TEMPORAL AND SPATIAL NONLINEARITIES IN FMRI BOLD RESPONSE IN HUMAN PRIMARY VISUAL CORTEX

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CEM BENAR
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We certify that we have read this thesis and that in our opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Science.

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ABSTRACT

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It is generally assumed that fMRI BOLD response (i.e., functional magnetic resonance imaging blood-oxygen-level-dependent signal) is linear and time-invariant. In this study, we investigated spatial and temporal nonlinearities in fMRI BOLD response at different flickering durations (nearly instantaneous and 1 s). We presented participants two successive flickering checkerboard wedge stimuli with stimulus onset asynchrony (SOA) of 0 s, 0.5 s, 1.5 s, and 6 s. The spatial locations of the stimuli were categorized as the same location in the same hemifield, adjacent locations in the same hemifield, and between hemifields. We demonstrated that fMRI BOLD response behaves nonlinearly when the successive stimuli spatially and temporally were close to each other for both flickering durations. Nonlinearity between the successive stimuli was the highest for the same location in the same hemifield, higher in adjacent locations in the same hemifield, and the lowest in between hemifields. In addition, nonlinearity at the shorter SOAs (0 s, 0.5 s, and 1.5 s) was found to be higher than nonlinearity at SOA 6.

Keywords: spatial nonlinearity, spatial summation, temporal nonlinearity, temporal summation, fMRI BOLD, primary visual cortex.

ÖZET

FMRG KAN OKSİJEN SEVİYESİNE BAĞIMLI (BOLD) SİNYALİN İNSAN BİRİNCİL GÖRME KORTEKSİNDE ZAMANSAL VE KONUMSAL NONLİNEERLİKLERİ

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Birçok çalışmada fMRG BOLD sinyalinin (fonksiyonel manyetik rezonans görüntüleme kan oksijen seviyesine bağımlı sinyal) genellikle lineer ve zamandan bağımsız olduğu kabul edilir. Bu çalışmada bu varsayımın doğru ve doğru olmadığı durumları inceledik. Farklı zaman aralıklarında (0 sn, 0.5 sn, 1.5 sn ve 6 sn) birbirinin ardından gelen ikili görsel uyaranın neden olduğu BOLD sinyalini iki farklı uyaran süresinde (çok kısa ve 1 sn) ölçtük. Bu ölçümleri uyaranların birbirlerine olan konumsal uzaklıklarının farklı olduğu üç ayrı durum için tekrarladık (uyaranlar aynı lokasyonda, uyaranlar aynı beyin yarısında birbirlerine komşu uzaklıkta ve uyaranlar farklı beyin yarılarında). Bu şekilde zamansal ve konumsal uzaklıklar arasındaki ilişkiye baktık. Buna ek olarak, iki farklı uyaran süresinde ölçmemiz zaman ve konum arasındaki ilişkilerin uyaran süresine bağlı olarak nasıl değiştiğini incelememize olanak sağladı. İki farklı uyaran süresinde, üç farklı uzaklıkta ve üç ayrı zaman aralığında yapılan bu ölçümlerde bulunan sonuçlar bize her iki uyaran süresi için uyaranların arasındaki konumsal uzaklığın azalması durumunda BOLD sinyalinin lineer sinyale göre daha düşük olduğunu gösterdi. Benzer şekilde, iki uyaran arasındaki zamanın kısa olduğu durumlarda (0 s, 0.5 s ve 1.5 s) BOLD sinyalinin lineer sinyale göre zaman aralığının 6 s oldugu duruma oranla daha düşük olduğu gözlemlendi. Bu çalışma, araştırmacılara fMRG BOLD sinyalinin yukarıda bahsedilen durumlarda lineer varsayılmasının yanlış olabileceğini göstermektedir.

Anahtar sözcükler: konumsal nonlineerlik, konumsal toplama, zamansal nonlineerlik, zamansal toplama, fMRG BOLD, birincil görme korteksi.

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Chapter 1

Introduction

1.1 Background

Functional magnetic resonance imaging (fMRI) is one of the most widely used techniques among neuroscientists to investigate underlying neuronal activity in response to a wide variety of stimulus. It is a non-invasive neuroimaging technique that measures concentration of deoxyhemoglobin in tissue, the form of hemoglobin without oxygen. FMRI BOLD signal (i.e., functional magnetic resonance imaging blood-oxygen-level-dependent signal) is measured by T2*-weighted (i.e., gradient-echo) imaging or T2-weighted (i.e., spin-echo) imaging. Spin-echo imaging is more commonly used in higher magnetic fields (at 7 T or higher). Both imaging techniques describe transverse relaxation (i.e. decay of MRI signal). When the concentration of deoxyhemoglobin (dHB) increases, transverse relaxation time decreases due to increasing local field inhomogeneities caused by paramagnetic properties of dHB, resulting in a reduction in image intensity. Conversely, it increases when concentration of deoxyhemoglobin decreases. In other words, there is an inverse relationship between concentration of deoxyhemoglobin and the BOLD signal. This contrast forms the basis of blood oxygen level-dependent (BOLD) mechanism [1, 2, 3, 4].

Concentration of deoxyhemoglobin and the corresponding BOLD signal depend on cerebral metabolic rate of oxygen ($CMRO_2$), cerebral blood volume (CBV), and cerebral blood flow (CBF) [5, 6, 7, 8]. Rising neuronal activity results in an increase in all these parameters [7], because neurons need oxygen to maintain their metabolic activities, get input from other neurons, and fire. Therefore, there is an indirect relationship between activity of neurons and BOLD response. The relationship between stimulus and BOLD response is characterized in Figure 1.1 [9, 10].

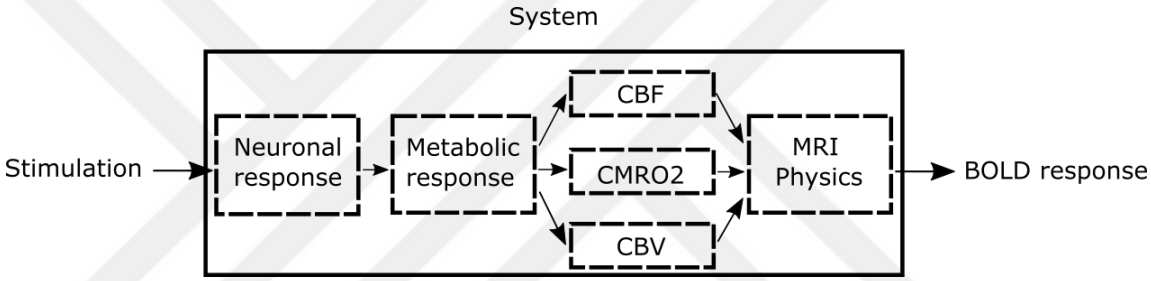

Figure 1.1: Relationship between stimulation and BOLD response. Neuronal response triggered by stimulus evokes the metabolic response. The metabolic response consists of CBF, $CMRO_2$, and CBV. These parameters together with MRI physics forms the BOLD response.

It is crucial to know this indirect relationship between the BOLD signal and neuronal activity in order to make correct inferences from fMRI experiments about the underlying neuronal activity. Previous studies have shown that local field potential (LFP) more successfully represents BOLD signal than multiunit activity (MUA) does [11]. This evidence shows that BOLD response is a better estimate of synaptic activity, since LFP and MUA are associated with synaptic and spiking activities, respectively. The fact that both inhibitory and excitatory input need oxygen is another evidence supporting the hypothesis that BOLD response represents synaptic activity more than spiking activity [12]. Overall, BOLD signal arises from excitatory and inhibitory synaptic activity, neural spiking and neuromodulation [13, 14].

The canonical shape of BOLD response can be described by four parameters: amplitude (gain), full width at half maximum (FWHM), peak delay (peak latency, time to peak), and onset delay as illustrated in Figure 1.2. Any deviations in these

measured parameters from the parameters expected from a linear system can be attributed to nonlinearity.

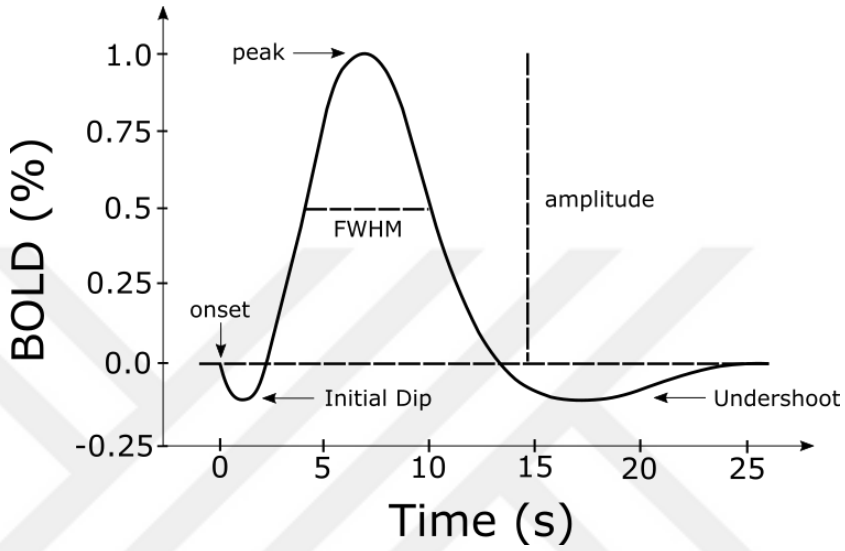

Figure 1.2: The canonical shape of BOLD response.

A system is said to be linear if it holds scaling (homogeneity) and additivity properties. Additivity and scaling principles are defined as:

$F(x_1 + x_2) = F(x_1) + F(x_2)$	Additivity
$F(ax) = aF(x)$	Homogeneity (Scaling)
for scalar a	

Scaling is a property which states that output of a linear system is proportional to magnitude of its input. If homogeneity (scaling) property holds, BOLD response would be proportional to the strength of neuronal activity. For example, doubling the strength of stimulus (i.e., contrast, luminance, stimulus duration) leads to the increase in BOLD response by a factor of its scaling constant. On the other hand, additivity requires that output of a linear system with more than one input is the sum of the responses to the individual inputs. If additivity property holds, BOLD response to two stimuli separated with a short lag would superimpose linearly (i.e., sum of individual responses of stimulus 1 and shifted stimulus 2). Additivity property also allows that BOLD response to short stimuli can predict BOLD response of longer stimuli. Besides, time-invariance, another property that usually comes with linearity, means that a time shift in the input function would

directly equate the same time delay in the output response given a system time-dependent output and time-dependent input functions. Additivity and scaling properties are illustrated in Figures 1.3 and 1.4, respectively.

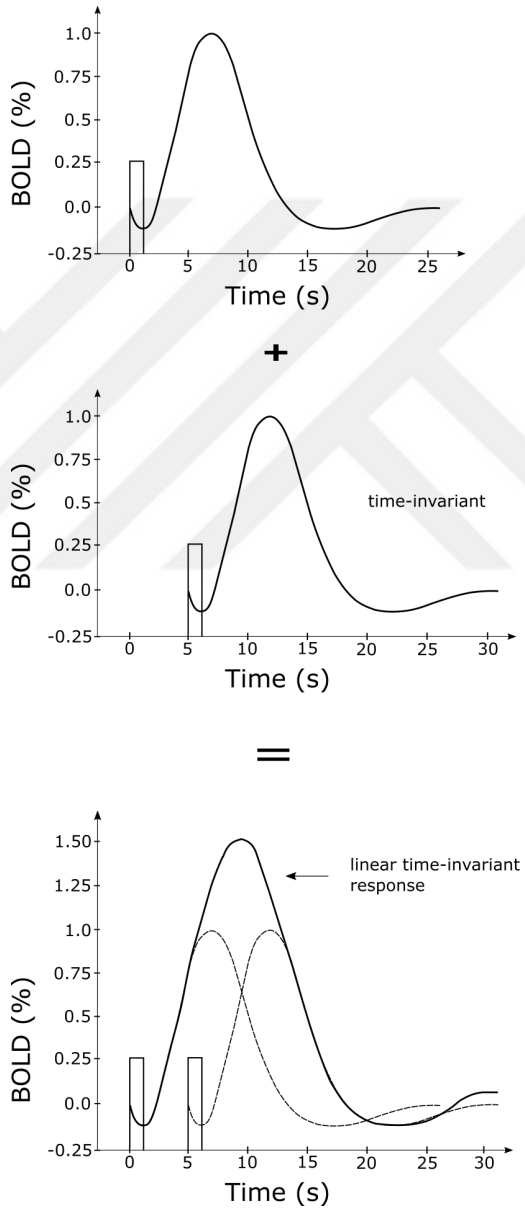

Figure 1.3: Additivity property of BOLD response.

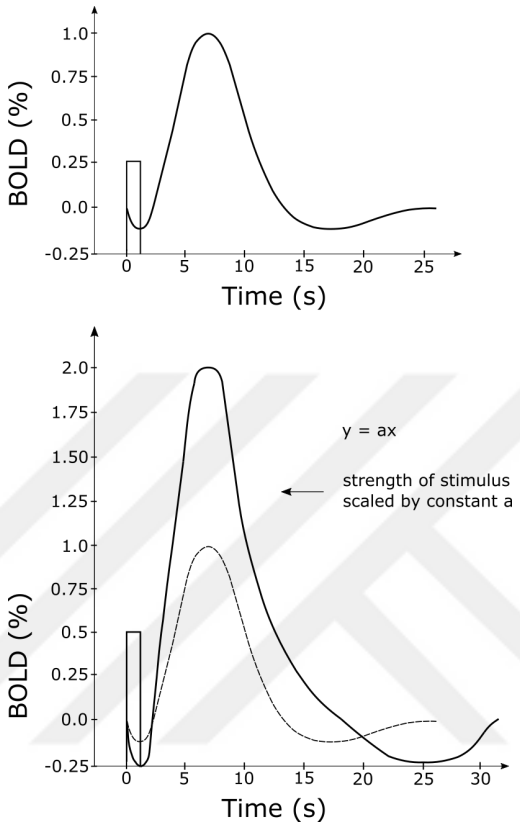

Figure 1.4: Scaling property of BOLD response. y=ax, where constant a assumed to be 1.

Neuroscientists investigate linearity between stimulus and BOLD response because disregarding nonlinearities in BOLD response create problems in rapid event related designs and may harm validity of studies. If BOLD response is a linear time-invariant system in response to stimulus, designing experiments and analyzing data would have been much simpler [15]. Data processing schemes such as General Linear Model (GLM) [16], correlation analysis [17] and some pRF models [18, 19, 20] assume that BOLD response is a linear time-invariant system with respect to stimulus. In addition, several research studies [21, 22, 23, 24] assume BOLD response linear in their analyses. Besides, since there is a long duration between the onset of stimulus and return to baseline, neuroscientists are required to design their experiments such that they adjust the onset time of events in time to minimize interactions between successive events and thereby successfully extract individual responses of events. If BOLD response is found to be linear and time-invariant, then subtractions of event responses to extract

individual event responses would be allowed and designs would be more efficient [25].

1.1.1 Temporal Linearity

Linear transform model proposed by [15, 26] aimed to model BOLD response. The model claims that BOLD response in human primary visual cortex can be obtained by convolving neuronal response with a hemodynamic response followed by adding Gaussian noise. Hemodynamic response function satisfied the scaling and additivity requirements of a linear system in [15, 26]. Meaning, smaller duration stimuli (e.g. 6 s) accurately predicted longer stimuli (e.g. showing 24 s checkerboard pattern). However, 3 s stimulus was not able to predict longer stimuli very well. The superimposed response appeared to be larger in amplitude than the actual response of the longer stimuli [15]. The authors noted that the nonlinearity with respect to stimulus contrast level was not because of the nonlinearity in shorter duration but because the response of the longer stimuli was reduced due to neuronal adaptation. In other words, the shorter stimuli (3 s) had no nonlinearity, whereas the longer stimuli (24 s) had nonlinearity due to the neuronal adaptation in response to longer stimulation (e.g., 24 s). Therefore, the authors asserted that the BOLD response became nonlinear due to nonlinear neural activity although it still satistied the linear transformation of neural activity. Besides, it was reported by [27] that there is a power law function between neuronal activity and hemodynamics response function although the relationship can be approximated by a linear function. Temporal additivity of BOLD response in the primary visual area (i.e., V1) was also tested in [28]. The authors used paired stimulus paradigm and presented different number of stimuli with checkerboard pattern. They measured BOLD responses of one stimulus, two stimuli (each separated by 2 s), and three stimuli (each separated by 2 s). In order to find individual contribution of the second stimulus, they subtracted the response of one stimulus from the response of the two stimuli. To find individual contribution of the third stimulus, the response of two stimuli was subtracted from the response of the three stimuli. They eventually found that individual

responses of first, second, and third stimulus are close to each other such that BOLD signal can be superposed in a linear fashion across successive trials at short (2 sec and 5 sec) inter stimulus intervals (ISIs) when presented 1 s full-field flickering checkerboard stimuli or 1 s right-left hemifield flickering checkerboard stimuli. However, they also pointed out that BOLD responses of the second and third stimulus were slightly lower than the response of the first stimulus in amplitude (a slight hemodynamic refractory effect was reported) and their peak latencies were slightly larger than the peak latency of the first stimulus. [29, 30] also found that linear approximation of BOLD response can be accurate in certain circumstances although there are small nonlinearities.

1.1.2 Temporal nonlinearity as a variable of stimulus duration

Nonlinearity of BOLD response was investigated with respect to stimulus duration ranging from 0.5 s to 12 s in the visual cortex in [31] and strong nonlinearity was observed at the shorter stimulus durations (< 3 s) when presented full-field circular flickering checkerboard stimuli at 8 Hz. BOLD response to longer stimulation appeared to be higher, wider and with delayed peaks than BOLD response to smaller stimulation. When examined maximum BOLD signal change (i.e., amplitude), time to peak, FWHM, and area under the curve with respect to stimulus duration, there was a nonlinear relationship only between amplitude and stimulus duration. That is, BOLD response decreasingly grew with respect to stimulus duration [31]. Therefore, when BOLD responses to shorter stimuli are superimposed to construct BOLD response to longer stimuli, the synthesized BOLD responses will appear to be larger than the observed BOLD response for stimulus durations between 1 s and 4 s. This finding is consistent with the study [15] at 3 s. This hypothesis was also supported by [32]. They also found that amplitude was nonlinearly dependent to stimulus duration.

Nonlinearity of BOLD and CBF with respect to stimulus duration (2 s, 6 s, and 18 s) was investigated by simultaneously measuring CBF and BOLD changes

with arterial spin labeling (ASL) method in response to flickering checkerboard pattern at 8 Hz [9]. BOLD response and CBF were correlated with each other and both were strongly nonlinear in the stimulus durations (2 s, and 6 s) to predict response of stimulus with 18 s in the primary visual cortex. The fact that the authors found nonlinearity at 6 s is contradictory to the study [15]. They also analyzed the primary motor cortex and found that CBF was linear in 2 s and 6 s to predict 18 s but BOLD responses to stimuli 2 s and 6 s did not accurately predict BOLD response to stimulus 18 s. Thus, although BOLD results gave consistent results in both primary visual cortex and primary motor cortex, CBF results differed across the regions.

In addition to investigating nonlinearity in the visual cortex with respect to stimulus duration, an auditory stimulus was presented to investigate nonlinearity in the auditory system in the study [33]. The stimulus consisted of a series of 100 ms tones and 100 ms pauses. 100 ms tones was played at 440 Hz. 100 ms tones and 100 ms pauses were successively combined to construct different stimulus durations (i.e., 100 ms, 300 ms, 700 ms, 1.5 s, 3.1 s, 6.3 s, 12.7 s, and 25.5 s). They found that BOLD response became linear when the stimulus duration was larger than 6 s and became nonlinear when it was less than 6 s. Stimulus duration with less than 6 s produced larger BOLD response than expected from a linear system.

1.1.3 Temporal nonlinearity as a variable of inter-stimulus duration

The refractory effect is a phenomenon that the activation of the first stimulus suppresses the activation of the second stimulus presented after a short ISI. The origin of the refractory effect can be neuronal or vascular. To investigate the refractory effect as a variable of ISI and the number of successive stimuli, four experiments were designed [34]. They simultaneously recorded EEG and fMRI data in the somatosensory cortex in rats in the first three experiments and fMRI data in primary visual area in human in the last experiment. The stimulus

used in rats was forepaw stimulation with pulse width 300 msec, and the pulsed current (0.4 mA to 1 mA), which is an electrical stimulation paradigm. In the first paradigm, they used up to 20 successive forepaw stimuli for two different ISIs (310 ms, 620 ms). For ISI of 310 ms, they found nonlinearity in BOLD response for number of stimuli greater than 2. For ISI of 620 ms, when the number of successive stimuli exceeded 4, BOLD became nonlinear. That is, the nonlinearity increased as the number of successive stimuli increased or as ISI became shorter. In the second experiment, they used a static stimulus duration (two successive stimuli) and a range of ISIs (20 to 750 ms). Both SEP (i.e., EEG) and fMRI stayed nonlinear until around 575 ms of ISI. Both experiment 1 and experiment 2 examined the effects of ISI and number of stimuli in nonlinearity of BOLD by presenting paired stimuli at the same region in the somatosensory cortex. Experiment 3 included two stimuli that activate separate brain regions in the opposite hemifields. Both SEP and fMRI results became nonlinear until 100 ms. It can be said that the nonlinearity in the experiment 1 and 2 (at the same location) are more severe than the nonlinearity in the experiment 3 (between hemifields). In the last experiment (experiment 4), they presented two very short (10 ms) visual stimuli at the same location in the primary visual cortex and examined nonlinearity of BOLD response. Although they reported that results substantially varied by subject, they found that nonlinearity of BOLD existed from 50 ms to 1000 ms of ISIs. It was reported that the second stimulus' response was nearly zero at ISI 200 ms. Nonlinearity of BOLD response caused by short ISI not only reduced amplitude of BOLD signal but also the width of the signal. They observed narrower BOLD response. In conclusion, both rat and human studies showed that nonlinearity of BOLD caused by refractory effect occurred at shorter ISIs and longer stimulus durations in the same location and between hemifields.

A similar study was conducted by [25] in human to investigate effect of ISIs in BOLD response. They designed paired stimuli paradigm and presented two 500 ms high contrast checkerboard stimuli located at the fixation with the specified SOAs (1 s, 2 s, 4 s, and 6 s) followed by intertrial interval (16-20 s). They also measured BOLD response of single stimulus of subjects. To extract BOLD

response evoked by the second stimulus, they subtracted one stimulus responses from two stimuli responses. They found that the BOLD response elicited by the second stimulus was smaller in amplitude and its time to peak was longer when compared to the first stimulus' BOLD response. If BOLD response was linear and time-invariant, amplitude and time to peak parameters of the first and second stimuli's BOLD responses had to be the same. The amplitude of BOLD response was modulated by SOA such that the response of the second stimulus was 55% of the response of the single stimulus at SOA 1 s, whereas this ratio recovered to 90% at SOA 6 s. In addition, they reported that longer time to peak (peak latency) were observed in response to shorter SOAs. Since longer time to peak and lower amplitude were observed at the same time, the findings are consistent with the former study [35], which showed that higher amplitude comes with earlier onset although the latter study wasn't able to explicitly detect onset latency but peak latency only.

1.1.4 Spatial linearity and nonlinearity

Assuming that fMRI BOLD response supports both temporal and spatial summation makes designing event-related experiments easier and extracting individual event-related responses more reliable. For example, consider that a pRF (population receptive field) is located at the horizontal midline of the visual field. It consists of upper and lower visual fields. When presented separate stimuli that cover the upper field only, the lower field only, or both upper and lower fields, individual responses of the lower and upper fields should be equal to the response of both fields if spatial and temporal linear summations exist. Consequently, this will make designing and analyzing event-related experiments simpler.

Spatial summation in V1 was investigated in the study [36]. They presented 3 s flickering at 8 Hz black-and-white checkerboard stimuli (rings, wedges, and intersections of rings and wedges) in both left and right visual fields with the maximum contrast. They assessed spatial linearity by comparing responses to the visual stimuli (wedges, and rings) with sum of responses to components of

wedges and rings. For example, rings consisted of three components in their design. They compared response to the ring with sum of individual responses to the components of the ring. They measured the shapes (e.g., rings) and components of shapes independently by using M-sequence. For example, a M-sequence measures response in the region in which the first individual component of a ring is located at. Another M-sequence measures response in the region where the second individual component of a ring is located at. M-sequences were separated with a blank duration of 30 s so that response in a region does not contaminate to a response in another region. They found that sum of responses to individual components of a shape were equal to response to a shape, meaning positive BOLD responses supported spatial summation in V1.

However, there are contradictory studies that show failure of spatial summation such as [37]. They reported that the prediction of spatial summation is slightly accurate in V1, V2, and in anterior extrastriate regions (e.g., LO-2, VO-2). Besides, spatial heterogeneity of nonlinearity within region and across regions exists, which might be due to spatial variation of neuronal firing or differences of cerebral vasculature [38, 39, 40]. As a consequence, this might lead to failure of linear spatial summation. It is also important to note that nonlinear surround suppression of neural activity can make BOLD responses spatially nonlinear [41]. This effect was previously reported in V1 [42, 43]. There are studies that reported facilitatory effects of the surrounding regions at the center, too [43].

Spatial summation was also investigated in MT by presenting moving Gabor function stimuli presented for 100 ms [44]. They found that the responses to pairs of these stimuli were importantly less than the sum of individual responses to the components. Likewise, the BOLD response to a group of nearby visual stimuli presented simultaneously for 250 ms was smaller than the sum of the individual responses of the stimuli in the areas of V1, V2, V3A, V4, TEO, and MT due to mutually suppressive interactions [45, 46, 47, 48]. They also found that this effect was even increased from V1 to V4 and concluded that the mutual suppression was correlated by the progressive increase in pRFs size of neurons. In addition, as the distance between the adjacent stimuli (i.e., spatial separation) were increased (from 2 degree to 7 degree), the suppression effect was lowered

and only seen in 2 degree in V1, V2 and V4. Besides, spatial summation was tested in V1 at different contrast levels (5%, 40%, and 90%) in [49] and similar results was found that the response to the simultaneously presented adjacent nine checkerboard wedge stimuli was less than the sum of the individual responses of the sequentially presented nine stimuli at all contrast levels due to mutually suppressive interactions between the adjacent stimuli. It was also found that mutual suppression became more dominant, resulting more severe nonlinearities as the contrast level decreased. As the contrast level increased, level of nonlinearity decreased [49].

Single-cell recording studies [50, 51] also found evidence that two groups of neurons that activate distinct regions in brain mutually modulate their firing rates which can be thought as an evidence for the interaction of two sets of neurons. Likewise, monkey studies also showed consistent results with the studies introduced earlier [45, 46, 47, 48].

1.2 Scope and Motivation of the Present Study

Our study focused on investigating spatial and temporal nonlinearities of BOLD response in V1 in response to black-and-white checkerboard wedge stimuli flickering at 8 Hz at the different flickering durations (nearly instantaneous, and 1 s). We investigated if linear summation holds in different spatial and temporal configurations and how spatial and temporal configurations interact with each other at different flickering durations.

For this purpose, we designed three experiments by repeating them two times for two different stimulus durations. We named early instantaneous as impulse. Stimulus duration lasting 1 second is called longer pulse. We used the impulse stimulus to discover how transient burst neural activity interacts with time and space. On the other hand, 1 sec (longer pulse duration) is a time duration where neural adaptation unlikely happens. Therefore it is important to show the interaction of neural activity without adaptation through BOLD response. Besides,

using different stimulus durations allowed to examine if space-time interactions differ at different flickering durations.

We used a wide range of SOAs where temporal nonlinearities may be expected due to vascular or nonlinear refractory effect. In addition, we observed the interaction between SOAs and spatial locations of the paired stimuli. We sought an answer if different spatial organizations have suppressive or facilitatory effects on the BOLD response at different SOAs. In short, we examined the interaction of time and space in BOLD response.

We used two different stimulus paradigms named SIRF and SOA experimental designs in this study. In SIRF paradigm, individual responses of two visual stimuli were measured. In SOA paradigm, the two visual stimuli were paired and presented successively at different SOAs (0 s, 0.5 s, 1.5 s, and 6 s). Both SIRF and SOA paradigms were conducted in three distinct spatial configurations and two distinct flickering durations. In SIRF paradigm, no temporal nonlinearity was expected because the stimuli were presented in separate time-intervals such that the former and latter stimuli will not affect each other. On the other hand, in SOA paradigm, we measured responses to the visual stimuli in the shared time-intervals (i.e. measuring them simultaneously). Therefore, SOA design allowed to measure not only single responses of the visual stimuli but also their mutual interactions since they were presented with the short SOAs. To assess linearity, we combined individual responses acquired by SIRF paradigm to each other in different SOAs to form the same paired stimuli responses we measured in SOA paradigms (see section 2.1.7.1 for more details). We named the combined individual responses as the predicted responses. Then we compared the predicted responses with observed responses acquired by SOA paradigm. If BOLD is linear and time-invariant system, the predicted and observed time-course responses are expected to be equal to each other. The linearity was evaluated by visual inspection and a quantitative way.

Chapter 2

Experiment 1: Interactions in the Same Visual Field and Between Visual Fields In Different Hemifields

We conducted this experiment for two purposes. The first purpose is to make sure that our method and analysis are compatible with the findings in the previous studies. For this purpose, we used the same conditions examined by many studies in the literature and compared our results with the previous findings.

The commonly used conditions in the literature were visual stimulations in same location with an interval of SOAs between successive stimulations. In other words, the experiment included conditions where the first and second visual stimuli were at the same spatial location. The conditions allowed us to investigate interactions between paired stimuli in the same location. It is known that a visual stimulus shown in the left visual field (i.e. left stimulus) forms a positive BOLD response in the right hemisphere because of the retinotopic organization of V1 [52]. However, the left stimulus can also modulate the ipsilateral hemisphere (i.e. left hemisphere in this case). We examined both contralateral and ipsilateral

activations of paired stimuli in the same location.

Our second purpose is to investigate whether there is any interaction between these two hemispheres as a variable of SOA. We presented two successive stimuli in opposite hemifields with varying SOAs.

In independently identified regions of interest (ROIs, see details of ROI localizer under section 2.1.5) in primary visual cortex (V1), we first identified hemodynamic impulse response functions using visual stimuli dispersed widely in time ('Single impulse response function (SIRF)' scans, see below for more details) and used them to predict responses to presentation of visual stimuli with shorter time between them ('SOA scans', see below for details). Any deviation between the predicted and observed BOLD responses is taken as a sign of nonlinearity.

2.1 Materials and Methods

2.1.1 Participants

Three subjects including the author CB (two females, ages ranged from 26 to 28) participated in the experiment. Participants were graduate students in National Magnetic Resonance Research Center (UMRAM), Bilkent University. All participants reported normal or corrected-to-normal vision, and had no history for neurological or visual disorders. Ethics approval was granted by Bilkent University Ethics Committee for Research with Human Participants. All participants gave written informed consent in accordance with the Declaration of Helsinki.

2.1.2 MRI Data Acquisition

A 3 Tesla MR scanner (Siemens Trio) using a 32-channel phase-array head coil at the National Magnetic Resonance Research Center (UMRAM), Bilkent University was used for scanning. Experiment 1 consists of two MR sessions for each subject. Each of the sessions started with an anatomical scan, followed by an V1 localization scan, 4 runs of SIRF scans, and 5 runs of SOA scans. It is known that subject's performance or attention may decrease over time. In addition, subject may tend to make more head motion towards the end of the scan. Therefore, 9 experimental scans, consisting of all SIRF and SOA runs, alternated in order to distribute equally the effect of subject's performance and head motion on the experimental scans. Anatomical scan was acquired using a high resoulution T1-weighted 3D MPRAGE sequence (TR: 2600 ms, TE: 2.92 ms, flip angle: 12 deg, slices per slab: 176, Bandwidth: 130 Hz/Px, FoV: 256 mm, slice thickness: 1 mm, spatial resolution: 1 mm x 1 mm x 1 mm). Functional localizer scan was performed with a gradient-echo echo-planar imaging (EPI) sequence (TR: 2000 ms, TE: 35 ms, flip angle: 75 deg, number of slices: 30, bandwidth: 1346 Hz/Px, FoV: 192 mm, slice thickness: 3 mm, in-plane resolution: 3 mm x 3 mm, slice orientation: parallel to calcarine sulcus). Functional experimental scans were acquired with a multi-band gradient-echo echo-planar imaging (EPI) sequence (TR: 250 ms, TE: 32 ms, flip angle: 30 deg, number of slices: 12, bandwidth: 1502 Hz/Px, FoV: 192 mm, slice thickness: 3 mm, multi-band acceleration factor: 4, in-plane resolution: 3 mm x 3 mm, slice orientation: parallel to calcarine sulcus). The first two volumes of the functional scans were discarded to allow for T1 saturation by the scanner.

