Characteristics of fMRI BOLD signal and its neurophysiological mechanism*

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Abstract The functional magnetic resonance imaging (fMRI) based on blood oxygen level dependent (BOLD) contrast has emerged as one of the most potent noninvasive tools for mapping brain function and has been widely used to explore physiological, pathological changes and mental activity in the brain. Exploring the nature and property of BOLD signal has recently attracted more attentions. Despite that great progress has been made in investigation of the characteristics and neurophysiological basis, the exact nature of BOLD signal remains unclear. In this paper we discuss the characteristics of BOLD signals, the nonlinear BOLD response to external stimuli and the relation between BOLD signals and neural electrophysiological recordings. Furthermore, we develop our new opinions regarding nonlinear BOLD response and make some perspectives on future study.

Keywords: functional magnetic resonance imaging, blood oxygen level dependent, nonlinear response, neural electrophysiological activity.

Blood oxygen level dependent (BOLD) contrast, which underlies functional magnetic resonance imaging (fMRI), was first described by Ogawa et al.[1] in 1990. The noninvasive and high resolution afforded by this technique has made it a powerful tool for mapping of brain function. Over the past decade, it has been widely used in various research fields such as physiological and pathological changes in the brain, and mental activities of human brain[2—4]. Because of its importance, searching for the neurophysiological mechanism of BOLD signal and its relation with brain neural activities has attracted growing interest, especially for the aspect of experimental study. Many experimental studies have explored the special-temporal characteristics of BOLD response to external stimulus (such as visual stimulation, auditory stimulation and finger movement, etc.), and have attempted to establish the relationship between BOLD response and external stimulus. Other animal studies attempted to establish the relationship between BOLD signal and electrophysiological signal changes by simultaneous measurement of the BOLD signal and electrophysiological signal in the animal brain, or comparing the results of the different studies. But because the experimental conditions differ across different previous studies, the resulting conclusions were not fully in accordance with each other. This article will briefly discuss the characteristics of BOLD signal, its non-linear response to external stimulation, and the relationship between BOLD signal and electrophysiological signal. In addition, we posit our explanations for the nature of nonlinear response, and give some perspectives for future studies.

1 Characteristics of the BOLD signal

It is well known that BOLD fMRI reflects indirectly neuronal activity by detecting the hemodynamic change coupling to neuronal activity in brain, therefore, it is necessary to clarify the physiological essence of the BOLD signal. In short, BOLD signal refers to the signal resulting from blood oxygen level dependent contrasts. With the presence of the external stimulation, the neuronal activity increases which is accompanied by the increased consumption of oxygen, leading to an increased amount of deoxyhemoglobin (dHb) in local brain tissue. The dHb is a paramagnetic substance, which destructing the stability of the local magnetic field around hydrogen proton (MRI primarily detect the signal coming from hydrogen proton), shortening the $T2^*$ relaxation time[5,6] and decreasing the MR signal. As a result, a negative BOLD response can be observed[7,8] in the early stage

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of the BOLD time course. Yet the negative signal is relatively weak and can only be measured in higher magnetic field scanner. In order to compensate the oxygen consumption, it is necessary to increase the blood flow in the local brain tissue. In fact, the increased blood flow is excessive relative to the actual metabolism requirements of brain activity, which resulting in the oversupply of blood oxygen concentration in the microvessels. The excessive oxygen level[9, 10] (relative to the metabolic requirements) results in a relatively decreased dHB and increased oxyhemoglobin concentration in microvessels and the activation of regional brain tissue. Due to the decreasing in the amount of dHb, the stability of magnetic field is better and the $T2^*$ relaxation time becomes relatively slow, and thus the resulting high MR signal can be detected. This MR signal change is derived from the hemodynamic alterations in the brain, which is a lagged response comparing to electrophysiological signals underlying neuronal activity. The onset of the stimulus-evoked hemodynamic response is typically delayed by 2—3 seconds. The BOLD signal gradually reaches plateau after 6—12 seconds (depending on the length of stimulation time), then drops down slowly and returns to its baseline about 9 seconds later (which also depending on the length of stimulation time). We now know that BOLD contrast depends not only on the ratio of deoxyhemoglobin to oxyhemoglobin but also on other influencing factors such as the regional blood flow and regional blood volume changes. Specifically, the BOLD signal is accompanied with the neuronal activity, which is necessary to fully understand the relationship between the BOLD signal and the stimulation as well as the neural signals.

