Original article

Temporally shifted hemodynamic response model helps to extract acupuncture-induced functional magnetic resonance imaging blood oxygenation-level dependent activities

Tsung-Jung Ho, Jeng-Ren Duann, Chun-Ming Chen, Jeon-Hor Chen, Wu-Chung Shen, Tung-Wu Lu, Jan-Ray Liao, Zen-Pin Lin, Kuo-Ning Shaw and Jaung-Geng Lin

Keywords: *acupuncture; magnetic resonance imaging, functional; blood oxygenation-level dependent responses*

Background The onsets of needling sensation introduced by acupuncture stimulus can vary widely from subject to subject. This should be explicitly accounted for by the model blood oxygenation-level dependent (BOLD) time course used in general linear model (GLM) analysis to obtain more consistent across-subject group results. However, in standard GLM analysis, the model BOLD time course obtained by convolving a canonical hemodynamic response function with an experimental paradigm time course is assumed identical across subjects. Although some added-on properties to the model BOLD time course, such as temporal and dispersion derivatives, may be used to account for different BOLD response onsets, they can only account for the BOLD onset deviations to the extent of less than one repetition time (TR).

Methods In this study, we explicitly manipulated the onsets of model BOLD time course by shifting it with –2, –1, or 1 TR and used these temporally shifted BOLD model to analyze the functional magnetic resonance imaging (fMRI) data obtained from three acupuncture fMRI experiments with GLM analysis. One involved acupuncture stimulus on left ST42 acupoint and the other two on left GB40 and left BL64 acupoints.

Results The model BOLD time course with temporal shifts, in addition to temporal and dispersion derivatives, could result in better statistical power of the data analysis in terms of the average correlation coefficients between the used BOLD models and extracted BOLD responses from individual subject data and the T-values of the activation clusters in the grouped random effects.

Conclusions The GLM analysis with ordinary BOLD model failed to catch the large variability of the onsets of the BOLD responses associated with the acupuncture needling sensation. Shifts in time with more than a TR on model BOLD time course might be required to better extract the acupuncture stimulus-induced BOLD activities from individual fMRI data.

Chin Med J 2009;122(7):823-829

The emergence of acupuncture, a traditional oriental healing technique, can be traced back to at least 2500 years ago. It was first named by western medical society as alternative medicine, and was now renamed as "complementary medicine" after its effectiveness in treating many conditions.[1,2] Recently, WHO published 64 symptoms, which acupuncture has proven effective to cure or relieve. For example, acupuncture has been successfully applied to chronic pain, fatigue, nausea, arthritis, and digestive problems.[3-6] In 1997, the US National Institute of Health issued a report claiming that acupuncture is a useful method for treating many conditions with fewer side effects compared with other medical procedures, such as surgery or pharmaceuticals. It also suggested that the acupuncture treatment should be covered by health insurance. This suggestion has had large impact on the status of acupuncture. However, as acupuncture has been gaining more and more attention in the medical society, the mechanism of how it can be of use is still controversial.

The discovery of opioid peptides release by acupuncture[7,8] and modern neurophysiological evidences,

DOI: 10.3760/cma.j.issn.0366-6999.2009.07.012
School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taiwan, China (Ho TJ)
Chinese Medicine Department, China Medical University Beigang Hospital, Taiwan, China (Ho TJ)
Institute for Neural Computation, University of California San Diego, La Jolla, CA, USA (Duann JR)
Department of Radiology, China Medical University Hospital, Taichung, Taiwan, China (Chen CM, Chen JH and Shen WC)
Department of Electric Engineering, National Chung-Shin University, Taichung, Taiwan, China (Chen CM and Liao JR)
Institute of Biomedical Engineering, National Taiwan University, Taipei, Taiwan, China (Lu TW)
Department of Holistic Wellness, MingDao University, Taiwan, China (Lin ZP)
ChangHwa Hospital, Department of Health, Executive Yuan, Taiwan, China (Shaw KN)
Graduate Institute of Acupuncture Science, China Medical University, Taiwan, China (Lin JG)
Correspondence to: Dr. Jaung-Geng Lin, Graduate Institute of Acupuncture Science, China Medical University, 91 Hsueh-Shih Rd., Taichung 404, Taiwan, China (Tel: 886-4-22053366 ext 3111. Email: jglin@mail.cmu.edu.tw)
Tsung-Jung Ho and Jeng-Ren Duann equally contributed to this work.
This study was supported by National Science Council (No. NSC93-WFD-240-5095 and NSC93-WFD-240-5129), Taiwan, China.