2.1.3 Visual Stimulus Presentation Setup

Visual stimuli were back-projected using a MR compatible LCD screen (refresh rate 60 Hz, resolution 1920x1080; TELEMED Solutions, Istanbul) that was viewed by participants with the help of a mirror attached to the head coil and located above their eyes while lying supine inside the scanner. The screen

had a width of 70 cm and was placed at a distance of 165 cm from the eyes of the participants. Gray scale look-up tables were prepared and used for correct luminance presentation.

2.1.4 Experimental Design

Presented stimuli was consisted of two wedges which have flickering contrast-reversing black and white checkerboard pattern with the flickering rate of 8 Hz. The widths of the two wedges were (90° circular angle). The wedges were located at the horizontal meridian and bilaterally symmetrical according to the fixation point. The wedges were named as left wedge and right wedge because we located the left and right wedges at the left and right visual fields, respectively. The distance from the innermost part of the wedges to the fixation point is 2° visual degree and the width of the wedges are 4° visual degree. The contrast of the wedges was 40% Michelson to keep the hemodynamic response below the saturation level. Background was isoluminant gray with luminance 86 in cd/m^2. The spatial configuration of the experiment is shown in Figure 2.1.

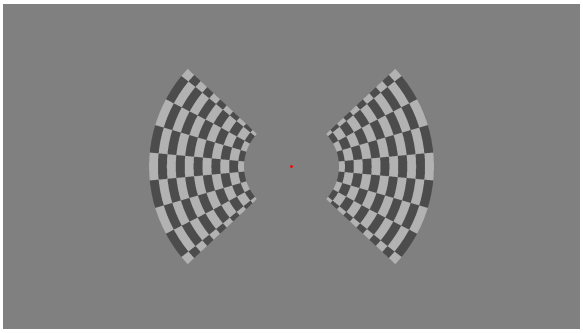

Figure 2.1: Experiment 1 configuration. The wedges were located at horizontal meridian and bilaterally symmetrical according to the fixation point. The left and right wedges were located at the left and right visual fields, respectively.

We used two flickering durations (impulse, and longer pulse) and repeated the experiment for each flickering duration. In the impulse version of the experiment 1, the flickering period consisted of one flick, meaning that black and white regions in the checkerboard pattern changed for once. Therefore, we named it as impulse

since the stimulus was nearly instantaneous. In the longer pulse version of the experiment, the flickering duration was 1 s.

2.1.4.1 Impulse Experimental SIRF Design

In SIRF scans we collected responses to widely dispersed single impulse stimuli, in other words responses to individual stimulation. Left and right stimuli alternate during the scan with a blank duration of 32 s between them. We used a long blank (32 s) in order to eliminate any effect of the former stimulus on the latter stimulus [53].

Each participant performed SIRF scans in two sessions. Each stimulus was repeated in 72 times in total, 36 times in each session. 36 repetitions of each stimulus was completed in 8 SIRF scans in each session. Since the experiment had three subjects, we had 216 trials for each stimulus in total. The number of trials was increased by a factor of two, since the left (216 trials) and right (216 trials) hemifields time-course data of a stimulus were combined during the data analysis, resulting 432 trials for each stimulus in total. Each SIRF run lasted 318 s including blank periods of 20 s at the start and 10 s at the end. Participants reported changes in the baseline color of the fixation point at the center of the visual presentation screen during the entire run. Figures 2.2 and 2.3 show the design of SIRF run.

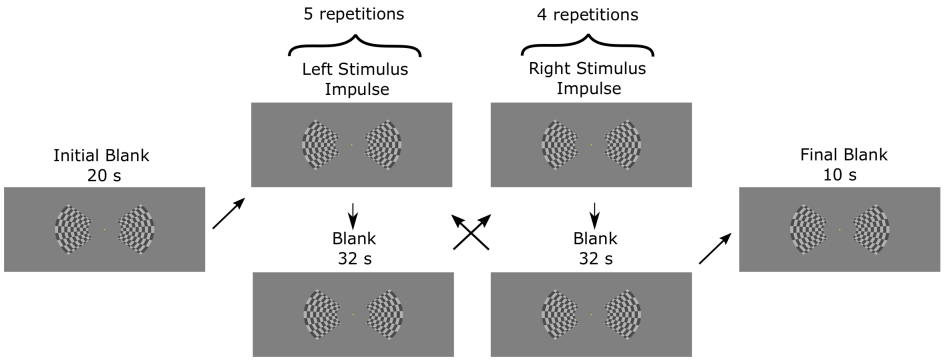

Figure 2.2: Impulse SIRF design for fMRI runs with odd number ID. It starts with 20 s initial blank where the wedges are visible but they are not flickering. It is followed by alternating the left and right stimuli with 32 s blank period in between (left stimulus = single flick in the left wedge, right stimulus = single flick in the right wedge). The alternation starts with the left stimulus.

2.1.4.2 Impulse Experimental SOA Design

In SOA scans, we collected responses to successively presented pairs of stimuli with shorter duration between. Each combination of Left and Right stimulation constituted a 'condition'. A condition consists of two stimuli whose onset differences were defined by SOA values. SOA is the amount of time between the onset of the first stimulus and the onset of the second stimulus.

The experiment had four conditions, which were Left-Right and Right-Left conditions with SOAs of 0 s, 0.5 s, and 6 s between them, and Left-Left and Right-Right conditions with SOAs of 0.5 s, and 6 s between them. To be more clear, for example, the condition Left 6 Right started with flickering left wedge (i.e., left stimulus) followed by flickering right wedge (i.e., right stimulus) 6 s later from the onset of the left stimulus.

Left-Left and Right-Right conditions are used to test any interaction in the same spatial location as a variable of different SOA values. These conditions were commonly applied in the literature to investigate nonlinearity of BOLD response in the temporal context. We also used these conditions in order to check if our results are consistent with the findings in the literature to ultimately prove if our

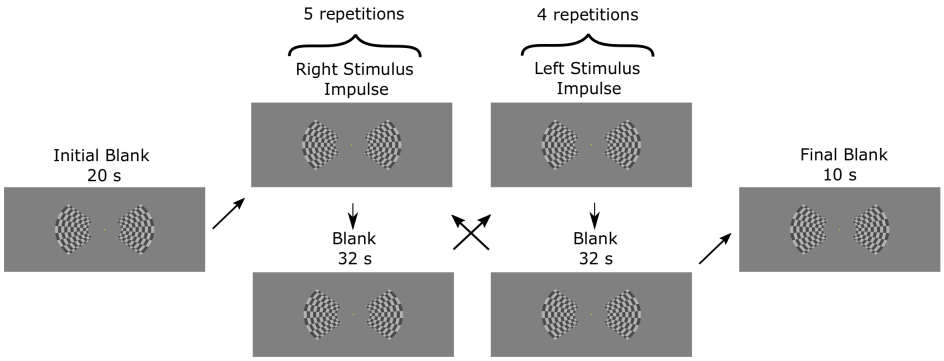

Figure 2.3: Impulse SIRF design for fMRI runs with even number ID. It starts with 20 s initial blank where the wedges are visible but they are not flickering. It is followed by alternating the left and right stimuli with 32 s blank period in between (left stimulus = single flick in the left wedge, right stimulus = single flick in the right wedge). The alternation starts with the right stimulus.

method and analysis are correct.

In addition to testing nonlinearity in the temporal context, we added Left-Right and Right-Left conditions to test spatial aspect of nonlinearity and its interaction with the temporal aspect. In Left-Right and Right-Left conditions, we test if any interaction causing nonlinearity exists between two hemispheres as a variable of SOAs.

There is a blank duration of 26 s between the conditions. In the blank period, the wedges were not flickering but they were rendered static on the screen. The blank period was set as a long duration to minimize any effect of the former condition on the latter condition [53], as shown in Figure 2.4. All conditions in a SOA run were randomly shuffled.

Each participant completed the SOA scans in two sessions. Each condition (e.g. Left 0.5 Right) was repeated in 20 times in total, 10 times in each session. 10 repetitions of each condition was completed in 5 SOA scans in each session. Since the experiment had three subjects, we had 60 trials for each condition in total. The number of trials was increased by a factor of two, since the left (60 trials) and right (60 trials) hemifields time-course data of a condition were combined during the data analysis, resulting 120 trials for each condition in total.

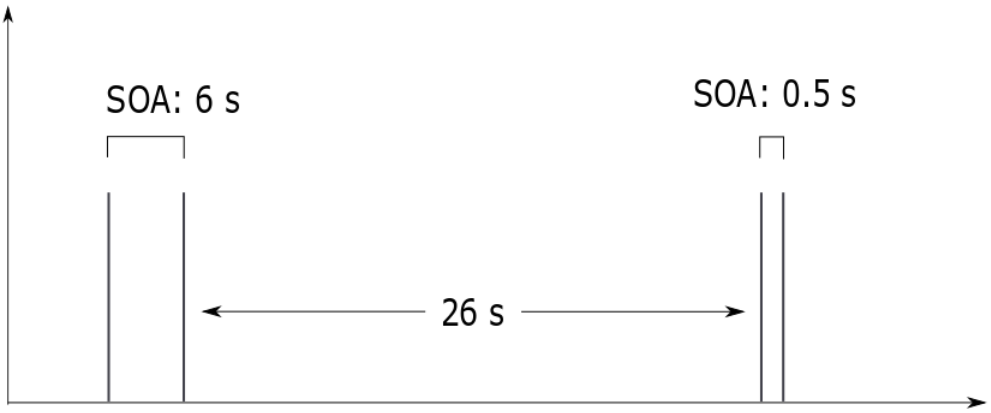

Figure 2.4: SOA Design

Each SOA run lasted 290 s including the blank periods of 20 s at the start and 10 s at the end. Figure 2.5 shows the design of an SOA run.

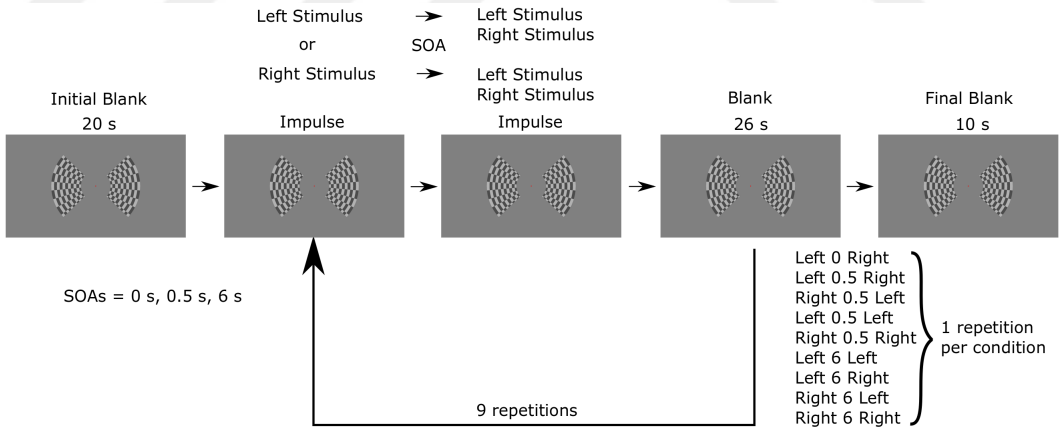

Figure 2.5: Impulse SOA Design. It starts with 20 s initial blank followed by a paired stimuli (condition). A paired stimuli consists of a combination of two stimuli (left and right) whose onset differences were defined by SOA values. Each condition was tested only once in single SOA run. The conditions were separated by 26 s blank period.

Participants conducted a fixation task during the entire run to maintain their visual gaze on the fixation point at the center of the visual presentation screen. They were asked to respond to the change of the fixation point's color when it became different from red.

2.1.4.3 Longer Pulse Experimental SIRF Design

In SIRF scans, we collected individual responses of left and right stimuli. Left and right stimuli alternate during the scan with a blank duration of 31 s. We used a long blank (31 s) in order to eliminate any effect of the former stimulus on the latter stimulus.

Each participant performed two sessions. Each stimulus was repeated 72 times in total, 36 times in each session. 36 repetitions of each stimulus was completed in 8 SIRF scans in each session. Since the experiment had three subjects, we had 216 trials for each stimulus in total. The number of trials was increased by a factor of two, since the left (216 trials) and right (216 trials) hemifields time-course data of a stimulus were combined during the data analysis, resulting 432 trials for each stimulus in total. Each SIRF run lasted 318 s including blank periods of 20 s at the start and 10 s at the end. Participants reported changes in the baseline color of the fixation point at the center of the visual presentation screen during the entire run. Figures 2.6 and 2.7 show the design of SIRF run.

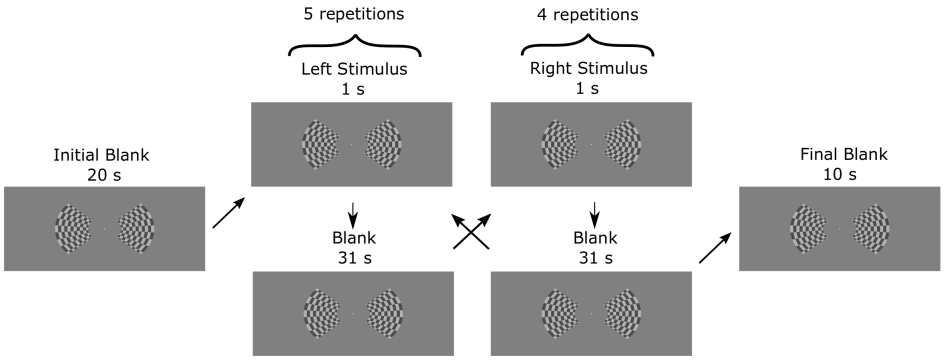

Figure 2.6: Longer pulse SIRF design for fMRI runs with odd number ID. It starts with 20 s initial blank where the wedges are visible but they are not flickering. It is followed by alternating the left and right stimuli with 32 s blank period in between (left stimulus = flickering left wedge for 1 s, right stimulus = flickering right wedge for 1 s). The alternation starts with the left stimulus.

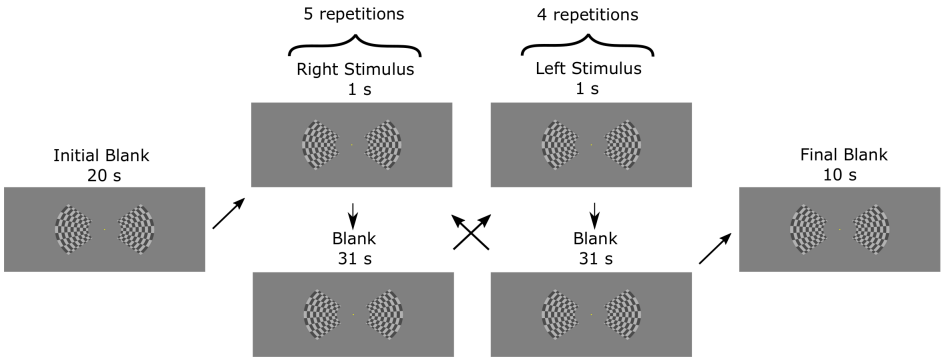

Figure 2.7: Longer pulse SIRF design for fMRI runs with even number ID. It starts with 20 s initial blank where the wedges are visible but they are not flickering. It is followed by alternating the left and right stimuli with 32 s blank period in between (left stimulus = flickering left wedge for 1 s, right stimulus = flickering right wedge for 1 s). The alternation starts with the right stimulus.

2.1.4.4 Longer Pulse Experimental SOA Design

Longer pulse design of SOA scans is the same with the one in the impulse version except the flickering duration and SOA values used. The flickering duration in this design was 1 s. In addition, we added 1.5 s as another SOA value in addition to SOA values of 0 s, 0.5 s, and 6 s because a SOA value used in Left SOA Left and Right SOA Right conditions cannot be smaller than the flickering duration (i.e., 1 s). As an example, if the flickering duration is 1 s, the condition Left 0.5 Left cannot exist, since the second left stimulus cannot start 0.5 s earlier from the offset of the first left stimulus.

As it was the case in the impulse SOA scans, we collected paired responses of the left and right stimuli. The experiment had four conditions, which were Left-Right and Right-Left conditions with SOAs of 0 s, 0.5 s, 6 s, and Left-Left and Right-Right conditions with SOAs of 1.5 s, 6 s. We used these conditions to fulfill the same goals described in Impulse SOA Design. All conditions in a SOA run were randomly shuffled.

Each participant completed the SOA scans in two sessions. Each condition was repeated in 20 times in total, 10 times in each session. 10 repetitions of each

condition was completed in 5 SOA scans in each session. Since the experiment had three subjects, we had 60 trials for each condition in total. The number of trials was increased by a factor of two, since the left (60 trials) and right (60 trials) hemifields time-course data of a condition were combined during the data analysis, resulting 120 trials for each condition in total.

Each SOA run lasted 292 s including blank periods of 20 s at the start and 10 s at the end. Participants focused on the fixation point at the center of the visual presentation screen during the entire run. Figure 2.8 shows the design of a SOA run.

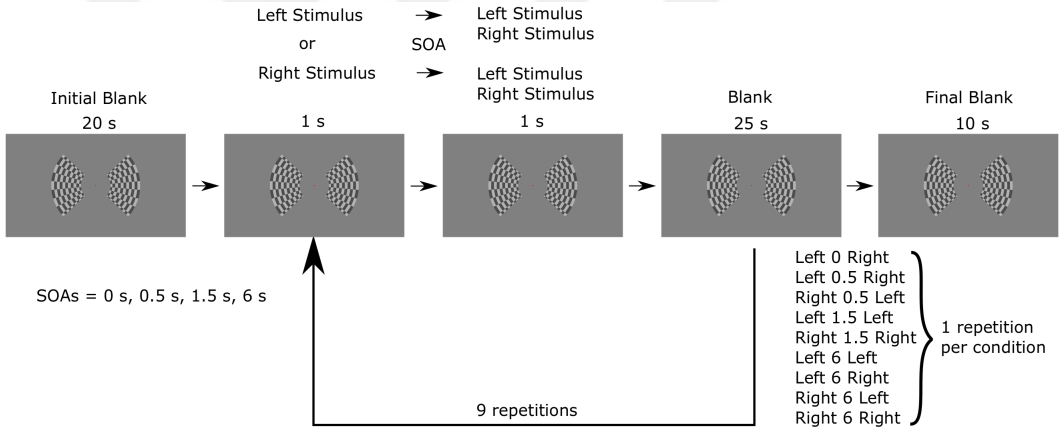

Figure 2.8: Longer pulse SOA Design. It starts with 20 s initial blank followed by a paired stimuli (condition). A paired stimuli consists of a combination of two stimuli (left and right) whose onset differences were defined by SOA values. Each condition was tested only once in single SOA run. The conditions were separated by 26 s blank period.

2.1.5 V1 ROI Localization

Region of interest (ROIs) in area V1 were identified through the functional localizer scan. It started with an initial blank period of 20 s, followed by flickering left wedge (i.e. left stimulus), a blank period, and flickering right wedge (i.e. right stimulus). Both the left and right stimuli lasted for 12 s. They alternated with each other with a blank period of 18 s between each other. In the blank period, the wedges were not flickering but they were rendered on the screen. This

sequence was repeated five times in a run. Participants focused on the fixation point at the center of the visual presentation screen during the entire run. Figure 2.9 shows the localizer design of the experiment 1.

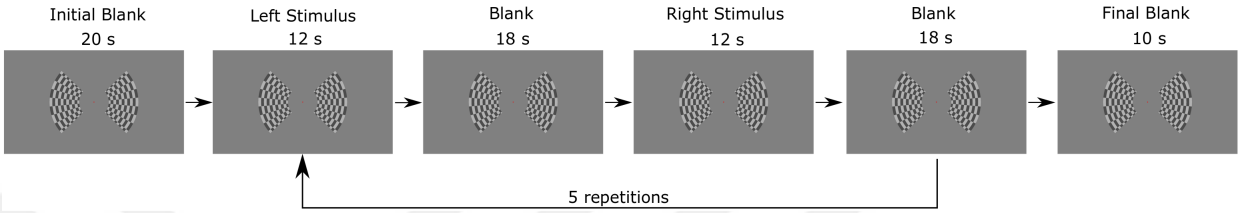

Figure 2.9: Functional Localizer Design

2.1.6 BrainVoyager Analysis

The magnetic resonance imaging data were analyzed using BrainVoyager QX 3.2 (Brain Innovation, Maastricht, the Netherlands). The data analysis was composed of several steps: preprocessing the data, defining ROIs, and extracted functional time-course data from the defined ROIs. These steps were repeated for each session and each participant and are explained below.

2.1.6.1 Anatomical Data Analysis

First of all, the anatomical data of brain were extracted from head MRI volume (i.e. extracting brain head MRI volume, that is brain peeling).

As the second step, since we had multiple sessions for the experiment in each participant, we chose the first session of each participant as the main session and applied manual anterior commissure-posterior commissure (i.e., AC-PC) transformation to transform anatomical images to align with the AC-PC coordinate system. We prefer to perform ACPC transformation rather than brain normalization such as Tailarach or MNI space transformation because transforming subjects' brains into common brain causes misalignments of macroanatomical structures such as sulci and gyri with deviations in the level of 1 cm. Shapes and sizes of

gyral and sulcal structures significantly vary across subjects. Besides, our analysis does not include group analysis but individual analysis therefore does not require brain normalization. ACPC transformation/space keeps original shape of brain, while it provides a common orientation for each brain because AC-PC plane forms the y-plane of the Tailarach coordinate system. ACPC transformation can be successfully used in individual analyses, which we only need to perform once. It is useful for subject-specific volumetry. We then applied anatomical-anatomical alignment between ACPC transformed anatomical images of the main session and native anatomical images of the other sessions. After this step, we only used the ACPC transformed anatomical images of the main session in the next steps.

As the final step, automatic cortex segmentation and reconstruction was applied in anatomical images of the main session to create cortical meshes of left and right hemispheres. To improve quality of the automatic segmentation, we adjusted brightness and contrast of anatomical because the better contrast between the white and gray matters results in a better segmentation. We skip to apply intensity inhomogeneity correction to remove intensity inhomogenities because automatic segmentation created worse meshes especially in the occipital cortex of both left and right hemispheres when intensity inhomogeneity correction had been applied. In terms of settings of automatic segmentation, we used standard resolution (1 mm iso-voxel), and filled ventricles and labelled subcortical structures as white matter (i.e., WM) by applying default brain mask in Tailarach space. Tailarach space transformation works well to extract subcortical brain structures. Besides, a threshold separating intensities of white matter and gray matter was manually selected through intensity histogram analysis as shown in Figure 2.10.

Then we labeled voxels containing white matter by using a region process. Then, to improve the quality of white matter segmentation, we dilated and smoothed white matter. Dilating white matter means expanding the white matter segmentation into the gray matter for one voxel. These two operations allowed a much more smoother boundary. Then topological errors called bridges were removed. This step is also important because when topological errors create undesired errors when the resulting meshes are inflated. Smoothed version of

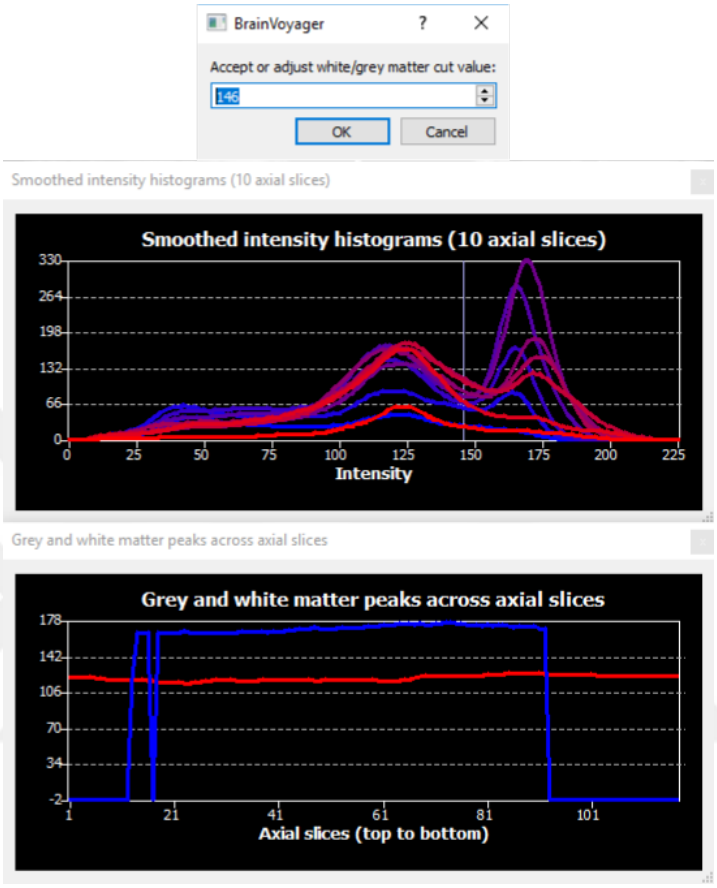

Figure 2.10: Intensity histograms of white and gray matter voxels.

reconstructed meshes of left and right hemispheres are shown in Figure 2.11.

To check how well the resulting mesh matches with the anatomical data (i.e., evaluating quality of segmentation results), we used the superposition tool allowing us to project the resulting mesh surface into the anatomical images, which is shown in Figure 2.12.

Lastly, each hemisphere's mesh was inflated by using mesh morphing. Then convex (gyrus) and concave (culcus) were colored with two colors as shown in Figure 2.13.

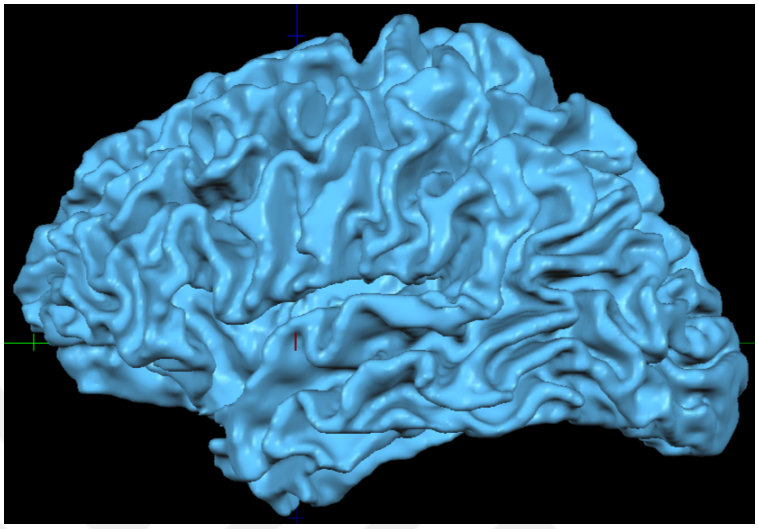

Figure 2.11: Smoothed version of reconstructed mesh of the left hemisphere

2.1.6.2 Functional Data Analysis

As the first step, preprocessing operations (slice scan time correction, 3D motion correction, and temporal filtering) was applied to raw functional (i.e., FMR) data. Slice scan time correction was applied because of the fact that slices were not acquired in MR at the same time but with a series of successive measurements. For example, the last slice is measured almost 250 milliseconds later than the first slice if parameter TR is 250 miliseconds. Slice scan time correction interpolates the data in a way that all of slices are scanned at the same time. Scan times of slices are stored in the CSA header of SIEMENS DICOM files. In multi-band settings, a number of slices depending on acceleration factor are simultaneously acquired. As an example, if there are 8 slices, the acceleration factor is 4 and the slice scanning order is ascending, slices 1, 3, 5, 7 and slices 2, 4, 6, 8 are grouped and acquired at the same time. BrainVoyager successfully handles multi-band measurements of slices, too.

Head motion detection and correction is another important step because the quality of fMRI data is significantly perturbed by head motion. Head movements are described by 6 parameters (3 translation and 3 rotation parameters). These parameters are concurrently calculated based on initial reference point during the

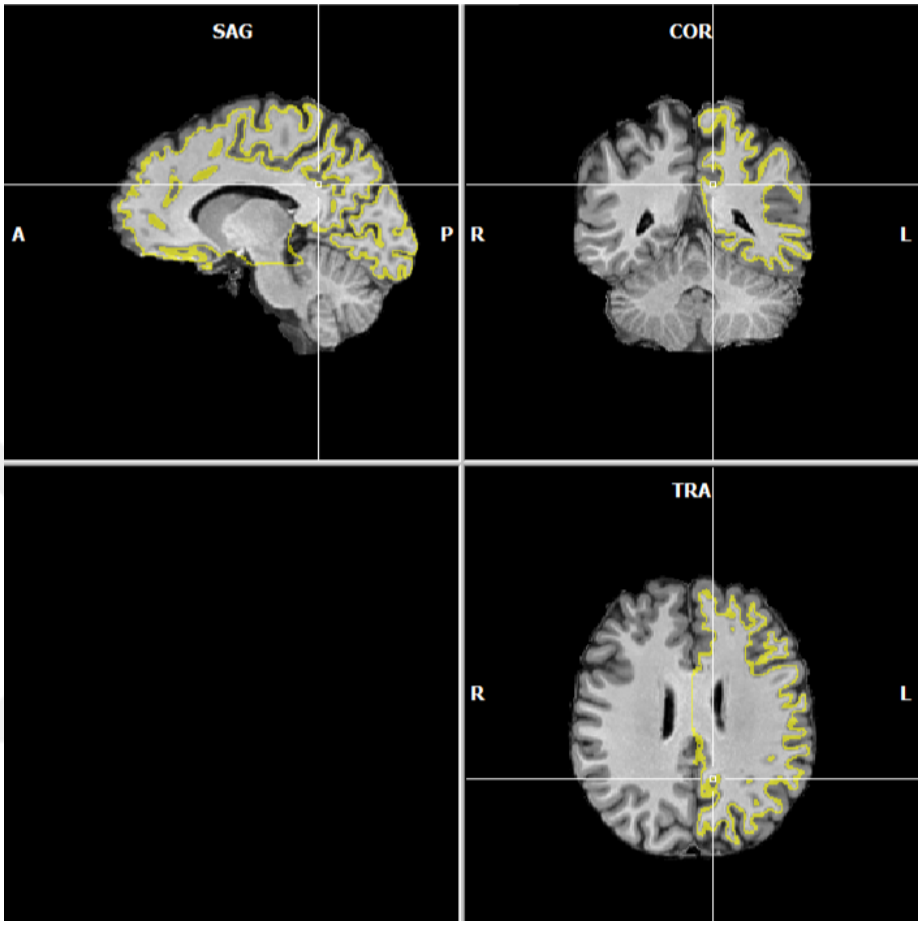

Figure 2.12: Verification of mesh segmentation in anatomical data

fMRI scan and BrainVoyager aligns the data based on these parameters. We also did intra-session alignment within a session by aligning functional scans within a session into the first functional scan. Therefore, we were able to account for head movements not only during a scan but also between the first and the other scans. We discarded the functional runs which had a trend of head motion or a substantial head movement difference compared to the first run.

