rate and functional magnetic resonance signal change in human primary motor cortex. J Cereb Blood Flow Metab 16:1250-1254 (1996)
10. **Cohen MS**: Parametric analysis of fMRI data using linear systems methods. NeuroImage 6:93-103 (1997)
11. **Friston KJ, Jezzard P, Turner R**: Analysis of functional MRI time-series. Human Brain Mapping 1:153-171 (1994)
12. **Buxton RB, Liu TT, Wong EC**: Nonlinearity of the hemodynamic response: modeling the neural and BOLD contributions. Proc. 9th ISMRM, 1164 (2001)
13. **Liu HL, Gao JH**: An investigation of the impulse functions for the nonlinear BOLD response in functional MRI. Mag Reson Med 18:931-938 (2000)
14. **Miller KL, Luh WM, Liu TT, et al**: Nonlinear temporal dynamics of the cerebral blood flow response. Human Brain Mapping 13:1-12 (2001)
15. **Johansen-Berg H, Rushworth M, Bogdanovic MD, Kischka U, Wimalaratna S, Matthews PM**: *The role of ipsilateral* premotor cortex in hand movement after stroke. Proc Natl Acad Sci 99:14518-14523 (2002)
16. **Gopinath KS, Briggs RW, Himes N**: Examination of the linearity of BOLD FMRI responses in a higher level cognitive system. Proc. 9th ISMRM, 1189 (2001)
17. **Christoff K, Prabhakaran V, Dorfman J**: Rostrolateral prefrontal cortex involvement in relational integration during reasoning. NeuroImage 14:1136-1149 (2001)
18. **Soltysik DA, Peck KK, White KD, Crosson B, Briggs RW**: Comparison of hemodynamic response nonlinearity across primary cortical areas. NeuroImage 22:1117-1127 (2004)
19. **Harrington GS, Downs III JH**: FMRI mapping of the somatosensory cortex with vibratory stimuli: is there a dependency on stimulus frequency? Brain Research 897:188-192 (2001)
20. **Francis ST, Kelly EF, Bowtell R, et al**: fMRI of the responses to vibratory stimulation of digit tips. Neuroimage 11:188-202 (2000)
21. **Briggs R, Dy-Liacco I, Malcolm M**: A pneumatic vibrotactile stimulation device for fMRI. Magnetic Resonance in Medicine 51:640-643 (2004)
22. **Lee HS**: The frequency effect in the somatosensory cortex response to vibrotactile stimulator in fMRI. Korean J Med Phys 15:128-132 (2004)
23. **Cox RW**: AFNI: software for analysis and visualization of functional magnetic neuroimages. Comput Biomed Res 9:162-173 (1996)
24. **Nangini C, MacIntosh BJ, Tam F, Staines WR, Graham SJ**: assessing linear time-invariance in human primary somatosensory cortex with BOLD fMRI using vibrotactile stimuli. Mag Reson Med 53:304-311 (2005)
25. **Krings T, Erberich SG, Roessler F, Reul J, Thron A**: MR blood oxygenation level-dependent signal differences in parenchymal and large draining vessels: implications for functional MR imaging. Am J Neuroradiol 20:1907-1914 (1999)
26. **Lee AT, Glover GH, Meyer CH**: Discrimination of large venous vessels in time-course spiral blood-oxygen-level-dependent magnetic-resonance functional neuroimaging. Mag Reson Med 33:745-754 (1995)

기능성 자기공명영상에서 진동자극에 대한 감각피질의 비선형성

상지대학교 의과대학 한방의료공학과

이 현 숙

기능성 자기공명영상을 이용하여 진동자극에 대한 감각피질의 비선형성에 대하여 연구하였다. 진동자극은 25 Hz의 주파수로 5개의 각기 다른 진동 자극 기간, 2초, 4초, 8초, 12초 그리고 16초와 함께 20초의 무자극 주기와 pseudo-random순서로 구성되었다. 감각피질에 대한 자극 기간의 변화에 따른 선형성을 이해하기 위하여 두 다른 방법(시스템의 선형성 조사법과 gamma-variate 함수를 적용하여 impulse response함수를 구하는 방법)을 사용하여 혈류반응 함수를 분석하였는데, 그 결과는 거의 비슷하였다. 감각피질에서의 BOLD 반응은 8초보다 작은 자극 기간 동안에는 비선형이고 8초 이상일 때는 선형성을 보였다. 자극 기간의 함수로 impulse response 함수의 진폭, 면적, 피크까지의 시간, FWHM을 계산하였고 진폭과 면적의 크기는 자극 기간이 증가할 때 감소함을 보여줌으로써 자극 기간 8초에서 BOLD 반응이 비선형성에서 선형성으로 변함을 뒷받침해 주었다.

중심단어: 기능성 자기공명영상, 진동자, 선형성, 감각피질, 뇌활성도