１．研究課題名：

A Bayesian Technique for Investigating Linearity in Event-Related BOLD fMRI

２．研究機関：

秋田県立脳血管研究センター

３．研究者名と所属 ：

Jeff Kershaw（科学技術振興事業団秋田研究室）

４．研究協力者名と所属：

柏倉健一（科学技術振興事業団秋田研究室）

Xiaojiang Zhang（科学技術振興事業団秋田研究室）

阿部清子（秋田県立脳血管研究センター）

菅野巌（秋田県立脳血管研究センター）

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６．要約

事象関連 BOLD fMRI データを時間不変線形システムとしてモデル化した。ベイズ推論法を用いて BOLD 応答特性における線形性を確認できる統計解析法を発展させた。この解析法を白黒チェッカーボードによる視覚刺激を行った８名のボランティア・データに実際に応用した。グループ解析の結果、BOLD 応答は明らかに非線形性を示していた。被験者ごとに解析したデータは、大部分は非線形性を示していたが、中には判断が困難なものもあった。この結果は、被験者個人の生理学的パラメータの推定に有効かもしれない。加えて、hemodynamic 応答関数を求めたが、刺激終了後の BOLD 信号低下を確実に示す証拠はなかった。

７．研究目的

Recently, event-related functional magnetic resonance imaging (ER-fMRI) has been employed to investigate temporal aspects of the blood oxygen level dependent (BOLD) response. The advantage of an ER-fMRI paradigm is that the response to sparse, short duration stimuli can be resolved without coupling to previous or subsequent stimulus presentations [1], [2], [3]. There is also evidence to suggest that the response to two or more closely spaced stimuli is additive of the response from the individual stimuli [4], [5]. This has prompted speculation that the temporal response to short duration stimuli in fMRI may be modeled by a linear time-invariant (LTI) system.

The first detailed study of the linearity assumption for the BOLD response was probably that of Boynton *et al.* [2] for human V1. Most of their results were consistent with, but did not prove that a linear system model is appropriate. In fact, for certain conditions they found a slight, but obvious, departure from linearity. By now, many other papers considering the linearity of the BOLD response (eg. [6], [7]) have arrived at a similar conclusion. Under some conditions the response is approximately linear, but there is also some departure from linearity. However, the degree of the nonlinearity varies from study to study and there is no clear agreement on the boundary of the linear domain.

One reason for the lack of agreement on the limitations of the linearity hypothesis may be the analysis techniques used. The present authors find the conclusions of these previous studies to be neither overly convincing nor rigorous. The tests for linearity are based on comparing only *estimates* for the response. Few give any consideration to the size of the error associated with these estimates. In fact, there is a relatively large uncertainty in any estimate for the measured BOLD response and consequently a simple comparison of predicted and measured responses can easily lead to an anomalous conclusion. Furthermore, the large error range brings into question conclusions about the post-stimulus undershoot because the signal-to-noise ratio in fMRI is small at that point. Some published results show no post-stimulus undershoot at all [8].

The goal of this paper is to introduce a signal model that can be used to not only estimate the form of the HRF, but can also be used to rigorously test the linearity of the BOLD response. The methodology is based on adapting a Bayesian approach to linear systems analysis of fMRI [9]. The advantage of a Bayesian framework is that the marginal posterior distribution of the HRF is derived. This probability distribution contains all information the data has to reveal about the HRF and can therefore be used to estimate the amplitude and shape of the response function. Most importantly, however, the distribution can be used in a hypothesis testing procedure to compare the HRFs from different experiments. The basis of the test for linearity shall be that if the system is truly linear then *the HRF calculated from each experiment should be the same*.

8．材料と方法

EXPERIMENTAL DETAILS

Eight healthy male subjects (age 21-39) were studied. All subjects gave informed consent according to the ethics committee of the Akita Research Institute of Brain and Blood Vessels. Data were acquired using a conventional 1.5T MRI scanner (Siemens Magnetom Vision, Erlangen, Germany) with a standard head coil. A T2*-weighted single-shot gradient-echo echo-planar imaging (EPI) sequence was applied with the following parameters: TR = 2 sec, TE = 60 msec, Flip Angle = 90 degrees, Matrix size = 64 × 64, FOV = 230 mm × 230 mm. Sixteen slices parallel to the AC-PC line with a slice thickness of 5 mm and slice gap of 1 mm were acquired. A head restraint was used to minimise head movement.