especially in the field of acupuncture analgesia, suggest that the effect of acupuncture may be transmitted through the neuronal system. In an acupuncture functional magnetic resonance imaging (fMRI) experiment with stimulus on the BL67 acupoint, Cho et al[9] presented the first evidence revealing the neurological effects induced by acupuncture, which equivalently induced increasing blood oxygenation-level dependent (BOLD) signal in the primary visual cortex as a passive visual stimulation of light could do. BOLD signal induced local cerebral oxygenation changes due to the neural activities in the brain areas involving in the brain processes in response to the endogenous or exogenous events. Such oxygenation effects can further alter the fractions of oxy- and deoxy-hemoglobin and, in turn, change the MR $T2^*$ properties in the brain areas. This changing signal evolving with time can be detected using specific MR pulse sequences and form so-called fMRI BOLD signal. This BOLD activity induced by acupuncture stimulation has proved related to the neurological mechanism of how acupuncture might work through altering the brain state and, in turn, encourages further research in finding the neural correlates of acupuncture stimulus using functional neuroimaging techniques.[7-9]

With almost identical settings to the study conducted by Cho et al,[9] Siedentoph and colleagues[10] successfully induced the activations in the primary visual cortex by stimulating the BL67 acupoint with laser acupuncture. Li and colleagues[11] were also able to successfully provoke the visual activations with an electro-acupuncture applied to more than one acupoint (connecting positive electrodes to the BL65 and BL67 acupoints and negative electrodes to the BL60 and BL66 acupoints) along the same meridian. However, also with almost identical settings to Cho′s study, except that the acupuncture stimulus was applied to the GB37 (instead of the BL67) acupoint, Gareus and colleagues[12] failed to find any acupuncture-related brain activities. In other similar studies, researchers reported activations in only the hypothalamus in addition to the pain matrix (M1/S1, anterior cingulate cortex, amygdala, hippocampus, superior temporal gyrus, insula, etc) instead of the brain areas supposed to associate with the acupoints stimulated.[13-15]

In the abovementioned studies, they all utilized a block-designed fMRI experiments with multiple ON/OFF blocks. Each block lasted for 20–40 seconds. Previous study has shown that once the needling sensation (the feeling of sourness, numbness, distension, and pain surrounding the needling point) was produced, it would last for from few minutes to even days.[16] In turn, the evoked BOLD responses could be carried over to the upcoming stimulation trials and possibly alter the baseline of the BOLD signals in a multi-block fMRI experiment with sub-minute block length. This might further affect the contrasts between ON and OFF conditions designated for and needed in the data analysis.[17] Furthermore, not only are the offsets of BOLD responses highly subject-dependent, but also are the onsets. The variability of the onsets of BOLD responses across subjects may also cause problems for the predefined model BOLD time course to catch in the data analysis. As a result, the inconsistency between the timings of the BOLD onsets and offsets and the structure of the predefined BOLD contrasts may together obscure finding the acupuncture-induced brain activities.

In this study, we conducted an fMRI study with acupuncture stimuli applied to three acupoints, namely Chong-Yang (ST42), Jing-Gu (BL64), and Qiu-Xu (GB40). As noted, the acupoints we tested in this paper are all the Yuan- (Primary-) acupoints of the corresponding meridians. According to Miraculous Pivot, the Yuan-acupoints are located in the vicinity of the wrist and ankle and thus are very easy to access for daily clinical treatment. The twelve Yuan-acupoints are closely related to the five zang and the six fu organs, and, most importantly, they are the acupoints where the primary Qi of the zang and fu organs is retained. Disorder of the zang-fu organs are usually relieved by needling the twelve Yuan-acupoints.[18] As a result, people have been interested in finding the neural correlates with needling the twelve Yuan-acupoints, especially after the evidence of the neural correlates with needling the acupoints in relation with the primary sensory organs.

However, as mentioned previously, due to the difficulties in conducting fMRI experiments with acupuncture paradigm (for example, the long carryover effects proposed by Ho et al[17]) as well as in analyzing fMRI data, the previous acupuncture fMRI studies have derived inconclusive results. Before the true hemodynamic BOLD responses in relation to the acupuncture stimuli can be pinpointed, it is extremely desirable to refine not only the experimental paradigms, which are able to avoid all sorts of confounding factors associated with acupuncture stimuli, but also the data analysis methods to account for great amount of inter-subject variability. Therefore, in this study, we specifically modeled the onsets of acupuncture stimulus-induced BOLD responses according to each individual-subject data set. The fMRI data were analyzed using general linear model (GLM) as implemented in SPM2 with a predefined model BOLD time course, however, further with the time-to-onset shifted in time with –2, –1, 0, and 1 TR. In so doing, we were to, first, reveal the wide variability of the onsets of the acupuncture-induced BOLD responses across subjects and, more importantly, to demonstrate a better approach to precisely catch the true BOLD onsets specifically to each of the individual subjects.

