Proceedings of the 28th IEEE
EMBS Annual International Conference
New York City, USA, Aug 30-Sept 3, 2006

Probing Fast Neuronal Interaction using fMRI

Nanyin Zhang, Xiao-Hong Zhu, and Wei Chen

Center for Magnetic Resonance Research, Department of Radiology,
University of Minnesota Medical School, Minneapolis, MN 55455, USA

Abstract

The paired-stimuli paradigms were used to study cross-modal neural interactions between the visual and auditory systems in human. It was found that the primary visual cortex was actively involved in the 'illusory double-flash' phenomenon. The similar paradigms were used to study the influence of MR scanner noise on human visual activities from the perspective of neural interaction. The results reveal that the gradient acoustic noise does interfere with the neural behavior in human visual cortex.

Introduction

Neuronal activity can elevate electromagnetic signal changes (the primary effect) accompanying with hemodynamic and metabolic changes (the secondary effect). These changes are the basic sources for the measurements of all modern neuroimaging technique. Depending on the signal sources, these imaging techniques can be divided into two categories. The first category directly detects the electromagnetic signal changes elevated by neuronal activity using single or multiple sensors at the brain surface. The common methods in this category are electroencephalography (EEG), event-related potentials (ERP) and magnetoencephalography (MEG). The other category is to detect hemodynamic changes such as cerebral blood flow (CBF), cerebral blood volume (CBV) and oxygenation level, and/or metabolic changes (glucose and oxygen utilization rates) or the combination of them [1, 2]. This category includes positron emission tomography (PET), single photon emission computed tomography (SPECT), optical imaging, near infrared spectroscopy (NIRS) and functional magnetic resonance imaging (fMRI). Though all these neuroimaging techniques have been successfully to map brain activation, most of them have limitations.

For example, MEG, EEG, ERP, optical imaging and NIRS have a high temporal resolution that might be capable of tracing the time courses of neuronal events at the time scale of millisecond. However, they suffer from the ambiguities in defining the spatial origins of brain activity due to their limited penetration, spatial resolution and the difficulty of solving the mathematical problems related to multiple activation sites. On the other hand, PET, SPECT and fMRI are good at mapping widespread activity covering the whole brain, but they are not suitable for providing the temporal information about neuronal events that occur within tens of millisecond due to the slow response of the secondary effects that are detected by these methods [3-7].

An alternative fMRI approach (referred as dynamic fMRI) has recently been proposed using the combination of conventional fMRI and a paired-stimuli paradigm [8]. This approach is capable of probing fast neuronal interaction occurring within tens of milliseconds. Since the neural interaction generates variation in the amplitude of the neuronal activity in a particular brain region, and this variation is dynamically sensitive to the inter-stimuli interval (ISI) between the consecutive stimuli for stimulating the neuronal groups being interacted, the temporal information of neural interaction can thus be embedded in the amplitude changes of the neuronal activities and can, in turn, be reflected by the corresponding signal changes in the slow BOLD response. Therefore, the dynamic fMRI approach is useful for providing both spatial and temporal information about brain activation and neural interaction.

So far, this dynamic fMRI approach was mainly used to study intracortical neural interaction. In this article, we extended the applications of this approach to the studies of cross-modal neural interaction, particularly, between visual and auditory sensory systems. Those applications include the study of illusory double-flash effect on human visual cortex [9] and the study of influence of gradient acoustic noise on fMRI response in human visual cortex [10]. Also based on this approach, we proposed a novel method for mapping human ocular dominance columns (ODCs) with the utilization of binocular inhibitory interaction. In these applications, we have further modified this dynamic fMRI approach allowing the use of the block paradigm designs for improving detection sensitivity of fMRI.

Results

Shams et al reported human behavior studies demonstrating the "illusory double-flash" effect due to the audio-visual cross-modal neural interaction during a combined visual and auditory stimulation [11, 12]. When a single physical light flash stimulus was accompanied by two short beep sounds with proper intervals amongst the stimuli, the subject could perceive two flashes, and this illusion effect was strong when the flash was presented in the peripheral visual field rather than in the central visual field [12]. These behavior studies indicate that visual perception can be significantly influenced by the auditory stimulation, and the degree of the influence may depend on the time delay (below 100 ms) between the auditory and visual stimuli and the visual field of the flash presentation.