2 The relationship between neuronal electrical activity and stimulation

As mentioned above, the BOLD fMRI is an indirect measurement of the neuronal electrical activity, thus prior to discussing the relationship between BOLD signal and the external stimulus, we should understand the relationship between neuronal electrical activity and the stimulation. Most of previous work involved solely measurement of electrophysiological signals or simultaneous measurement of BOLD signal and electrical activities by animal experiments.

2.1 A few types of electrophysiological activity signals

The measurement of neuronal electrical activity can be done by both the non-invasive and invasive methods. The former includes electroencephalogram or magnetoencephalogram techniques, and the latter is mainly microelectrode recording. The electroencephalogram has a high temporal resolution, but a poor spatial resolution which limits its application.

The electrophysiological event of the neurons is a complex phenomenon. According to the different measurement techniques and the site of recording electrodes placed, it can be roughly expressed as a spike potential (or an action potential) or the so-called extracellular field potentials (EFPs). It is generally considered that neurons are embedded in an extracellular medium that acts as a huge volume conductor with a high impedance between 200 and 400 Ω/cm[11—14]. This resistance generates EFPs that can be measured by the electrode. The signal measured by an electrode placed at a neural site represents the mean EFP (m EFP) from the weighted sum of all inward and outward currents[15, 16]. If a microelectrode with a small tip is placed close to the soma or axon of a neuron which is spiking, the spike potential can be detected in the mEFP.

When a relatively large tip of a microelectrode is placed on the extracellular medium, and is a bit farther from the spiking-generating sources, the recorded mEFP under such conditions is related both to integrative processes (dendritic events) and to spiking generated by several hundreds of neurons. These signals can be segregated into two parts by frequency band separation[17, 18]. A high pass filter (cutoff frequency 300—400 Hz) obtains the single-unit spiking activity (SUA, with a single microelectrode) or multiple-unit spiking activity (MUA, with multiple microelectrodes), and a low pass filter (cutoff frequency 200 Hz) generates the so-called local field potential (LFP) which primarily reflects the synaptic potentials. The amplitude of MUA changes with the different neural site, but within the same brain area the MUA is relatively invariable. The size of a neural cell is one important factor determining the amplitude of MUA[19, 20].

The LFP is a kind of mEFP signals with the low frequency range, representing most slow electrical current and sub-threshold electrical events. Up to now, these signals were generally considered to represent exclusively the synapse activities. The supporting evidence came from the combined measurements

of electroencephalogram (EEG) and intra-cortical recording, which shows that the slow wave action of EEG is quite independent of the action potential of the neurons[21—24]. Unlike MUA, the amplitude of LFP is irrelevant to the cell size, but instead reflecting the extent and geometric characteristic of each recording point. The LFP mainly reflects the weighted average of the synchronized dendrosomatic components of the synaptic signals from the neural population within 0.5 mm—3 mm of the sharp tip of the microelectrode[25, 26]. In addition, the LFP also represents other types of slow activity unrelated to synaptic events, such as voltage-dependent membrane oscillation and spiking post potential[27]. In summary, we should know that LFP compromises much richer neural information. It is not only capable of affecting the local neural excitation[28] but also reflects the input of a given cortical area as well as its local intracortical processing. In contrast to MUA, the LFP does not represent the action potential that mainly reflects the output of the neurons.