METHODS

Participants

In total, 56 healthy right-handed subjects (26 females, age range (21.7 ± 2.7) years) participated in this study. None

of these subjects has had pathological history of head trauma, neurological diseases, and substance abuse. None of them reported painful or stressful responses to the experiment and its environment before and after experimental sessions. The Institutional Review Board (IRB) of China Medical University Hospital approved this experimental protocol. All subjects provided their signed consents prior to experiment and understood that they could withdraw from the experiment any time when they felt uncomfortable.

Experimental paradigms

This study included three different acupuncture experiments. They were conducted with exactly the same experimental paradigm; however, the acupuncture stimuli were applied to different acupoints: left ST42, left GB40, and left BL64. After subjects arrived, they were randomly assigned to one of these three experimental groups. Because subjects in ST42 group were scanned for three fMRI runs (with repetitions), we assigned only 11 subjects in this group. For GB40 and BL64 groups, 23 and 22 subjects were assigned to these groups, respectively. For subjects in these two groups, only one fMRI run was scanned.

All participants were requested to come 20 minutes before fMRI sessions. After explaining to them their rights and experimental procedures, an experienced acupuncturist (TJH) performed acupuncture on the subjects′ left ST42, GB40, or BL64 acupoint using an aseptic acupuncture needle (0.25 mm in diameter and 25.4 mm in length). Needle was manipulated by twisting in both clockwise and counterclockwise at a rate of 2 Hz to produce needling sensation and to make sure the needle was inserted in the right position. After needling sensation was produced, the subjects were asked to subjectively rate the strength of their needling sensation, from 0 to 10. The highest score (10) was defined as the maximum level of needling sensation the subjects could ever imagine.[19,20] In all three experiments, all subjects reported needling sensation greater than 8 on average in the prescreening phase.

Subjects were then positioned in the MR scanner after their needling sensation returned to baseline. Before the first acupuncture fMRI run was performed, subjective needling sensation rating was recorded again to confirm that subjects′ needling sensation had returned to baseline (<2 on average). In ST42 experiment, three fMRI runs with acupuncture stimulation followed. Each acupuncture fMRI run consisted of one alternation of 26-second OFF and 26-second ON blocks, starting with OFF condition. During ON period, the acupuncturist manipulated the needle at the same pace as was used in the prescreening phase; during OFF period, acupuncturist kept his right hand off the needle; however, his left hand kept holding subjects′ foot during the entire acupuncture run to avoid subjects′ anticipating the onsets of needle manipulation. In between fMRI runs, we acquired one structural (T1-weight images with identical slice position as prescribed for fMRI scans) and high-resolution 3D anatomical scans to allow subjects′ needling sensation to die down (with at least 8 minutes separation between two consecutive fMRI scans). Subjects′ needling sensation scores were recorded after all three fMRI runs were finished. In GB40 and BL64 experiments, the same experimental paradigm of single 26-second-ON-and-26-second-OFF block was used; however, only one fMRI run was acquired for each individual subject.

Image acquisition

MR images were acquired using a 1.5-T MR scanner (GE Excite-2, Milwaukee, MI, USA) installed in China Medical University Hospital, Taichung, Taiwan, China. For each subject, the fMRI image data were acquired using an echoplanar image sequence (EPI, TR/TE = 2000/60 ms, flip angle = 90°, image matrix = 64 × 64, FOV = 23 cm × 23 cm, resolving a 3.6 mm × 3.6 mm in-plane resolution, slice thickness = 7 mm plus 0.7 mm gap). Eighteen axial slices parallel to the AC-PC line were acquired from brain base to vertex. Each fMRI run consisted of 26 image volumes. Dummy scans were discarded before image data were stored. Anatomical image data were obtained using a 3D Space SPGR sequence (TR/TE = 33/3 ms, flip angle = 35°, image matrix = 256 × 256, FOV 23 cm × 23 cm resulting in a 0.9 mm × 0.9 mm in-plane resolution). A series of 2D T1-weighted images were also acquired using a T1 FLAIR sequence for registering functional images to individual subjects′ brain anatomies.