A rectangular black and white checkerboard with a black cross at its centre was displayed on a translucent screen placed at the foot of the scanner bed. During stimulation the checkerboard was reversing at a frequency of 8Hz. The visual patterns were generated by in-house software running on a PC, and projected onto the backside of the screen via a LCD video. The PC and MRI scanner were connected by an optical fibre and the onset of each visual stimulus and fMRI acquisition were synchronised. Three event-related experiments were performed for each subject, each with a different stimulus duration. The stimulus durations were all multiples of TR so that their lengths were 2, 4, and 6 seconds. Four of the subjects were presented with the visual stimulus in the order 2, 4, 6, while for the remaining subjects the order was 6, 4, 2. Each run consisted of 11

cycles and each cycle consisted of 10 frames (20 seconds). The first cycle was discarded to avoid magnetic saturation effects. In addition, all subjects performed a block paradigm experiment of 10 frames on followed by 10 off. This was used when selecting suitable activated pixels for the regions of interest.

Tracking the image centre of mass in time showed no appreciable interframe motion. No spatial nor temporal smoothing, nor movement correction were applied to the data before applying statistical analysis. Activated areas were obtained using two separate techniques developed in-house [10]. ROIs of between 2 to 17 contiguous pixels based around these areas of persistent activation were then chosen for each stimulus duration. In the case where persistent activation extended over several slices, separate ROIs were made for each slice. The algorithms were then applied to each ROI separately, as well as to the combined ROI created for each subject. A group analysis was also performed by combining the ROIs from all subjects for each stimulus duration. Each test returns a value P_o that is interpreted as the probability that the system is linear or nonlinear with respect to the chosen significance level.

９．結果

A. Estimation of the HRF

Figure 1 contains some examples of the expected HRF derived from the fMRI data. The first example is taken from slice 6 of subject 1 (Fig. 1a), the second from slice 6 of subject 3 (Fig. 1b), and the final example from slice 8 of subject 4 (Fig. 1c). Under visual examination it appears that the three expected HRFs in the first example are the most likely to be from a linear system as they are quite similar. However, taking into account the error in the estimates, even in the other two examples there is still enough similarity between the HRFs that those systems may be linear. However, as has been discussed previously, it is precisely this uncertainty in the estimates that this paper seeks to address and any conclusions about the linearity/nonlinearity should be left until the hypothesis test is applied in the next section.

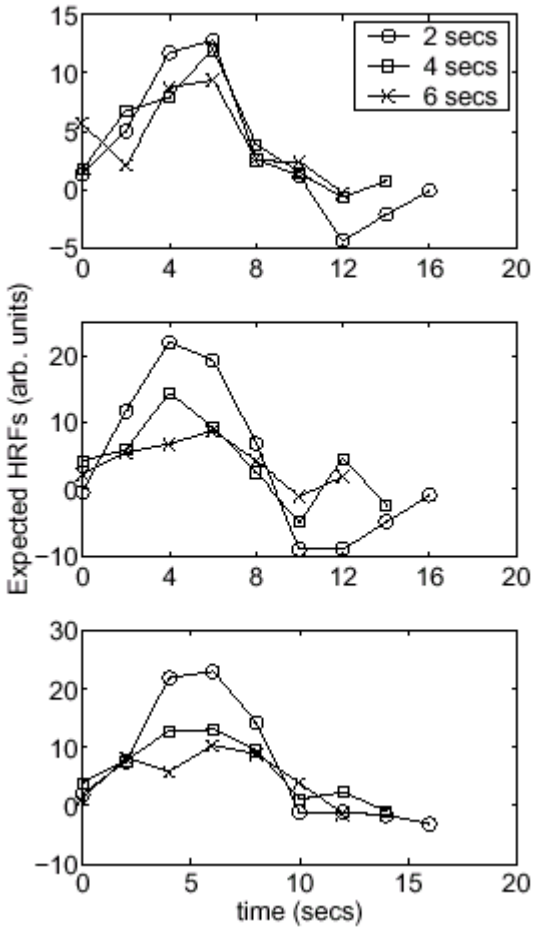

Fig 1: Example expected HRFs calculated from single slices of different subjects: (a) slice 6 of Subject 1, (b) slice 6 of Subject 3, and (c) slice 8 of Subject 4. The legend in (a) refers to the stimulus duration used in the experiment that each curve is calculated from. It is the same for each part of the figure.