Figure 1 shows the blood oxygenation-level dependent (BOLD) signals in the primary visual cortex (V1) detected by fMRI in the conditions of a single flash accompanied with two beep sounds (1F&2B), two physical flashes (2F) and one single flash (1F), respectively, from a representative subject. The BOLD amplitude in the condition of 'illusory double flashes' is significantly larger than that in the condition of single physical flash, even though the light stimulation was the same in the two conditions. The average from five subjects indicate that there is a 20% increase in the BOLD amplitude for the 1F&2B condition and a 34% increase for the 2F condition compared with the 1F condition. Paired t-test indicates that the BOLD amplitude elicited at the 1F&2B condition is significantly larger than that at the 1F condition ($p < 0.01$, n = 5). Nevertheless, statistical significance is not reached in the BOLD amplitude between the 1F&2B condition and the 2F condition ($p = 0.29$, n = 5).

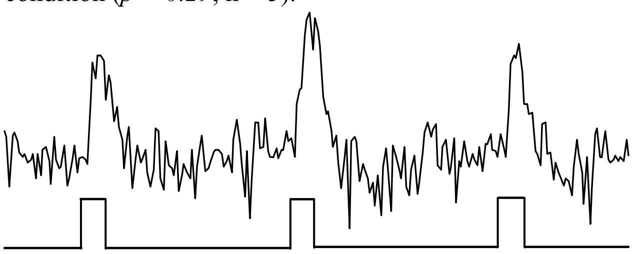

Figure 1: Averaged BOLD time course (single subject result) in the activated region in the visual cortex in three brain simulation conditions: 1F&2B (one flash and two beep sounds), 2F (two flashes) and 1F (one flash), respectively.

The effect of the gradient acoustic noise on the fMRI response in human V1 from the perspective of audio-visual cross-modal neural interaction was also studied using the paired stimuli paradigm. The gradient noise generated during fMRI acquisition was used as the primary stimulus and a single flashing light was used as the secondary stimulus with an inter-stimulus interval (ISI) between them. Six tasks were designed with different ISIs ranging from 50 to 700 ms. Figure 2 illustrates the dependence of the normalized BOLD signal intensity upon the relative time delay between the MRI scanner noise and the flashing light (i.e., ISI) from the averaged result for all nine experiments. This result indicates that the BOLD signal intensity in the visual cortex in response to the flashing light stimulation is reduced by the scanner gradient noise when the ISI is between 200 ms and 400 ms. The most significant reduction occurs at ISI = 300 ms approximately, and this suppression effect gradually disappears when the ISI is longer than 400 ms. This result also clearly demonstrates that the neural interaction between the auditory and visual sensory systems is modulated by a change in the relative delay between the consecutive auditory-visual stimuli. Student t-test shows that the BOLD signal intensity elevated by the flashing light stimulation with ISI = 300 ms is significantly smaller than the averaged BOLD signal intensity from all the six tasks ($p = 0.03$, $n = 9$).

A similar trend of the correlation between the activated pixel number and ISI is also evident from the average results of nine experiments (data not shown). Student t-test shows that the number of activated pixels with ISI = 300 ms is significantly smaller than the number of activated pixels averaged for all the six tasks ($p = 0.038$, $n = 9$). The number of pixels at an ISI of 300 is about 30% lower as compared to the average over all ISI's.