2.2 The adaptation and transient electrophysiological signals response to a specific stimulation

In the primary cortex V1 area, the characteristics of the neural activity response to a short time stimulus are: at the early onset of the stimulus the neurons in V1 show a relatively large instantaneous electrical response, then descending rapidly within a few hundred milliseconds[29], and gradually returning[30] to the baseline after a long time (4—30 seconds) stimulation, which indicates that the neurons have entered an adaptation period. The transient response in V1 area might arise from attention. At the early onset of the stimulus, these neurons may be automatically engaged in attention and a transient stimulus may evoke a disproportionate larger neural response[31].

The transient response and adaptation of neural signals play an important role in the investigation of non-linear properties of BOLD signal, some experiments with combined fMRI and electrophysiological methods have revealed this speciality. For instance, the LFP or MUA signal from the experiment of Logothetis et al.[32, 33], in which BOLD signal and electrodes were simultaneously recorded in monkey brain under visual stimulations, directly showed this feature. The resulting refractory period of Somato-evoked potential (SEP) in rat brain under electrical stimulation from the simultaneous experimenting of the fMRI and EEG by Ogawa et al.[34] also indirectly reflected this feature. Though square wave was used as the form of stimulation, the nerve response signal obtained was not a square wave, which indicates that the neural signal's response to the stimulation is nonlinear, and the corresponding BOLD signal's response to stimulation is also nonlinear.

3 Linear response of BOLD signal to stimulation or neural activity

To discuss the linear response of BOLD signal to stimulation or neural activity, it is necessary to understand the characteristics of the stimulation or neural activity. For most studies, the stimulations of single square wave, with constant strength or periodic square waves and isometric short interval, are always used in the same group of experiments (see Fig. 1). Obviously, this kind of stimulation is periodic. If the linear response exists, the time invariance should be satisfied firstly, that is, the BOLD signal caused by the stimulation (or neural signals) of two time cycles should equal the signal caused by the second time cycle plus the other signal that was caused by the first time cycle and delayed by one period on the time axis. And the same should be true for those of multiple cycles. In addition, scaling property should also be satisfied. Here the scaling property means that, if the stimulation strength (or neural signal strength) doubles, the BOLD signal strength should also double. Noting at the same time that the neural signal caused by the stimulation of single square wave has a transient response and adaptation period, if the adaptation period is flat, this kind of neural signal must be partially periodic. In that case, if the time invariance

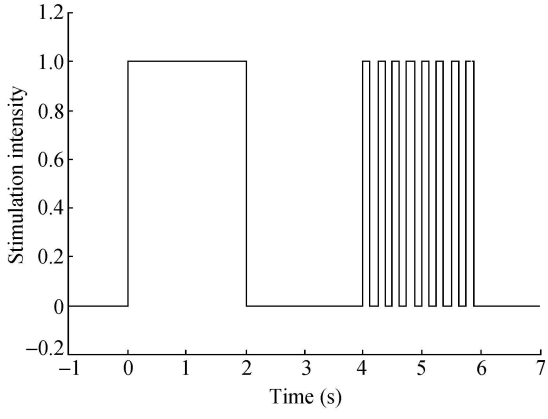

Fig. 1. The sketch map of square wave stimulation function. The single square wave was from −1 to 3 s along time axes, and periodic muti-square waves were from 3 to 7 s.

cannot be observed, it is necessary to test whether there is a linear relationship between BOLD signal strength and length of stimulation duration; if it is the case, the linear response of BOLD to the neural signal cannot be denied still. Therefore, while discussing the issue concerning the linear response of BOLD signal, it is necessary to consider that such a linear response is related to stimulation or to neural signal.