Nevertheless, the estimates are still useful for visualising some of the qualitative aspects of the response. Figure 2 shows the expected responses corresponding to the expected HRFs of Fig. 1. The first thing to note about these responses is that they don't necessarily begin at zero. This is not to say that the true response doesn't begin from zero. The discrepancy most probably develops because of the inaccuracy of the estimate of the baseline and the relatively low signal-to-noise of ER-fMRI data. Another thing to note about the curves is that the rising slope of the response is reasonably constant with respect to stimulus duration in all three examples. The response then appears to peak between 4 and 6 seconds after the onset of stimulation. Moreover, the peak heights of the responses in the latter two examples, Figs. 2b and c, are about the same for all three curves, perhaps indicating that the signal has already saturated, even for a stimulus duration of only 2secs. Finally, as the signal decreases again towards the equilibrium position there is no consistent appearance of a post-stimulus undershoot. In fact, only the 2sec stimulus curves of Figs. 2a and b can be said to have a significant undershoot, although several other curves marginally drop below the zero line. Again, this inconsistency is most likely due to the low signal-to-noise ratio, and therefore it is not possible to conclusively say from these

results whether a post-stimulus undershoot exists or not for event-related responses.

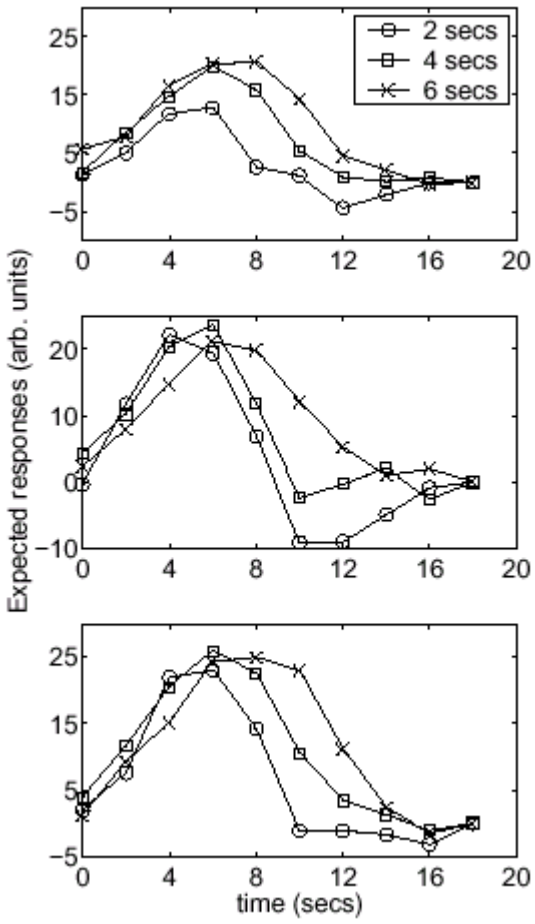

Fig 2: Expected responses corresponding to the same expected HRFs used in Fig. 1: (a) slice 6 of Subject 1, (b) slice 6 of Subject 3, and (c) slice 8 of Subject 4. The legend in (a) refers to the stimulus duration used in the experiment that each curve is calculated from and is the same for each part of the figure. Only the responses to the 2~second stimulus in parts (a) and (b) appear to have definite post-stimulus undershoots.

As a final result for this section, the expected HRFs and corresponding responses calculated from the grouped ROIs are presented in Fig. 3. The response to the 2sec stimulus in Fig. 1b has a clear undershoot, but the other two responses do not.

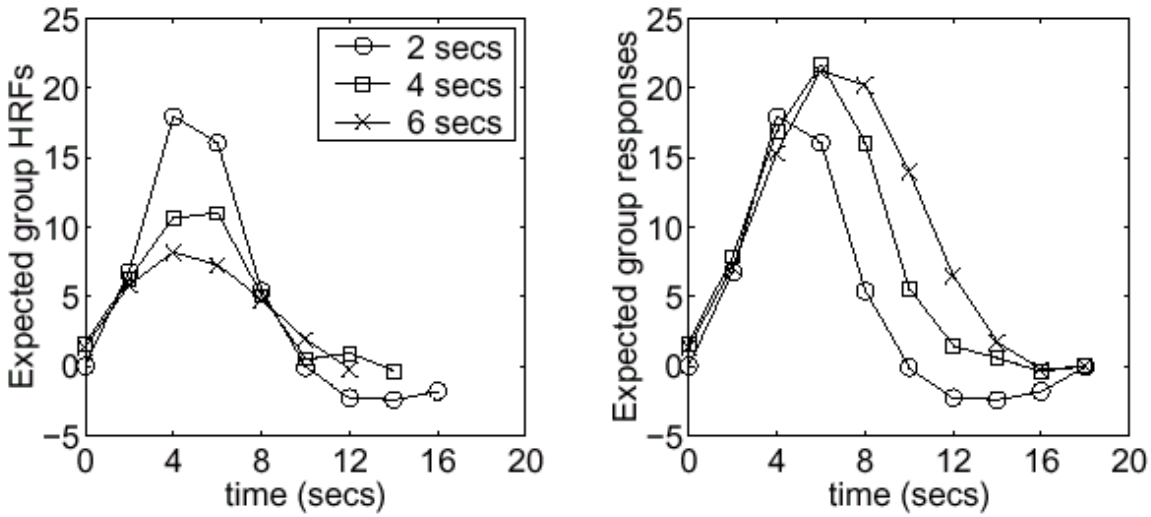

Fig. 3: Expected HRFs, (a), and expected responses, (b), obtained when the ROIs from all subjects are combined for the group analysis. The numbers in the legend refer to the stimulus duration and apply to both parts of the figure.