Data analysis

FMRI data were analyzed using SPM2 running in a Windows XP computer. For ST42 experiment, the data obtained from multiple fMRI runs were analyzed separately as were from three different sessions. All the functional imaging data were first slice timing adjusted to compensate the inhomogeneity introduced by acquiring different images slices at slightly different times. The image volumes were then realigned to the middle (14th) image volume of the image sequence of each fMRI run for motion correction. After motion correction, image data were spatially normalized to the standard MNI brain template and then spatially smoothed using an 8-mm FWHM Gaussian kernel. The preprocessed data were then subjected to GLM analysis to derive fixed effects against the model BOLD signal created by convolving a canonical hemodynamic response function (HRF) with a step function representing the OFF/ON stimulus design time course. Temporal and dispersion derivatives were added to model the onset variability of the stimulus-induced BOLD responses.

In addition, we also temporally shifted the model BOLD time course with –2, –1 and 1 TR to test if the temporal shifts applied to the BOLD model could help to more precisely catch the onsets of the stimulus-induced BOLD responses. The best onset timing for each individual

subject was determined by cross-correlation between the extracted (fitted) BOLD time course resulted from the derived fixed effects and the temporally shifted model BOLD time courses. That is, four GLM analyses with different temporally shifted BOLD models were performed. Subsequently, the one with maximum correlation between the BOLD model and the extracted BOLD response would be selected as the best onset timing. To further evaluate if the temporal shifts helped to improve the statistical power of the GLM analysis, the correlation coefficients between the best fitted BOLD model (with shift) and its corresponding extracted BOLD effects were compared with the correlations between the ordinary BOLD model (without shift) and its extracted BOLD time courses. Paired *t* test was used for the comparison. Furthermore, the fixed effects at individual level obtained with and without temporal shift were grouped using SPM2 second level analysis, respectively, and the statistical power of the group effects would be also compared against each other. A P <0.05 was considered statistically significant.

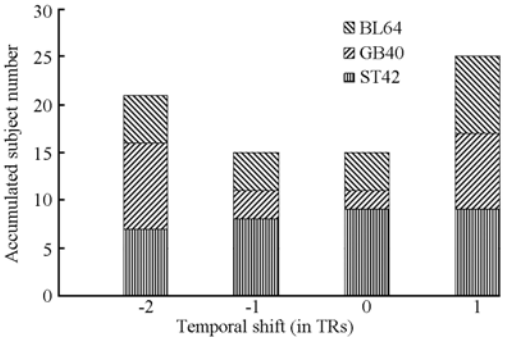

Figure 1. Temporal shifts (in TRs) in hemodynamic response model that gave the optimal correlations between model time course and detected BOLD responses in individual subjects/sessions. Three different shade areas indicated the temporal shift histograms obtained from different acupuncture fMRI studies (stimulation site: ST42, GB40, and BL64, respectively). In ST42 session, there was no significant difference in amount of temporal shifts across subjects. However, in GB40 and BL64 sessions, subjects tended to have late (shifted 1 TR) or very early (shifted –2 TR) BOLD responses to the acupuncture stimuli.

RESULTS

In order to make sure that the needle manipulation during the fMRI runs could successfully produce needling sensation in each subject, a post-interview after the entire fMRI runs was finished confirmed with average needling sensation score higher than 8.

In order to precisely catch the evoked BOLD responses by acupuncture stimulation applied to subjects′ left ST42, GB40, or BL64 acupoint, an explicit temporal shift was applied to the model BOLD signal with the amount of –2, –1, 0 (no shift), or 1 TR (TR = 2 seconds). Figure 1 showed the histogram of the temporal shifts applied to the model BOLD signal to result in maximum correlations between the model BOLD time course and the time courses of extracted BOLD responses for all fMRI runs. Different acupuncture experiments were indicated by different shades in the figure. The size of the bars indicated the number of subjects/sessions having best fitted BOLD responses when the model BOLD time courses were temporally shifted the amount of TRs as indicated by the x-axis. It was clearly seen that most of the subjects tended to have late onset (one TR shift) in response to acupuncture stimulation. This was mainly because that the needling itself took some time to develop a needling sensation. However, there were also considerable amount of subjects who had earlier onsets, which might reflect subjects′ anticipation or the needling sensation induced by the needle itself without further needle manipulation as the needle stayed in the acupoint from the beginning of the fMRI session. This has to be further examined. On the other hand, the analysis with ordinary BOLD model gave relatively worse fit between the time courses of BOLD model and extract BOLD responses.