In addition to slice scan time correction and head motion correction, the fMRI data was filtered by a high-pass filter (number of cycles is 2) because physiological or scanner-related noise have low frequency drifts. We checked whether applying the high-pass filter eliminated the event-related responses of impulse and longer pulse and found no evidence as shown in Figures 2.14, 2.15, 2.16, and 2.17. The filter also allowed us to remove linear trend in the data.

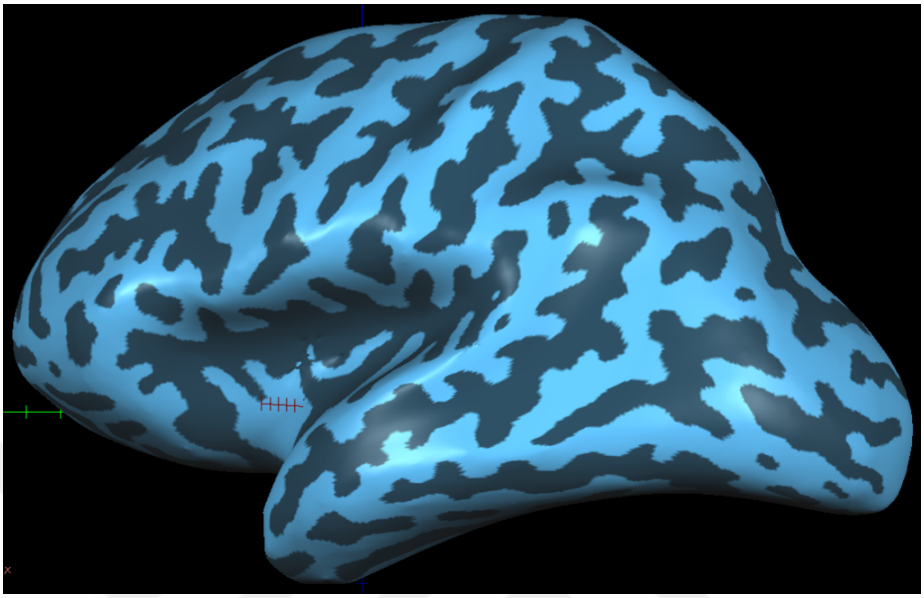

Figure 2.13: Two colored inflated mesh of the left hemisphere of a participant. Convex (gyrus) and concave (culcus) were colored with different colors.

Besides, we did not prefer to apply low-pass filter to remove high-frequency noise because it may be possible to eliminate the signal associated with stimulus, as well.

As the second step, functional-anatomical data alignment was applied to align functional images with anatomical images for each session. Most of the alignment was successfully done. Partially unsuccessful alignments were manually corrected.

As the last step, we converted functional data files to VTC files for each FMR run by using transformation (i.e., TRF) files obtained during anatomical-anatomical and functional-functional alignment steps. VTCs were linked to VMR files and allowed us to visualize the brain data in anatomical space with higher spatial resolution. Functional and anatomical spatial resolutions were 3 mm x 3 mm x 3 mm, and 1 mm x 1 mm x 1 mm, respectively. Interpolation was applied due to difference in their spatial resolutions to align functional data into anatomical data during the creation of VTC files.

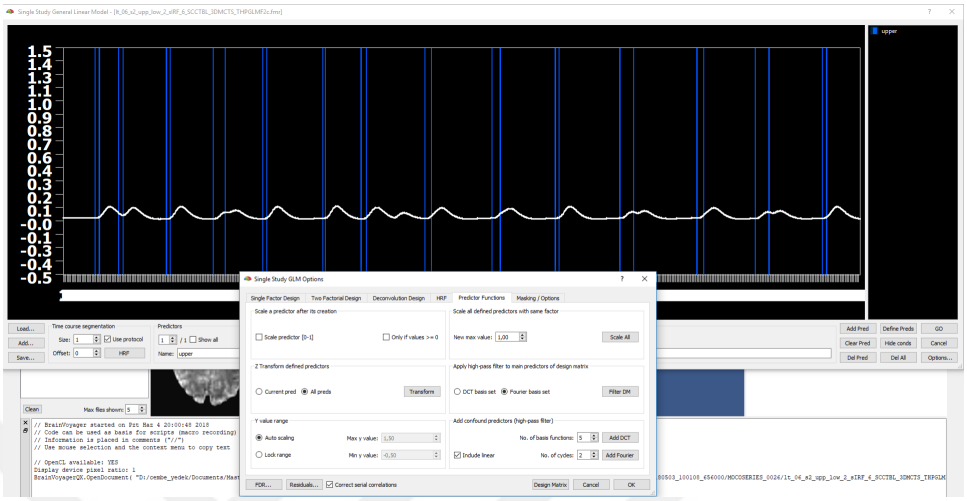

Figure 2.14: Impulse No. cycles 0 (no temporal high-pass filtering)

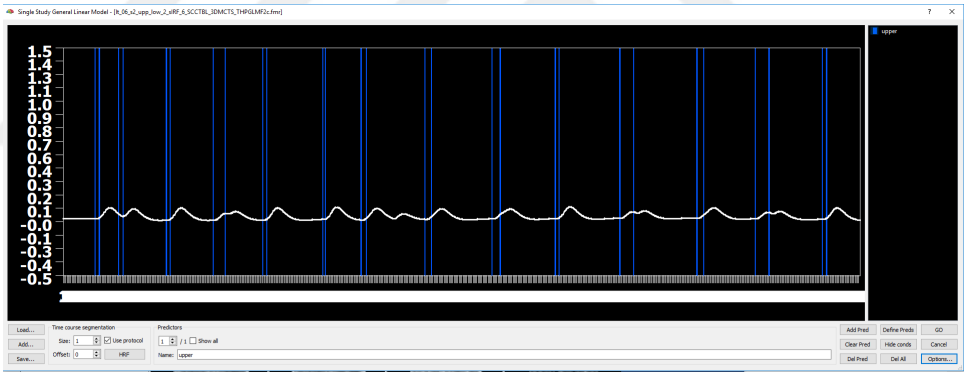

Figure 2.15: Impulse No. cycles 2

2.1.6.3 V1 ROI Analysis

General Linear Model (i.e., GLM) was applied for the V1 localizer data to determine the active voxels in primary visual cortex (i.e., V1). There were three stimuli (i.e., left, right, and blank stimuli) and two conditions (i.e., left vs. blank, right vs. blank). See section 2.1.5 for the detailed description of the localizer protocol. Difference of two gamma distribution functions [30] was used since it is a good approximation of the real HRF in region V1 [15]. GLM results of a subject (right stimulus vs. blank stimulus in the left hemifield) is shown in Figure 2.18.

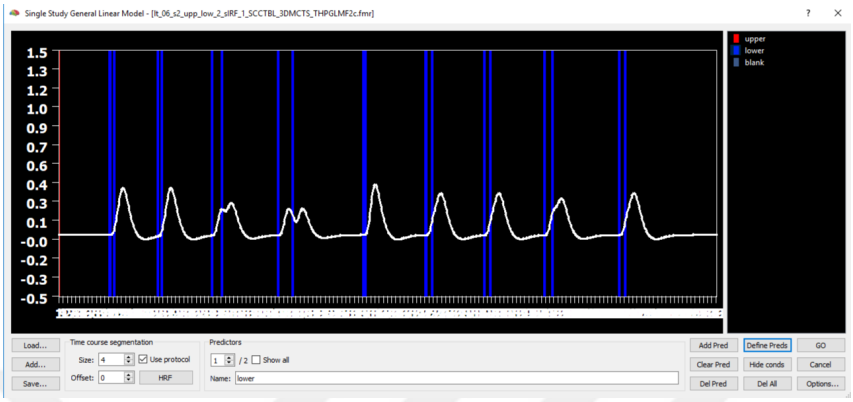

Figure 2.16: Longer pulse No. cycles 0 (no temporal high-pass filtering)

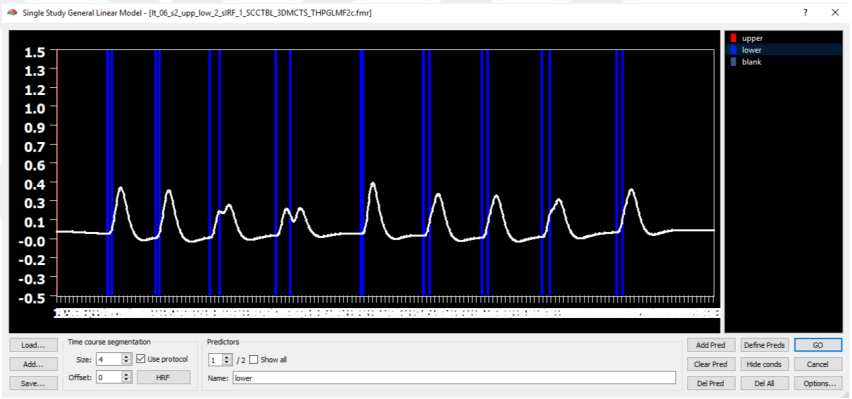

Figure 2.17: Longer pulse No. cycles 2

After the GLM analysis was performed, the activation was projected onto the meshes from anatomical-VTC space as shown in Figure 2.19. VOIs (i.e., volumes of interest) were defined for each condition based on the activations of calcarine sulcus on the meshes of both left and right hemispheres. Defined VOIs were Left VOI and Right VOI. As an example, the left VOI was activated by the right wedge (i.e. the wedge in the right visual field) because of the retinotopic organization of V1 [52]. Then the time course data of all the active voxels within the VOI were averaged for each time point and the average data for all the experimental runs (i.e., SIRF and SOA) were extracted.

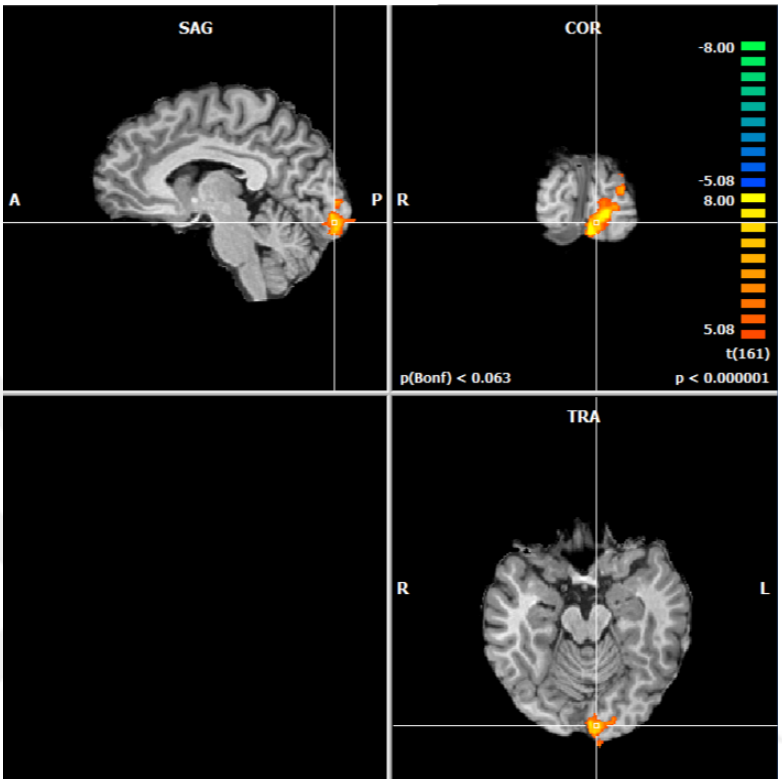

Figure 2.18: VMR activation

2.1.7 Data Visualization

The extracted time course data were normalized by the mean BOLD signal across the scan and computed percent BOLD signal change. Average BOLD response of each stimulus (left or right stimulus) was computed by averaging BOLD responses of all trials of each stimulus in all the SIRF runs. In a similar vein, average BOLD response of the paired stimuli (i.e. conditions) were obtained by averaging BOLD responses of all trials of each condition in all the SOA runs.

To reduce the number of the graphs in the experiment 1, we combined the same type of conditions. To be more clear, for example, Left 6 Right in LH and Right 6 Left in RH were merged as the condition named Ipsilateral 6 Contralateral (i.e., Ipsi 6 Contra). It is because ipsilateral and contralateral hemispheres of the left stimulus are left and right hemispheres, respectively, while the ipsilateral and contralateral hemispheres of the right stimulus are right and left hemifields,

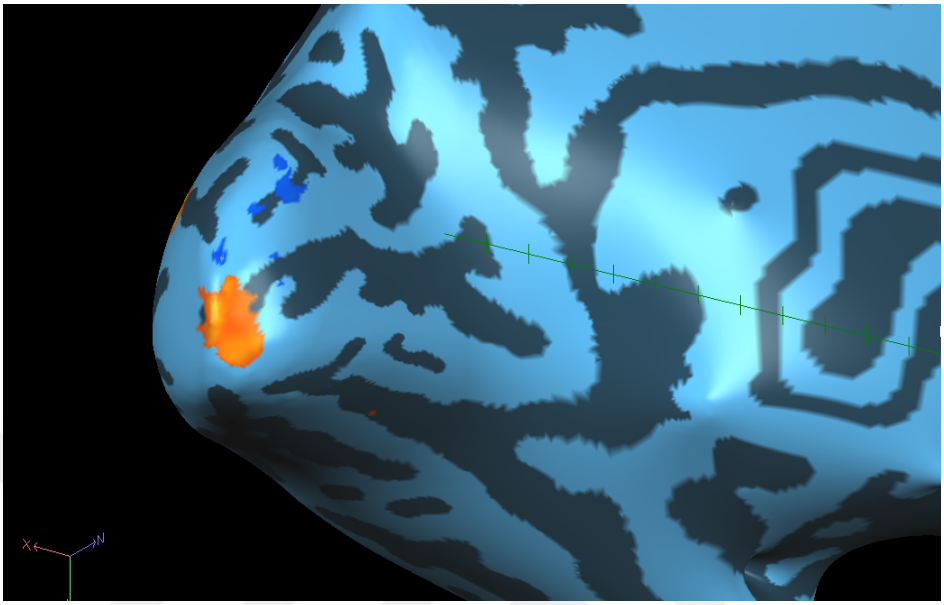

Figure 2.19: Left hemisphere (LH) mesh activation. After the GLM analysis was performed, functional localizer's activation was projected onto the meshes to define VOIs.

respectively. As the last step, SIRF and SOA data of all the subjects for each condition were averaged and visualized by using Matplotlib library in Python.

2.1.7.1 Computing predicted responses from individual responses

BOLD response of single stimulus was obtained from SIRF runs, while BOLD response of paired stimuli was extracted from SOA runs. Since our aim is to compare the predicted and observed responses for each condition, we added BOLD responses of single stimuli acquired from SIRF data to each other to construct the corresponding conditions in SOA runs and named as the predicted response. As an example, to construct the predicted response of the condition Contra 6 Contra, we shifted SIRF response of the Contralateral stimulus by 6 seconds and added it into the SIRF response of the Contralateral stimulus. Figure 2.20 illustrates how to compute the predicted response of Contra 6 Contra condition from the individual response of Contralateral stimulus.

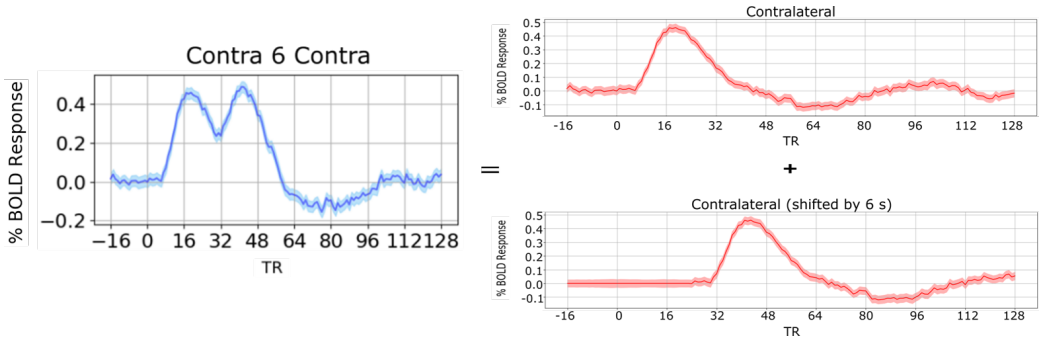

Figure 2.20: Computing predicted responses from individual responses.

2.1.8 Statistical Analysis

We quantitatively analyzed differences between the two time-course data (predicted vs. observed) to detect nonlinearity in a condition. For this purpose, we came up with a residual (nonlinearity) index that measures the difference between the predicted and observed time-course data in each condition.

The nonlinearity index is simply mean squared error between the predicted and observed data normalized by variance of the data. It is defined as follows:

$$r = \sum_{tr=0}^{m-1} \frac{(\mu_{observed_{tr}} - \mu_{predicted_{tr}})^2}{\sigma_{tr}^2}$$

$$\sigma_{tr}^2 = \frac{1}{N-1} \sum_{j=sample}^{N} (x_{tr_j} - \mu_{observed_{tr}})^2$$

TR represents a specific time point in the time-course data. $\mu_{observed_{tr}}$ describes the mean of observed samples in a specific TR. σ_{tr}^2 is the variance in a specific TR. x_{tr_j} corresponds to j'th sample in i'th TR. For example, the experiment 1 had 216 samples (i.e., trials) in each TR for SOA runs. N and m describe number of samples in each TR and number of TRs, respectively.

We calculated the nonlinearity between predicted and observed response for all TRs (time points) and obtained a single nonlinearity index. In addition, in order

to see how the nonlinearity values differ temporally, we divided the time-course data of a condition into time windows and calculated a nonlinearity index for each time window (i.e., sliding window procedure). Our windows are overlapping with each other because the window size and window step size are 16 TRs and 8 TRs, respectively. In other words, the first window is between 0 TR and 16 TR, while the second window is between 8 TR and 24 TR, and so on. After we calculated a nonlinearity value for each window, we grouped all nonlinearity values (r_{tcd}) as follows:

$$r_{tcd} = [r_8, r_{16}, ..., r_{m-8}]$$

$$r_i = \sum_{tr=i-8}^{i+8} \frac{(\mu_{observed_{tr}} - \mu_{predicted_{tr}})^2}{\sigma_{tr}^2}$$

Then, we plotted all nonlinearity values in a condition to see how it differs temporally. r and r_{tcd} are shown in "Results" section.

2.1.8.1 Comparing Groups with ANOVA

The nonlinearity metric offered a quantitative way of detecting nonlinearities in a condition in addition to visual inspection. With ANOVA, we divided conditions into groups (independent variables) and statistically compared means of those groups and their interactions. We had four groups which were explained in the following paragraphs.

First group was spatial configuration to examine how nonlinearity differed with respect to spatial configuration. Therefore, all conditions of the experiments were grouped by their spatial configurations. For example, Ipsi-Ipsi and Contra-Contra conditions in the experiment 1 were named as the same location group, and Ipsi-Contra and Contra-Ipsi conditions in the experiment 1 were named as the between hemifields groups. Likewise, Inn-Out and Upp-Low conditions in the experiment 2 and 3 were named as horizontally adjacent locations and vertically adjacent locations, respectively. Second group was SOA duration

(i.e., 0 s, 0.5 s, 1.5 s, and 6 s). Conditions within a spatial group were separated by their SOAs. As an example, between hemifield spatial configuration consists of Ipsi-Contra and Contra-Ipsi conditions with varying SOAs. Ipsi-Contra with SOA of 0 s as the SOA 0 group, Ipsi-Contra and Contra-Ipsi with SOA of 0.5 s as the SOA 0.5 group, Ipsi-Contra and Contra-Ipsi with SOA of 6 s as the SOA 6 group. Thus, we examined how nonlinearity differed with respect to SOAs within a spatial group. Third group was flickering duration (i.e., impulse, longer pulse). We grouped conditions by their flickering duration to examine how nonlinearity changes with respect to flickering duration. Fourth and last group was TR. As mentioned in section 2.1.8, we calculated a nonlinearity index for each time window to investigate how nonlinearity differs with respect to time.

We performed 3-way ANOVA for each experiment with independent variables SOA, TR, and flickering duration. To investigate spatial configuration, we combined all experiments and performed 4-way ANOVA with independent varianbles SOA, TR, flickering duration, and spatial configuration. Tukey's post-hoc test and Bonferroni correction was applied for multiple comparisons.

2.2 Results

2.2.1 Impulse SIRF results

Figure 2.21 displays SIRF results of the experiment for impulse flickering duration. As expected, we see a positive response in Contra stimulus, and baseline activation in Ipsi stimulus.

2.2.2 Impulse SIRF vs. SOA Nonlinearity Comparison

Figures 2.22 and 2.23 show a comparison between SIRF and SOA results in impulse flickering duration.

We compared the differences between the predicted and observed results in Figure 2.22 by visual inspection and in Figure 2.23 with the help of the nonlinearity index. Ipsi 0 Contra and Contra 0.5 Contra were the most nonlinear conditions. Their observed responses stayed to be positive and as a result the width of their signals were wider than the widths of the corresponding predicted responses. In addition, Ipsi 6 Ipsi, Ipsi 0.5 Ipsi, Ipsi 0.5 Contra, Contra 0.5 Ipsi, Contra 6 Contra were the conditions which had small nonlinearities. However, the nonlinearity in Ipsi 6 Contra might be negligible because predicted response of Contra 6 Ipsi fitted well to its observed response. In addition, Figure 2.23 shows us that most of the conditions have higher nonlinearities in their tails.

2.2.3 Longer Pulse SIRF Results

Figure 2.24 displays SIRF results of the experiment for longer pulse flickering duration. As expected, we see a positive response to contralateral stimulation, and baseline activation to ipsilateral stimulation.

2.2.4 Longer Pulse SIRF vs. SOA Nonlinearity Comparison

Figures 2.25 and 2.26 show a comparison between SIRF and SOA results in longer pulse flickering duration.

We compared the differences between the predicted and observed results in Figure 2.25 by visual inspection and in Figure 2.26 with the help of the nonlinearity metric. Contra 1.5 Contra and Ipsi 1.5 Ipsi were the most nonlinear conditions. In addition, it appears that the response of the second Contra stimulus in Contra 6 Contra were lower than the corresponding predicted response. Contrary to the linear response of Contra 0.5 Ipsi, Ipsi 0.5 Contra had small nonlinearity. In addition, Figure 2.26 shows us that most of the conditions have higher nonlinearities in their tails.

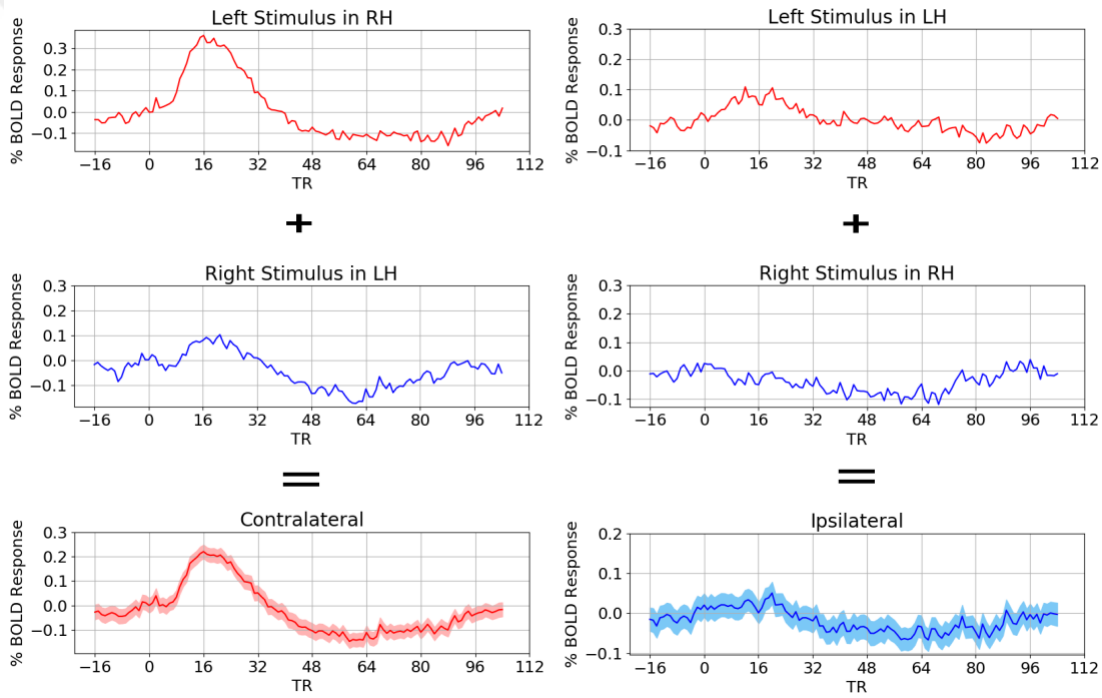

Figure 2.21: BOLD responses to impulse stimulation (Impulse SIRF). Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

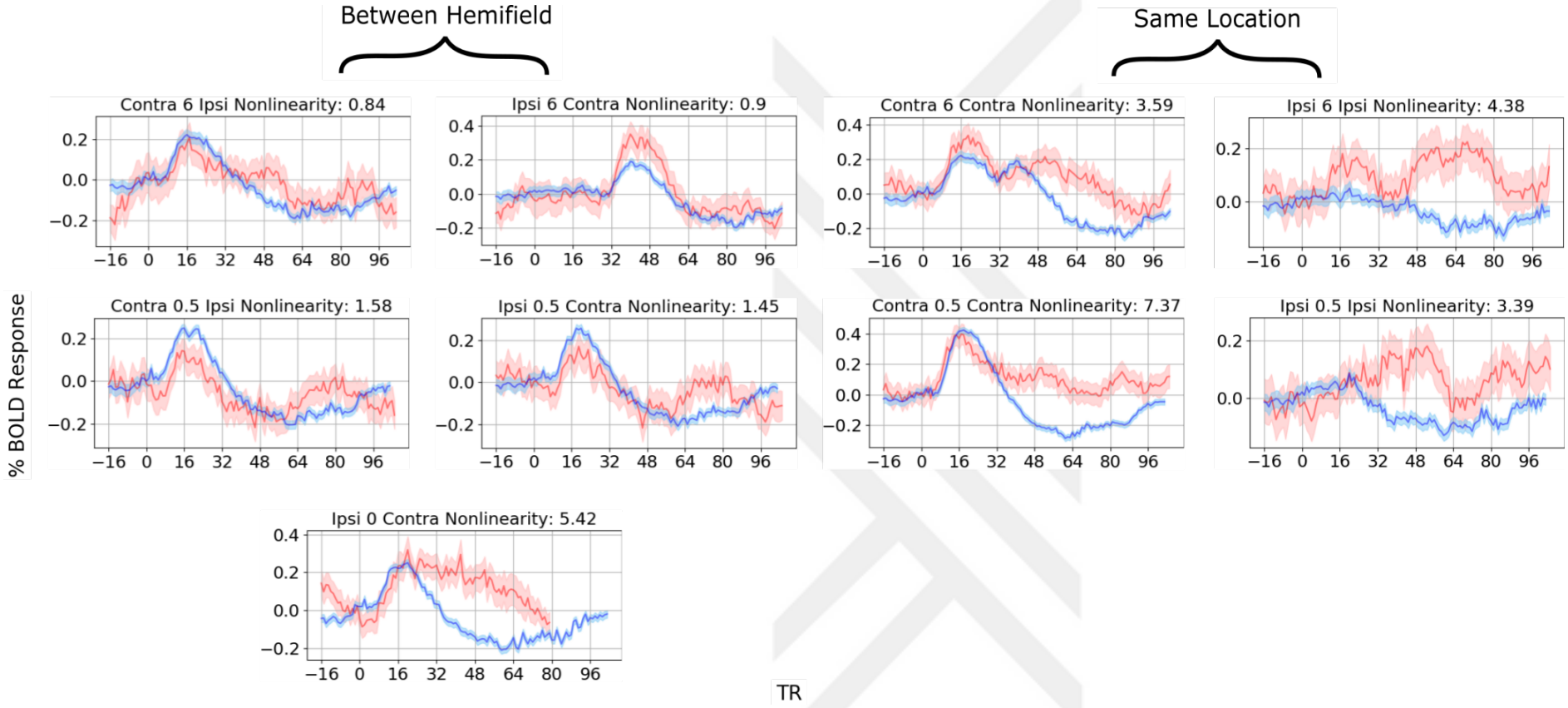

Figure 2.22: Impulse Experiment 1 SIRF vs. SOA. Blue is the predicted response. Red is the observed response. The nonlinearity index measures the degree of the difference between the predicted and observed responses and was calculated based on the residual (nonlinearity) formula for all TRs. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

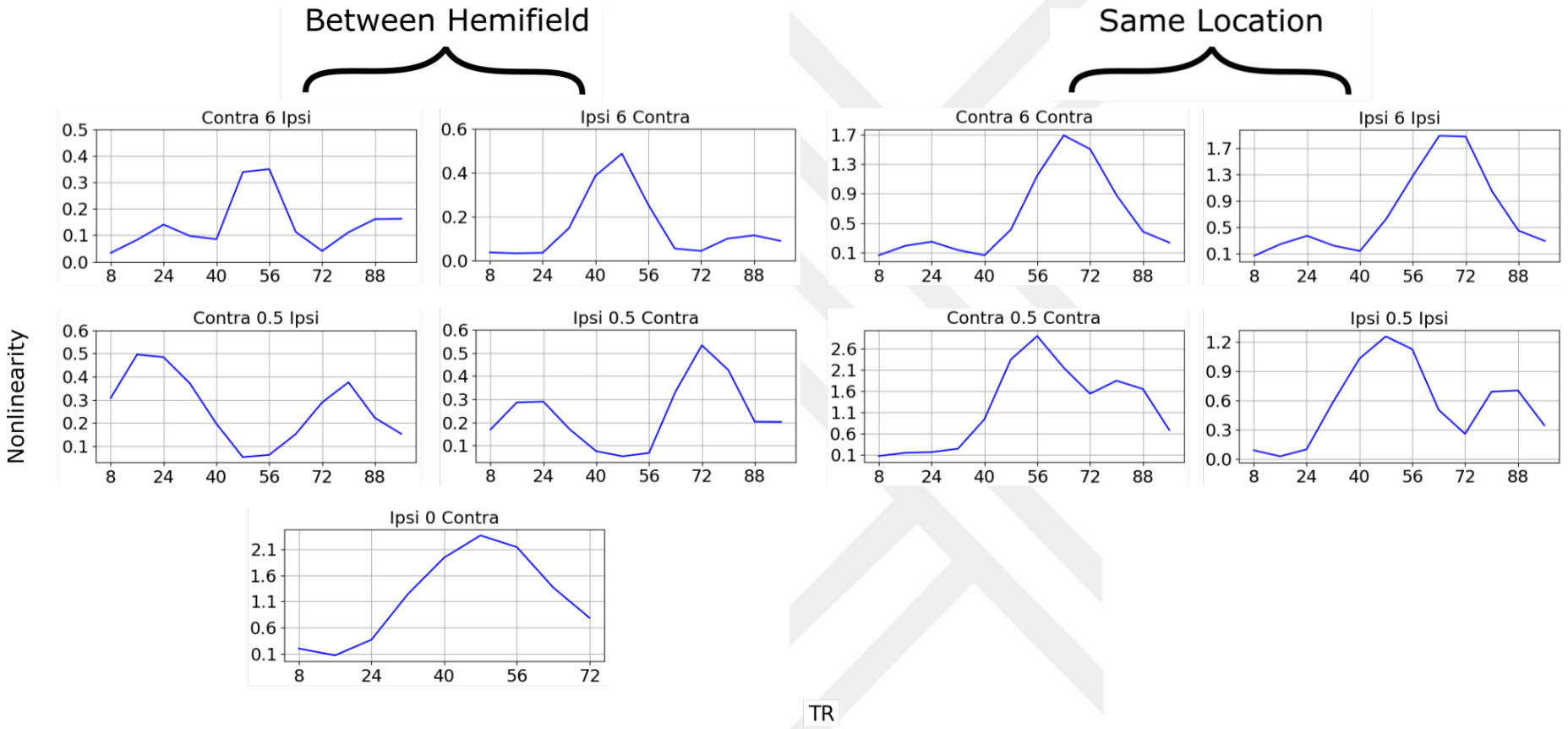

Figure 2.23: Impulse Experiment 1. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

