International Journal of Biological, Life and Agricultural Sciences
ISSN: 2415-6612
Vol:5, No:10, 2011

Mirror Neuron System Study on Elderly Using Dynamic Causal Modeling fMRI Analysis

R. Keerativittatayut, B. Kaewkamnerdpong, J. Laothamatas, and W. Sungkarat

Abstract**—**Dynamic Causal Modeling (DCM) functional Magnetic Resonance Imaging (fMRI) is a promising technique to study the connectivity among brain regions and effects of stimuli through modeling neuronal interactions from time-series neuroimaging. The aim of this study is to study characteristics of a mirror neuron system (MNS) in elderly group (age: 60-70 years old). Twenty volunteers were MRI scanned with visual stimuli to study a functional brain network. DCM was employed to determine the mechanism of mirror neuron effects. The results revealed major activated areas including precentral gyrus, inferior parietal lobule, inferior occipital gyrus, and supplementary motor area. When visual stimuli were presented, the feed-forward connectivity from visual area to conjunction area was increased and forwarded to motor area. Moreover, the connectivity from the conjunction areas to premotor area was also increased. Such findings can be useful for future diagnostic process for elderly with diseases such as Parkinson's and Alzheimer's.

Keywords**—**Mirror Neuron System (MNS), Dynamic Causal Modeling (DCM), Functional Magnetic Resonance Imaging (fMRI)

I. Introduction

MIRROR Neuron System (MNS) is the brain system that neurons are activated due to a surrogate perception. In 1992, MNS was discovered from single-neuron microelectrode recordings in macaque monkey. Since then, other evidences of imitation or mirror system have been found [5-9]. In 1999, the discovery of MNS in human was published and become one of the most important discoveries in the field of cognitive neuroscience [10-12]. MNS studies in human have shown the activation in premotor area while viewing movies, hearing sounds, or reading action-related sentences [8]. The neuroimaging research in human [10, 11, 13-18] suggested that the main areas composed in MNS system include Brodmann area (BA) 44 in the premotor cortex, the temporal lobe, and the parietal lobe. Moreover, another mirror system was discovered in auditory system [8]; it was found that the activated areas for auditory stimuli were in left temporal–parietal–frontal, right temporal–parietal–frontal, medial frontal and medial occipital. Because invasive MNS studies are not appropriated to conduct in human, fMRI (functional Magnetic Resonance Imaging) is the method of choice for MNS studying.

Visual stimuli are commonly used in fMRI experiments because they are easy to be presented to subjects in MRI scanners. Many research use fMRI for MNS study to identify the related area in MNS system. In this study, the mechanism of MNS system is investigated. There are many research models addressing functional brain network. Dynamic Causal Model (DCM), a method creatively applying engineering techniques to analyze neuroimaging data, is used in this study. DCM is used to test designed hypotheses on neuronal interactions and effects among brain regions. An MNS responding to visual stimuli provided to the system is studied in this research using DCM- fMRI. Dynamic Causal Modeling (DCM) was introduced by Friston et. al. in 2003 [1]. The authors defined and viewed the meaning of DCM as the model of effective connectivity, i.e., the causal influences of system elements exerting over others, which are essential for studying the functional integration of neuronal populations and for understanding the mechanisms that underlie neuronal dynamics [2]. In the past, a variety of models have been proposed for inferring effective connectivity from neuroimaging data, e.g., regression-based model for psycho-physiological interactions [3], structural equation model [3, 4], multivariate autoregressive models, and dynamic causal model [1]. The main idea of DCM is to treat the brain as a deterministic nonlinear dynamic system that is subject to inputs and produces outputs [1]. Effective connectivity is parameterized in terms of coupling among unobserved brain states (neuronal activities in different regions). The objective is to estimate these parameters by perturbing the system and measuring the response. This is in contradistinction to established methods for estimating effective connectivity from neurophysiological time series, which include structural equation modeling and models based on multivariate autoregressive processes.Therefore, the aim of this work is to study the functional brain network model focused on the use of visual tasks to explore the Mirror Neuron System in the elderly group with fMRI images. Our goal is to use DCM to characterize the effective connectivity of Mirror Neuron System and, possibly, to use the obtained information for future diagnostic investigation in elderly patients. This paper is elaborated into 5 sections: I – introduction; II – methodology, comprising participants, stimuli and procedure, functional MRI and data acquisition, Statistical Parametric Mapping (SPM) analysis, and Dynamic Causal Modeling (DCM) analysis and describing how to construct the models; III – the result of standard fMRI and DCM analysis; IV– discussion; V – conclusion.