It was also worth noting that in ST42 experiment the amount of temporal shifts giving best time course fit was not significantly different from setting to setting; however, in GB40 and BL64 experiments, 0 TR shift was significantly less than –2 and 1 TR shifts. This might be because that in ST42 experiment, some of the experimental runs were repetitions and subjects might be more experienced and thus had fewer false alarms regarding the needling sensation. To this end, we explicitly took the onset timings associated with each session and compared, first, if they were significantly deviating from zero and, second, if the onset timings were significantly different across sessions using Wilcoxon signed ranked test. The result showed that there was no significant difference between the onset timings associated with different sessions. However, the onset timings found in the first session were slightly more negative (earlier, P=0.043) compared with the onset timings found in the second (P=0.125) and third (P=0.42) sessions. This further confirmed that for the first session, subjects tended to have earlier onsets due partly to the anticipatory responses to the acupuncture stimulation or the needling sensation induced by the inserted needle with no manual manipulation. In addition, the wide spread of onset timings found in the ST42 experiment also lends itself a good evidence showing the individual differences in the acupuncture-induced BOLD responses across subjects or even across different runs within the same subjects. As a result, manipulation of model BOLD time courses is indeed necessary to extract the evoked BOLD responses with large inter-subject or inter-session variability.

Figure 2 shows the average correlation coefficients between the model BOLD time course (with (shaded) and without (clear) temporal shifts) and the extracted BOLD responses from all the individual fMRI runs. Although both model BOLD time courses with and without

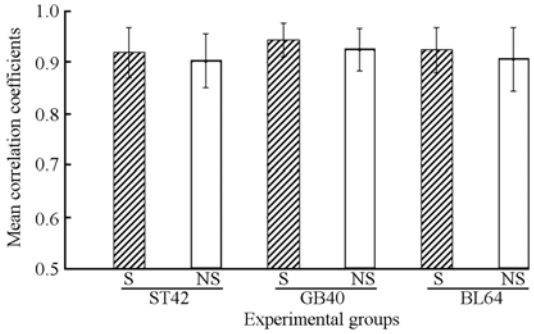

Figure 2. Average correlation coefficients between the model hemodynamic response time course and detected BOLD responses after (indicated by "S") and before (indicated by "NS") temporally shifted the model time course to derive the best fit. All comparison pairs were significant under the confidence interval of P <0.001 using a paired t-test.

temporal shifts all fitted the extracted BOLD response time courses quite well, the resulting average correlations from the BOLD model temporally shifted to better fit the onset timings were still significantly higher (P <0.001) than the correlations resulted from the ordinary ones in all cases.

After fixed effects were extracted from each individual fMRI run using the model BOLD time courses with and without temporal shifts, these individual fixed effects were thresholded with the criterion of FDR-corrected P <0.05 and then spatially smoothed using the Gaussian kernel with 8 mm of full width at half maximum (FWHM). The spatial smoothing was to account for the individual differences in brain anatomies. The processed fixed effects at the individual level were then group analyzed using SPM2 second-level analysis with the "one-sample t-test" option.

Figure 3 shows the group results derived from the individual fixed effects obtained using the model BOLD time courses with (left panel) and without (right panel) temporal shifts. Figure 3A, 3B, and 3C illustrated the 3 glass brain views of the results of ST42, GB40, and BL64 experiments, respectively. In the table, the top two most significant activation clusters as well as their sub-clusters were listed. The table lists the x-, y-, and z-coordinate of the centroid of the main clusters (in mm) as well as the t-values of the activation clusters and the size of the main clusters (in voxel counts). On the left, it showed the results of the group effects obtained with temporal shifts applied to the BOLD model and the ones without on the left.

In these results, the centroid of the main clusters with higher t-values found with and without temporal shifts remained similar to each other; however, for the lower t-value ones started to deviate from each other. In the group effect maps derived from the individual fixed obtained with temporal shifts (left panel in Figure 3), they were more sensitive to find the smaller activation clusters compared with the one derived from the ordinary BOLD model. Most importantly, the results obtained with temporal shifts derived significantly higher t-values (paired t-test, P <0.00002) and broader coverage of the activation clusters in all cases (cluster sizes listed in the Table).