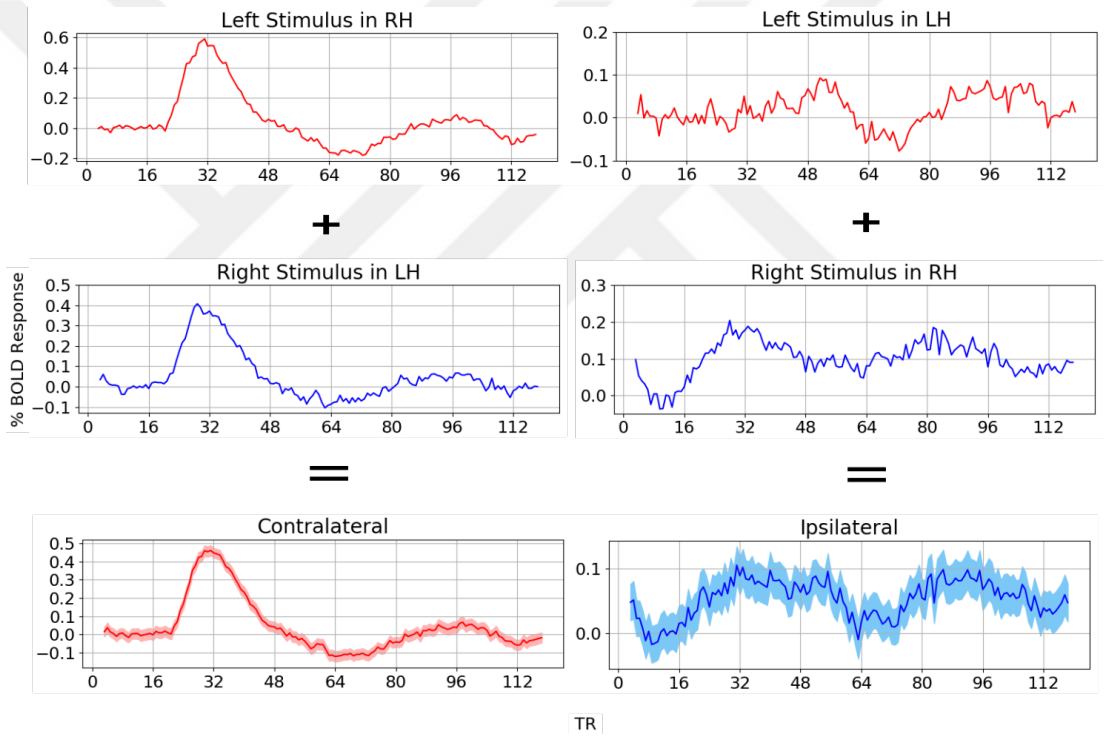

Figure 2.24: BOLD responses to 1 s stimulation (Longer Pulse SIRF). Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

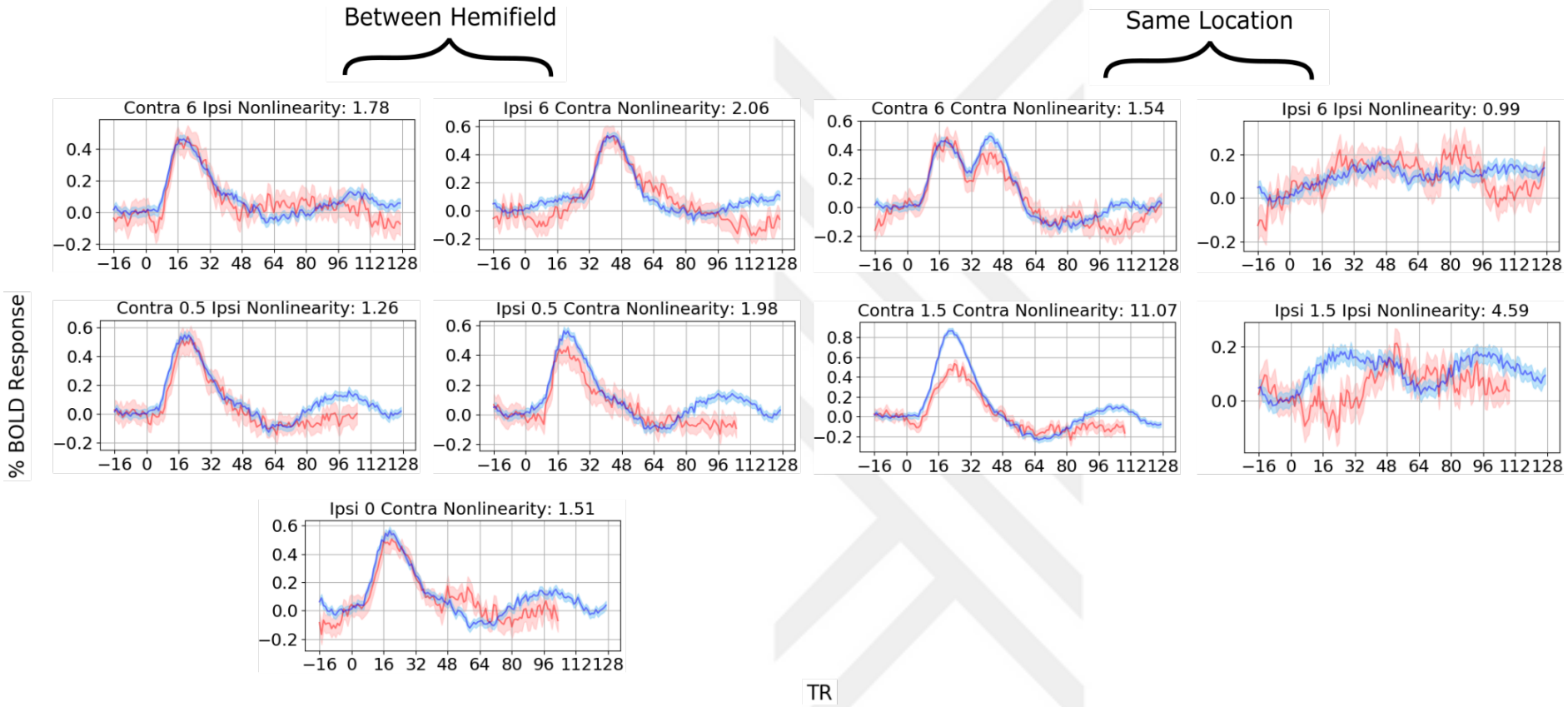

Figure 2.25: Longer Pulse Experiment 1 SIRF vs. SOA. Blue is the predicted response. Red is the observed response. The nonlinearity index measures the degree of the difference between the predicted and observed responses and was calculated based on the residual (nonlinearity) formula for all TRs. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

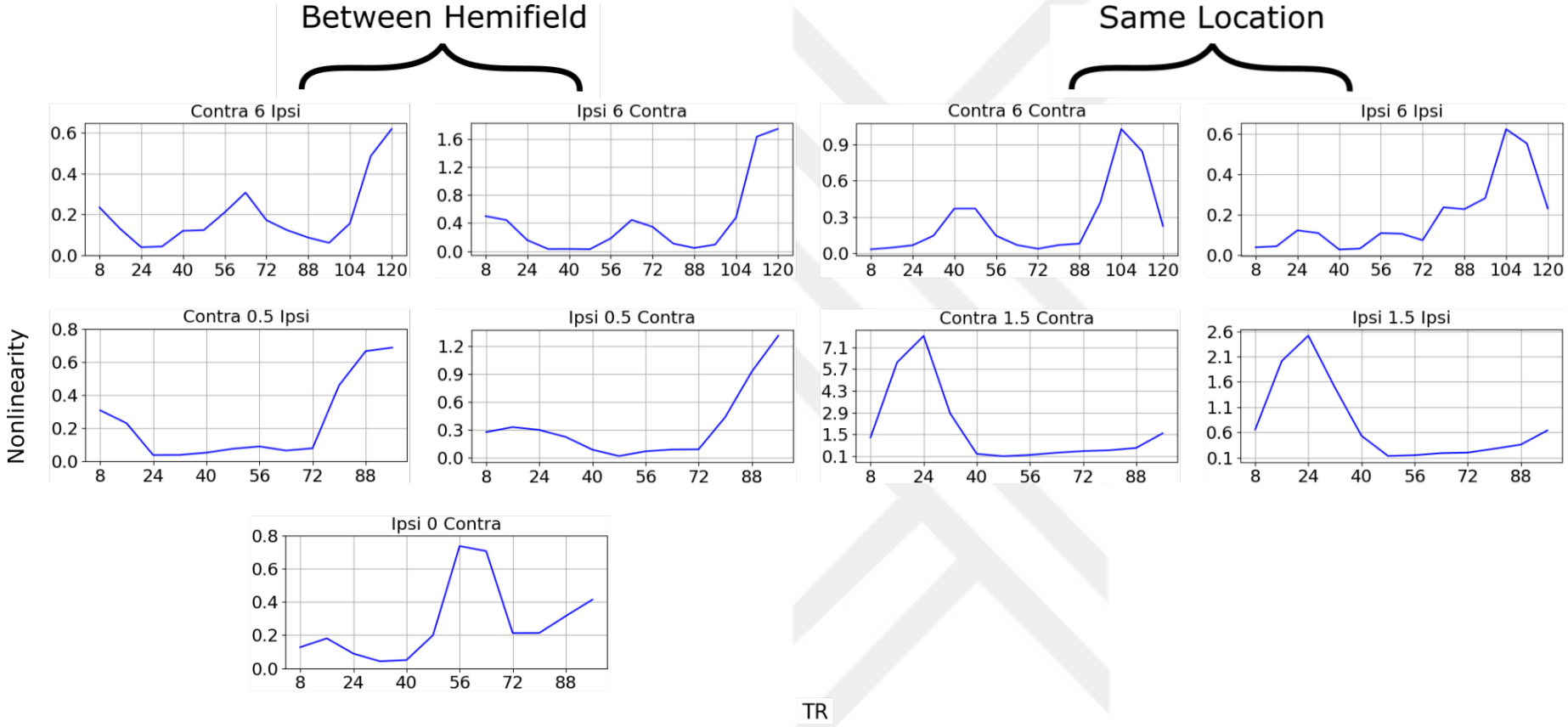

Figure 2.26: Longer Pulse Experiment 1. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

2.2.5 Statistical Results

We separately performed 3-way ANOVA and Tukey's post-hoc test for each spatial configuration (e.g., between hemifield, and same location). The dependent variable was the nonlinearity index and the independent variables were TR, SOA, and flickering duration.

In between hemifield configuration, statistical significance between levels of an independent variable were found in all of the independent variables ($F_{TR} = 8.9, p < 0.001$); $F_{SOA} = 52.9, p < 0.001$; $F_{FlickDur} = 40.9, p < 0.001$). Besides, there were statistically significant two-way interactions between SOA and TR (F = 5.5, p < 0.001), between SOA and flickering duration (F = 35.8, p < 0.001), and between TR and flickering duration (F = 5.6, p < 0.001). In addition, there was a statistically significant three-way interaction between TR, SOA, and flickering duration (F = 3.8, p < 0.001).

In same location configuration, statistical significance was found only in SOA ($F_{SOA} = 14.3, p < 0.001$) and flickering duration ($F_{FlickDur} = 5.2, p < 0.05$) . Besides, there was a statistically significant two-way interaction only between SOA and TR (F = 2.8, p < 0.005).

2.2.5.1 Flickering Duration Comparison

All conditions within a spatial group (e.g., between hemifields, same location) were grouped by their flickering durations. Figure 2.27 compares the flickering durations (impulse and longer pulse) in the conditions of between hemifields. The nonlinearity of the impulse conditions is statistically bigger than the nonlinearity in the longer pulse conditions (p < 0.001).

Figure 2.28 compares the flickering durations in the conditions of the same location. There is no statistical difference found between impulse and longer pulse conditions, although nonlinearity in impulse is slightly bigger than nonlinearity in longer pulse.

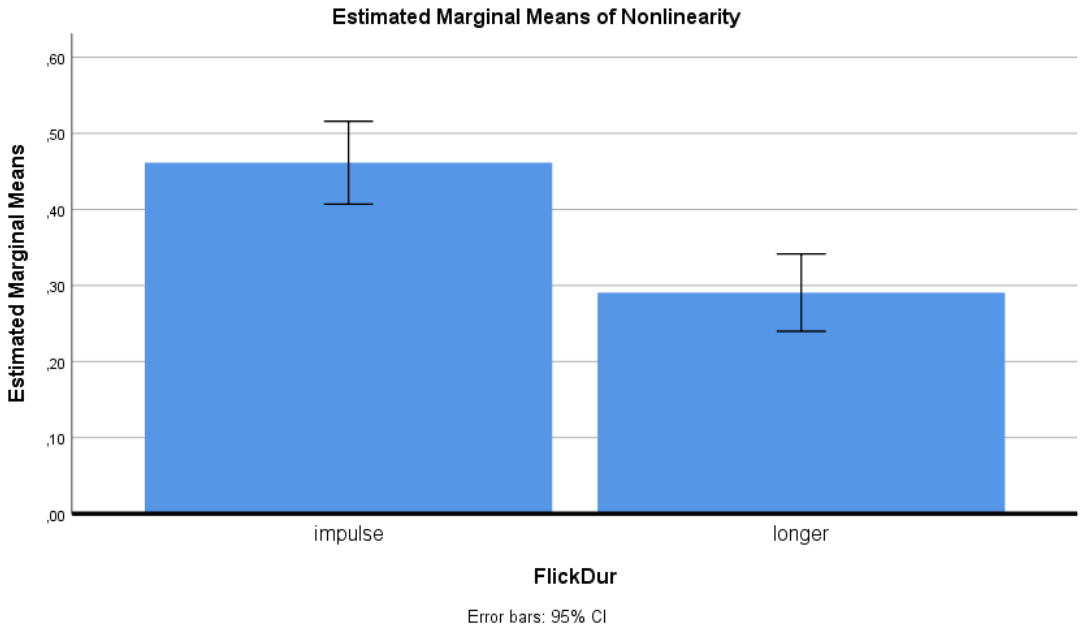

Figure 2.27: Nonlinearity as a variable of flickering duration between visual fields in different hemifields. The difference between impulse and longer pulse is statistically significant ($p < 0.001$).

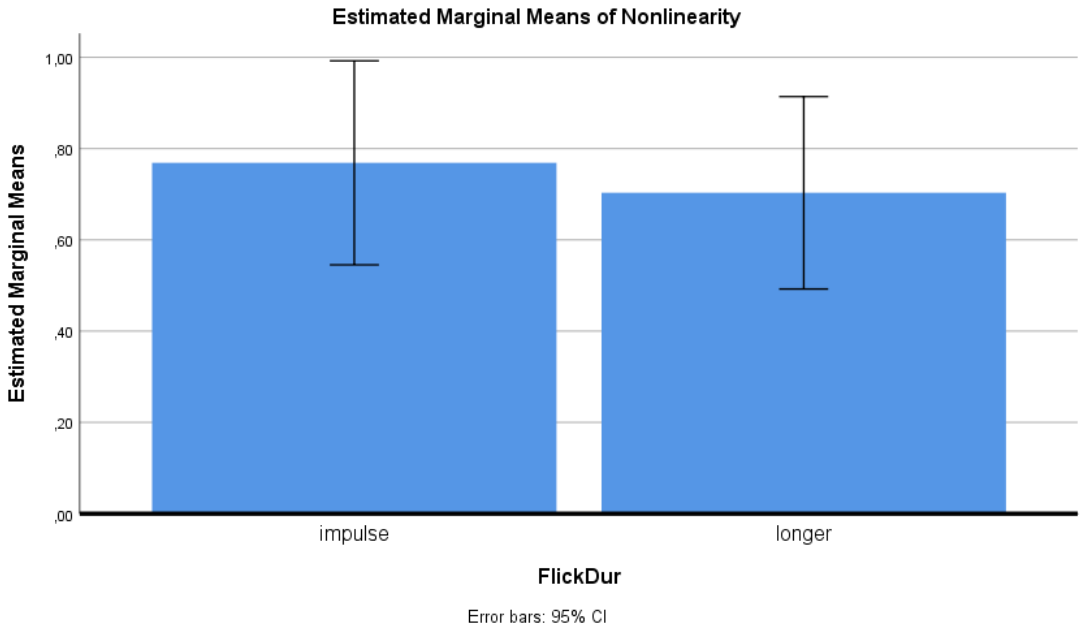

Figure 2.28: Nonlinearity as a variable of flickering duration between visual fields in the same location. The difference between impulse and longer pulse is not statistically significant.

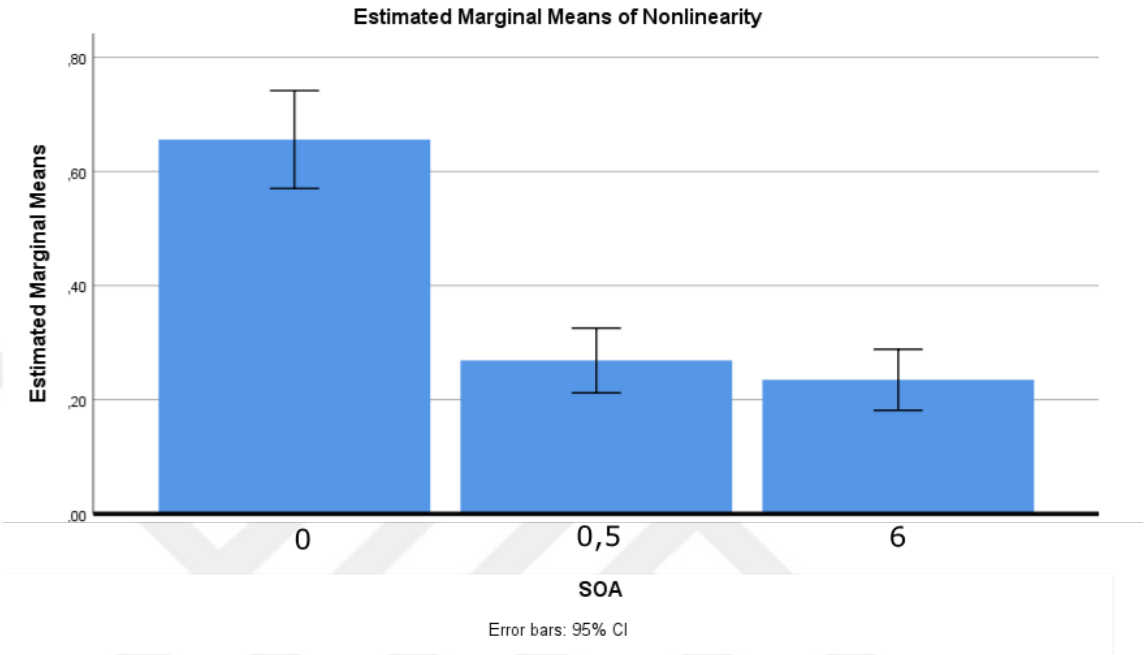

Figure 2.29: Nonlinearity as a variable of SOA duration between visual fields in different hemifields. The difference between SOA 0 and SOA 0.5 is statistically significant ($p < 0.001$). The difference between SOA 0 and SOA 6 is statistically significant ($p < 0.001$). There is no statistical difference between SOA 0.5 and SOA 6.

2.2.5.2 SOA Duration Comparison

We grouped all conditions within a spatial group (e.g., between hemifields, same location) by their SOA durations (see section 2.1.8.1 for more details). Figure 2.29 compares the SOA durations (0 s, 0.5 s, and 6 s) in the conditions of between hemifields. The nonlinearity in SOA 0 is statistically bigger than the nonlinearities in SOA 0.5 and SOA 6 ($p < 0.001$, $p < 0.001$). There is no statistical difference between SOA 0.5 and SOA 6.

Figure 2.30 compares the SOA durations in the conditions of the same location. The corresponding SOA durations were 0.5 s and 6 s for impulse and were 1.5 s and 6 s for longer pulse. Nonlinearities in SOA 0.5 and 1.5 are statistically bigger than the nonlinearity in SOA 6 in the conditions of the same location ($p < 0.05$, $p < 0.001$).

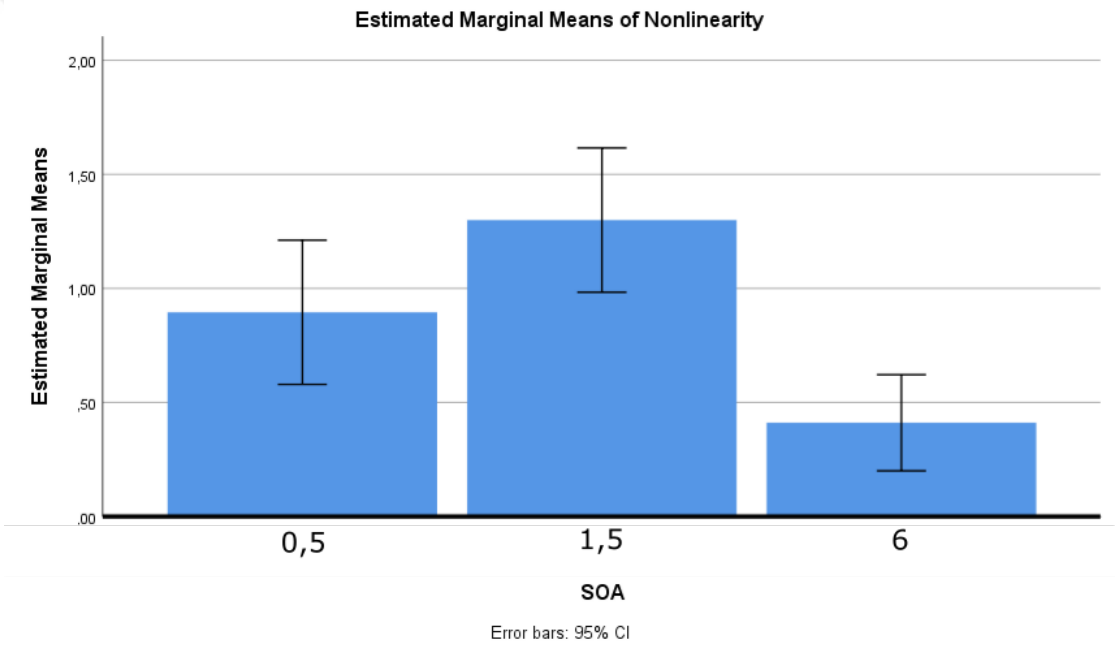

Figure 2.30: Nonlinearity as a variable of SOA duration between visual fields in the same location. The difference between SOA 0.5 and SOA 6 is statistically significant ($p < 0.05$). The difference between SOA 1.5 and SOA 6 is statistically significant ($p < 0.001$). There is no statistical difference between SOA 0.5 and SOA 1.5.

2.3 Intermediate Discussion

2.3.1 Impulse SIRF

As expected, we see a strong activation in the contralateral hemisphere and a baseline activation in the ipsilateral hemisphere due to the retinotopic organization of V1 [52].

2.3.2 Impulse SIRF vs. SOA Nonlinearity Comparison

In the SOA version of Ipsi 6 Ipsi and Ipsi 0.5 Ipsi conditions, we see a suppressive effect at the onset of the stimulus, followed by the positive response. It seems that the visual stimulus evokes an inhibitory response at first, followed by a facilitatory response in the ipsilateral hemifield of V1 region. This effect was not seen in the SIRF results. We observed nonlinearity not only in Ipsi-Ipsi conditions but also in Contra 0.5 Contra. The SOA response of Contra 0.5 Contra had no post-stimulus undershoot nonlinearity. Therefore, one can conclude that conditions of the same location (i.e., Contra-Contra, Ipsi-Ipsi) shows nonlinearity. The results are consistent with the nonlinearity studies [34, 25]. The highest degree of nonlinearity was observed when two stimuli were close in time and space. This phenomenon can be explained by refractory effect [34]. Besides, neurons may fire more at the onset of the stimulus duration than the rest of the remaining stimulus duration [26]. This mechanism might also lead to nonlinearity between predicted (from SIRF) and observed (from SOA) responses of impulse. Finally, when two stimuli are presented simultaneously, response to a visual stimulus is suppressed by the other stimulus located at the same location [54, 55, 51] due to mutual suppression mechanism.

Ipsi 0 Contra was another nonlinear condition. In addition, Ipsi 0.5 Contra, and Contra 0.5 Ipsi had small nonlinearities, too. This might suggest that mutual suppression mechanism [54, 55, 51, 45, 47] may take place between hemifields. We

also observed that nonlinearity was decreased as the SOA duration was increasing in the conditions of between hemifields. The fact that nonlinearity was observed between separate hemifields (i.e., spatial distance between activated brain regions is big) shows that space and time interact with each other. The observed nonlinearity between hemifields also shows that V1 neurons in one hemifield modulates the V1 neurons in the other hemifield. Interhemispheric connections were found between V1 neurons in the left and right hemifields through corpus callosum [56].

Ipsi 0 Contra and Contra 0.5 Contra were the conditions that share sustained positive post-stimulus response. It has been reported that the increase in CMRO2 accompanies with larger increase in CBF, resulting in positive BOLD response [57]. They simultaneously recorded EEG and fMRI data and found that a EEG signal associated with cortical inhibition correlated with post-stimulus BOLD response, meaning that post-stimulus BOLD response might be neuronal in origin. Therefore, one can conclude that the sustained positive post-stimulus responses in Ipsi 0 Contra and Contra 0.5 Contra may represent cortical excitation (i.e., additional neuronal activity) in post-stimulus interval.

However, it is difficult to determine in some conditions (e.g., Ipsi 0.5 Contra, and Contra 0.5 Ipsi) if the deviations between the predicted and observed responses arised due to nonlinearity or small signal to noise ratio. Nevertheless, since we did not observe a reduction in the signal at Ipsi 6 Contra and Contra 6 Ipsi, the decrease in the SOA response might be a sign for nonlinearity.

2.3.3 Longer Pulse SIRF

As expected, we see a positive activation in the contralateral hemisphere and a baseline activation in the ipsilateral hemisphere due to the retinotopic organization of V1 [52].

2.3.4 Longer Pulse SIRF vs. SOA Nonlinearity Comparison

As expected, we found stronger nonlinearity when two stimuli were spatially and temporally close to each other. Contra 1.5 Contra, Ipsi 1.5 Ipsi, and Contra 6 Contra (i.e., conditions of the same location) were the conditions found nonlinear. On the contrary, other conditions were found linear roughly. It was found that nonlinearity of BOLD response was increased when the onsets of two successive stimuli that activate the same region became closer in time [34]. Explanations about possible reasons were made in the section 2.3.2.

2.3.5 Impulse SIRF vs. Longer Pulse SIRF

Longer pulse activation in the contralateral hemifield was stronger than the impulse activation in the contralateral hemifield. The relative increase in the activation of the contralateral hemisphere can be explained by strength of stimulus. Stronger stimuli typical evoke stronger positive BOLD response [11, 34]. Therefore, due to longer stimulation duration, longer pulse results may have evoked higher BOLD response in the contralateral hemifield.

Stronger stimulus causes larger spread in the BOLD response, resulting stronger positive responses in the surrounding regions, too [58, 59]. However, their activations in the ipsilateral hemisphere did not differ. It might be due to the fact that the contralateral and ipsilateral activations are driven by spatially distinct vasculature and do not share their blood supply with the adjacent dilated vessels, resulting in that the activation in the contralateral hemifield cannot spread to the ipsilateral hemifield or vice versa. On the other hand, it has been reported that there are interhemispheric connections between V1 neurons [56].

2.3.6 Flickering Duration and SOA Duration Comparisons

Figure 2.27 shows that impulse nonlinearity is significantly bigger than longer pulse nonlinearity in the conditions of between hemifields ($p < 0.001$). On the other hand, Figure 2.28 shows that impulse and longer pulse nonlinearities are roughly equal to each other. Therefore, one can conclude that overall impulse nonlinearity is slightly more than longer pulse nonlinearity. Besides, it can be observed by visual inspection that impulse conditions are more nonlinear than longer pulse conditions in the post-stimulus undershoot. It has been reported that post-stimulus undershoot represents neuronal inhibition in origin [57]. In addition, the impulse data is noisier than the longer pulse data. The differences between impulse and longer pulse results suggest that a care should be taken in designing experiments with very short stimulus duration. Besides, Figures 2.29 and 2.30 show that nonlinearity is bigger at shorter SOAs. These results suggest that there is a three-way interaction between space, time, and flickering duration.

Chapter 3

Experiment 2 and Experiment 3: Interactions Between Adjacent Visual Locations In The Same Hemifield

3.1 Experiment 2: Interactions Between Horizontally Adjacent Locations

Experiment 2 (i.e., Experiment Inner-Outer) was conducted to examine the interaction between the paired stimuli as a variable of SOAs when they are located at adjacent spatial locations along x axis in the same hemisphere.

In independently identified regions of interest (ROIs, see details of ROI localizer under section 3.1.1.6) in primary visual cortex (V1), we first identified hemodynamic impulse response functions using visual stimuli dispersed widely in time ('Single impulse response function (SIRF)' scans, see below for more details) and used them to predict responses to presentation of visual stimuli with shorter

time between them ('SOA scans', see below for details). Any deviation between the predicted and observed BOLD responses in the SOA scans is taken as a sign of non-linearity.

3.1.1 Materials and Methods

3.1.1.1 Participants

Three subjects including the author CB (two males, ages ranged from 22 to 26) participated in the experiment. Participants were graduate students in National Magnetic Resonance Research Center (UMRAM), Bilkent University. The same participants attended the Experiment 'Upper-Lower' that will be described below. They reported normal or corrected-to-normal vision, and had no history for neurological or visual disorders. Ethics approval was granted by Bilkent University Ethics Committee for Research with Human Participants. All participants gave written informed consent in accordance with the Declaration of Helsinki.

3.1.1.2 MRI Data Acquisition

Scanning protocols were the same with the experiment 1 (see Section 2.1.2).

3.1.1.3 Visual Stimulus Presentation Setup

The setup was the same with the experiment 1 (see Section 2.1.3).

3.1.1.4 Experimental Design

Similar to the experiment 1, a flickering wedge stimulus with contrast-reversing checkerboard pattern was used with a flickering rate of 8 Hz. The experiment 2

consisted of two stimuli named 'Inner' and 'Outer'. As distinct from the experiment 1, both inner stimulus and outer stimulus were composed of two flickering wedges. The widths of the two wedges were (90° circular angle). The paired wedges (i.e., inner stimulus' wedges, outer stimulus' wedges) were symmetrical to each other with respect to y-axis. One was located at the left visual field, the other was located at the right visual field. Likewise, the outer stimulus had also two wedges located in a similar way. The inner stimulus' wedges were closer to the fixation point than the outer stimulus' wedges. Background was isoluminant gray with luminance 86 in cd/m^2. The spatial configuration of the experiment is shown in Figure 3.1.

The distance from the fixation point to the innermost part of the inner wedge is 3° visual degree. The distance between the outermost part of the inner wedge and innermost part of the outer wedge is 2° visual degree. The widths of inner and outer wedges are 2.5° visual degree. The Michelson contrast of the wedges was 40% to keep the hemodynamic response below the saturation level.

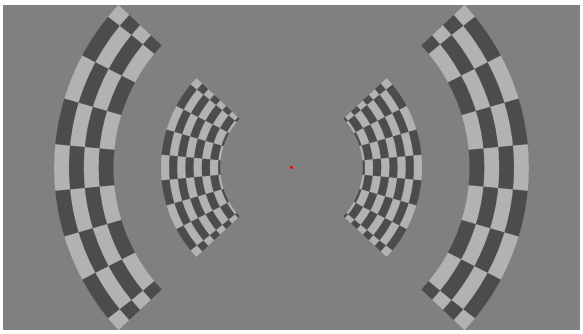

Figure 3.1: Experiment 2 Inner-Outer configuration. Inner wedges were the ones which were closer to the fixation point. Outer wedges were located more distant to the fixation point than the inner wedges.