R. Keerativittayayut and B. Kaewkamnerdpong are with the Biological Engineering Program, King Mongkut's University of Technology Thonburi (KMUTT),Bangkok,Thailand(email:ruadeerat_321@hotmail.com,boonserm.kae@kmutt.ac.th).

J. Laothamatas and W. Sungkarat are with Radiology Dept. and Advanced Diagnostic Imaging and Image-Guided Minimal Invasive Therapy Center, Ramathibodi Hospital, Faculty of Medicine, Mahidol University, Bangkok, Thailand (email: sungkarat@gmail.com).

II. Methodology

A. Participants

The fMRI data were collected from 20 healthy elderly volunteers that are recruited by Ramathibodi hospital for Thai Brain Mapping and/or Surveying and Following-up Dementia in Thai Adults research projects. The inclusion criteria were: 60 -70 years of age, no neurologic or psychiatric disorder, and no cognitive complaint. Demographic and health characteristics of the sampled group are shown in Table I.

TABLE I
DEMOGRAPHIC AND HEALTH CHARACTERISTICS OF THE ELDERLY VOLUNTEERS

Demographic & health characteristic	**Elderly Group n = 20 Mean (SD)/n(%)**
Age	66.50 (4.18)
Female	18 (90%)
Education year	14.55 (2.62)
MMSE* score	19
Health characteristic	
- Hypertension	4 (20%)
- Dyslipidemia	9(45%)
- Angina	0(0%)
- Myocardial infarction	0(0%)
- DM	0(0%)
- Smoking	0(0%)
- Drinking	0(0%)

*MMSE = The mini–mental state examination, the test for screening cognitive impairment patient

B. Stimuli and procedure

The block-design fMRI visual stimuli (3 kinds) were: tearing-paper movie watching, fixation-point watching, and tearing-paper still picture watching. Figure 1 is the graphical plot of hemodynamic response function convolved sequences.

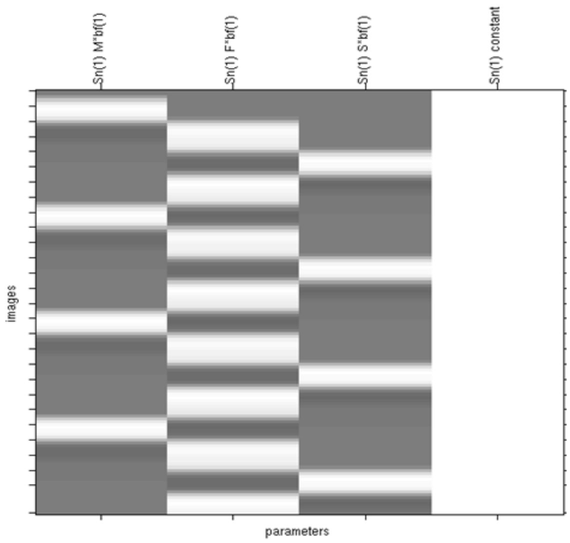

Fig. 1 SPM's design matrix of the stimulus sequence

TABLE II
PERIOD AND TIME FOR EACH STIMULUS CONDITION

Condition	**Period**	**Time(s)**
Movie	15	0, 70, 140, 210
Fixed point	20	15, 50, 85, 120, 155, 190, 225 260
Still movie	15	35, 105, 175, 245

C. Functional MRI and data acquisition

Functional MRI was conducted on a Philips Achieva 3.0-T scanner. One hundred and forty echo-planar images (EPI), blood oxygenation level-dependent (BOLD) effect sensitive images, were collected (28 axial slices to cover the whole brain, 4 mm slice thickness, 128x128 image matrix, TR = 2000 ms). The visual stimuli were presented via a fiber optic goggle display. For anatomical details, a T1-weighted image was scanned.