B. Linearity in BOLD ER-fMRI data?

Application of the linearity test to the fMRI data is summarised in Tables 1 and 2. The first table presents the results of individually applying the test to each ROI from each subject. In the majority of cases (34 out of 48) the algorithm has, to within numerical accuracy, returned a value of 1. This means that the linearity hypothesis is rejected for these cases regardless of the chosen significance level. Also, there are another four cases where $P_o > 0.99$ so that the linearity hypothesis would be rejected for a 1% significance level. Altogether, these results show that for ≈79% of the cases tested, the linearity hypothesis is inappropriate. Of the remaining 10 instances where $P_o \leq 0.99$, 6 of these have P_o's greater than 0.9, and the rest have much lower values, suggesting that there is a strong probability that the linearity hypothesis is acceptable for comparisons between these experiments.

The results can also be interpreted in terms of what they say about the system dynamics of each slice. This is summarised in the ``Dynamics'' column of Table 1, where one of the five symbols L, NL, L→NL, NL→L, or sNL is placed. The first two, L and NL, are used when linearity is respectively either accepted or rejected for all three tests on a particular slice. The latter symbol, NL, is the most common with nine instances, whereas only one of the slices sufficiently meets the conditions for linearity. This case, slice 6 of Subject 1, was highlighted in the previous section as the example that had similar expected HRFs for all stimulus durations (Fig. 1a). The other two examples from that section are both accorded the NL symbol (Figs. 1b and c).

The third symbol, L→NL, is used to indicate that linearity is accepted for the 2↔4 test, but is rejected for both the 4↔6 and 2↔6 tests. Thus, the system seemingly evolves from linearity to nonlinearity as the stimulus duration increases. Similarly, the fourth symbol, NL→L, denotes the case where linearity is accepted for the 4↔6 test, but is rejected for both the 2↔4 and 2↔6 cases. The only occurrence of L→NL is for the single slice from Subject 2, whereas NL→L is

attached to four slices: slice 7 of Subject 3, the single slice of Subject 5, and both slices of Subject 7.

Table 1
Hypothesis Test Results for all ROIs from each Subject

Subject	Slice	ROI size [a]			P_o [b]			Dynamics[c]
		2 secs	4 secs	6 secs	2 ↔ 4	4 ↔ 6	2 ↔ 6	$\alpha = 0.01$
1	6	3	5	6	0.584	0.920	0.959	L
	7	4	4	7	0.905	0.914	1	sNL
2	5	8	10	13	0.930	1	1	L→NL
3	5	4	6	9	1	1	1	NL
	6	3	5	8	1	1	1	NL
	7	2	4	5	1	0.508	1	NL→L
4	6	6	12	17	0.999	1	1	NL
	7	4	10	13	1	1	1	NL
	8	5	9	15	1	1	1	NL
5	6	2	3	3	0.991	0.731	1	NL→L
6	5	3	3	11	0.997	1	1	NL
	6	4	11	12	0.994	1	1	NL
7	5	3	2	2	1	0.736	1	NL→L
	6	2	6	7	1	0.842	1	NL→L
8	5	4	6	6	1	1	1	NL
	6	4	9	12	1	1	1	NL

[a]Times refer to the stimulus duration used in the corresponding experiment.
[b]X↔Y denotes the hypothesis test using the ROIs from the X and Y second experiments.
[c]L = linear, NL = nonlinear, L→NL = from linear to nonlinear, NL→L = from nonlinear to linear, sNL = *slow* nonlinear.