3.1 The results of linear response

Boynton et al.[35] have revealed the linear response of BOLD signal to stimulation by exploring the time invariance between the stimulation and the BOLD response and the scaling property between BOLD signal amplitude and stimulation strength. They compared the time course of the BOLD signals respond to visual stimulations with different time period, that is 3 s, 6 s, 12 s, and 24 s, respectively. They revealed that the time course of BOLD signal caused by the stimulation of long duration can be predicted by parallel aggregating the time course of the short duration, which suggests that the time invariance can be satisfied. In the mean time, they analyzed the relationship between the BOLD signal amplitude and the stimulation strength (the white-black contrast of checkboard) and suggested the existence of a nonlinear relation. However, they proposed that the existence of such a nonlinear relation did not imply that the linear transformation model cannot be fited, because the neural response to this kind of contrast stimulation is indeed nonlinear[36—40], which indicates that the linear response of BOLD signal to neural activity is still possible.

The results of Boynton et al.'s study also provided the evidence for the violation of time invariance. When checking the time invariance carefully they found an overestimation when the signal produced by the 3-second stimulation was used to predict the signals caused by 6 s, 12 s, and 24 s stimulations. The underestimation of the 3 s signal occurred when a uniform model was used to predict all the signals. They argued that it was caused by the adaptation of neural signals, which was to say that once transient response and adaptability of the neural signal were considered, the BOLD signal could still be predicted using the linear model of the neural signal. At the same time they suggested that the result of Savoy et al.[41] could also be predicted this way.

Even there is evidence from some experiments showing the BOLD signal response to stimulation is nonlinear, it is more important to verify whether the BOLD signal response to neural signal is linear too, because these data do not mean that the linear transformation model of BOLD signal to neural signal cannot sustain. Another experiment performed by Dale and Buckner[42] aimed to verify the linearity without giving any consideration to transient response and adaptability of nerve signal, and proved the near linearity of the BOLD signal response to visual stimulation by examining the time invariance. Noting that the stimulations they used were periodic short square wave with intervals, and because of the intervals each square wave would evoke transient response, and if the amplitude of this transient response is much greater than the signal amplitude during the adaptation period, then the neural signal caused by this kind of stimulation is still periodic, and thus the time invariance can sustain. Their final result has indeed proved this point.

Ogawa et al.[34] also reported that characteristics of the linear relation will be changed as stimulation interval alteration. They observed that there is suppression to BOLD signal in the V1 area of the brain, that means the BOLD signal caused by the two same stimulations will be lower than two times of single stimulation. In short, the signal of the second stimulation has been depressed. It indicated that the BOLD signal has a refractory period. This suppression depends on the stimulation interval time. When the stimulation interval is longer than 1 s, the BOLD signal will totally recover from the suppression. Because the stimulation interval is shorter than several seconds of the blood vessel response time, they considered that the refractory period is possibly generated by the neural cells.

Logothetis et al.[32] have carried out the simultaneous measurement of the functional magnetic resonance imaging and the electrophysiological signal recording. They directly used the convolution relation to explore the linear relation of the BOLD signal and neural signal. In their study, they have measured the static state activity[43] without any external stimulation at every recording site for estimating hemodynamic response function (HRF) to LFP. According to the model of linear transformation, they found that the BOLD signal evoked by visual stimulation could be predicted by the convolution of the estimating

HRF and the evoked neural signal LEP. Comparing with the actual measured BOLD signal, both of them were roughly coincident. Thus they considered that as a first approximation, for a short stimulation, there is a linear relation between the BOLD signal and nerve signal.

As for the research of the scaling property, the related study involved the comparisons of the BOLD signal with spike potential of single neural cell, and the BOLD signal amplitude with the EEG signal. The first one was on the awaked monkey brain and the human brain, which showed that the BOLD signal is directly proportional to the average firing rate of the neurons[44,45]. Using the available spike potential data of a single neural cell, Rees et al.[44] calculated the average firing rate of neurons in macaque MT area which was linearly increased with the coherence of the visual motion[46], and then they also revealed that the response of the BOLD signal in the human brain V5 area has an almost linear relation with the coherence of visual motion too. Their results supported the viewpoints in Ref. [47].