D. Statistical parametric mapping analysis (SPM)

The signal change induced by the BOLD effect is very subtle and hard to be directly detected. Therefore, repeated measurements are needed for a statistical analysis. In this study, Statistical Parametric Mapping (SPM) was used to identify activated voxels for every volunteer and to conduct the group analysis. SPM is an open source statistical software package for analyzing neuroimage data. In brief, for each data set the anatomical image (T1-weighted) was registered to the EPI images. Next, slice timing correction was done to temporally interpolate multi-slice data with different sampling time points to be as if the whole volume image was sampled at the same time. Then, normalization was performed. In the process, EPI and anatomical T1-weighted images are morphed into a Montreal Neurological Institute (MNI)'s brain template. The normalization refers to stretching, rotating and warping brains from individuals so that the result images are aligned in the standard space (MNI space in this study). Once a volume image has been normalized, its brain size and shape approximately matches those of normalized brain images of the group. This allows us to make a group comparison of the results. The last pre-processing step was image data smoothing with 8 mm full width at half maximum (FWHM) Gaussian kernel. SPM uses General Linear Model (GLM) to fit the time-series image data voxel by voxel. The hypothesis testing of the data is based on t-statistics. After a certain threshold was set (p-value), voxels with t-scores surpassing the threshold corresponding to the p-value could be displayed in color. Finally, the results from all individual data sets were analyzed as a group using one-sample t-test (group analysis) mode in SPM.

E. Dynamic causal modeling analysis

Dynamic Causal Modeling (DCM) tool in SPM2 package was utilized to analyze the functional connectivity of the MNS in fMRI data. In brief, DCM is a model to estimate the parameters of neuronal state and hemodynamic equation when a brain system is disturbed by a specific stimulus. The meaning of "causal" is the effective connectivity influences among neuronal populations [1][19]. Therefore, the denotation of this model is the model of causal interaction explaining regional effects in terms of interregional connectivity. The parameters in DCM including the extrinsic influence of inputs on regional responses, intrinsic connections between regions, and modulatory effects can be estimated.

a) *Region selection*

According to DCM, regions or volumes of interest (VOIs) have to be chosen for functional connectivity analysis. The fMRI group analysis result of "tearing-paper movie watching" against "fixation-point watching" (M>F) was used for choosing VOIs. Each region was defined by using a VOI with the diameter of 10 mm, centered around the most significant voxel (the area with most activated color) at $p < 0.001$, corrected. Four activated areas that are precentral gyrus, inferior parietal lobule, inferior occipital gyrus, and supplementary motor area (SMA) were selected for the DCM analysis.

b) *Definition of inputs and model selection*

Because only partial information about the interaction among all regions was known, plausible models were designed in order to find the optimal model; Bayesian model selection (BMS) method was used. To compare the models, Bayes factor (BF) was calculated based on Bayesian information criterion (BIC) and Akaike information criterion (AIC). Firstly, we defined a basic model consisting of the four regions (precentral gyrus, inferior parietal lobule, inferior occipital gyrus, and SMA) with full reciprocal connections and visual stimulus input at the visual area (inferior occipital gyrus). It is well-known that visual area plays an important role as a processor and an interpreter of the sensory information from the eyes and, then, sends the information to upper cortical areas, SMA and precentral gyrus to work in concert in moving body parts. Then, parietal lobe deals with perception and integrates sensory inputs. However, among those associated areas of this MNS, interaction, modulation, feed-backward, and feed-forward information have not been established. Therefore, all possible modulatory models were generated with various modulatory effects specifying onto the intrinsic connections in the basic DCM model.

c) *DCM Group Average*

Finally, the parameters of the best model were averaged across all volunteers.