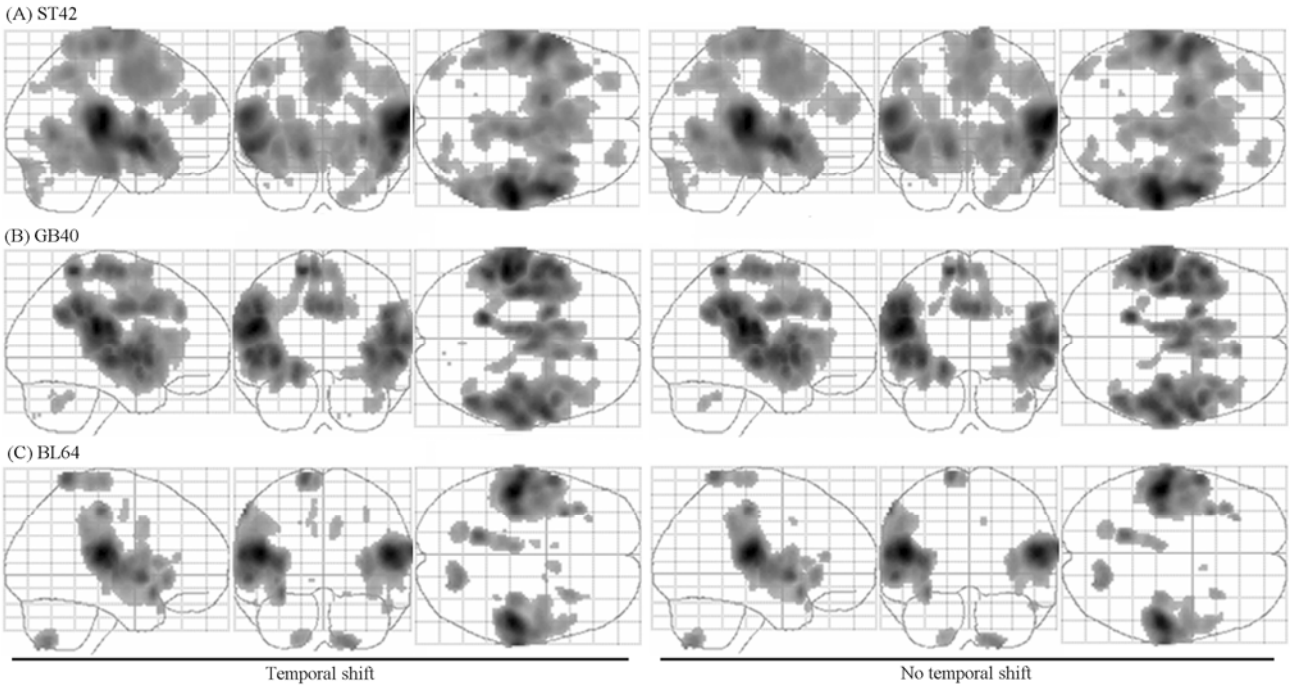

Figure 3. Group effect maps obtained from the individual results derived from the model hemodynamic response function time course with (left panel) and without (right panel) temporal shifts: (**A**) ST42, (**B**) GB40, and (**C**) BL64. There was no significant difference between the two group effect maps in all three fMRI studies. However, with temporal shifts, the group effect maps tended to render broader activation brain areas, some of which might even cross their borders and become one larger group. In addition, the group effects obtained with temporal shifts gave higher statistical powers (seen in the Table).

Table. Comparison of statistical powers of group analysis results derived from the individual results obtained using a temporally shifted version of model hemodynamic response function (columns marked as "shift") versus a fixed version (columns marked as "no shift")

Variables	Cluster	*t* values	Sizes
ST42 (shift)	**62 −24 14**	10.24	23 958
	56 4 −6	8.95	
	−58 −24 16	7.89	
	12 −24 72	5.91	8554
	6 −4 78	5.55	
	6 −6 50	5.26	
ST42 (no shift)	**62 −24 12**	10.16	24 250
	56 4 −6	8.84	
	−58 −24 16	7.90	
	12 −24 72	5.59	8264
	8 −6 74	5.13	
	4 2 54	5.00	
GB40 (shift)	**−52 −30 24**	8.53	14 570
	−54 −22 24	7.45	
	−16 −48 66	6.86	
	56 −2 2	6.86	9215
	52 −34 22	6.62	
	62 −18 14	6.56	
GB40 (no shift)	**−52 −30 24**	7.74	8880
	−54 −22 24	7.04	
	−50 −42 36	6.81	
	62 −18 14	6.36	8283
	56 −2 2	6.20	
	52 −32 18	6.17	
BL64 (shift)	**−48 −24 16**	8.44	6729
	−60 −18 16	7.09	
	−38 −24 10	6.36	
	52 −26 16	8.12	4334
	68 −22 18	6.52	
	36 −26 6	4.94	
BL64 (no shift)	**−48 −24 16**	8.16	5950
	−60 −18 16	6.85	
	−38 −24 10	6.11	
	52 −24 16	7.11	3317
	68 −22 20	6.06	
	34 −24 10	4.39	

This table listed the x-, y-, and z-coordinates of the centroid of the first two most significant activation clusters (in bold face) along with one to two subclusters within these main clusters (in thin face). Table also listed the *t* values of the centroids of all the main- and sub-clusters. The sizes of the main clusters were also given in voxel numbers as listed. The *t* values obtained with and without temporally shifting the HRF model were compared using a paired *t* test. The statistical power obtained with temporal shift was significantly higher compared with the one without (P <0.000 02).

