NEW fMRI APPROACHES FOR ACUPUNCTURE STUDIES

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Purpose

From the aspect of Chinese Medicine, the effect of acupuncture stimulation could last for quite awhile and even for days. In addition, the onset (De-Qi) timings for different individuals can vary widely. Data analysis, when closely tied to the experimental paradigm, might account for some other brain processes, such as anticipation; since the true De-Qi sensation might arrive later. On the other hand, the lasting effect can make the baseline of the consecutive block dangled from the "true" baseline. Thus, in a common fMRI setting with multiple on/off blocks, the contrast between conditions may be smeared out due mainly to the baseline drifting induced by the lasting effect of acupuncture stimuli. In this study, we first conducted a psychophysical test to reveal the lasting effect of acupuncture stimulation. Accordingly, we also conducted an fMRI experiment on the same group of subjects with single-block experimental design to avoid the contamination by the lasting effect. We analyzed the fMRI data using a GLM method with and without temporal shifts on the reference time course to account for the different onset timing of De-Qi for different subjects. Finally, we compared the results obtained with different analytical methods.

Methods

Sixteen subjects (27 +/- 2.7 years old) participated in this study. A psychophysical study for testing the lasting effect of acupuncture stimulation was conducted first. The subjects were acupunctured at acupoint ST42 (Chong Yuan) of the left foot. Acupuncture was done using a single-needle protocol. The needle was inserted and manipulated clockwise and counterclockwise at a frequency of 1-2 Hz to produce a De-Qi sensation. The subjects were requested to report continually their De-Qi sensation subjectively for every ten seconds. The De-Qi sensation was rated with score from 0 (no De-Qi sensation at all) to 10 (the highest De-Qi sensation that the subject can hardly endure). The De-Qi scores were recorded for up to hours to assess the decay of the sensation. At a separate occasion, the subjects were recalled for the fMRI experiment. The subjects underwent acupuncture at the same acupoint ST42 with the same needle technique producing De-Qi sensation. Having waited for five minutes to allow the De-Qi sensation to return to its baseline, the subject was sent into MR scanner for fMRI experiment. We adopted the block-designed fMRI experiment with only single on/off block to test the active brain areas in response to acupuncture stimulation. The single on/off block consisted of 24 s resting period followed by 32 s needle manipulations. At the end of experiment, the needle was pulled out. The MR images were obtained with a 1.5 T MR scanner. Three image data sets were obtained: (1) high-resolution 3-D T1-weighted images, (2) functional images, and (3) a series of 2D T1-weighted images. The fMRI data were analyzed using SPM99 under Matlab installed in a Windows PC. After preprocessing, a GLM regression was then applied to test the parameters of interest resembling the acupuncture stimulation time course (reference function). The reference time course resolving the experimental paradigm was temporally shifted for -4, -2 (accounting for earlier onsets), 0, and 2 (accounting for later onset) TRs (TR = 2 s) to create time-delayed versions of reference functions. These functions were input into SPM as parameters of interest. Thus, for each single subject, there were four different activation maps corresponding to four different reference functions. The average correlation coefficient between the reference function and the time courses of the resultant activation maps by both GLM with and without temporal shifts was compared. The difference between the active brain areas was estimated using a two samples t-test, a module for second-level inference provided by SPM2. The group effects of the selected activation maps by both methods were overplotted on top of an inflated cortical surface from the MNI T1 template

Results

In Fig. 1, the lasting effect is estimated by averaging the subjective De-Qi sensation rated by the subjects themselves in a separate psychophysical test prior to the fMRI experiment. A subgroup consists of five subjects showing higher De-Qi sensation is highlighted with pink trace. In GLM, the reference time course was temporally shifted with -4, -2, 0, and 2 TRs to account for the possibly different onset for each individual subject. Note that the individual difference in onset timing is significant and should be taken into considered in data analysis. For each method, the time course of the active brain voxels was calculated subject by subject. The 16 time courses were compared to the experimental paradigm (reference function) using correlation coefficient. For GLM with temporal shifts, the average correlation coefficient was 0.57 +/- 0.1229; for the traditional one, the average correlation was 0.32 +/- 0.3098 (mean +/- standard deviation). Apparently, with temporal shifts, the GLM was able to find for each individual subject the best brain responses to the experimental paradigm.

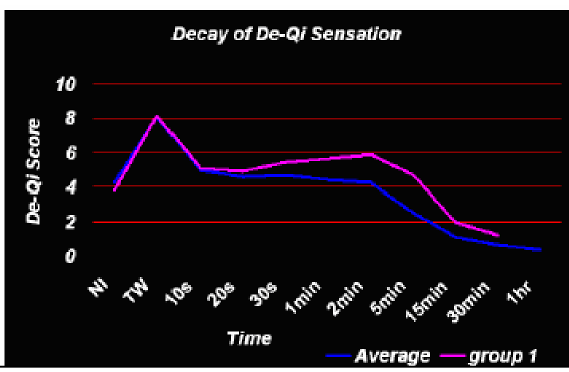

Fig. 1 Lasting effect of De-Qi sensation averaged across 16 subjects. The De-Qi sensation could last for 2-5 minutes (and up to days for some subjects) after reaching a De-Qi state. Group 1 shows the average De-Qi score from a subgroup (five subjects) whose members have relatively higher De-Qi sensation compared to others. NI stands for needle insertion and TW for 30-s needle twisting.

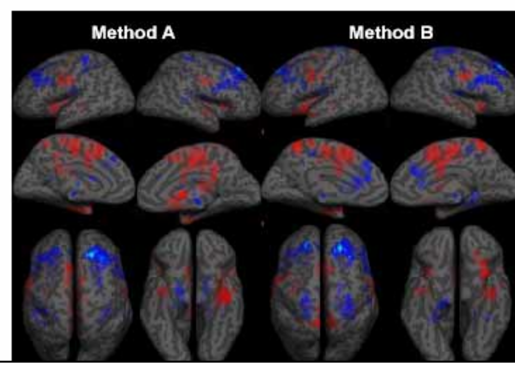

Fig. 2 Group effect, obtained by SPM2 second-level inference, overplotted on top of an inflated cortical surface from the MNI T1 template. Method A shows the result obtained using a GLM with temporal shifts; Method B the traditional GLM (threshold uncorrected $p < 0.01$).

In Fig. 2, the group effect based on the activation maps obtained by both methods were overplotted on top of an inflated cortical surface from the MNI T1 template. Although these two methods rendered very similar activation patterns from the same group, GLM with temporal shifts has rendered the activation in the right thalamus, amygdala, ventral anterior cingulate, and posterior cingulate. GLM without temporal shifts additionally found the primary sensory cortex corresponding to foot area with positive correlation and anterior cingulate with negative correlation.

Conclusion

As expected, the single-block experimental design and the data analysis with multiple temporal offsets improve the sensitivity needed by acupuncture studies. Higher temporal correlation to the reference function and more deep brain structure can be obtained with our new approach. In the further study, we will need to compare our result to the fMRI results on sham condition as a control to further distinguish the brain processes in response to acupuncture.

References [1] Wu MT, et al. *NeuroImage,* **16**: 1028-1037. [2] Cho ZH, et al. *Proc. Natl. Acad. Sci. USA.,* **95**: 2670-2673.