III. RESULTS

A. Statistical parametric mapping analysis results

SPM2 was used for image processing and statistical analysis. The common brain areas engaged in stimulus conditions were identified by a group analysis. The statistical threshold was set at $p < 0.001$, uncorrected. The general network of brain areas involved during visual search was defined by the group analysis of both task conditions relative to the visual fixation baselines. A large number of cortical regions including parietal, frontal, occipital–temporal cortical regions and primary visual cortex, as well as several sub-cortical structures were activated with a significant threshold of $p<0.001$ (FDR corrected) as shown in Fig. 2.

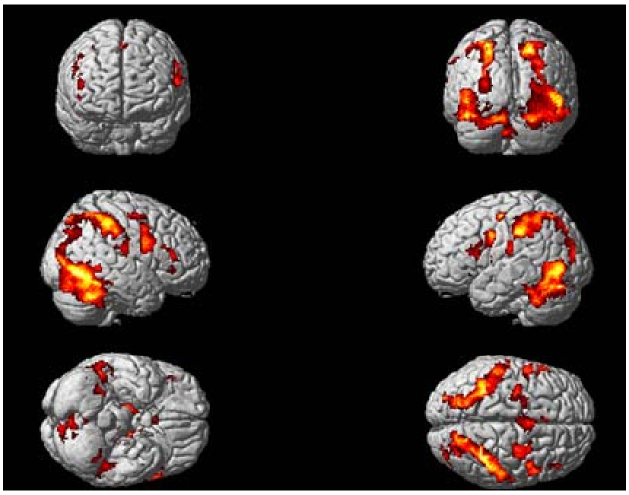

Fig. 2 fMRI group analysis result

In defining the voxel of interest (VOI) for DCM analysis, four regions were selected based on the most activated areas relating to the experiment hypothesis (Mirror Neuron System). The locations of all regions were verified with SPM anatomy toolbox at precentral Gyrus, inferior parietal lobule, inferior occipital gyrus, and supplementary motor area (SMA); the voxel of interest locations are included in Table III.

TABLE III
THE LOCATIONS OF VOIS IN CONTROL GROUP

Region	Location		
	X	Y	Z
pre central gyrus	-28	-10	52
inferior parietal lobule	-36	-42	44
inferior occipital gyrus	-46	-78	2
supplementary motor area SMA	2	-2	52

B. Dynamic Causal Modeling results

When comparing all candidate models (Figure 3 shows 4 example models of 30 models), the model with feed-forward connection from occipital gyrus (Figure 3(a) or Figure 5) was better than the rest. Therefore, the best model in this study is compared with the basic model (with full reciprocal connection as shown in Figure 4). The intrinsic connection of the basic model with posterior densities is equal to 0.1946. After providing the visual stimulus into the system, the feed-forward connectivity between inferior occipital gyrus to inferior parietal lobule, inferior occipital gyrus to SMA, inferior parietal lobule to precentral gyrus, and SMA to precentral gyrus are all increased (when comparing with basic model without stimulus as shown in Figure 4). Nevertheless, the feed-backward connectivity (from premotor area comeback to input receiver) is fairly constant.

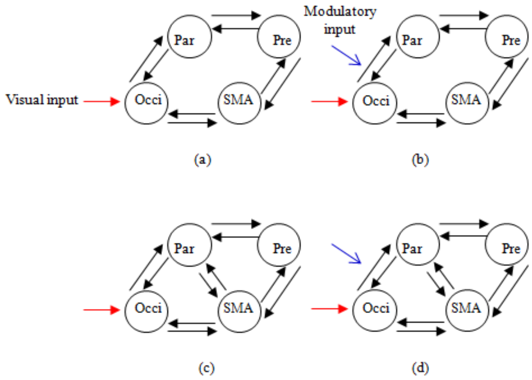

Fig. 3 (a) The model with visual stimulus; (b) the model including a modulatory input; (c) the model with the connection between inferior parietal lobule and SMA; (d) the model with modulatory input and the connection between inferior parietal lobule and SMA