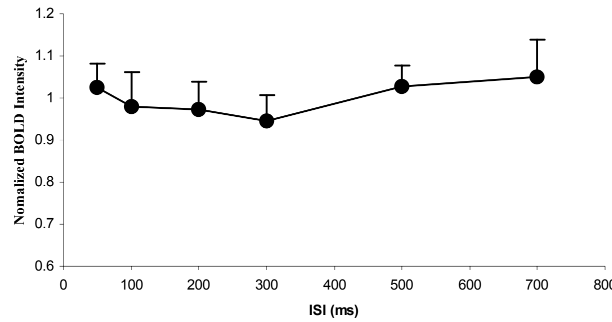

Figure 2: Dependence of BOLD signal intensity on the relative delay (ISI) between the gradient acoustic noise and the flashing light stimulation from the average of nine experiments from eight subjects. The BOLD intensities were normalized to the average BOLD from all the six tasks.

Discussion

Though the illusory double-flash effect illustrates an important phenomenon in cognitive brain function, the mechanisms underlying this phenomenon are not well understood. One particularly interesting question is whether the human primary visual cortex (V1) involves in the illusion phenomenon? To answer this question, one has to choose a neuroimaging modality with the capability of studying both the spatial and temporal aspects regarding the audio-visual neural interaction. The dynamic fMRI approach combined with a paired-stimuli paradigm can provide a suitable tool for this purpose [8].

The results from this study reveal that the illusory double-flash effect can significantly affect the neuronal activities in the peripheral visual cortical area, and the degree of this effect is sensitive to the inter delay between the auditory and visual stimuli. The fMRI findings were consistent with the behavioral measures, indicating a tight correlation between the behavioral performance and the BOLD signal which reflects the brain activity; they further suggest that V1 may be involved in high-level brain processing beyond the retinotopic perception.

Similarly, the paired-stimuli paradigm was used to study the influence of scanner acoustic noise on visual processing. The results reveal that the gradient acoustic noise does interfere with the neural behavior in human visual cortex. They provide important evidence of the cross-modal neural interaction between the visual cortex and auditory cortex and have a potential impact on fMRI studies involving visual stimuli following or during image acquisitions. The BOLD signal detected from the visual stimulation under this circumstance can be sensitive to the delay between the image acquisition and visual stimulation or the configuration between the fMRI gradient sounds and visual stimuli. The proposed approach by appropriately combining the paired-stimuli with a variable ISI and the block fMRI task design provides a robust and efficient tool for quantitatively studying the mechanism underlying the neuronal interaction. The BOLD reduction in the visual cortex caused by the gradient acoustic noise is, though significant, small, and it should not alter conclusions for most fMRI studies involving visual stimulation. However, it can become important for fMRI studies in which major conclusions are based on a small BOLD difference between control and task conditions and/or between different task conditions, as well as for fMRI studies for addressing the issues regarding cross-modal neural interaction between different sensory systems or within the same sensory system (e.g., the auditory cortex in response to the gradient acoustic sound and desired auditory stimuli).

In addition to study fast neural interactions, the paired-stimuli paradigm can in principle be used to spatially separate two ocular dominance columns (ODCs). We have already demonstrated that the selective stimulation of one eye can considerably suppress the activity induced by subsequent stimulation of the other eye if the delay between the monocular stimulations is as short as 30-90 ms; this suppression gradually disappears when the delay exceeds 300~400 ms [13]. Therefore, the fMRI data at long inter-stimulus interval (ISI) of ~300 ms can generate fMRI maps including the activated pixels covering both eyes ODCs in V1, while at short ISI (~40ms), the regions activated by the eye experiencing the second stimulation are significantly suppressed. Consequently, the separation of the left and right eye ODCs depends on the degree of suppression in terms of the BOLD responses between the two stimulation conditions (short ISI vs. long ISI). Since this method uses the reference of intrinsic neuronal activities within the same ODC group at different conditions instead of referring to the activities from the neighboring ODCs, it does not rely on the assumption of symmetric BOLD activities from the neighbor ODCs, which is the assumption underpinning the traditional ODC mapping methods, and therefore can further improve the spatial specificity of fMRI mapping. Moreover, the reliability of ODC maps generated using this technique can be independently examined from multiple aspects: human ODC morphology, difference between low-resolution and high-resolution maps and mapping reproducibility. In addition, the mapping reliability can be further examined by switching the order of the paired-monocular stimuli between two different sessions (e.g. session one uses the stimuli of ‘left-eye first, right-eye trailing’, session two uses the stimuli “right-eye first, left-eye trailing’). In reliable ODC maps, one should expect the suppressed ODC population in the first session become unsuppressed ODC population and vice versa.