Heeger et al.[45] carried out the same measurements of the primary visual cortex activity of human brain and monkey brain which had been reported by themselves before[47—49]. They used the black and white contrast as an individual component, and found that almost all neurons in the V1 area monotonously increased their firing rate with the increasing contrast. They further analyzed the average firing rate of V1 area in the monkey brain and the BOLD signal of human brain, both of the curves were superposed. This finding once more indicated a close relation between the fMRI signal and the average firing rate. However, both of these two studies were based on a series of calculations of the average firing rate of neurons from the data of neural electrophysiology. And the analysis data collected were not only from the different areas of the brain, but also from the brain of different species.

3.2 The results of nonlinear response

Many investigators applied different methods such as deconvolution, Volterra kernels and Bayesian technique to reveal the experimental evidence of nonlinearity[41,50—53]. Other studies[54,55] simply employed the violation of time invariance to explain the nonlinearity. In these results, although the integral of the BOLD time curve is not directly proportional to stimulation duration, it was still in a linear relation. The similar experimental results reported by us[56] have proved this point (Figs. 2 and 3). As discussed at the beginning of this chapter, this result cannot deny the linear response of BOLD signal to the neural signals.

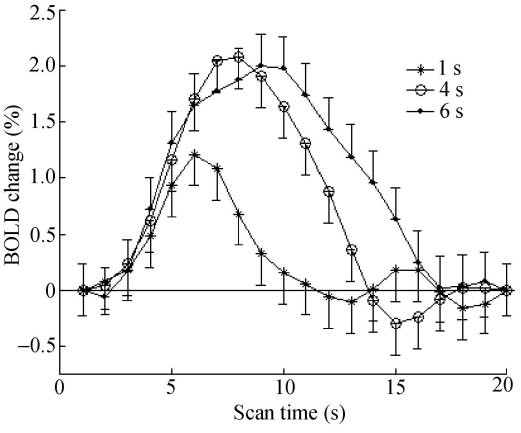

Fig. 2. The BOLD response curves at the voxel with the most statistical significance in primary visual cortex with several stimulus duration.

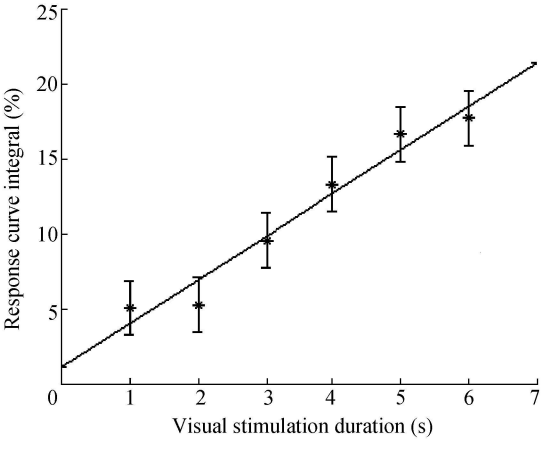

Fig. 3. The linear relationship between BOLD response and stimulus duration.

Most of the existing studies suggested that the nonlinear response of the neural signal to the stimulation probably depends on the inherently nonlinear characteristic of hemodynamics[31,57,58]. For example, when the regional blood flow increases to a certain level, the BOLD signal might have been saturated already[57,59,60], the influence of the decreased deoxyhemoglobin could be ignored. As a result, even if the stimulus intensity has not reached the greatest value, it could have evoked the greatest BOLD response, leaving no room to reflect the much stronger stimulation evoked BOLD response, however, the stronger stimulation can raise much greater neuronal activities.