We used two flickering durations (impulse, and longer pulse) and using the same experimental protocol as describe below. In the impulse version of the experiment Inner-Outer, the flickering period consisted of one flick, meaning that black and white regions in the checkerboard pattern changed for once. In the longer pulse version of the experiment, the flickering duration was 1 s.

3.1.1.4.1 Impulse Experimental SIRF Design

In SIRF scans we collected responses to widely dispersed single impulse stimuli, in other words responses to individual stimulation. The inner and outer stimuli alternate during the scan with a blank duration of 32 s. We used a long blank duration (32 s) in order to eliminate any effect of the former stimulus on the latter one [53].

Each participant performed SIRF scans in two sessions and completed 72 trials for each stimulus, 36 times in each session. 36 repetitions of each stimulus was completed in 8 SIRF scans in each session. Since the experiment had three subjects, we had 216 trials for each stimulus in total. The number of trials was increased by a factor of two, since the left (216 trials) and right (216 trials) hemifields time-course data of a stimulus were combined during the data analysis, resulting 432 trials for each stimulus in total. Each SIRF run lasted 318 s including blank periods of 20 s at the start and 10 s at the end. Participants focused on the fixation point at the center of the visual presentation screen during the entire run. Figures 3.2 and 3.3 show the design of SIRF run.

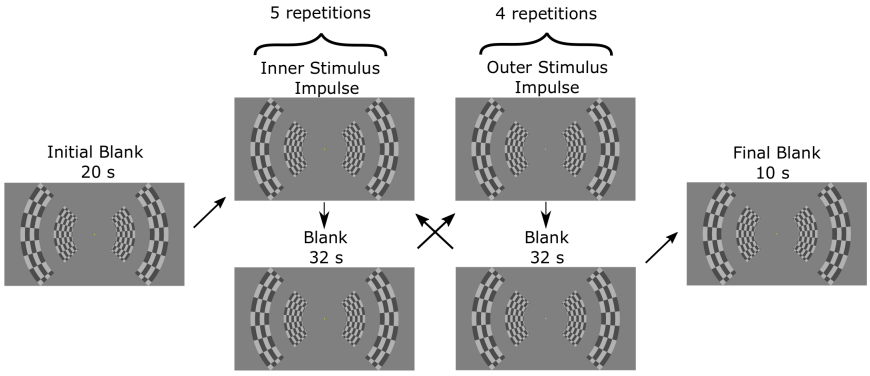

Figure 3.2: Experiment Inner-Outer Impulse SIRF design for fMRI runs with odd number ID. It starts with 20 s initial blank where the wedges are visible but they are not flickering. It is followed by alternating the inner and outer stimuli with 32 s blank period in between (inner stimulus = single flick in the inner wedge, outer stimulus = single flick in the outer wedge). The alternation starts with the inner stimulus.

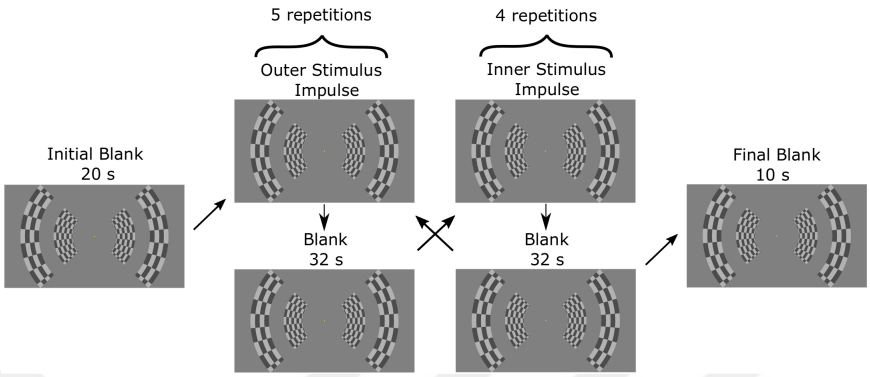

Figure 3.3: Experiment Inner-Outer Impulse SIRF design for fMRI runs with even number ID. It starts with 20 s initial blank where the wedges are visible but they are not flickering. It is followed by alternating the inner and outer stimuli with 32 s blank period in between (inner stimulus = single flick in the inner wedge, outer stimulus = single flick in the outer wedge). The alternation starts with the outer stimulus.

3.1.1.4.2 Impulse Experimental SOA Design

In SOA scans, we collected responses to successively presented pairs of stimuli with shorter duration between. Each combination of Inner and Outer stimulation constituted a 'condition'. A condition consists of two stimuli whose onset differences were defined by the SOA values.

The conditions were, in this experiment, Inner-Outer and Outer-Inner with SOAs of 0 s, 0.5 s and 6 s. To be more clear, the condition Inner 6 Outer started with flickering inner wedges (i.e., inner stimulus) followed by flickering outer wedges (i.e., outer stimulus) 6 s later from the onset of the inner stimulus. Since both stimuli consist of two wedges located at left and right hemifields, they activate both hemifields.

Inner-Outer and Outer-Inner are the conditions which are used to test any interaction between horizontally adjacent spatial locations along x-axis in the same hemisphere with respect to SOA values.

There is a blank duration of 26 s between the conditions. In the blank period, the wedges were not flickering but they were rendered on the screen. The blank

period was set as a long duration to minimize any effect of the former condition on the latter condition [53], as shown in Figure 3.4. All conditions in a SOA run were randomly shuffled.

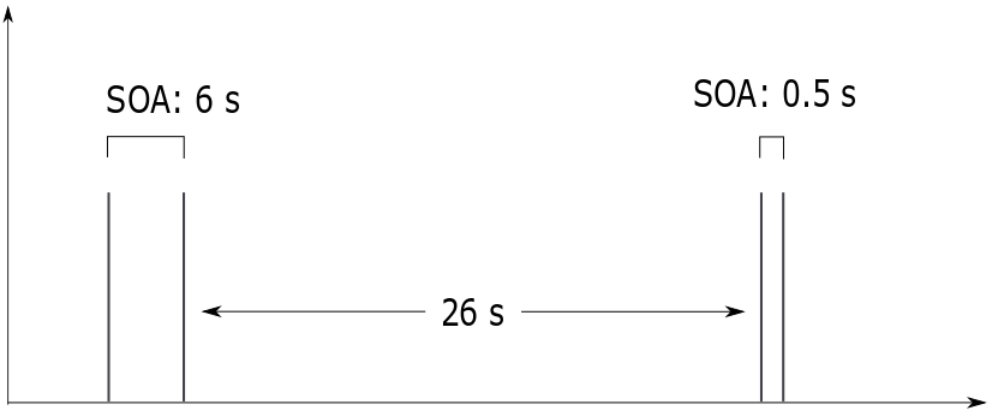

Figure 3.4: SOA Design

Each participant completed the SOA scans in two sessions. Each condition (e.g. Inn 0.5 Out) was repeated in 20 times in total, 10 times in each session. 10 repetitions of each condition was completed in 5 SOA scans in each session. Since the experiment had three subjects, we had 60 trials for each condition in total. The number of trials was increased by a factor of two (resulting 120 trials for each condition in total), since two BOLD responses to a condition were extracted from both left (60 trials) and right hemifields (60 trials) and combined during the data analysis. Each SOA run lasted 316 s including blank periods of 20 s at the start and 10 s at the end. Figure 3.5 shows the SOA run's design.

Participants conducted a fixation task during the entire run to maintain their visual gaze on the fixation point at the center of the visual presentation screen. They were asked to respond to the change of the fixation point's color when it became different from red.

3.1.1.4.3 Longer Pulse Experimental SIRF Design

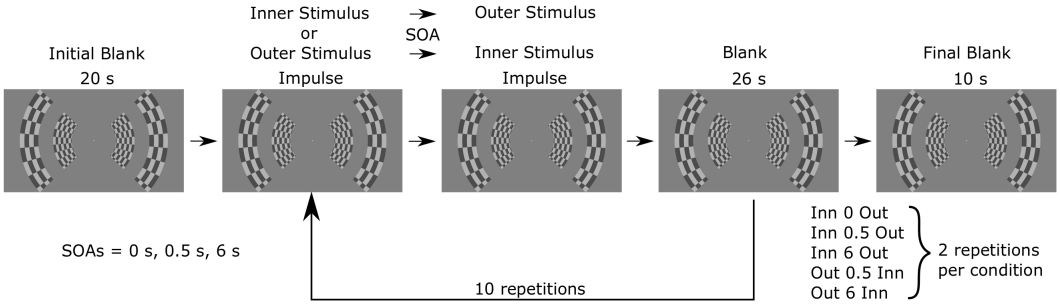

Figure 3.5: Experiment Inner-Outer Impulse SOA Design. It starts with 20 s initial blank followed by a paired stimuli (condition). A paired stimuli consists of a combination of two stimuli (inner and outer) whose onset differences were defined by SOA values. Each condition was tested only once in single SOA run. The conditions were separated by 26 s blank period.

All except the flickering duration are the same with the impulse SIRF design (see section 3.1.1.4.1). Flickering duration is 1 s in the longer pulse SIRF. Figures 3.6 and 3.7 show the longer pulse design of the SIRF run.

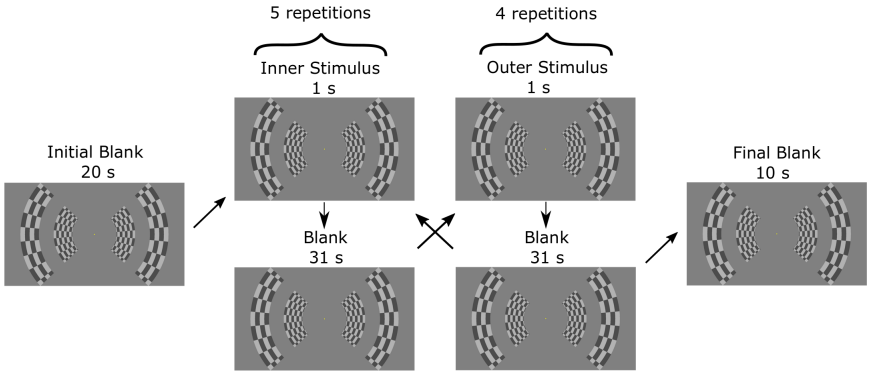

Figure 3.6: Experiment Inner-Outer Longer Pulse SIRF design for fMRI runs with odd number ID. It starts with 20 s initial blank where the wedges are visible but they are not flickering. It is followed by alternating the inner and outer stimuli with 32 s blank period in between (inner stimulus = flickering inner wedge for 1 s, outer stimulus = flickering outer wedge for 1 s). The alternation starts with the inner stimulus.

3.1.1.4.4 Longer Pulse Experimental SOA Design

All except the flickering duration are the same with the impulse SOA design (see section 3.1.1.4.2). Flickering duration is 1 s in the longer pulse SIRF. Figure

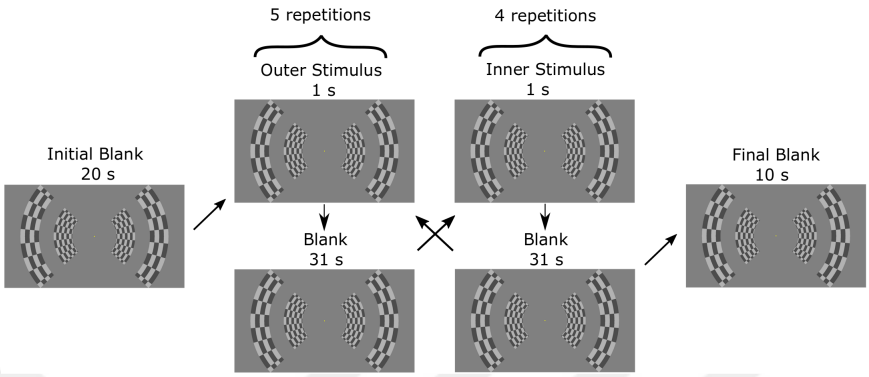

Figure 3.7: Experiment Inner-Outer Longer Pulse SIRF design for fMRI runs with even number ID. It starts with 20 s initial blank where the wedges are visible but they are not flickering. It is followed by alternating the inner and outer stimuli with 32 s blank period in between (inner stimulus = flickering inner wedge for 1 s, outer stimulus = flickering outer wedge for 1 s). The alternation starts with the outer stimulus.

3.8 shows the longer pulse design of the SIRF run.

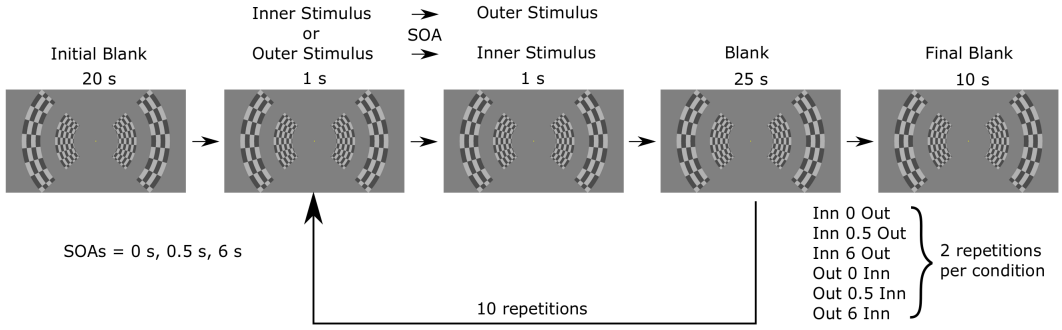

Figure 3.8: Experiment Inner-Outer Longer Pulse SOA Design. It starts with 20 s initial blank followed by a paired stimuli (condition). A paired stimuli consists of a combination of two stimuli (inner and outer) whose onset differences were defined by SOA values. Each condition was tested only once in single SOA run. The conditions were separated by 26 s blank period.

3.1.1.5 Pilot Functional Localizer Experiments to Determine Design parameters

Since BOLD specificity is larger than the specificity of underlying neuronal activity, active neurons activate BOLD in a wider area [58, 59]. For this reason, when

two closely spaced stimuli are presented, neurons of the one which are spatially close to the region of the other stimuli may cause increase or decrease BOLD response in the other region. Since one of the closely spaced stimuli unintentionally may increase or decrease BOLD response of the other one as it might be the case in this study [44], it may invalidate the assumption of spatial linear summation.

To minimize this effect, pilot functional localizer experiments were conducted to find optimal size of the wedges, distance between the wedges, and distance between the fixation point and the wedges in order to have non-overlapping brain activations for the inner and outer stimuli.

Having separate ROI activations for each type of stimuli did not not only depend on the parameters and the ability of the fMRI analysis program but also the subject's brain structure. Although our subjects' brain structures (i.e., calcarine sulcus) varied, we used a common set of parameters for each subject by caring to select non-overlapping activations as ROIs in BrainVoyager as far as possible (see the section 3.1.1.7 for more details).

3.1.1.6 V1 ROI Localization

Regions of interest (ROIs) in area V1 were identified through the functional localizer scan. The scan started with an initial blank period of 20 s, followed by flickering the inner wedges (i.e. inner stimulus), a blank period, and flickering the outer wedges (i.e. outer stimulus). Both the inner and outer stimuli lasted for 12 s. They alternated with each other with a blank period of 18 s between each other. In the blank period, the wedges were not flickering but they were rendered on the screen. This sequence was repeated five times in a run. Participants focused on the fixation point at the center of the visual presentation screen during the entire run. Figure 3.9 shows the localizer design of the experiment Inner-Outer.

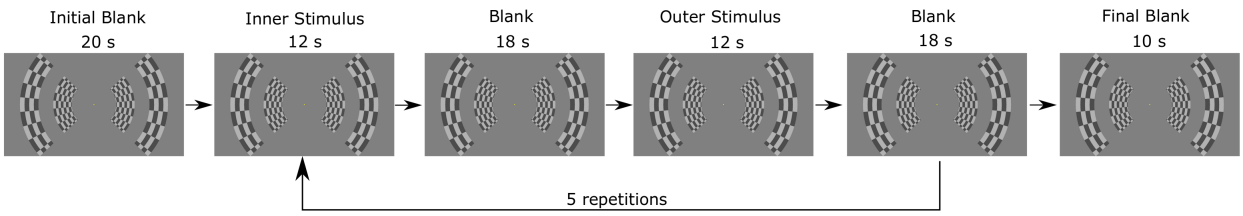

Figure 3.9: Experiment Inner-Outer Functional Localizer Design

3.1.1.7 BrainVoyager V1 ROI Analysis

The analysis steps were the same with the ones in the experiment 1 (see section 2.1.6) except V1 ROI Analysis (see 2.1.6.3).

We followed the same procedure to perform GLM (see section 2.1.6.3). There were three stimuli (i.e., inner, outer and blank stimuli) and two conditions (i.e., inner-blank, outer-blank). See section 3.1.1.6 for the detailed description of the localizer protocol. Difference of two gamma distribution functions [30] was used since it is a good approximation of the real HRF in region V1 [15]. GLM results of a subject is shown in Figure 3.10. As it is seen in Figure 3.10, both inner and outer stimuli have activations in both hemispheres. Therefore, we have two ROIs per stimulus. The inner stimulus activates posterior part of V1, whereas the outer stimulus activates anterior part of the brain at each hemisphere.

After the GLM analysis was performed, the activation was projected to the meshes from anatomical-VTC space as shown in Figure 3.11. VOIs (i.e., volumes of interest) were defined for each condition based on the activations of calcarine sulcus on the meshes of both left and right hemispheres. Defined VOIs were Inner VOI in LH, Inner VOI in RH, Outer VOI in LH, and Outer VOI in RH. As an example, Inner VOI in LH was activated by the inner wedge in the right visual field because of the retinotopic organization of V1 [52]. Then the time course data of all the active voxels within the VOI were averaged for each time point and the average data for all the experimental runs (i.e., SIRF and SOA) were extracted for each VOI.

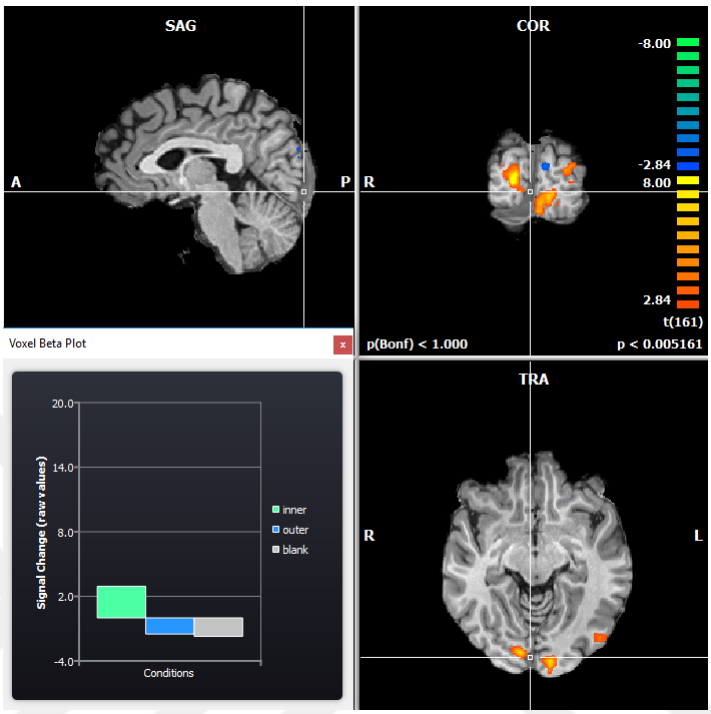

Figure 3.10: GLM activation of inner stimulus vs. blank stimulus

3.1.1.8 Data Visualization

The extracted time course data were normalized by the mean BOLD signal across the scan and computed percent BOLD signal change. Average BOLD response of each stimulus (i.e., inner or outer stimulus) in each ROI was computed by averaging BOLD responses of all trials of each stimulus in each ROI in all the SIRF runs. As an example, first we found average BOLD responses of Inner stimulus both in Inner ROI LH and Inner ROI RH by averaging time course data of all trials extracted from the corresponding ROI. Then we averaged them to find average BOLD response of Inner stimulus in Inner ROI. Likewise, we calculated average BOLD response of Inner stimulus in Outer ROI to examine the effect of Inner stimulus in Outer ROI. The same steps were repeated for Outer stimulus, too. Therefore, we obtained four average BOLD responses from SIRF data (i.e., Inner stimulus in Inner ROI, Inner stimulus in Outer ROI, Outer stimulus in Inner ROI, Outer stimulus in Outer ROI)

In a similar vein, average BOLD response of the paired stimuli (i.e. conditions)

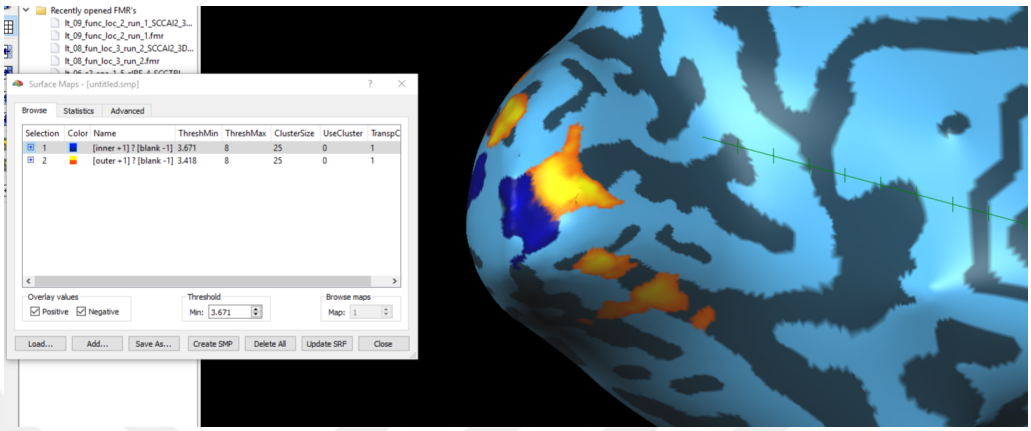

Figure 3.11: Mesh activation Inn-Out LH

were obtained by averaging BOLD responses of all trials of each condition in all the SOA runs. As another example, after average BOLD responses of "Inner 6 Outer in Inner ROI LH" and "Inner 6 Outer in Inner ROI RH" were found, we calculated average BOLD response of "Inner 6 Outer in Inner ROI". The same steps were followed to calculate average response of all conditions in Outer ROI.

BOLD response of single stimulus was obtained from SIRF runs, while BOLD response of paired stimuli was extracted from SOA runs. Our aim is to compare the SIRF and SOA data of each condition in both ROIs (i.e., Inner ROI, Outer ROI). Therefore, we added BOLD responses of single stimuli (e.g., Inner stimulus in Inner ROI) acquired from SIRF data to each other within ROI in order to construct the corresponding conditions in SOA runs (e.g. Inner 6 Outer in Inner ROI). As an example, to construct the condition Inner 6 Outer in Inner ROI, we shifted SIRF response of the outer stimulus in Inner ROI by 6 seconds and added it into the SIRF response of the inner stimulus in Inner ROI. SIRF and SOA data of all conditions were compared in both ROIs (i.e., Inner ROI, Outer ROI). All aforementioned analysis steps were performed in Python. Figures were constructed with Matplotlib library in Python.

3.1.1.9 Statistical Analysis

Procedures in the statistical analysis were the same with the Experiment 1 (see section 2.1.8). The only exception was that the the conditions in this experiment (i.e., Inner-Outer) consisted of one spatial configuration (i.e., adjacent spatial locations in the same hemifield along x-axis), whereas the conditions in the experiment 1 consisted of two distinct spatial configurations (i.e., between hemifields, and the same location).

3.1.2 Results

3.1.2.1 Impulse SIRF Results

Figure 3.12 displays SIRF results of the experiment for impulse flickering duration. As expected, we observed positive BOLD responses in Inner and Outer ROIs in response to Inner and Outer stimuli, respectively due to the retinotopic organization of V1 [52]. It was surprising that Outer and Inner stimuli also induce positive BOLD responses in Inner and Outer ROIs, respectively (i.e., Outer stimulus in Inner ROI, and Inner stimulus in Outer ROI). However, these positive effects in the surrounding regions were smaller in amplitude than the responses at the center.

3.1.2.2 Impulse SIRF vs. SOA Nonlinearity Comparison

Figures 3.13, 3.14, 3.15, and 3.16 show comparisons between SIRF and SOA results for impulse flickering duration in Inner and Outer ROIs, respectively.

We compared the differences between predicted (from SIRF) and observed (from SOA) results in Figures 3.13 and 3.15 by visual inspection, and in Figures 3.14 and 3.16 with the help of the nonlinearity index. Inn 0.5 Out and Out 0.5 Inn were the most nonlinear conditions in both Inner and Outer ROIs. In addition,

Inn 6 Out and Out 6 Inn had small nonlinearities in both ROIs. Surprisingly, Inn 0 Out had small nonlinearity although its SOA duration was the smallest one.

3.1.2.3 Longer Pulse SIRF Results

Figure 3.17 shows SIRF results of the experiment for longer pulse flickering duration. As expected, we observed positive BOLD responses in Inner and Outer ROIs in response to Inner and Outer stimuli, respectively due to the retinotopic organization of V1 [52]. It was surprising that Outer and Inner stimuli also induce BOLD positive responses in Inner and Outer ROIs, respectively (i.e., Outer stimulus in Inner ROI, and Inner stimulus in Outer ROI). However, these positive effects in the surrounding regions are smaller in amplitude than the responses at the center.

3.1.2.4 Longer Pulse SIRF vs. SOA Nonlinearity Comparison

Figures 3.18, 3.19, 3.20, and 3.21 show comparisons between SIRF and SOA results for longer pulse flickering duration in Inner and Outer ROIs, respectively.

We compared the differences between predicted (from SIRF) and observed (from SOA) results in Figures 3.18 and 3.20 by visual inspection, and in Figures 3.19 and 3.21 with the help of the nonlinearity index. Except the nonlinearity of Out 0.5 Inn in Inner ROI, all conditions had small or no nonlinearity in both ROIs. To be specific, Inn 0.5 Out and Out 6 Inn had small nonlinearities in Inner ROI. On the other hand, Inn 0 Out, Out 0.5 Inn, Inn 6 Out had small nonlinearities in Outer ROI. Inn 0.5 Out, Out 6 Inn had very small nonlinearities in Outer ROI.

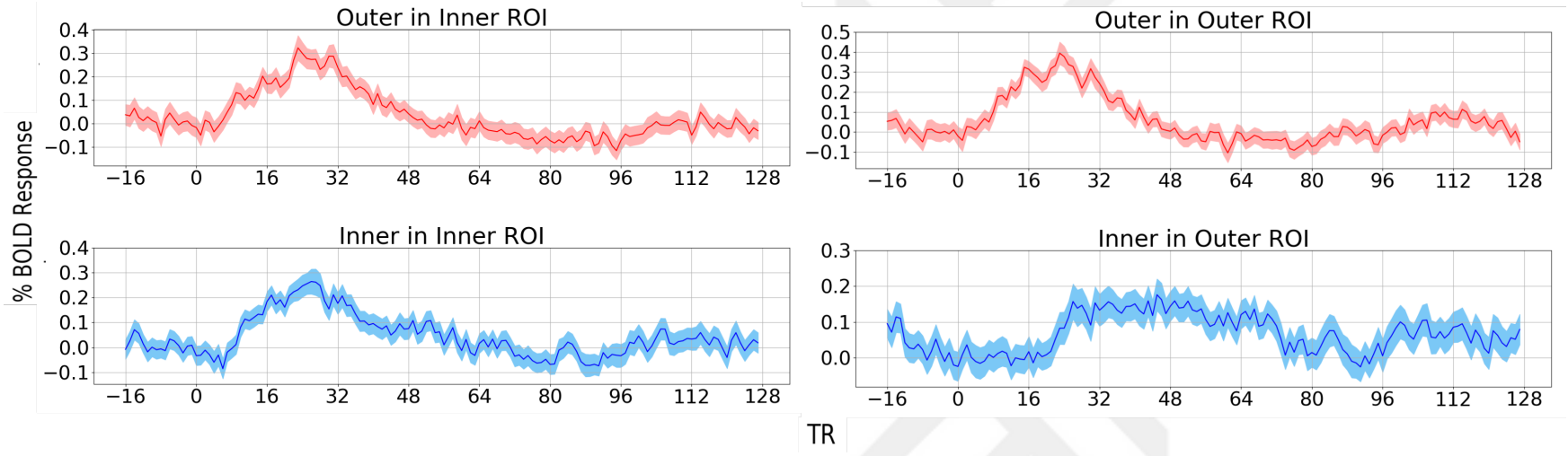

Figure 3.12: BOLD responses to impulse stimulation (Impulse Inn-Out SIRF). Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

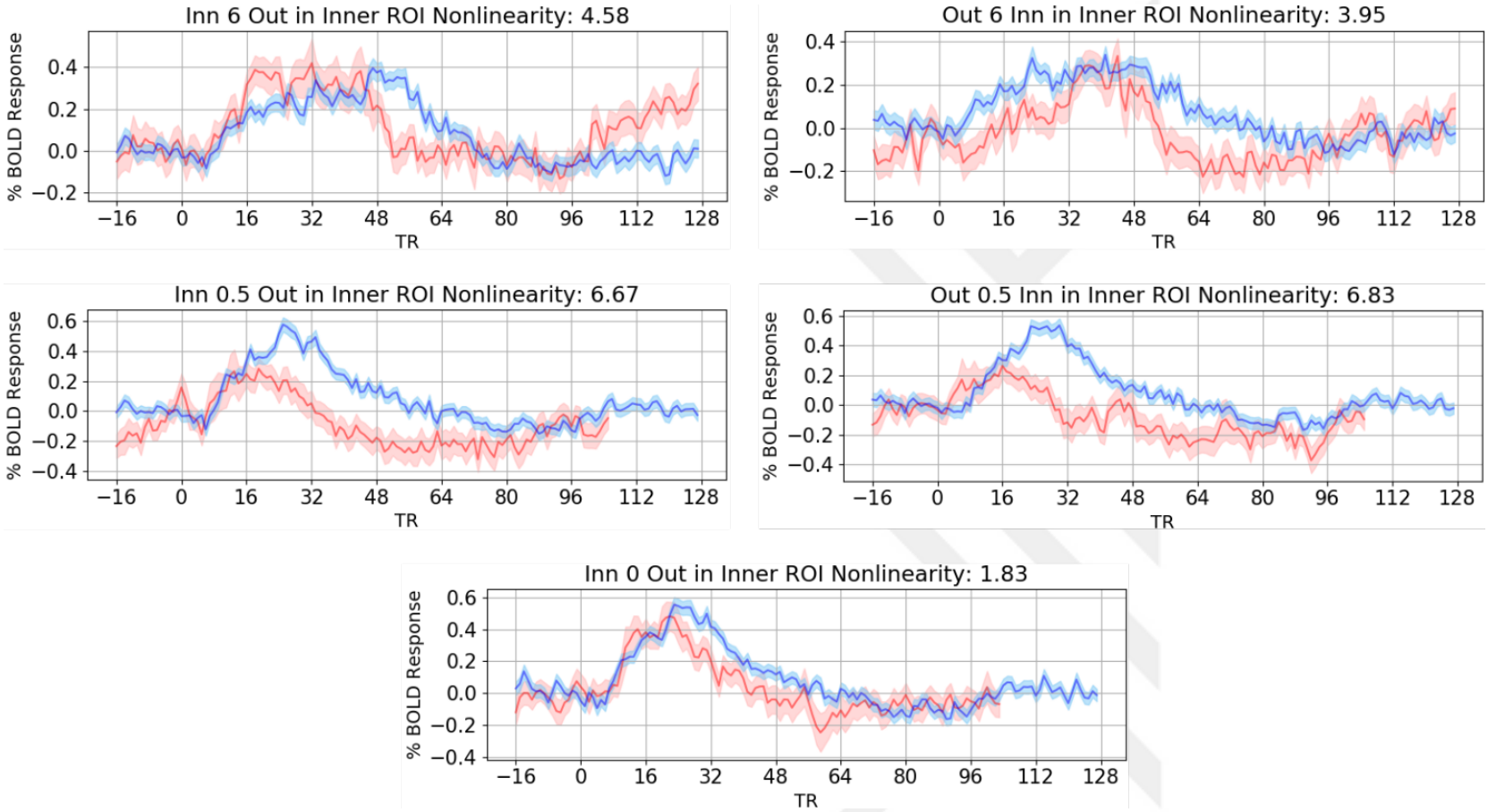

Figure 3.13: Impulse Inn-Out SIRF vs. SOA in Inner ROI. Blue is the predicted response. Red is the observed response. The nonlinearity index measures the degree of the difference between the predicted and observed responses and was calculated based on the residual (nonlinearity) formula for all TRs. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