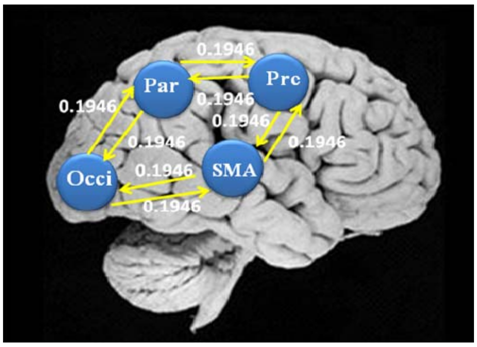

Fig. 4 The basic model without the visual stimulus

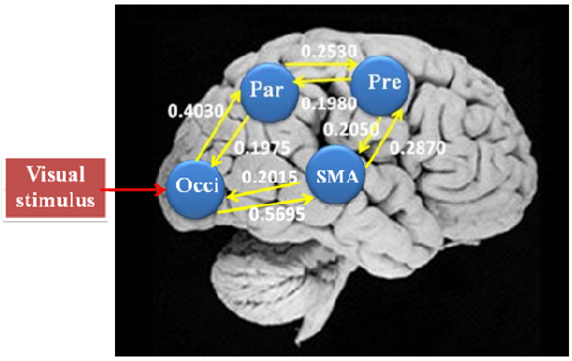

Fig. 5 The best model with the visual stimulus

IV. Discussion

The result from fMRI analysis revealed four brain regions that are related to the provided visual stimulus; these regions are precentral gyrus, inferior parietal lobule, inferior occipital gyrus, and supplementary motor area (SMA). From many hypotheses of the pathway for MNS mechanism, using DCM analysis the model as illustrated in Figure 3(a) and Figure 5 is the most plausible representative of MNS mechanism. The visual stimulus is presented to inferior occipital gyrus (located in visual cortex). There are two reciprocal connection paths from inferior occipital gyrus to precentral gyrus; one is through inferior parietal lobule while the other is through supplementary motor area. When compared with the basic model without visual stimulus, the mirror neuron system mainly responds to the stimulus only in the feed-forward connectivity from visual cortex to premotor area but merely in the feed-backward connectivity.

The results indicate that the signal from the visual area is transferred in parallel connectivity to the premotor area. Nevertheless, we designed 30 candidate models in total with distinct hypotheses and conducted the experiments. The models with reciprocal connectivity between inferior parietal lobule and SMA as shown in Figure 3(c) are also included. After comparing the model by using Bayesian model selection (BMS), we found that the model without the connectivity between these areas was better than other models. Additionally, there was no better model even those with modulation effects. Therefore, the mechanism of mirror neuron effects in the elderly can be illustrated in Figure 4 and 5. According to the results, the simple connection system that premotor area responding to the visual stimulus occurred when a subject watching an action such as tearing paper; there is no complex mechanism involved.

V. Conclusion

We investigated the mirror neuron system in an elderly group. When the subject views tearing-paper movie, not only the visual area was activated but also the effective connectivity was increased in the premotor area. Our findings from DCM-fMRI analysis suggested that the MNS system that we observed is consisted of four main regions: precentral gyrus, inferior parietal lobule, inferior occipital gyrus, and supplementary motor area (SMA). The feed-forward connectivity in the connection between the visual area to inferior parietal lobule and to SMA facilitates the cascade of neuronal signals to premotor area (increased connectivity in each connection). Our results are just from a preliminary study; however, they may be useful information for a diagnostic MRI investigation in the future, for an example, using DCM-fMRI to investigate the connectivity change of a MNS. It may help to determine the risks for diseases such as Parkinson’s or Alzheimer’s disease. Moreover, it may be useful for evaluating the disease state.

Acknowledgment

This research is supported by Advanced Diagnostic Imaging and Image–Guided Minimal Invasive Therapy Center (AIMC) at Ramathibodi Hospital, Thai Brain Mapping Project, Surveying and Following-up Dementia in Thai Adults Research Project. Moreover, this research is supported by National Research Council of Thailand (NRCT).

REFERENCES

[1] Friston, K.J., Harrison, L., and Penny, W., 2003, "Dynamic Causal Modelling", NeuroImage, Vol. 19, pp. 1273–1302.

[2] Friston, K.J., 2002, "What Can Neuroimaging Tell Us Abut Distributed Circuitry? Ann. Rev", Neuroscience, Vol. 25, pp. 221–250.