DISCUSSION

In this study, we demonstrated that by altering the onset timing of the model BOLD time course, we were able to find for each subject a specific onset for his/her brain BOLD response to the acupuncture stimulus. These specific BOLD onsets widely varied across subjects/sessions and across the temporal shifts we used (–2, –1, 0, and 1 TR). Most of the subjects tended to have early (–2 TRs) or late BOLD response onsets (1 TR) instead of as specified by the ordinary BOLD model. Although the regular GLM analysis based on the predefined BOLD model can be incorporated with temporal and dispersion derivatives to account for the BOLD onset variability across subjects and fMRI runs, the effectiveness to account for the onset timing variability across different subjects is limited. If the deviation of the BOLD onset is more than one TR, temporal and dispersion derivatives might fail to do the adjustment. This in turn affects the statistical power of data analysis. We showed that by more precisely fitting the onsets of individual BOLD responses, we were able to not only improve the goodness-of-fit between the BOLD model and the associated BOLD responses but also significantly increase the spatial coverage and *t*-values of the derived activation clusters. Some smaller active brain regions were also found by the approach with better BOLD onset-fitting, meaning that the proposed approach could improve the sensitivity and detection rate as well. These smaller activation clusters could otherwise be overlooked if the ordinary BOLD model was used.

Interestingly, with repetition of fMRI runs as was done in ST42 experiment, the histogram of temporal shifts tended to flat out across different amount of shifts. That is to say, the histogram became more evenly distributed. Unlike the cases of GB40 and BL64, wherein only one fMRI run was conducted for each individual subject, the histogram was more toward the two extremes, either early or late onset. This difference might be due to that the subjects′ BOLD activations were more consistent with the onset of needle manipulation when the subjects underwent more than one acupuncture stimulus. However, the wide dispersion of the temporal shifts implies that specific adjustments on the model BOLD time course are needed in data analysis.

Together with the carryover effect introduced by acupuncture-type stimulus, which makes the offset of BOLD activation uncertain and affects data analysis by altering the baseline BOLD signal associated with upcoming stimuli,[17] the uncertainty of BOLD onsets and offsets makes the fMRI data analysis for acupuncture or alike studies non-trivial. This uncertainty might also give an answer to why the results of acupuncture fMRI studies in the literature remain so incongruent. Therefore, a better experimental design as well as data analysis strategy for acupuncture fMRI study needed to be reconsidered.

Based on the results of the current study, we found that the temporal shifts applied to the model BOLD time course were essential to more specifically find the acupuncture-induced BOLD activities in individual subjects. In so doing, it gave significantly better goodness-of-fit between model and extracted BOLD effects as well as higher statistics of the resultant activation brain clusters though the differences in spatial activation maps were subtle. However, such an analysis can sometimes be very time-consuming because at least four analyses will be needed for each single data set (depending on how many temporal shifts users may want to incorporate). Therefore, a data-driven analysis approach may be more preferable for this purpose. With data-driven analysis methods, one can extract the stimulus-related BOLD activities from the data without

specifying the model BOLD time course.[21,22] This in turn gets rid of the tests for best BOLD onsets for each individual image data set and may help to better register the acupuncture-induced BOLD activations without tedious test procedure in data analysis.

Acknowledgment: The authors would like to thank Mr. Chang-Hai Tsai, Chairman of China Medical University and Hospital, for his great support on this study.