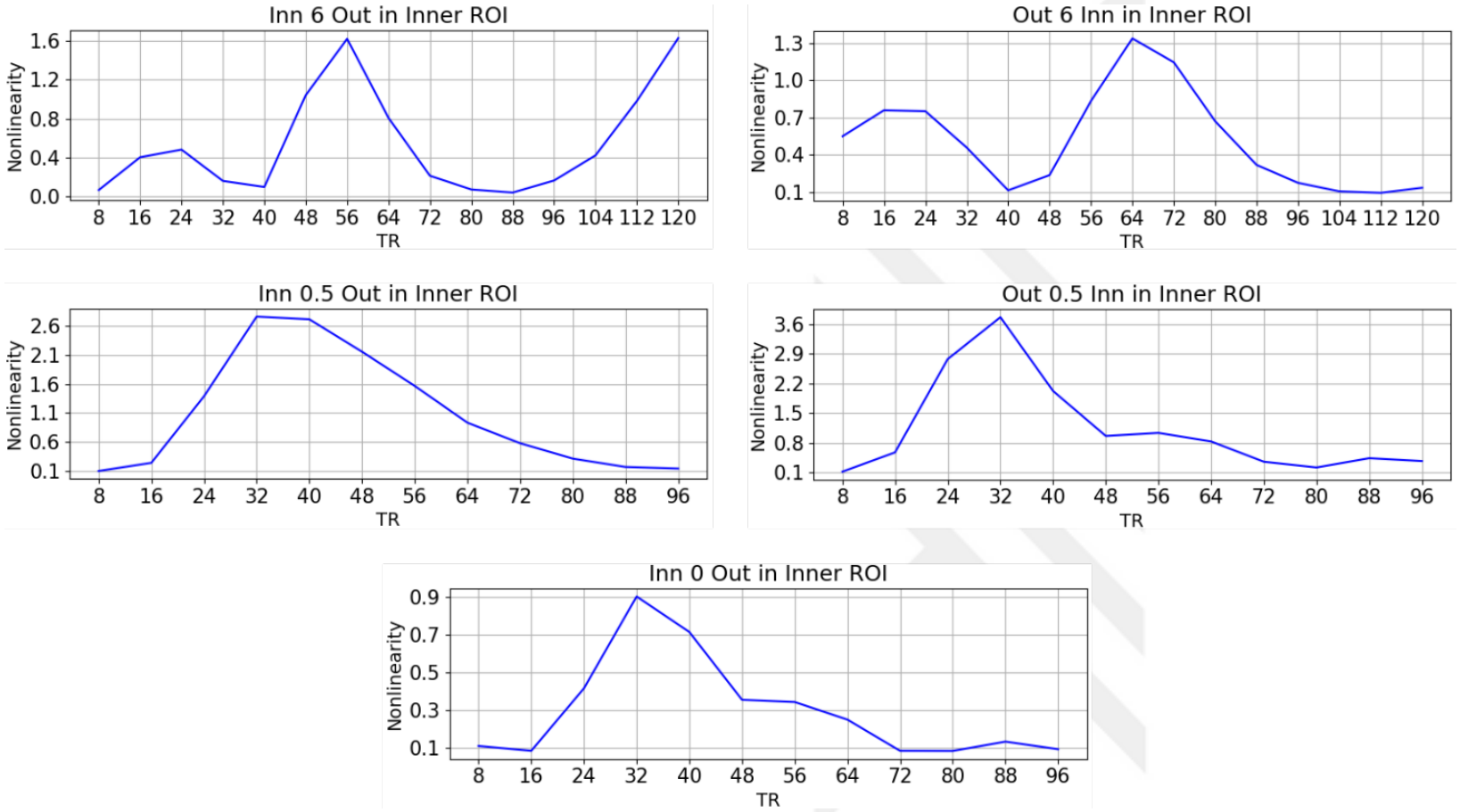

Figure 3.14: Impulse Inn-Out in Inner ROI. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

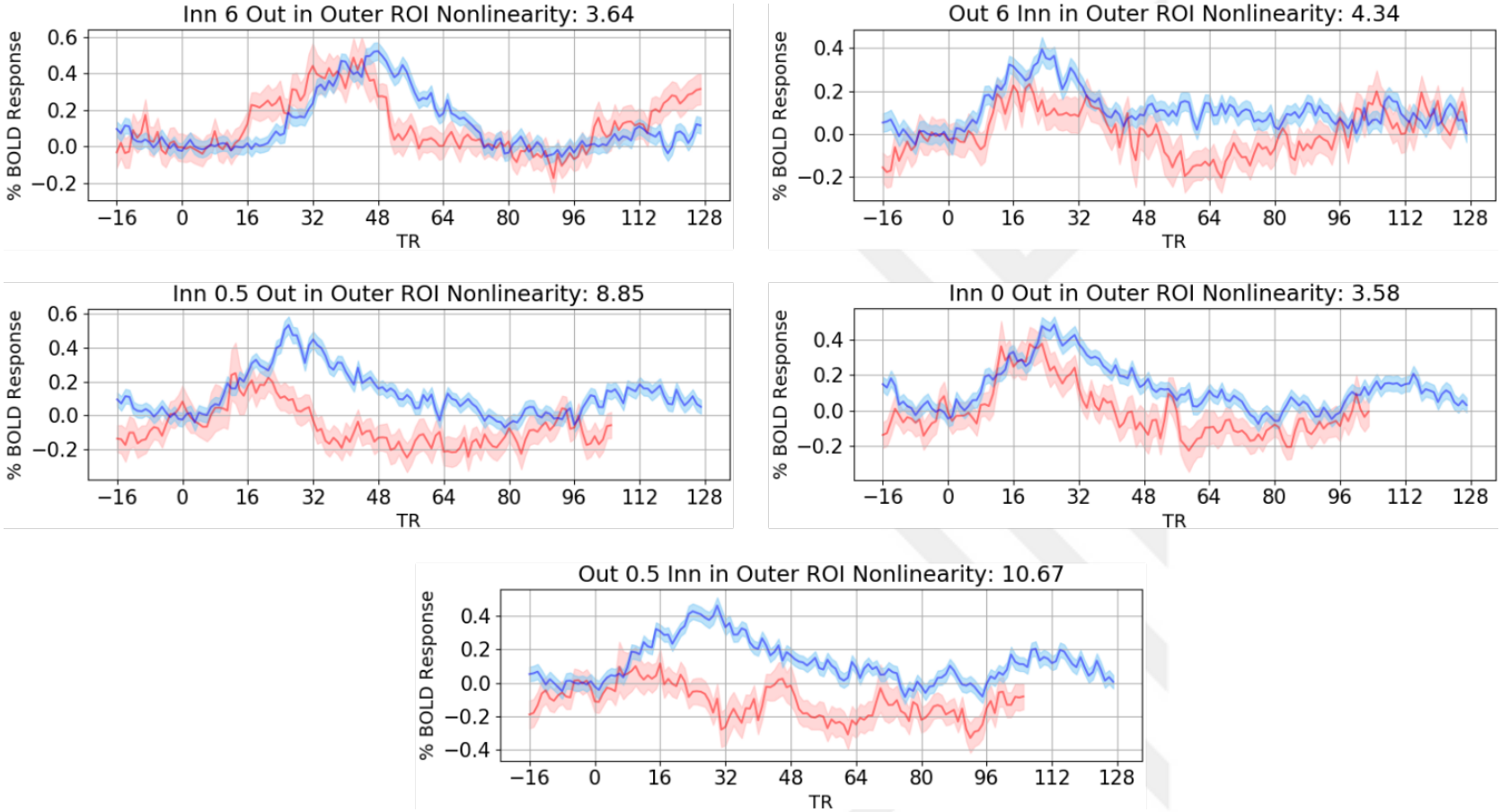

Figure 3.15: Impulse Inn-Out SIRF vs. SOA in Outer ROI. Blue is the predicted response. Red is the observed response. The nonlinearity index measures the degree of the difference between the predicted and observed responses and was calculated based on the residual (nonlinearity) formula for all TRs. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

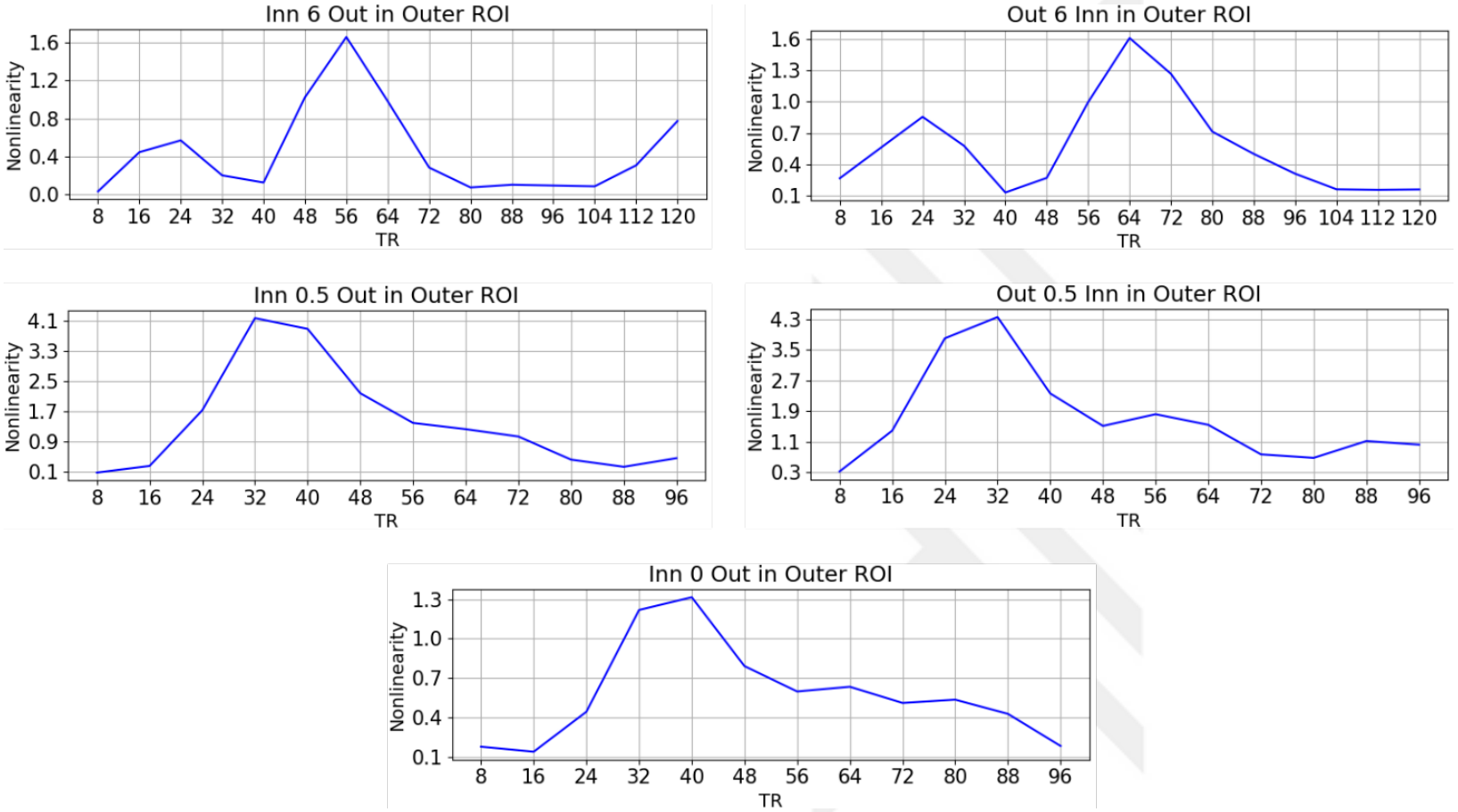

Figure 3.16: Impulse Inn-Out in Outer ROI. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

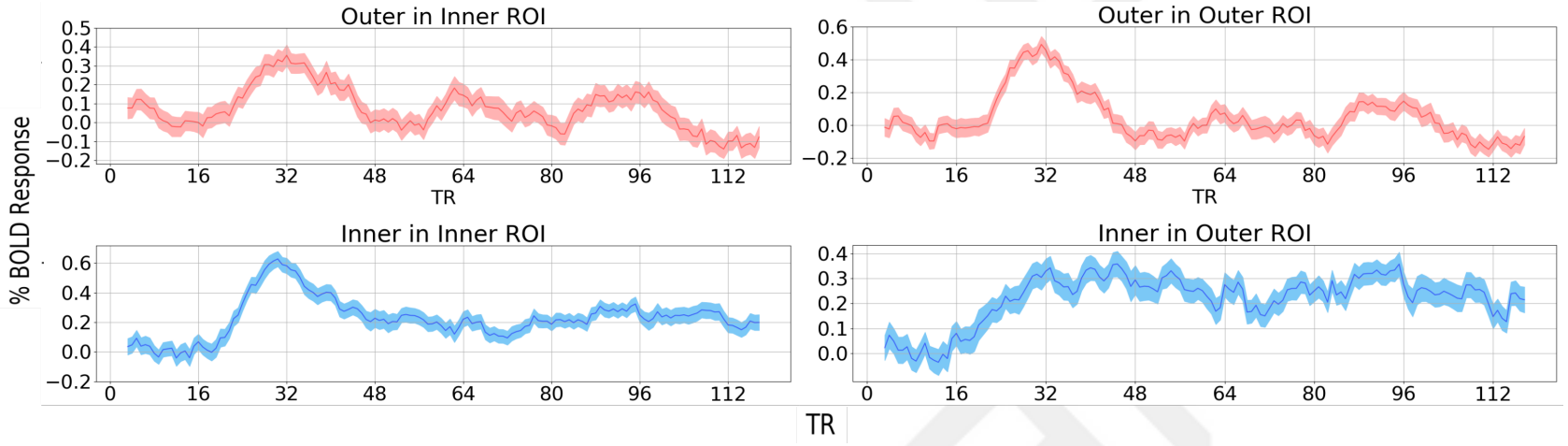

Figure 3.17: BOLD responses to 1 s stimulation (Longer Pulse Inn-Out SIRF). Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

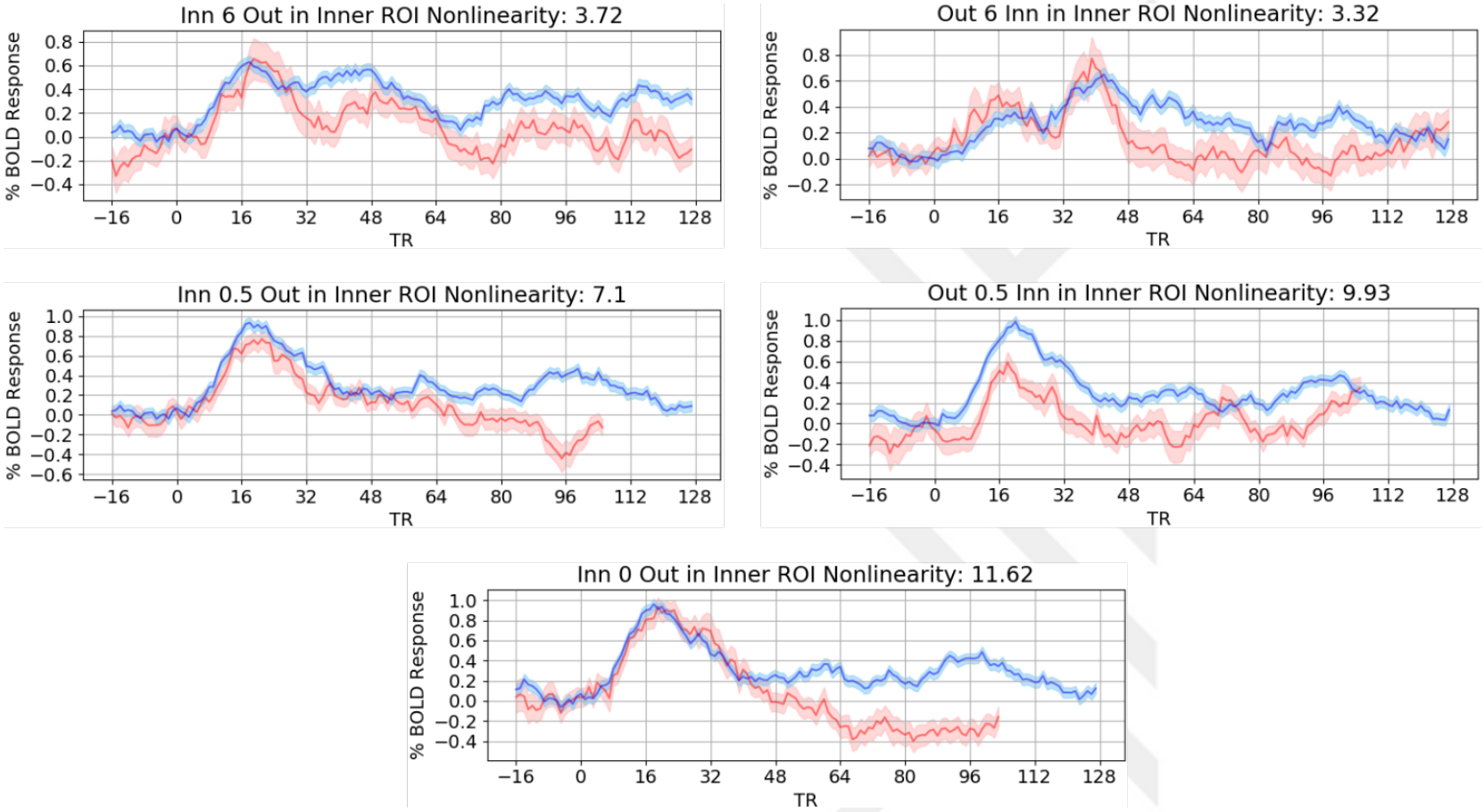

Figure 3.18: Longer Pulse Inn-Out SIRF vs. SOA in Inner ROI. Blue is the predicted response. Red is the observed response. The nonlinearity index measures the degree of the difference between the predicted and observed responses and was calculated based on the residual (nonlinearity) formula for all TRs. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

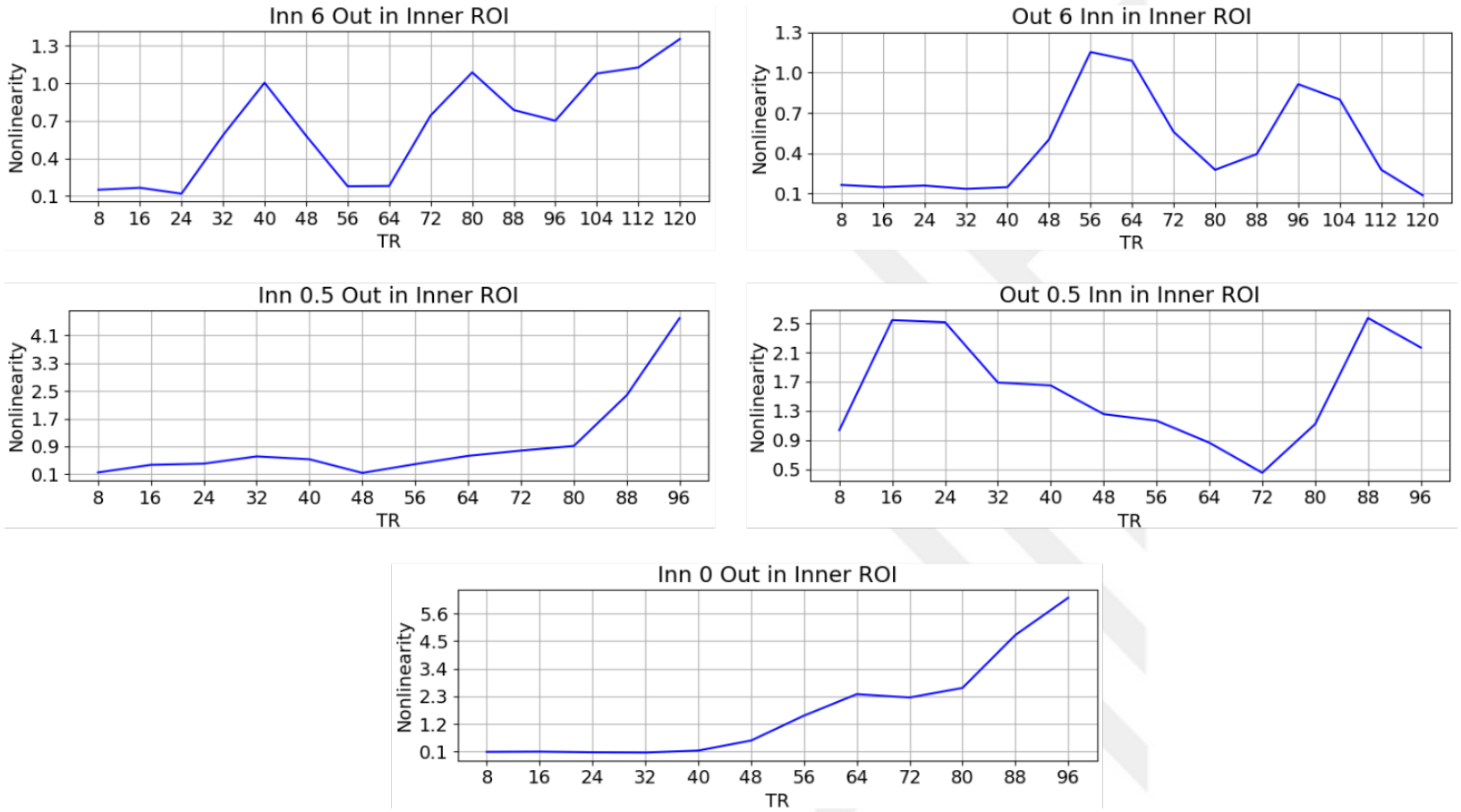

Figure 3.19: Longer Pulse Inn-Out in Inner ROI. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

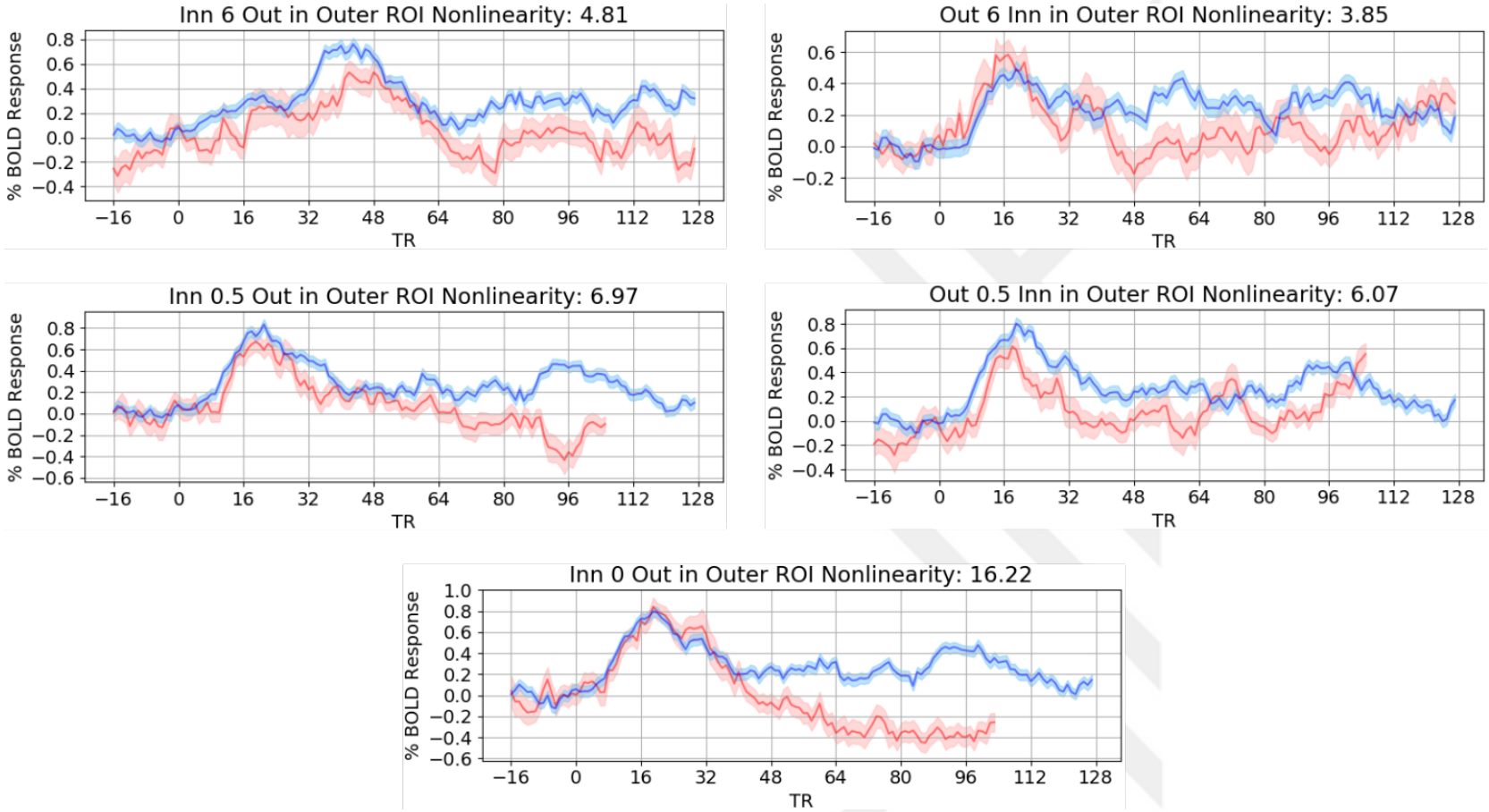

Figure 3.20: Longer Pulse Inn-Out SIRF vs. SOA in Outer ROI. Blue is the predicted response. Red is the observed response. The nonlinearity index measures the degree of the difference between the predicted and observed responses and was calculated based on the residual (nonlinearity) formula for all TRs. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

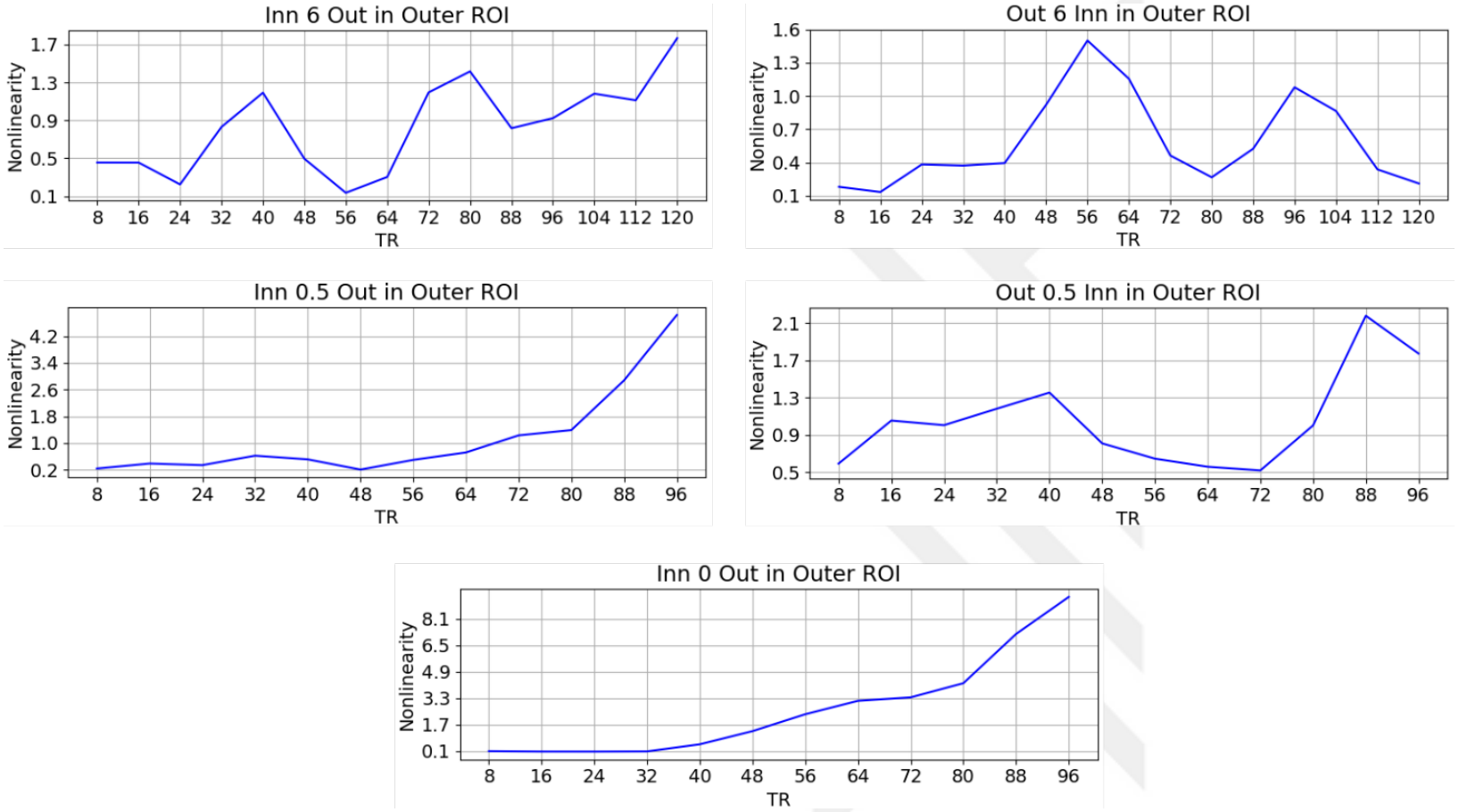

Figure 3.21: Longer Pulse Inn-Out in Outer ROI. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

3.1.2.5 Statistical Results

We performed 3-way ANOVA and Tukey's post-hoc test. The dependent variable was the nonlinearity index and the independent variables were TR, SOA, and flickering duration. Statistical significance between levels of an independent variable were found in all of the independent variables ($F_{TR} = 12.4, p < 0.001$), $F_{SOA} = 51.7, p < 0.001$, $F_{FlickDur} = 66.1, p < 0.001$). Besides, there were statistically significant two-way interactions between SOA and TR (F = 10.8, p < 0.001), between SOA and flickering duration (F = 54.4, p < 0.001), and between TR and flickering duration (F = 25.6, p < 0.001). In addition, there was a statistically significant three-way interaction between TR, SOA, and flickering duration (F = 8.9, p < 0.001).

3.1.2.5.1 Flickering Duration Comparison

We grouped all conditions within a spatial group (e.g., horizontally adjacent spatial locations in the same hemifield along x-axis) by their flickering durations (see section 2.1.8.1 for more details). Figure 3.22 compares the flickering durations (impulse and longer pulse) in the conditions of horizontally adjacent spatial locations in the same hemifield. The nonlinearity of the longer pulse conditions is significantly bigger than the nonlinearity in the impulse conditions (p < 0.001).

3.1.2.5.2 SOA Duration Comparison

We grouped all conditions within a spatial group (e.g., horizontally adjacent spatial locations in the same hemifield along x-axis) by their SOA durations (see section 2.1.8.1 for more details). Figure 3.23 compares the SOA durations (0 s, 0.5 s, and 6 s) in the conditions of adjacent spatial locations in the same hemifield along x-axis. Nonlinearities in SOA 0 and SOA 0.5 are significantly bigger than nonlinearity in SOA 6 (p(SOA 0 vs. 6) < 0.001, p(SOA 0.5 vs. 6) < 0.001). There is no significant difference between SOA 0.5 and SOA 6.