[3] Friston, K.J., Büchel, C., Fink, G.R., Morris, J., Rolls, E., and Dolan, R.J., 1997, "Psychophysiological and Modulatory Interactions in Neuroimaging", NeuroImage, Vol. 6, pp. 218-229.

[4] McIntosh, A.R., Grady, C., Ungerleider, L.G., Haxby, J.V., Rapoport, S.I., and Horwitz, B., 1994, "Network Analysis of Cortical Visual Pathways Mapped with Pet", neuroscience, Vol. 14, pp. 655-666.

[5] Fogassi, L., 2011, "The Mirror Neuron System: How Cognitive Functions Emerge from Motor Organization", Journal of Economic Behavior & Organization, Vol. 77, pp. 66–75.

[6] Fogassi, L., Ferrari, P.F., Gesierich, B., Rozzi, S., Chersi, F., and Rizzolatti, G., 2005, "Parietal Lobe: From Action Organization to Intention Understanding", Science, Vol. 308, pp. 662–667.

[7] Fogassi, L. and Luppino, G., 2005, "Motor Functions of the Parietal Lobe", Current Opinion in Neurobiology, Vol. 15, pp. 626-631.

[8] Galati, G., Committeri, G., Spitoni, G., Aprile, T., Russo, F.D., Pitzalis, S., and Pizzamiglio, L., 2008, "A Selective Representation of the Meaning of Actions in the Auditory Mirror System", NeuroImage, Vol. 40, pp. 1274–1286.

[9] Gallese, V., Fadiga, L., Fogassi, L., and Rizzolatti, G., 1996, "Action Recognition in the Premotor Cortex", Brain, Vol. 119, 2, pp. 593–609.

[10] Iacoboni, M., 2005, "Neural Mechanisms of Imitation", Current Opinion in Neurobiology, Vol. 15, 6, pp. 632–637.

[11] Iacoboni, M. and Dapretto, M., 2006, "The Mirror Neuron System and the Consequences of Its Dysfunction", Nature Reviews Neuroscience, Vol. 7, 12, pp. 942–951.

[12] Iacoboni, M., Woods, R.P., Brass, M., Bekkering, H., Mazziotta, J.C., and Rizzolatti, G., 1999, "Cortical Mechanisms of Human Imitation", Science, Vol. 286, pp. 2526–2528.

[13] Decety, J., Chaminade, T., Grezes, J., and Meltzoff, A.N., 2002, "A Pet Exploration of the Neural Mechanisms Involved in Reciprocal Imitation", NeuroImage, Vol. 15, pp. 265–272.

[14] Fabbri-Destro, M. and Rizzolatti, G., 2008, "Mirror Neurons and Mirror Systems in Monkeys and Humans", Physiology, Vol. 23, pp. 171–179.

[15] Grafton, S.T., Arbib, M.A., Fadiga, L., and Rizzolatti, G., 1996, "Localization of Grasp Representations in Humans by Positron Emission Tomography. 2. Observation Compared with Imagination", Exp. Brain Res, Vol. 112, pp. 103–111.

[16] Grezes, J., Armony, J.L., Rowe, J., and Passingham, R.E., 2003, "Activations Related to “Mirror” and “Canonical” Neurones in the Human Brain: An Fmri Study", NeuroImage, Vol. 18, pp. 928–937.

[17] Lamm, C., Fischer, M.H., and Decety, J., 2007, "Predicting the Actions of Others Taps into One's Own Somatosensory Representations—a Functional Mri Study", Neuropsychologia, Vol. 44, pp. 2480–2491.

[18] Rizzolatti, G., Fogassi, L., and Gallese, V., 2001, "Neurophysiological Mechanisms Underlying the Understanding and Imitation of Action", Nat. Rev. Neurosci, Vol. 2, pp. 661–670.

[19] Marreiros, A.C., Kiebel, S.J., and Friston, K.J., 2008, "Dynamic Causal Modelling for Fmri: A Two-State Model", NeuroImage, Vol., pp. 269–278.