Deconvolution analyses with tent functions reveal delayed and long-sustained increases of BOLD signals with acupuncture stimulation

Tomokazu Murase[1], Masahiro Umeda[2], Yuko Kawai[2], Yasuharu Watanabe[2], Shoji Naruse[3], Chuzo Tanaka[1], and Toshihiro Highchi[1]

[1]Department of Neruosurgery, Meiji University of Integrative Medicine., Nantan, Kyoto, Japan, [2]Department of Medical Informatics, Meiji University of Integrative Medicine., Nantan, Kyoto, Japan, [3]Daini Okamoto General Hospital, Uji, Kyoto, Japan

Introduction Typically, functional magnetic resonance imaging (fMRI) studies of acupuncture have been performed using block designs and analyzed using a general linear model (GLM). However, recent studies have questioned the equivalence of stimulations with sensations in block-design acupuncture experiments [1-2]. Furthermore, a previous study showed that prolonging of the needling sensation introduced by acupuncture needling could occur [3]. We reported that changes in the blood-oxygen-level-dependent (BOLD) signals caused by acupuncture stimulation was sustained for approximately 15 s, even after the cessation of acupuncture stimulation, by using independent component analysis (ICA) [Murase et al, ISMRM 2012:2146]. However, by using the ICA method, the temporal BOLD signal changes of each activation area could not be obtained separately. Therefore, we focused on the temporal changes in brain activity caused by acupuncture stimulation with deconvolution analysis to analyze brain responses without the expected reference function.

Methods Twenty-six healthy right-handed subjects (men, 16; women, 10; age range, 20–33 years) were divided into 2 groups. One group (N = 13; 8 men and 5 women) received real acupuncture stimulation with manual manipulation; the other group (N = 13; 8 men and 5 women), which was considered as the control, received tactile stimulation with sham acupuncture (noninsertive) stimulation and scrubbing stimulation. Acupuncture stimulation was applied by bidirectional needle rotation to approximately 180° with even motion at a frequency of 1 Hz. Tactile stimulation consisted of 2 types: tapping the skin at the LI4 with a size 5.88 von Frey monofilament (sham acupuncture stimulation) and scrubbing the skin on the palm using a sponge at 4 Hz.

All fMRI runs consisted of block designs with four 15-s stimulation blocks (on) interspersed between one 30-s and four 45-s rest blocks (off). All experiments were performed using a GE 1.5-T Signa MRI system with a standard head coil. The subjects underwent gradient echo type-echo planar imaging (GRE-EPI) with the following parameters: thickness, 5 mm; matrix, 64 × 64; field of view (FOV), 22 × 22 cm^2; repetition time (TR), 3000 ms; echo time (TE), 50 ms, 30 axial slices, and 90 time points.

Data analysis was performed using a combination of analysis packages, including Statistical Parametric Mapping 8, MarsBaR, and Analysis of Functional NeuroImages (AFNI) software. For statistical analysis, 3dDeconvolve, which is part of the AFNI package, was used to extract the impulse response functions (IRFs) of the fMRI signals on a voxel-wise basis. First, we assumed that 20 TRs, which included 5 TR periods for stimulation, were long enough for extracting IRFs. Then, the 11 tent basis functions (^{1}T–^{11}T) covering -2 to 18 TRs (relative to the stimulus onset) were used to estimate the fitting coefficient (beta estimate). To eliminate the variance in each condition of interest across subjects, a random-effects analysis was performed using a 1-sample *t* test at each voxel across subjects based on their individual beta maps ($p < 0.001$, uncorrected). Further, to examine the IRF, a cubic region of interest was defined using a set of voxels in a 4 × 4 × 4-mm^3 portion centered in the maximum *t* value for the area of activation cluster within the Brodmann area. Finally, the time courses of the extracted IRFs were tested at each time point across the stimulations. A one-way ANOVA, followed by a Bonferroni correction were performed for statistical comparisons.

Results & Discussion Figure 1 shows the extracted IRFs in the various brain regions. These data were consistent with the IRFs obtained after deconvolution analysis. In real acupuncture, areas of stimulus-induced activation were observed in the primary somatosensory cortex (SI), secondary somatosensory cortex (SII), insula, anterior cingulate cortex (ACC), thalamus, and prefrontal cortex. Delayed and long-sustained increases of the signal induced by the real acupuncture were observed after stimulation in these areas. Conversely, in sham acupuncture and scrubbing stimulations, areas of stimulus-induced activation were observed in the SI, SII, and insula. In the SI and SII, scrubbing-induced signal increases during the period of stimulation were significantly larger than that during other periods. Sham acupuncture and scrubbing evoked responses that decreased more rapidly after cessation of the stimuli than those evoked in real acupuncture. Especially, in real acupuncture, significantly delayed and long-sustained increases of BOLD signals were observed in several brain regions related to pain perception than those observed in sham acupuncture and palm scrubbing. We suggest that the delayed and long-sustained signal increases were caused by peripheral nociceptors, flare responses, and processing of the central nervous system.

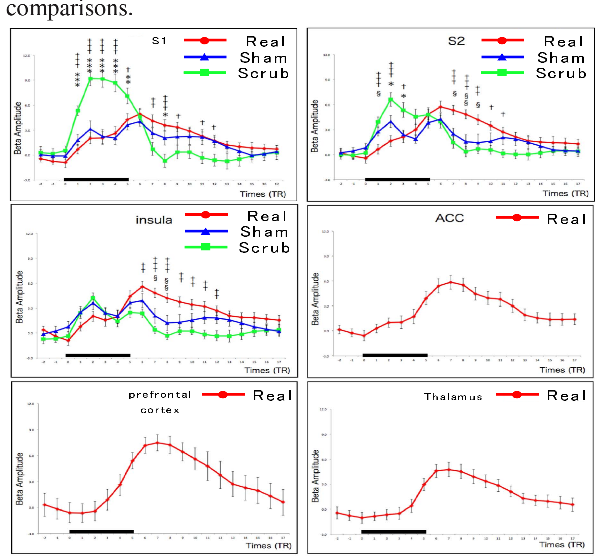

Figure 1 Time-course of the extracted impulse response functions (IRFs; means ± standard error [SE]) for real acupuncture (red), sham acupuncture (blue), and scrubbing (green) stimulations in the area of the activation cluster.

$P < 0.05$: §, †, *; $P < 0.01$: §§, ††, **; $P < 0.001$: §§§, †††, ***; Real-Sham: §; Real-Scrub: †; Sham-Scrub: *

Conclusion We used deconvolution with tent basis function for processing the fMRI data for acupuncture stimulation, and we found delayed increasing and delayed decreasing BOLD signal changes in areas related to pain perception. Further, deconvolution analyses with tent functions are considered as useful in the extraction of complicated, associated brain activity that is delayed and sustained for a long period after various stimulations.

Reference [1] Ho TJ, et al. Am J Chin Med. 2008; 36(1):55-70; [2] Bai L, et al. Hum Brain Mapp. 2009; 30(11):3445-60; [3] Ho TJ, et al. J Altern Complement Med. 2007; 13(1):13-14.