Pfeuffer et al.[61] have explored the nonlinear response and the spatial dependence of BOLD signal to short stimulation by using the magnetic resonance imaging with different magnetic field intensity and different spatial resolution. Under the short stimulation duration condition (<2 s), the data obtained by 4T MRI scanner have showed the index of nonlinearity can reach 400%. But 7T data showed the index of nonlinearity can only reach 40%. Because the spatial resolution of 7T is higher than that of 4T, they suggested that the nonlinear effect might be a tissue-specific phenomenon. Having considered the transient response of neural signals in their model, the authors argued that the observations of the magnetic field dependence of non-linear BOLD response support the hypothesis that the hemodynamic effect has great contribution to the non-linear source under a short duration stimulation. Although they had taken the transient response of neural signal into consideration, the correction of the model itself remains uncertain, along with the changeable magnetic field intensity and spatial resolution in their experiment, Thus, the dependence mainly derived from the hemodynamic change or the tissue specificity, or from both of them, cannot be explained clearly only by their study.

In the aspect of scaling property, in disagreement with the results of Rees et al.[44] and Heeger et al.[45], Logothetis and colleagues found that the BOLD signal and neural response did not simply have the direct proportion each other, it showed the failture of the scaling property. The stimulation of 12% black and white contrast approximately evoked half of the greatest response (at 100% contrast) of BOLD signal, but the evoked signals of LFP and MUA are far less than half of their maximum value (at 100% contrast). This means even if the relation is the same monotony but nonlinear with the contrast, in the low contrast region (<12%) BOLD signal will rise faster than the response of neural cell, but in the contrast range of 12%—100%, the change of BOLD signal will be much slower than that of the response of neural cell. It must be noticed that, although the measuring results of the neurons will reach half of their maximum firing rate under 10%—15% of the contrast reported by Logothetis et al. they are obviously different from those by Heeger et al.[31] and Geisler et al.[49], the measuring results of monkey brain BOLD signal by Logothetis et al. are the same as those of human brain BOLD signal by Heeger et al.[41] and Boynton et al.[48] So far it is not clear that the discrepancy of the neural response is only due to different measuring methods, or due to the difference of experimental tools. Otherwise, if BOLD signal and neural response are really not directly proportional, then it will be difficult to explain why there has been a convolution relation presented by Logothetis et al. as mentioned above. Because their results are from simultaneous measurements of the functional nuclear magnetic resonance imaging and electrophysiologic signal, and the other results are from individual measurements, we cannot exclude the influence of high magnetic field and excitation signal emitted from the loop to the measurement of electric physiologic signal.

4 The electrophysiological mechanism of BOLD signals

It is well known that fMRI takes the advantage of the coupling between neuronal activity and hemodynamics in the brain to mapping brain function, however, the exact mechanism underlying this process is only partially understood. Prior to discussing this question, we should learn some basic concepts of this process. The first is how to describe neural activity. In fact, the nature of neural activity is electrical events. As the above discussed, the MUA mainly reflects the electrical activities of the multiple neurons and the LFP mainly reflects the electrical events related to synaptic activity. The second concerned issue is which changes are contained during the hemodynamic processes. The processes comprise of the blood flow and blood volume changes.

The BOLD signals originate from the surplus oxygen supply resulting from the dismatch of the oxygen supply and the actual consumption required by the activating neurons. The exact mechanism underlying this process remains unclear till now. One of the generally accepted viewpoints suggests that the astrocytes play a crucial role in this process[62]. It has been widely recognized that neuron activity requires a large energy provision and most of consumptive energy is related to clear the glutamate from the extra-cellular space and convert it to glutamine, which is one of very important excitable neurotransmitters in the brain. The glucose is one of the main energy producing materials in the brain. There are two ways by which the glucose transfers to the energy material—ATP. One is glycolysis way, which does not require oxygen available, and the other is oxidative glucose metabolism route which needs the oxygen to produce

energy material. The former is a fast way to generate ATP, but the produced amount of ATP is relatively small. The latter is a slower way to produce ATP with a large amount of ATP generated than the former. The increased neural activity requires correspondingly the increased energy provision and the energy consumption triggers hemodynamic changes, including elevated blood flow and blood volume, to deliver the glucose and oxygen. It is suggested that the elevated oxygen and glucose in the vasculature is appropriate for the metabolic needs, which exactly matches the ratio of glucose and oxygen demand of the aerobic process. The electrical events of the neurons take place fairly quickly with milliseconds order, in contrast, the companying hemodynamic response is relatively sluggish, thus the brain is able to produce the energy material by the use of non-oxidative mechanism to meet the metabolic needs, and then starts the powerful energy production system to generate large amounts of energy. Because the non-oxidative process has consumed some glucose in advance without taking advantage of the available oxygen, the necessary consequence is the surplus oxygen available in the brain.