Conclusion

The paired-stimuli paradigms were used to study cross-modal neural interactions between the visual and auditory systems in human. It was found that the primary visual cortex was actively involved in the illusory double-flash phenomenon. The similar paradigms were used to study the influence of MR scanner noise on human visual activities from the perspective of neural interaction. The results reveal that the gradient acoustic noise does interfere with the neural behavior in human visual cortex.

References

[1] M. Raichle, "Circulatory and metabolic correlates of brain function in normal humans," *In: Mountcastle VB, Plum F, Geiger SR, Editors. Handbook of Physiology-The Nervous System. Bethesda: American Physiological Society*, pp. 643-674, 1987.

[2] L. Sokoloff, "Localization of functional activity in the central nervous system by measurement of glucose utilization with radioactive deoxyglucose," *J. Cereb. Blood Flow Metab*, vol. 1, pp. 7-36, 1981.

[3] P. A. Bandettini, E. C. Wong, R. S. Hinks, R. S. Tikofsky, and J. S. Hyde, "Time course EPI of human brain function during task activation," *Magn Reson Med*, vol. 25, pp. 390-7, 1992.

[4] A. M. Blamire, S. Ogawa, K. Ugurbil, D. Rothman, G. McCarthy, J. M. Ellermann, F. Hyder, Z. Rattner, and R. G. Shulman, "Dynamic mapping of human visual cortex by high-speed magnetic resonance imaing," *Proc. Natl. Acad. Sci. USA*, vol. 89, pp. 11069-11073, 1992.

[5] A. F. Cannestra, P. N., M. H. Shomer, and T. A.W., "Refractory periods observed by intrinsic signal and fluorescent dye imaging," *J Neurophysiol*, vol. 80, pp. 1522-32, 1998.

[6] K. K. Kwong, J. W. Belliveau, D. A. Chesler, I. E. Goldberg, R. M. Weisskoff, B. P. Poncelet, D. N. Kennedy, B. E. Hoppel, M. S. Cohen, R. Turner, and et al., "Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation," *Proc Natl Acad Sci U S A*, vol. 89, pp. 5675-9, 1992.

[7] S. Ogawa, D. W. Tank, R. Menon, J. M. Ellermann, S. G. Kim, H. Merkle, and K. Ugurbil, "Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging," *Proc Natl Acad Sci U S A*, vol. 89, pp. 5951-5, 1992.

[8] S. Ogawa, T.-M. Lee, R. Stepnoski, W. Chen, X. H. Zhu, and K. Ugurbil, "An approach to probe neural systems interaction by functional MRI at neural time scale down to milliseconds," *Proc*

Natl Acad Sci U S A, vol. 97, pp. 11026-11031, 2000.

[9] N. Zhang and W. Chen, "A dynamic fMRI study of illusory double-flash effect on human visual cortex," *Exp Brain Res*, pp. 1-10, 2005.

[10] N. Zhang, X. H. Zhu, and W. Chen, "Influence of gradient acoustic noise on fMRI response in the human visual cortex," *Magn Reson Med*, vol. 54, pp. 258-63, 2005.

[11] L. Shams, Y. Kamitani, and S. Shimojo, "Illusions. What you see is what you hear," *Nature*, vol. 408, pp. 788, 2000.

[12] L. Shams, Y. Kamitani, and S. Shimojo, "Visual illusion induced by sound," *Brain Res Cogn Brain Res*, vol. 14, pp. 147-52, 2002.

[13] X. H. Zhu, X. L. Zhang, S. Tang, S. Ogawa, K. Ugurbil, and W. Chen, "Probing fast neuronal interaction in the human ocular dominate columns based on fMRI BOLD response at 7 Tesla," presented at 9th International Society for Magnetic Resonance in Medicine Annual Meeting, Glasgow, UK, 2001.