Table 2
Hypothesis Test Results by Subject and as a Group

Subject	Slices	ROI size [a]			P_o [b]			Dynamics[c]
		2 secs	4 secs	6 secs	2 ↔ 4	4 ↔ 6	2 ↔ 6	$\alpha = 0.01$
1	6, 7	7	9	13	0.991	0.997	1	NL
2	5	8	10	13	0.930	1	1	L→NL
3	5, 6, 7	9	15	22	1	1	1	NL
4	6, 7, 8	15	31	45	1	1	1	NL
5	6	2	3	3	0.991	0.731	1	NL→L
6	5, 6	7	14	23	1	1	1	NL
7	5, 6	5	8	9	1	0.869	1	NL→L
8	5, 6	8	15	18	1	1	1	NL
Group	All	61	105	146	1	1	1	NL

[a]Times refer to the stimulus duration used in the corresponding experiment.
[b]X↔Y denotes the hypothesis test using the ROIs from the X and Y second experiments.
[c]NL = nonlinear, L→NL = from linear to nonlinear, NL→L = from nonlinear to linear.

The final symbol, sNL, denotes the case where linearity is acceptable for 2↔4 and 4↔6, but not for 2↔6. This can be interpreted as indicating that the differences in the HRFs from the 2sec to the 4sec stimuli and from the 4sec to the 6sec stimuli are small enough that the linearity hypothesis is accepted in those cases. However, when comparing the 2sec and 6sec experiments, the change in the HRF is significant enough for linearity to be rejected. This case is therefore called ``slow nonlinearity'' meaning that the system is probably nonlinear, with the HRF changing from experiment to experiment, but the change is too *slow* to be resolved from tests on data taken with sufficiently similar stimulus durations. Such a case only occurs for slice 7 of Subject 1.

It should also be noted that there are some cases of the dynamics that do not occur. All of these are consistent with the observation that the null hypothesis is never accepted for the 2↔6 test without it also being accepted for the two other tests. In fact, acceptance for the 2↔6 case only occurs for the solitary linear slice.

The second table, Table 2, summarises the results of the linearity test when applied to the joint ROI of each subject. Subjects 2 and 5 have only one slice containing a ROI so their results are the same as in Table 1. Of the remaining subjects, all are found to be nonlinear except for Subject 7 who is NL→L. The most distinctive result is that Subject 1, who had one slice linear and

the other sNL, is found to be nonlinear when the two ROIs are combined. Under closer consideration this is not so surprising. Since the combined ROIs contain elements from two different types of systems, the joint system will most likely be nonlinear. This is probably also the case for Subject 3 when slice 7, which is NL→L, is combined with the other two slices that are NL. In contrast, the joint ROI for Subject 7 is a combination of two ROIs with the same dynamics so that the combined result is the same as the individual results.

Also contained in Table 2 are the results of the group analysis. They clearly show that the dynamics are nonlinear, the reason undoubtedly being that since there seems to be little consistency of the HRF across slices from the same subject, then there is no reason to expect that it should be consistent across subjects.

Finally, it is important to remember that the interpretation of the dynamics presented here is dependent on the significance level, and a higher or lower choice for it can easily change the classification.

10. 考察

Event-related BOLD fMRI data is modeled as a linear time-invariant system. Together with Bayesian inference techniques, a statistical test is developed for rigorously detecting linearity/nonlinearity in the BOLD response system. The test is applied to data collected from eight subjects using an event-related paradigm with a switching checkerboard as the visual stimulus. Analysed as a group, the results clearly find the response to be nonlinear. When each subject is analysed individually, however, the results are predominately nonlinear but there is some evidence to suggest that there may be a crossover from a linear to a nonlinear regime and vice versa. This could be important when estimating physiological parameters for individuals.

Aditionally, estimates of the HRF and the corresponding expected response did not consistently show the existence of a post-stimulus undershoot in either the group or individual analyses.

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13. 研究業績

13-1. 原著論文：
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13-2. 総説など：なし

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14. A Bayesian Technique for Investigating Linearity in Event-Related BOLD fMRI
15. Akita Research Institute of Brain and Blood Vessels
16. Jeff Kershaw (JST Akita)
17. Kenichi Kashikura (JST Akita)
    Xiaojiang Zhang (JST Akita)
    Sumiko Abe (Akita Research Institute of Brain and Blood Vessels)
    Iwo Kanno (Akita Research Institute of Brain and Blood Vessels)
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19. Abstract

Event-related BOLD fMRI data is modeled as a linear time-invariant system. Together with Bayesian inference techniques, a statistical test is developed for rigorously detecting linearity/nonlinearity in the BOLD response system. The test is applied to data collected from eight subjects using an event-related paradigm with a switching checkerboard as the visual stimulus. Analysed as a group, the results clearly find the response to be nonlinear. When each subject is analysed individually, however, the results are predominately nonlinear but there is some evidence to suggest that there may be a crossover from a linear to a nonlinear regime and vice versa. This could be important when estimating physiological parameters for individuals. Additionally, estimates of the haemodynamic response function and corresponding response were obtained, but there was no consistent appearance of a post-stimulus undershoot in the event-related BOLD response.