REFERENCES

1. Diehl DL, Kaplan G, Coulter I, Glik D, Hurwitz EL. Use of acupuncture by American physicians. J Altern Complement Med 1997; 3: 119-126.
2. Eisenberg DM, Kessler RC, Foster C, Norlock FE, Calkins DR, Delbanco TL. Unconventional medicine in the United States. Prevalence, costs, and patterns of use. New Engl J Med 1993; 328: 246-252.
3. al-Sadi M, Newman B, Julious SA. Acupuncture in the prevention of postoperative nausea and vomiting. Anaesthesia 1997; 52: 658-661.
4. Cheng XD, Wu GC, He QZ, Cao XD. Effect of continued electroacupuncture on induction of interleukin-2 production of spleen lymphocytes from the injured rats. Acupunct Electrother Res 1997; 22: 1-8.
5. Du LN, Wu GC, Cao XD. Modulation of orphanin FQ or electroacupuncture (EA) on immune function of traumatic rats. Acupunct Electrother Res 1998; 23: 1-8.
6. Dundee JW, Ghaly RG, Bill KM, Chestnutt WN, Fitzpatrick KT, Lynas AG. Effect of stimulation of the P6 antiemetic point on postoperative nausea and vomiting. Br J Anaesth 1989; 63: 612-618.
7. Cheng RS, Pomeranz BH. Electroacupuncture analgesia is mediated by stereospecific opiate receptors and is reversed by antagonists of type I receptors. Life Sci 1980; 26: 631-638.
8. Clement-Jones V, McLoughlin L, Tomlin S, Besser GM, Rees LH, Wen HL. Increased beta-endorphin but not met-enkephalin levels in human cerebrospinal fluid after acupuncture for recurrent pain. Lancet 1980; 2: 946-949.
9. Cho ZH, Chung SC, Jones JP, Park JB, Park HJ, Lee HJ, et al. New findings of the correlation between acupoints and corresponding brain cortices using functional MRI. Proc Natl Acad Sci U S A 1998; 95: 2670-2673.
10. Siedentopf CM, Golaszewski SM, Mottaghy FM, Ruff CC, Felber S, Schlager A. Functional magnetic resonance imaging detects activation of the visual association cortex during laser acupuncture of the foot in humans. Neurosci Lett 2002; 327: 53-56.
11. Li G, Cheung RT, Ma QY, Yang ES. Visual cortical activations on fMRI upon stimulation of the visual-implicated acupoints. Neuroreport 2003; 14: 669-673.
12. Gareus IK, Lacour M, Schulte AC, Hennig J. Is there a BOLD response of the visual cortex on stimulation of the visual-related acupoint GB 37? J Magn Reson Imaging 2002; 15: 227-232.
13. Hsieh JC, Tu CH, Chen FP, Chen MC, Yeh TC, Cheng HC, et al. Activation of the hypothalamus characterizes the acupuncture stimulation at the analgesic point in human: a positron emission tomography study. Neurosci Lett 2001; 307: 105-108.
14. Wu MT, Hsieh JC, Xiong J, Yang CF, Pan HB, Chen YC, et al. Central nervous pathway for acupuncture stimulation: localization of processing with functional MR imaging of the brain — preliminary experience. Radiology 1999; 212: 133-141.
15. Wu MT, Sheen JM, Chuang KH, Yang P, Chin SL, Tsai CY, et al. Neuronal specificity of acupuncture response: an fMRI study with electroacupuncture. Neuroimage 2002; 16: 1028-1037.
16. Ho TJ, Duann JR, Shen WC, Lin JG. Needling sensation: explanation of incongruent conclusion drawn from acupuncture FMRI study. J Altern Complement Med 2007; 13: 13-14.
17. Ho TJ, Duann JR, Chen CM, Chen JH, Shen WC, Lu TW, et al. Carryover effects alter FMRI statistical analysis in an acupuncture study. Am J Chin Med 2008; 36: 55-70.
18. Long Z, Tang Y, Geng E. Acupuncture and moxibustion. 1st ed. Seattle: Beijing University of Traditional Chinese Medicine Academy Press; 1999: 53.
19. Beijing College of Traditional Chinese Medicine, Shanghai College of Traditional Chinese Medicine, Nanjing College of Traditional Chinese Medicine, The Acupuncture Institute of the Academy of Traditional Chinese Medicine. Essentials of Chinese acupuncture. Beijing: Foreign Language Press; 1993.
20. Stux G, Pomeranz B. Basics of acupuncture. Berlin: Springer-Verlag; 1998.
21. Duann JR, Jung TP, Kuo WJ, Yeh TC, Makeig S, Hsieh JC, et al. Single-trial variability in event-related BOLD signals. Neuroimage 2002; 15: 823-835.
22. McKeown MJ, Makeig S, Brown GG, Jung TP, Kindermann SS, Bell AJ, et al. Analysis of fMRI data by blind separation into independent spatial components. Hum Brain Mapp 1998; 6: 160-188.

(Received August 20, 2008)
Edited by WANG Mou-yue