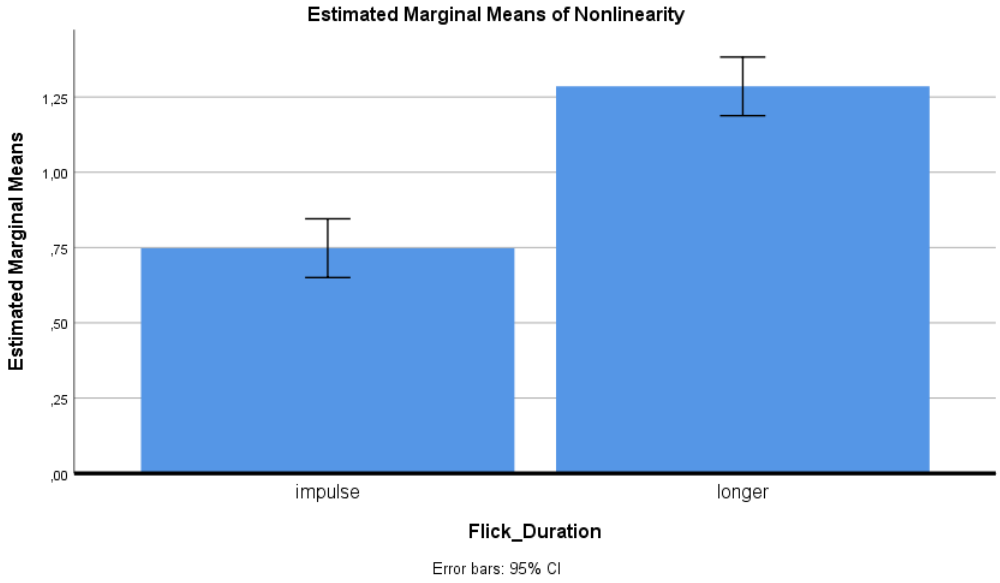

Figure 3.22: Nonlinearity as a variable of flickering duration between horizontally adjacent visual fields in the same hemifield along x-axis. The difference between impulse and longer pulse is statistically significant ($p < 0.001$).

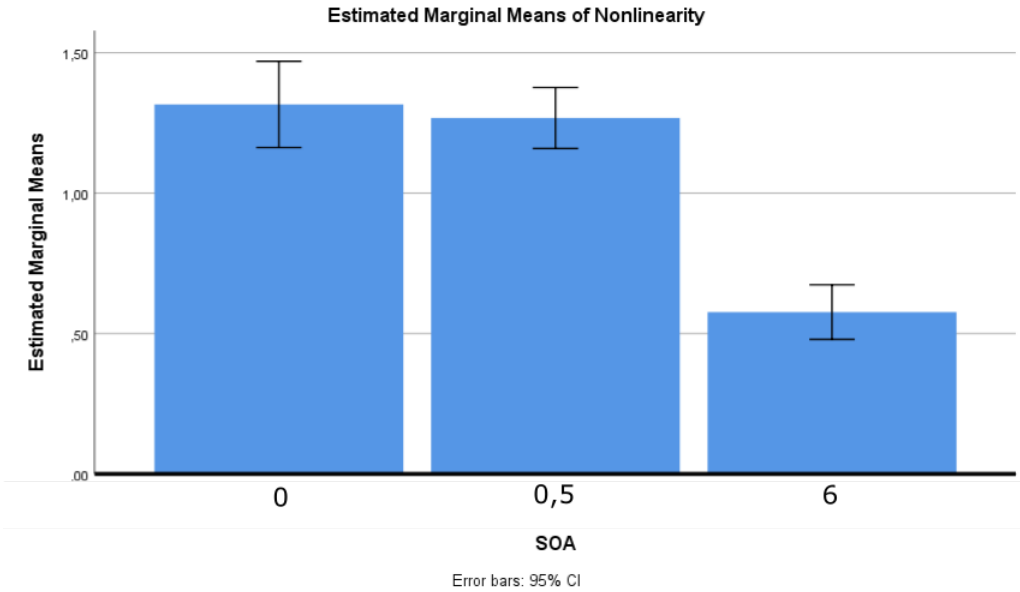

Figure 3.23: Nonlinearity as a variable of SOA duration between adjacent visual fields in the same hemifield along x-axis. The difference between SOA 0 and SOA 6 is statistically significant ($p < 0.001$). The difference between SOA 0.5 and SOA 6 is statistically significant ($p < 0.001$). There is no statistical difference between SOA 0 and SOA 0.5.

3.1.3 Intermediate Discussion

3.1.3.1 Impulse SIRF

As expected, we saw positive responses for the Inner stimulus in the Inner ROI and for Outer the stimulus in the Outer ROI due to the retinotopic organization of brain [52]. However, we also saw weaker but still positive responses in Inner stimulus in Outer ROI and Outer stimulus in Inner ROI. This effect might be caused by the spatial extent of BOLD response (i.e., its point spread function) [58, 59]. The positive responses in the surrounding regions were also found in V1 [49].

To minimize the effect of point spread function of BOLD response, we adjusted the design parameters of the experiment such that the resulting ROI activations of the stimuli did not overlap with each other and cared to define non-overlapping ROIs for the stimuli (see sections 3.1.1.5 and 3.1.1.7 for more details). However, ROI size of the stimuli depend on the statistical threshold in GLM which can be adjusted manually. When we reduce the statistical threshold manually, we saw wider brain activation for each stimulus as expected. Consequently, we saw that non-overlapping ROIs started to overlap with each other. The reason that we saw positive responses in adjacent regions can be because the point spread function still had a positive effect in the adjacent regions.

Apart from the large spread of the BOLD response to the localized neuronal activity, facilitatory effects in V1 were found between nearby stimuli in both electrophysiological [60] and fMRI [61], which might also explain the positive responses in the surrounding regions. However, there are studies that prove the existence of surround inhibition in the visual cortex [43, 42, 41].

Nevertheless, the existence of the positive BOLD responses in the surrounding regions or surround inhibition/facilitation is irrelevant to our aim and does not invalidate our study since our aim is to investigate in which spatial (i.e., between hemifields, adjacent spatial locations in the same hemisphere, and the

same location) and temporal (i.e., SOAs: 0 s, 0.5 s, 6 s) configurations linear summation can successfully be conducted and how temporal and spatial configurations interact with each other. If spatial linear summation exists in one of the spatial configurations, we expect that the positive response in the surrounding region and surround inhibition/facilitation obtained by SIRF data should stay the same in SOA data, too. Therefore, point spread function and surround inhibition/facilitation will not make any difference to conduct this study.

3.1.3.2 Impulse SIRF vs. SOA Nonlinearity Comparison

The conditions with SOAs 0.5 s had substantial nonlinearities in both Inner and Outer ROIs, which was elicited as lower BOLD response. The nonlinearity at SOA 0.5 s was more severe than it was at SOA 0 s in both Inner and Outer ROIs. Besides, the conditions in Outer ROI had small nonlinearities even at SOA 6 s.

The two adjacent stimuli which are located in a similar way as it was in the experiments Inner-Outer and Upper-Lower (described next) mutually suppressed each other resulting a decrease in the BOLD response [45, 46, 47, 62]. Computation capacity in the visual system is limited [63, 64, 65]. Due to the limited processing capacity, simultaneously presented objects in the scene compete with each other to have enough neural representation. Consequently, when two stimuli are presented simultaneously, response to a visual stimulus is suppressed by the other stimulus located at the same location [54, 55, 51] or the adjacent location [45, 47]. This mechanism is called mutual suppression. The effect size of mutual suppression mechanism is increased by pRF size [46, 62]. Therefore its effect is stronger in the higher visual regions (e.g., V2, VP, V4) than in V1. In fact, aforementioned studies showed that V1 was not affected by mutual suppression mechanism. Besides, the mutual suppression can be modulated by bottom-up stimulus driven processes such as visual salience in V2/VP and V4 and by top-down selective attention (attention eliminates the effect of mutual suppression) in V2, V4, and MT [66, 45, 67, 50, 68, 51, 69]. In addition, mutual suppression is context dependent. For example, it was found that its effect was stronger when the heterogeneous stimuli (i.e., stimuli presented at the scene differ from

each other) were presented than when the homogeneous stimuli (i.e., stimuli presented at the scene are the same) were presented [62]. In our study, we presented homogeneous stimuli in V1. Therefore, the fact that no suppressive effect was observed in longer pulse conditions (except Out 0.5 Inn in Inner ROI) is consistent with the longer pulse results. The suppression effect was not found for neither heterogeneous nor homogeneous stimuli in V1 because RF size of V1 is smaller [62, 66]. However, decreasing display size of visual stimuli can induce stronger neural competition in earlier visual areas such as V1 and V2 since their pRF size are small [70]. In fact, the same study reported that suppressive interactions were twice as larger in V1 and V2 in response to 2x2 visual degree visual stimuli than they were in response to 4x4 degree visual stimuli. Even though the spatial distance between Inner and Outer wedges are 2 visual degree and width of the wedges are 2.5 visual degree, mutual suppression mechanism may take place in V1, too. Then this raises the question why nonlinearity in the longer pulse at shorter SOAs was not observed but observed in the impulse flickering duration by visual inspection. Since selective attention reduces the degree of mutual suppression [66, 45, 67, 50, 68, 51, 69], selective attention mechanism may be involved in longer pulse but not in impulse flickering duration to modulate V1. Since impulse flickering duration is very short, it might be impossible that selective attention mechanism modulates V1. Therefore it will not able to reduce the effect of mutual suppression in V1 for impulse. Consequently, the effect of mutual suppression can be stronger in impulse than it is in longer flickering duration.

It is also interesting to find that nonlinearity was observed at SOA 0.5 s, but not in SOA 0 s in longer pulse. It might imply that an inhibitory mechanism that makes SOA 0.5 s nonlinear cannot be involved in when two stimuli flicker at the same time.

In addition to the mutual suppression mechanism, surround suppression is another mechanism that may invalidate spatial summation [49]. It has been shown that the response to a bar stimulus presented in a RF was lower when the stimulus was surrounded by a similar bar presented outside the RF than the response to the same bar when there was no surrounding bar. In other words, activation to a stimulus in its receptive field is lowered when there is a

surrounding stimulus. The surround inhibition mechanism exists in V1 [71, 72]. This mechanism can be effective in V1 up to 10-12 degree [72, 73, 74]. However, it has been reported not only inhibitory [43, 42, 41] but also facilitatory [43] effects at the center by the surrounding stimuli. Nevertheless, as explained in section 3.1.3.1 in a more detailed way, surround inhibitory and facilitatory effects modulate both SIRF and SOA data. Therefore, any deviation between predicted (from SIRF) and observed (from SOA) responses might not be explained by surround inhibition and facilitation mechanisms.

Besides, we do not expect that any nonlinearity caused neuronal or vascular adaptation to the stimulus duration because the impulse stimulus duration is nearly instantaneous. However, we found that the degree of nonlinearity (i.e., the reduction in amplitude) depends on SOAs. Although the nonlinearity can be ignored at the relatively longer SOAs, it is substantial at the SOAs 0 s and 0.5 s in impulse and at the SOA 0.5 s in longer.

3.1.3.3 Longer Pulse SIRF

As expected, we saw positive responses for Inner stimulus in Inner ROI and Outer stimulus in Outer ROI due to the retinotopic organization of brain [52]. However, we also saw weaker but still positive responses for the Inner stimulus in the Outer ROI and Outer stimulus in the Inner ROI. Possible explanations for the positive responses in the surrounding regions was mentioned in the section 3.1.3.1.

3.1.3.4 Longer Pulse SIRF vs. SOA Nonlinearity Comparison

All conditions in both Inner and Outer ROIs (except the substantial nonlinearity in Out 0.5 Inn in Inner ROIs) have small nonlinearities, which was elicited as lower BOLD response.

The same mechanism (i.e., mutual suppression) can be the underlying reasons for the emerging nonlinearities (see section 3.1.3.2 for more details).

3.1.3.5 Impulse SIRF vs. Longer Pulse SIRF

Main (i.e., Inner stimulus in Inner ROI, Outer stimulus in Outer ROI) and surrounding activations (i.e., Inner stimulus in Outer ROI, Outer stimulus in Inner ROI) in longer pulse are very roughly two times bigger in amplitude than the main and surrounding activations in impulse. This could be due to the fact that stimulus duration (i.e., strength of stimulus) was longer in the longer pulse than it was in the impulse because stronger stimuli typically evoke stronger BOLD response [11, 34]. However, nonlinearity of BOLD response with respect to stimulus duration was observed as reported in Table 3.1. If the BOLD response holds the scaling property, longer pulse responses would have been much bigger in amplitude than twice impulse responses since the longer pulse duration is much longer than twice the impulse duration.

Table 3.1: Amplitudes of main and surrounding activations in Inner-Outer SIRF

Duration	**Main**	**Surrounding**	**ROI**
Impulse	0.4	0.15	Outer ROI
Impulse	0.3	0.3	Inner ROI
Longer	0.5	0.35	Outer ROI
Longer	0.6	0.35	Inner ROI

3.1.3.6 Flickering Duration Comparison

Figure 3.22 shows that the nonlinearity in the longer pulse results is more extreme than the nonlinearity in the impulse results. On the contrary, when we compared the impulse figures 3.13 and 3.15 with the longer pulse figures 3.18 and 3.20 by visual inspection, we perceived that the impulse results were more nonlinear than the longer pulse results. Therefore, one can conclude that there are inconsistencies between the visually inspected results and quantitative results. There are two possible explanations.

The first explanation is that, in general, the longer pulse results were found to be more nonlinear in tails than the impulse results in tails. In general, when

we visually judge the difference between predicted and observed responses, we tend to focus on the time interval where stimulus-evoked responses are dominant rather than tails. It is because responses in tails may represent noise rather than stimulus-evoked responses. As an example, the time frame where stimulus-evoked response are more dominant could be between 0 TR and 80 TR (i.e., 0-20 s). However, in the quantitative results, we took responses in tails into consideration, as well. Therefore, Figure 3.22 might be modulated by noise as well.

The second explanation is that longer pulse results can be potentially found more nonlinear than impulse results because of the nonlinearity (residual) formula. The formula computes the mean squared error (i.e., distance) normalized by variance. Therefore, we might have bigger nonlinearities in longer pulse because longer pulse BOLD responses are generally bigger than impulse results (see section 3.1.3.5). To be clear, assume that peaks of predicted and observed responses are 0.6 and 0.3 for impulse and 1.2 and 0.9 for longer pulse. Assume that variances of impulse and longer pulse are equal. Then the nonlinearity formula will produce the same value for both impulse and longer pulse. However, when the differences between predicted and observed responses are visually judged for both flickering duration, the impulse result will appear more nonlinear than the longer pulse results since the relative difference between predicted and observed responses are higher in the impulse ($0.3/0.6 = 0.5$ in impulse; $0.9/1.2 = 0.75$ in longer pulse).

If the data is reanalyzed by discarding responses in tails, the nonlinearity in longer pulse will be decreased. Since there seems to be a mismatch between the visually judgment and quantitative results, we hesitate to draw a conclusion regarding the comparison between impulse and longer pulse. However, the following paragraphs discuss why the impulse results were found to be more nonlinear than the longer pulse results (according to the visual judgment).

There are three mechanisms (point spread function, surround inhibition, and mutual suppression) involved in the process. Point spread function of BOLD response facilitates the activations in the surrounding regions. Conversely, mutual

suppression and surround inhibition cause negative activations in the surrounding regions. These mechanisms are modulated by strength of stimulus (e.g., stimulus duration, and contrast).

The degree of mutual suppression increased as the contrast level was lowered [49]. It is known that both neuronal [75] and hemodynamic responses [76, 11] rise monotonically as the level of contrast increases. It is, therefore, intuitive to expect that the degree of spreading of activation of BOLD response in response to the increased neuronal activation was increased as the contrast level increased. In a similar vein, we may expect that the same relationship can also exist between the stimulus duration and the degree of spreading of activation. That is, increased stimulus duration results in an increase in the neuronal activity accompanying an increase in spreading of the activation. In this context, impulse and longer pulse results can be thought as lower and higher contrast results, respectively. The spread is bigger in longer pulse, whereas it is smaller in the impulse.

It has been reported that reduced stimulus strength results in a reduction in the neuronal suppression mechanism accompanying with stronger spatial summation [77]. Conversely, stronger stimulus causes the stronger suppression in the neuronal activity. Therefore, impulse results may show less suppressive effects in the surrounding regions. On the contrary, the degree of the neuronal mutual suppression is higher in the longer pulse.

Both point spread function and surround inhibition took place in SIRF and SOA data. Since we compare SIRF and SOA data and investigate their differences, the only mechanism that exists in the SOA data but not in SIRF data is the mutual suppression. Mutual suppression is involved in case two group of neurons located close to each other in space suppress each other only when they are activated in temporally close in time due to the neuronal competition. We see that, in impulse results, the balance between surround inhibition and the positive spread collapses when mutual suppression mechanism is also included. However, there is a balance between the facilitatory (i.e., spread) and inhibitory (i.e., surround inhibition, and mutual suppression) effects. As an explanation, it can be concluded that as the stimulus duration increases, the spread increases

more than the increase in the neuronal suppression, resulting an almost linearity in the longer results. As another possible explanation, it has been reported that selective attention reduces mutual suppression [66, 45, 67, 50, 68, 51, 69]. Since impulse may have the pop-out effect, selective attention mechanism cannot be involved in modulating V1, that is it cannot reduce the effect of mutual suppression. Consequently, the effect of mutual suppression can be stronger in impulse than it was in longer pulse. It is also possible that the effect of mutual suppression is significantly reduced, since selective attention is able to modulate V1 in longer pulse. Then mutual suppression might be the reason for the nonlinearity in impulse.

Since spreading of activation may be lower in the impulse results than the longer pulse results, mutual suppression may take a more effective role and may become the dominant factor, resulting more severe signal reductions (i.e., spatial nonlinearity) in the impulse results. Conversely, since spreading of activation is higher in the longer pulse results, there may not be a signal reduction thanks to the relative increase in spreading of activation even though mutually suppressive interactions between the adjacent stimuli are more powerful in the longer pulse. In other words, in the longer pulse results, increased spreading of activation may cancel out the increase in the mutual and surround inhibition. Table 3.1 also shows that the positive activation of the surrounding region was higher in the longer pulse than it was in the impulse.

3.1.3.7 SOA Duration Comparison

Figure 3.23 showed that a strong nonlinearity was observed at SOA 0 s and SOA 0.5 s in both impulse and longer pulse. The nonlinearity in SOA 0 and SOA 0.5 were significantly bigger than the nonlinearity in SOA 6 and SOA 6 ($p(\text{SOA } 0.5 \text{ vs. } 0) < 0.001$, $p(\text{SOA } 0.5 \text{ vs. } 6) < 0.001$). There was no significant difference between SOA 0 and SOA 0.5.

Therefore, one conclude that shorter SOAs caused higher nonlinearities. Many

studies showed that nonlinearity exists in V1 due to neuronal or vascular refractory effects and mutual suppression when two visual stimuli are close in time to each other. The strength of these inhibitory effects decreases as the SOA duration increases (see section 1.1.3).

3.2 Experiment 3: Interactions Between Vertically Adjacent Locations

Experiment 3 (i.e., Experiment Upper-Lower) was conducted to examine the interaction between the paired stimuli as a variable of SOAs when they are located at adjacent spatial locations along y axis in the same hemisphere. We examine if the results are similar to the one in the experiment Inner-Outer or changing the location of the paired visual stimuli makes any difference for the interaction.

In independently identified regions of interest (ROIs, see details of ROI localizer under section 3.2.1.6) in primary visual cortex (V1), we first identified hemodynamic impulse response functions using visual stimuli dispersed widely in time ('Single impulse response function (SIRF)' scans, see below for more details) and used them to predict responses to presentation of visual stimuli with shorter time between them ('SOA scans', see below for details). Any deviation between the predicted and observed BOLD responses in the SOA scans is taken as a sign of non-linearity.

3.2.1 Materials and Methods

3.2.1.1 Participants

Three subjects including the author CB (two males, ages ranged from 22 to 26) participated in the experiment. Participants were graduate students in National Magnetic Resonance Research Center (UMRAM), Bilkent University. The same participants attended the Experiment Inner-Outer, too. They reported normal or corrected-to-normal vision, and had no history for neurological or visual disorders. Ethics approval was granted by Bilkent University Ethics Committee for Research with Human Participants. All participants gave written informed consent in accordance with the Declaration of Helsinki.

3.2.1.2 MRI Data Acquisition

Scanning protocols were the same with the Experiment 1 and the Experiment 2 (see Section 2.1.2).

3.2.1.3 Visual Stimulus Presentation Setup

The setup was the same with the Experiment 1 and the Experiment 2 (see Section 2.1.3).

3.2.1.4 Experimental Design

Similar to the experiments 1 and 2, a flickering wedge stimulus with contrast-reversing checkerboard pattern was used with a flickering rate of 8 Hz. The experiment had two stimuli named 'Upper' and 'Lower'. Similar to the experiment Inner-Outer, both upper stimulus and lower stimulus consisted of two flickering wedges. The widths of the two wedges were (65° circular angle). The paired wedges (i.e., upper stimulus' wedges, and lower stimulus' wedges) were symmetrical to each other with respect to x-axis. The symmetrical wedges of each stimulus allow the both upper and lower stimuli to be located in both left and right visual fields. The upper stimulus was located in the left and right upper visual fields (above the fixation point), while the lower stimulus was located in the left and right lower visual fields (below the fixation point). Background was isoluminant gray with luminance 86 in cd/m^2. The Michelson contrast of the wedges was 40% to keep the hemodynamic response below the saturation level. The spatial configuration of the experiment Upper-Lower was shown in Figure 3.24.

The distance between innermost part of the both types of the wedges and fixation point is 3° visual degree. The distance between the bottommost part of upper wedge and the topmost part of lower wedge is 0.5° visual degree. The widths of both types of the wedges are 3° visual degree.

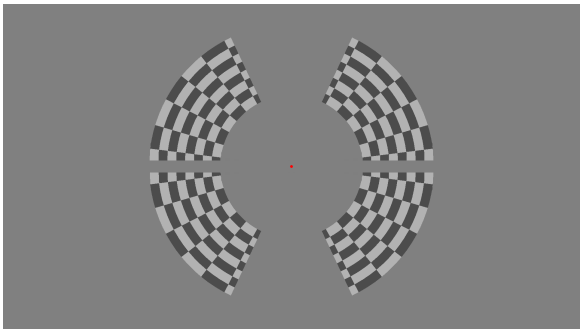

Figure 3.24: Experiment 3 Upper-Lower configuration. The upper wedges and lower wedges were located at the upper and lower visual fields, respectively.

We used two flickering durations (impulse, and longer pulse) and repeated the experiment for each of them.

3.2.1.4.1 Impulse Experimental SIRF Design

In SIRF scans, we collected single responses of the upper and lower stimuli. The upper and lower stimuli alternate during the scan with a blank duration of 32 s. We used a long blank duration (32 s) in order to eliminate any effect of the former stimulus on the latter one.

Each participant performed SIRF scans in two sessions and completed 72 trials for each stimulus, 36 times in each session. 36 repetitions of each stimulus was completed in 8 SIRF scans in each session. Since the experiment had three subjects, we had 216 trials for each stimulus in total. The number of trials was increased by a factor of two, since the left (216 trials) and right (216 trials) hemifields time-course data of a stimulus were combined during the data analysis, resulting 432 trials for each stimulus in total. Each SIRF run lasted 318 s including blank periods of 20 s at the start and 10 s at the end. Participants focused on the fixation point at the center of the visual presentation screen during the entire run. Figures 3.25 and 3.26 show the design of SIRF run.

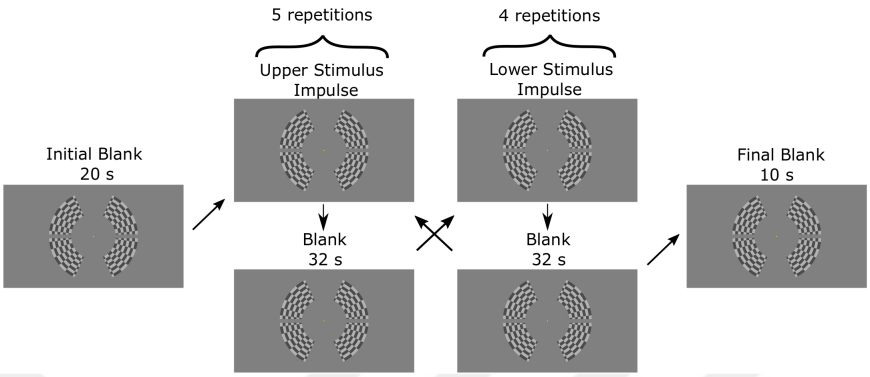

Figure 3.25: Experiment Upper-Lower Impulse SIRF design for fMRI runs with odd number ID. It starts with 20 s initial blank where the wedges are visible but they are not flickering. It is followed by alternating the upper and lower stimuli with 32 s blank period in between (upper stimulus = single flick in the upper wedge, lower stimulus = single flick in the lower wedge). The alternation starts with the upper stimulus.

3.2.1.4.2 Impulse Experimental SOA Design

In SOA scans, we collected responses to successively presented pairs of stimuli with shorter duration between. Each combination of Upper and Lower stimulation constituted a 'condition'. A condition consists of two stimuli whose onset differences were defined by the SOA values.

The conditions were Upper-Lower and Lower-Upper with SOAs of 0 s, 0.5 s, and 6 s. To be more clear, the condition Upper 6 Lower started with flickering upper wedges (i.e., upper stimulus) followed by flickering lower wedges (i.e., lower stimulus) 6 s later from the onset of the lower stimulus. Since both stimuli consist of two wedges located at left and right hemifields, they activate both hemifields.

Upper-Lower and Lower-Upper are the conditions which are used to test any interaction between vertically adjacent spatial locations along y-axis in the same hemisphere as a variable of SOA values.

There is a blank duration of 26 s between the conditions. In the blank period, the wedges were not flickering but they were rendered on the screen. The blank period was set as a long duration to minimize any effect of the former condition

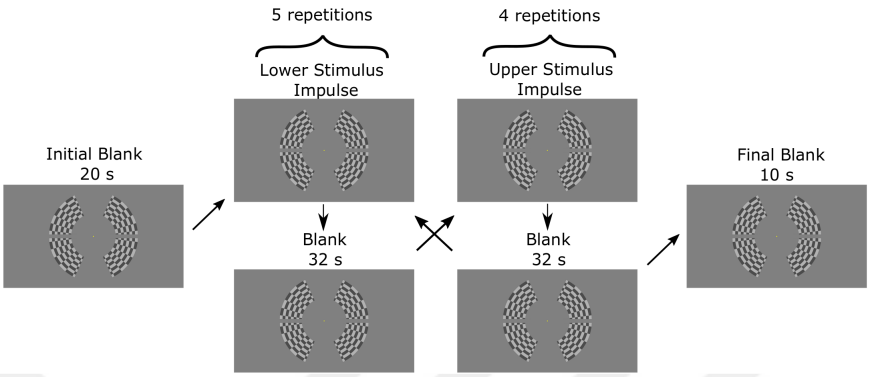

Figure 3.26: Experiment Upper-Lower Impulse SIRF design for fMRI runs with even number ID. It starts with 20 s initial blank where the wedges are visible but they are not flickering. It is followed by alternating the upper and lower stimuli with 32 s blank period in between (upper stimulus = single flick in the upper wedge, lower stimulus = single flick in the lower wedge). The alternation starts with the lower stimulus.

on the latter condition [53], as shown in Figure 3.27. All conditions in a SOA run were randomly shuffled.

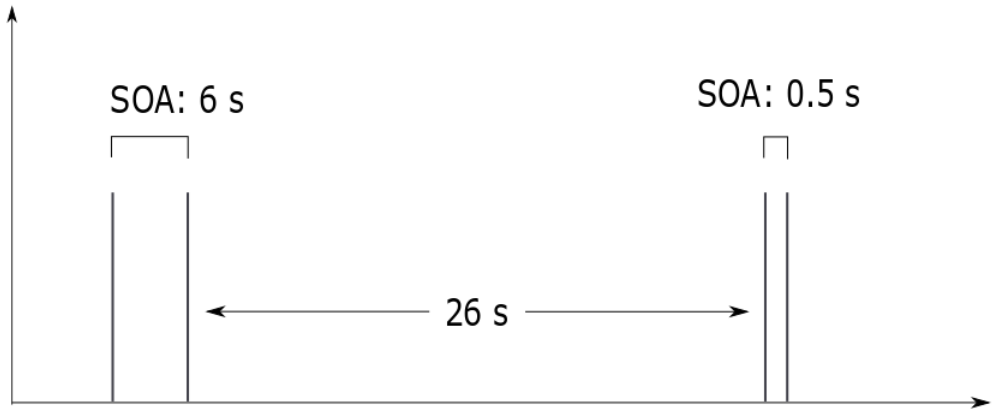

Figure 3.27: SOA Design

Each participant completed SOA scans in two sessions. Each condition (e.g. Upp 0.5 Low) was repeated for 20 times in total, 10 times in each session. 10 repetitions of each condition was completed in 5 SOA scans in each session. Since the experiment had three subjects, we had 60 trials for each condition in total. The number of trials was increased by a factor of two (resulting 120 trials for

each condition in total), since two BOLD responses to a condition were extracted from both left (60 trials) and right hemifields (60 trials) and combined during the data analysis. Each SOA run lasted 316 s including blank periods of 20 s at the start and 10 s at the end. Figure 3.28 shows the SOA run's design.

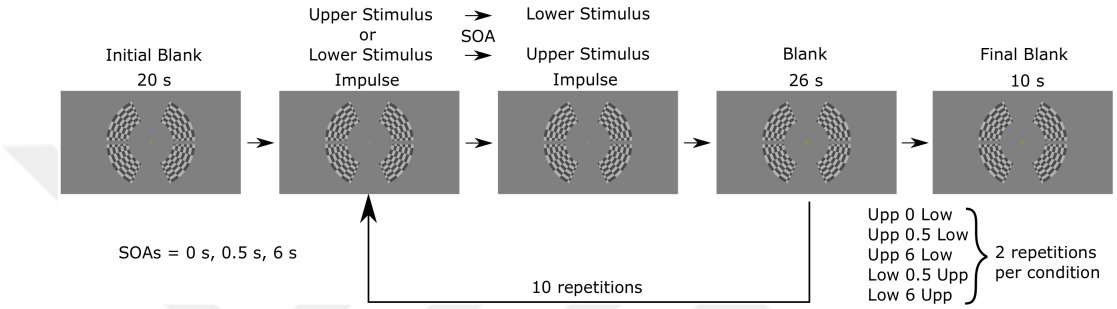

Figure 3.28: Experiment Upper-Lower Impulse SOA Design. It starts with 20 s initial blank followed by a paired stimuli (condition). A paired stimuli consists of a combination of two stimuli (upper and lower) whose onset differences were defined by SOA values. Each condition was tested only once in single SOA run. The conditions were separated by 26 s blank period.

Participants conducted a fixation task during the entire run to maintain their visual gaze on the fixation point at the center of the visual presentation screen. They were asked to respond to the change of the fixation point's color when it became different from red.

3.2.1.4.3 Longer Pulse Experimental SIRF Design

All except the flickering duration are the same with the impulse experimental SIRF design (see section 3.2.1.4.1). Flickering duration is 1 s in the longer pulse SIRF. Figures 3.29 and 3.30 show the longer pulse design of the SIRF run.

3.2.1.4.4 Longer Pulse Experimental SOA Design

All except the flickering duration are the same with the impulse experiment SOA design (see section 3.2.1.4.2). Flickering duration is 1 s in the longer pulse SIRF. Figure 3.31 shows the longer pulse design of the SOA run.