Another crucial issue worthy of emphasis is what neural information is indeed reflected by the BOLD signals underlying neuronal activity? As mentioned above, the MUA and LFP could describe certain characteristics of the neural activity to some extent and contain crucial neural information. The MUA reflects the electrical activity related mainly to neuronal population, and the LFP primarily reflects the electrical events involved in synaptic activity. At present, it is widely considered that the synaptic activity is closely related to aspects of the input signal and the local intracortical information processing. Now we know that electrical activities are complex and information-rich signals, but what information on earth do the BOLD signals mainly reflect? Some studies have revealed that both the MUA and LFP are related to BOLD signals. The great work done by Logthetis and colleagues[32] with a high field magnetic resonance scanner in animal study has shown that BOLD signals are mostly related to the LFP than other neural activity events. It is suggested that the BOLD signals to a great extent reflect the synaptic activity among the neural activity events.

5 Prospective

Much progress has been made with regard to many aspects of the functional magnetic resonance imaging, especially, in its application areas, however, there are still a large number of questions regarding the characteristics of the BOLD signals and its relation to neural activity remains to be solved in the future studies. There are no confirmative conclusions have been reached on the linear relation between BOLD signals and the underlying neuronal activity signal. The major rationales of the disagreeable results from the most previous studies are the lack of comparison study under the same conditions. Either the experimental tools or the detailed process that occurs in the experiment are not unified. At present, a key issue to be resolved is how to modify some aspects of the current neural activity measurement methods. We need to know much more of the relation between the measured values obtained from different experiments, including the fire rates of single neuron and multi neuronal population, and the local field potentials. Based on these knowledge we can thoroughly learn whether they reflect the different aspects of neural activity. In addition, the stimulation induced external environment change is another consideration. The characteristic neuronal response includes the instantaneous signal and the adaption period which have been demonstrated in numerous studies, but there are still no comprehensive results and we lack a reasonable theoritical model to describe and explain it.

The linear model is the simplification and approximation to the complicated problem, using the model we can obtain many hidden information under a special condition. If we can confirm the linear relation between BOLD signal and nervous signal under special conditions and comprehensively know about the neural signals (including those that can be modeled), then it is possible to extract the underlying neural activity from the BOLD signals[31, 34]. In this way we will measure the human brain neural activity noninvasively and quantitatively, but not relying on the BOLD signal to do a qualitative analysis only on them. To test this linear relation, the ideal situation will be just like in the studies[32, 34] with the same subjects and the simultaneous measurement with different measuring tools (including the measurements of BOLD signal and neural signal). But similarly there is possible signal distortion caused by the simultaneous measurement and this will make the disturbance among all different measuring tools, and will also affect the results in the end. If employing the multiple time measurements, the physiological signal

differences at different time will probably be smoothed, therefore, it is worth to consider again whether the simultaneous measurement is appropriate. Undoubtedly, even if it is not simultaneous measurement, it still needs the same subjects but with different measuring tools. In the correlation studies of fMRI BOLD intensity and histochemical analysis of AD model rat[63, 64], we have carried out the similiar experiment successfully with the same subjects but with different tools and different time measurements.

The presence of the linear relation needs a certain condition, for most cases nonlinearity will appear. Although the nonlinear issues are more complicated compared to the linear ones, there is also a regularity to be sought. To explore the precise model of nonlinearity in BOLD response by experiment is also specially important for the experimental design with the fast time-related type of short random presenting[61, 65].

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