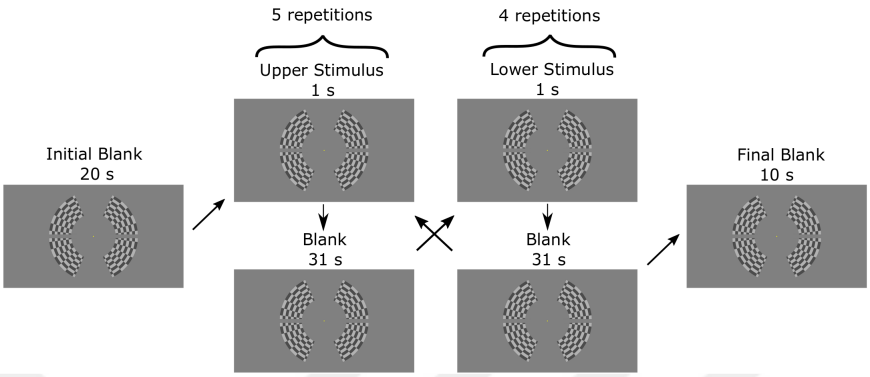

Figure 3.29: Experiment Upper-Lower Longer Pulse SIRF design for fMRI runs with odd number ID. It starts with 20 s initial blank where the wedges are visible but they are not flickering. It is followed by alternating the upper and lower stimuli with 32 s blank period in between (upper stimulus = flickering upper wedge for 1 s, lower stimulus = flickering lower wedge for 1 s). The alternation starts with the upper stimulus.

3.2.1.5 Pilot Functional Localizer Experiments to Determine Design Parameters

The motivation and the procedure were the same with the section 3.1.1.5.

3.2.1.6 V1 ROI Localization

Region of interest (ROIs) in area V1 were identified through the functional localizer scan. It started with an initial blank period of 20 s, followed by flickering the upper wedges (i.e. upper stimulus), a blank period, and flickering the lower wedges (i.e. lower stimulus). Both the upper and lower stimuli lasted for 12 s. They alternated with each other with a blank period of 18 s between each other. In the blank period, the wedges were not flickering but they were rendered on the screen. This sequence was repeated five times in a run. Participants focused on the fixation point at the center of the visual presentation screen during the entire run. Figure 3.32 shows the localizer design of the experiment Upper-Lower.

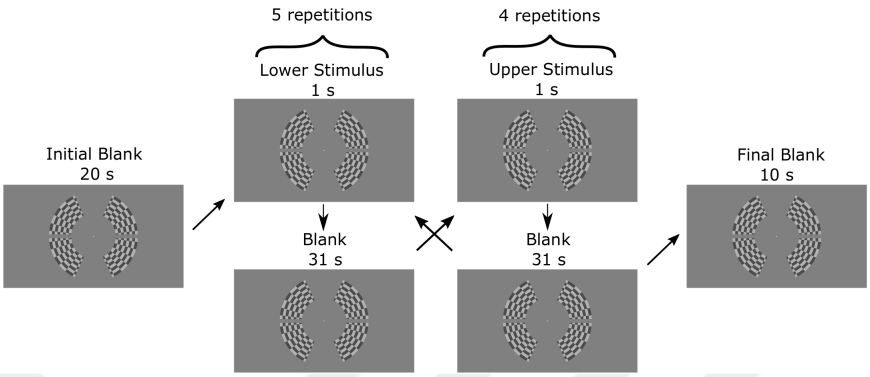

Figure 3.30: Experiment Upper-Lower Longer Pulse SIRF design for fMRI runs with even number ID. It starts with 20 s initial blank where the wedges are visible but they are not flickering. It is followed by alternating the upper and lower stimuli with 32 s blank period in between (upper stimulus = flickering upper wedge for 1 s, lower stimulus = flickering lower wedge for 1 s). The alternation starts with the lower stimulus.

3.2.1.7 BrainVoyager V1 ROI Analysis

The analysis steps were the same with the ones in the experiment Inner-Outer (see section 3.1.1.7).

We followed the same procedure to perform GLM (see section 2.1.6.3). There were three stimuli (i.e., upper, lower and blank stimuli) and two comparisons (i.e., upper vs. blank, lower vs. blank). See section 3.1.1.6 for the detailed description of the localizer protocol. GLM results of a subject is shown in Figure 3.33. As it is seen in Figure 3.33, both upper and lower stimuli have activations in both hemispheres. Therefore, we have two ROIs per stimulus. Upper stimulus leads to activation in ventral parts of V1, while lower stimulus activates dorsal parts of V1.

After the GLM analysis was performed, the activation was projected to the meshes from anatomical-VTC space as shown in Figure 3.34. VOIs (i.e., volumes of interest) were defined for each condition based on the activations of calcarine sulcus on the meshes of both left and right hemispheres. Defined VOIs were Upper VOI in LH, Upper VOI in RH, Lower VOI in LH, and Lower VOI in RH. As an example, Upper VOI in LH was activated by the lower wedge in the right

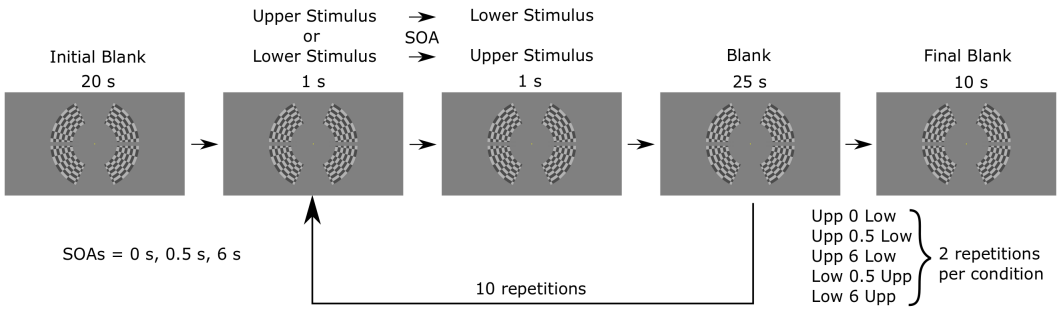

Figure 3.31: Experiment Upper-Lower Longer Pulse SOA Design. It starts with 20 s initial blank followed by a paired stimuli (condition). A paired stimuli consists of a combination of two stimuli (upper and lower) whose onset differences were defined by SOA values. Each condition was tested only once in single SOA run. The conditions were separated by 26 s blank period.

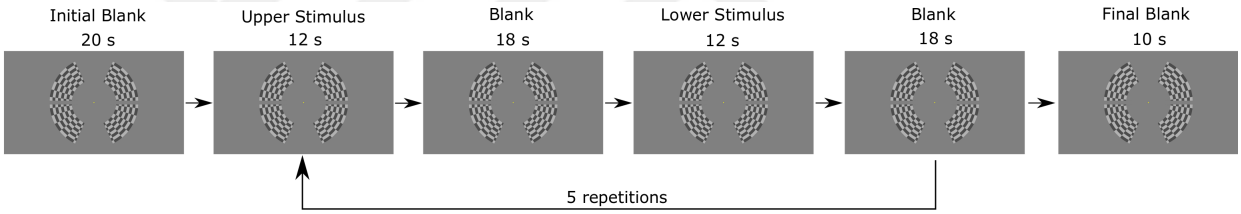

Figure 3.32: Functional Localizer Design

visual field because of the retinotopic organization of V1 [52]. Then the time course data of all the active voxels within the VOI were averaged for each time point and the average data for all the experimental runs (i.e., SIRF and SOA) were extracted for each VOI.

3.2.1.8 Data Visualization

The analysis steps were the same with the ones in the experiment Inner-Outer (see section 3.1.1.8).

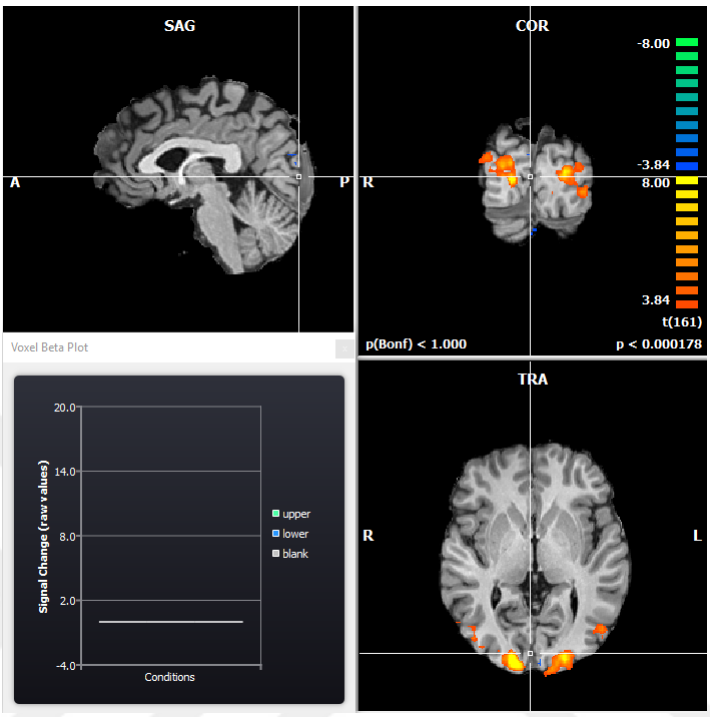

Figure 3.33: GLM activation of the upper stimulus vs. blank stimulus

3.2.1.9 Statistical Analysis

Procedures in the statistical analysis were the same with the experiments 1 and 2 (see section 2.1.8). The only exception was that the the conditions in this experiment (i.e., Upper-Lower) consisted of one spatial configuration (i.e., adjacent spatial locations in the same hemifield along y-axis), whereas the conditions in the experiment 1 consisted of two distinct spatial configurations (i.e., between hemifields, and the same location).

3.2.2 Results

3.2.2.1 Impulse SIRF Results

Figure 3.35 shows SIRF results of the experiment for impulse flickering duration. As expected, we observed positive BOLD responses in Upper and Lower

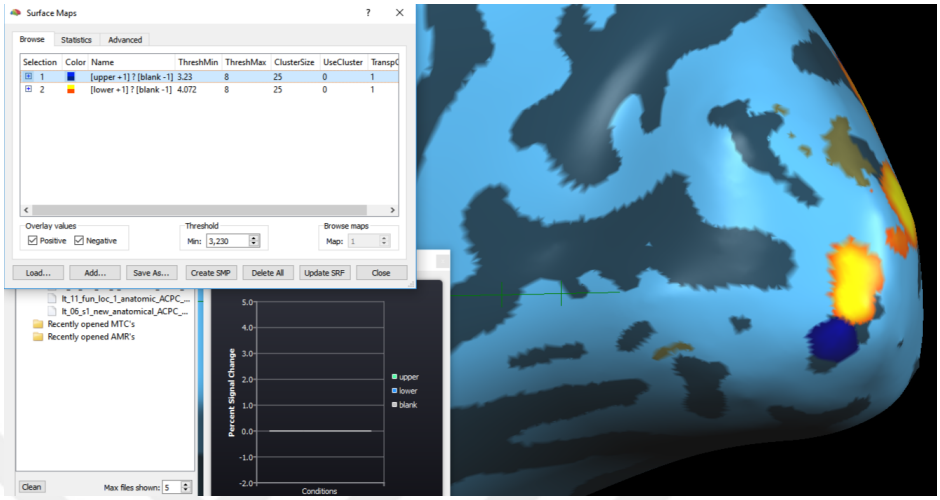

Figure 3.34: Mesh activation Upp-Low RH

ROIs in response to Upper and Lower stimuli, respectively due to the retinotopic organization of V1 [52]. A stimulus located at the upper visual field activates ventral parts of the brain, while a stimulus located at the lower visual field activates dorsal parts of the brain. Therefore, it was surprising that Upper and Lower stimuli also induce positive BOLD responses in Lower and Upper ROIs, respectively (i.e., Upper stimulus in Lower ROI, and Lower stimulus in Upper ROI). However, these positive effects in the surrounding regions are smaller in amplitude than the responses at the center.

3.2.2.2 Impulse SIRF vs. SOA Nonlinearity Comparison

Figures 3.36, 3.37, 3.38, and 3.39 show comparisons between SIRF and SOA results for impulse flickering duration in Upper and Lower ROIs, respectively.

We compared the differences between predicted (from SIRF) and observed (from SOA) results in Figures 3.36, and 3.38 by visual inspection and in Figures 3.37 and 3.39 with the help of the nonlinearity index. Upp 0.5 Lower in Lower ROI had important nonlinearity. In addition, Upp 0 Low and Low 0.5 Upp had small nonlinearities in Lower ROI. Similarly, Upp 0.5 Low and Low 0.5 Upp had small nonlinearities in Upper ROI.

3.2.2.3 Longer Pulse SIRF Results

Figure 3.40 shows SIRF results of the experiment for longer pulse flickering duration. As expected, we observed positive BOLD responses in Upper and Lower ROIs in response to Upper and Lower stimuli, respectively due to the retinotopic organization of V1 [52]. A stimulus located at the upper visual field activates ventral parts of the brain, while a stimulus located at the lower visual field activates dorsal parts of the brain. Therefore, it was surprising that Upper and Lower stimuli also induce positive BOLD responses in Lower and Upper ROIs, respectively (i.e., Upper stimulus in Lower ROI, and Lower stimulus in Upper ROI). However, these positive effects in the surrounding regions were smaller in amplitude than the responses at the center.

3.2.2.4 Longer Pulse SIRF vs. SOA Nonlinearity Comparison

Figures 3.41, 3.42, 3.43, and 3.44 show comparisons between SIRF and SOA results for longer pulse flickering duration in Upper and Lower ROIs, respectively.

We compared the differences between predicted (from SIRF) and observed (from SOA) results in Figures 3.41, and 3.43 by visual inspection, and in Figures 3.42 and 3.44 with the help of the nonlinearity index. Upp 0 Low in both Upper and Lower ROIs had important nonlinearity in post-stimulus undershoot. In addition, Low 0.5 Upp in Lower ROI, Low 6 Upp in Lower ROI, and Low 6 Upp in Upper ROI had small nonlinearities.

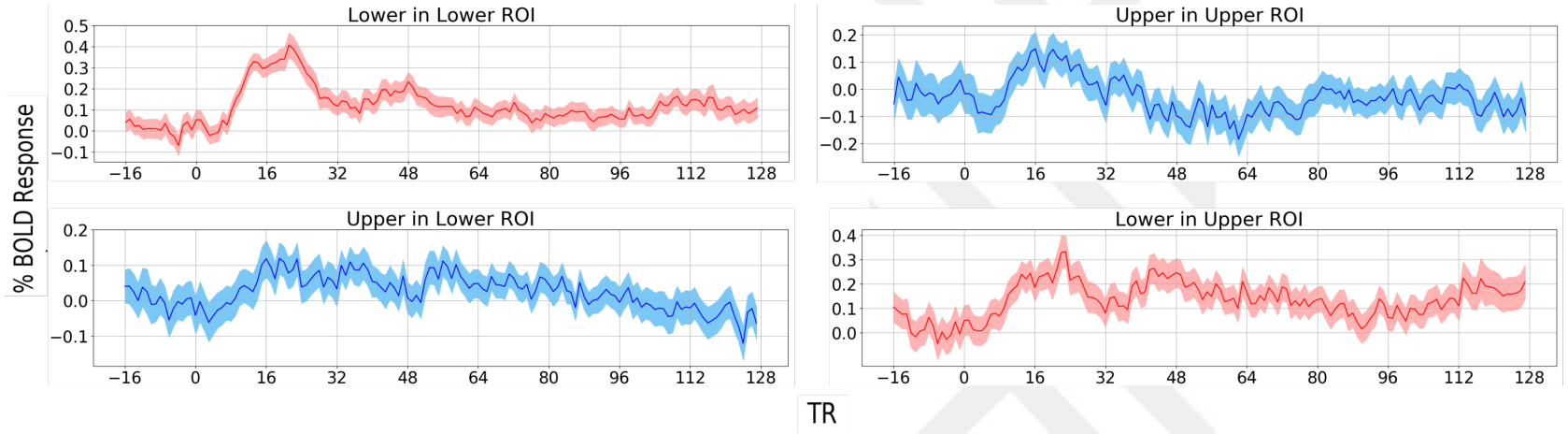

Figure 3.35: BOLD responses to impulse stimulation (Impulse Upp-Low SIRF). Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

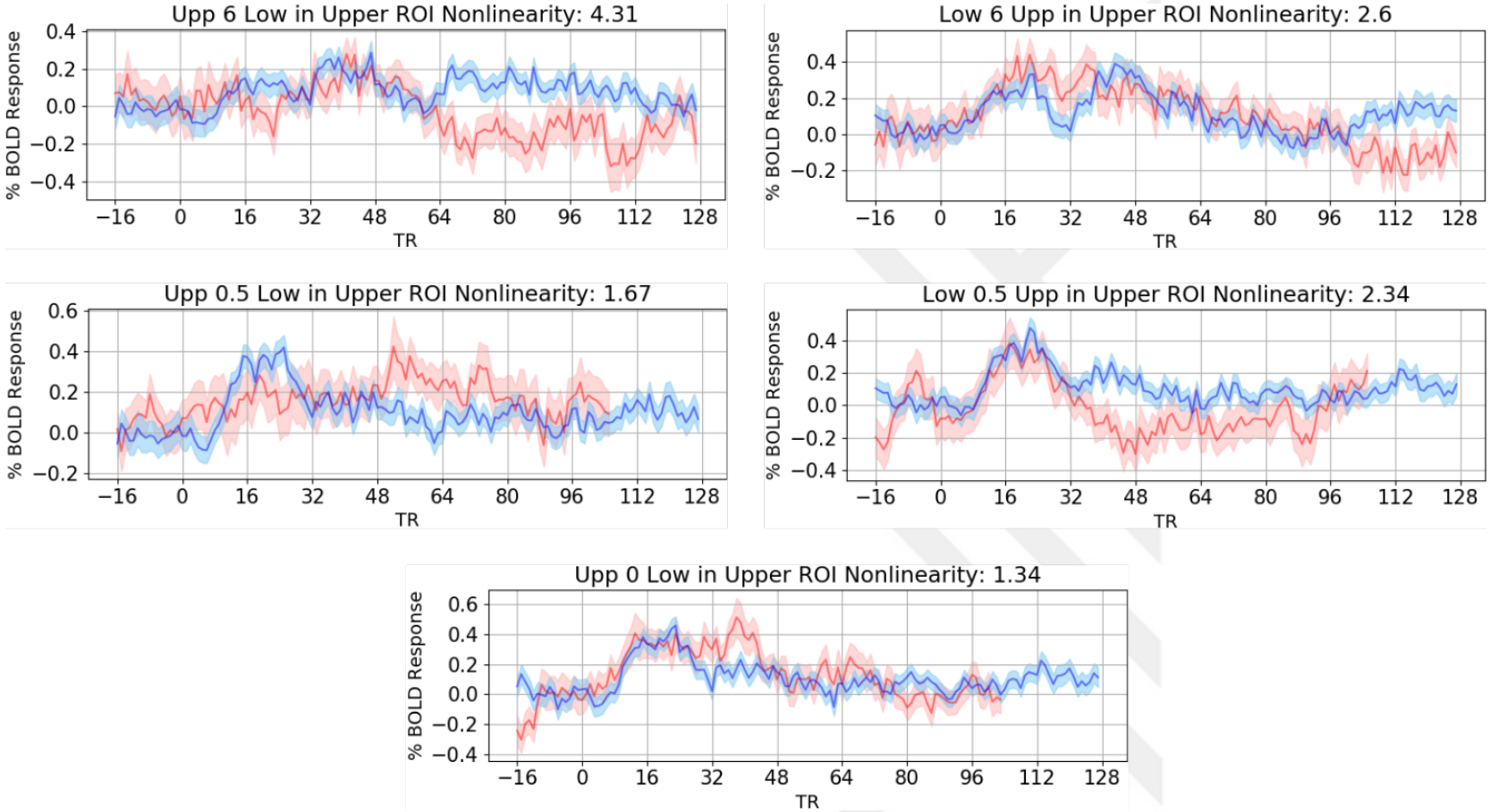

Figure 3.36: Impulse Upp-Low SIRF vs. SOA in Upper ROI. Blue is the predicted response. Red is the observed response. The nonlinearity represents the difference between the predicted and observed responses and was calculated based on the residual (nonlinearity) formula for all TRs. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

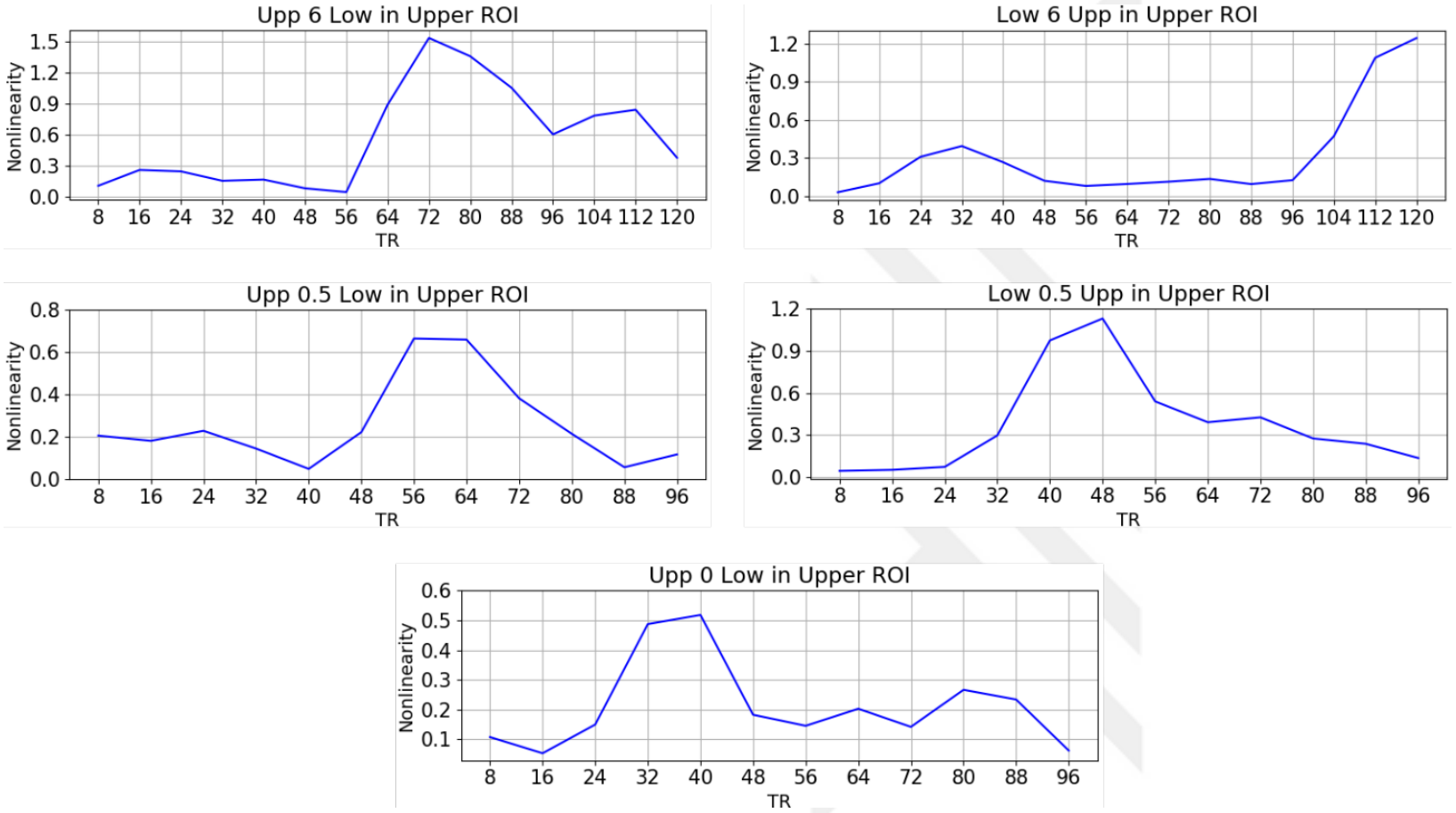

Figure 3.37: Impulse Upp-Low in Upper ROI. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

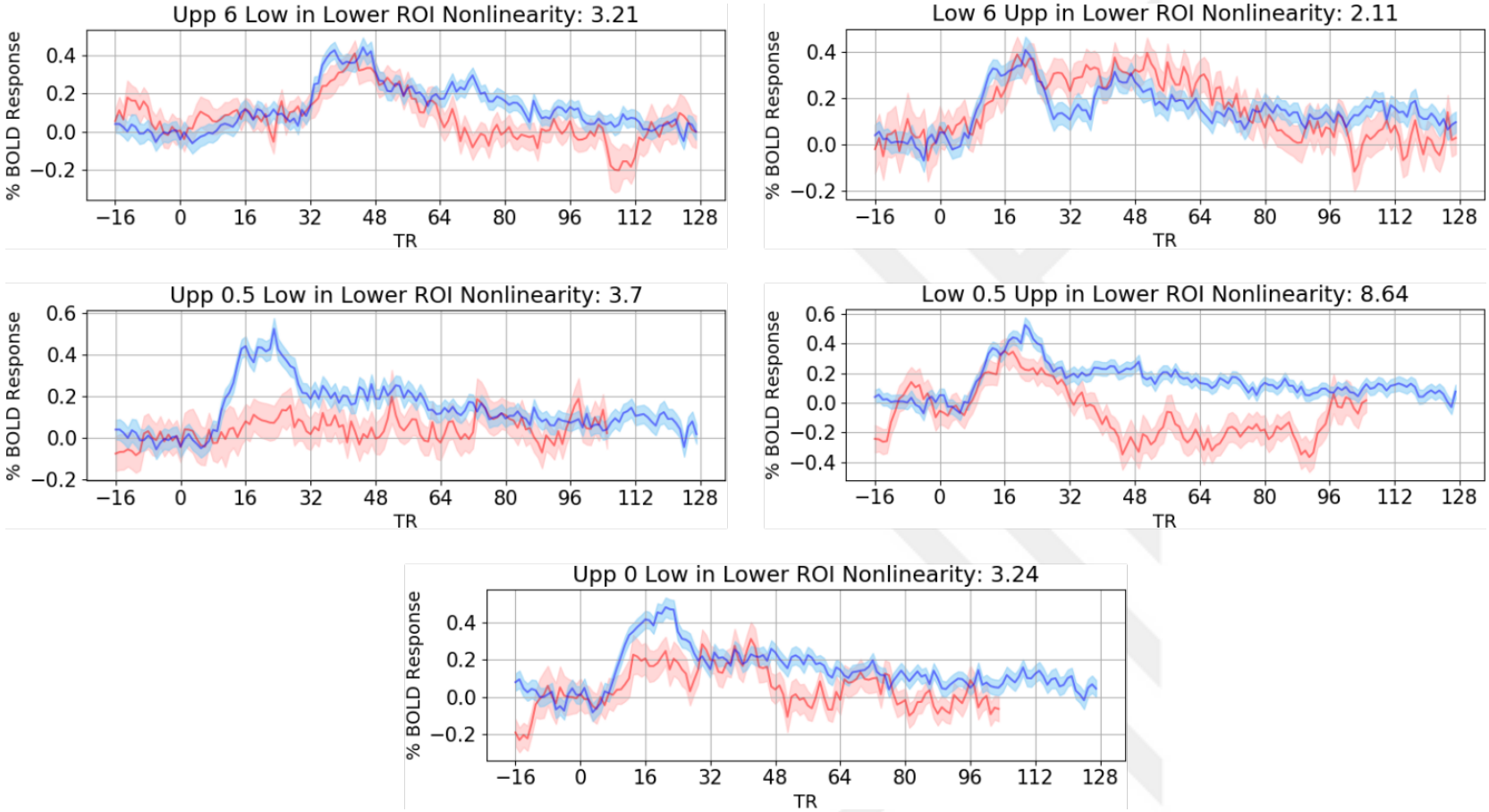

Figure 3.38: Impulse Upp-Low SIRF vs. SOA in Lower ROI. Blue is the predicted response. Red is the observed response. The nonlinearity represents the difference between the predicted and observed responses and was calculated based on the residual (nonlinearity) formula for all TRs. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

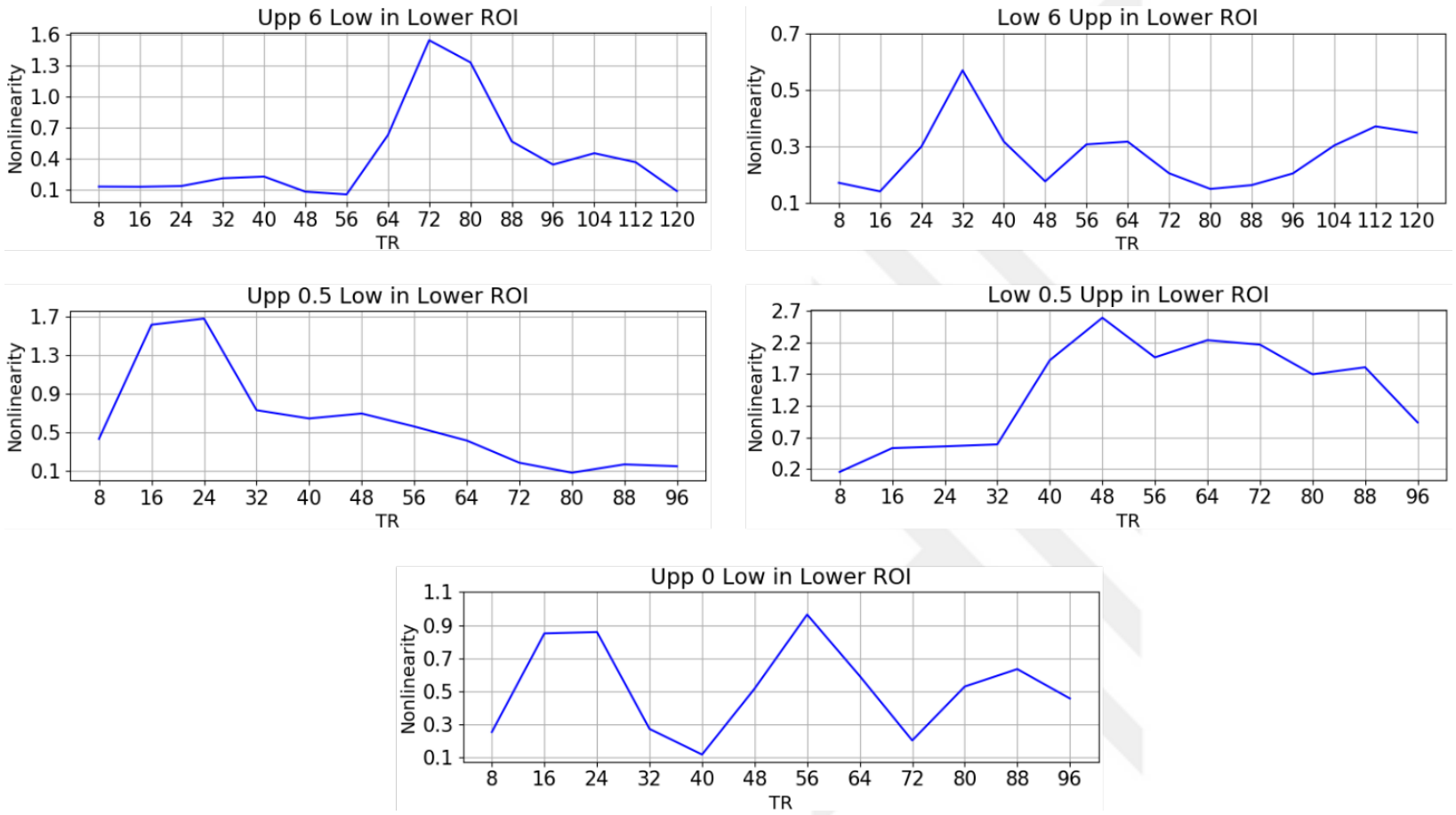

Figure 3.39: Impulse Upp-Low in Lower ROI. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

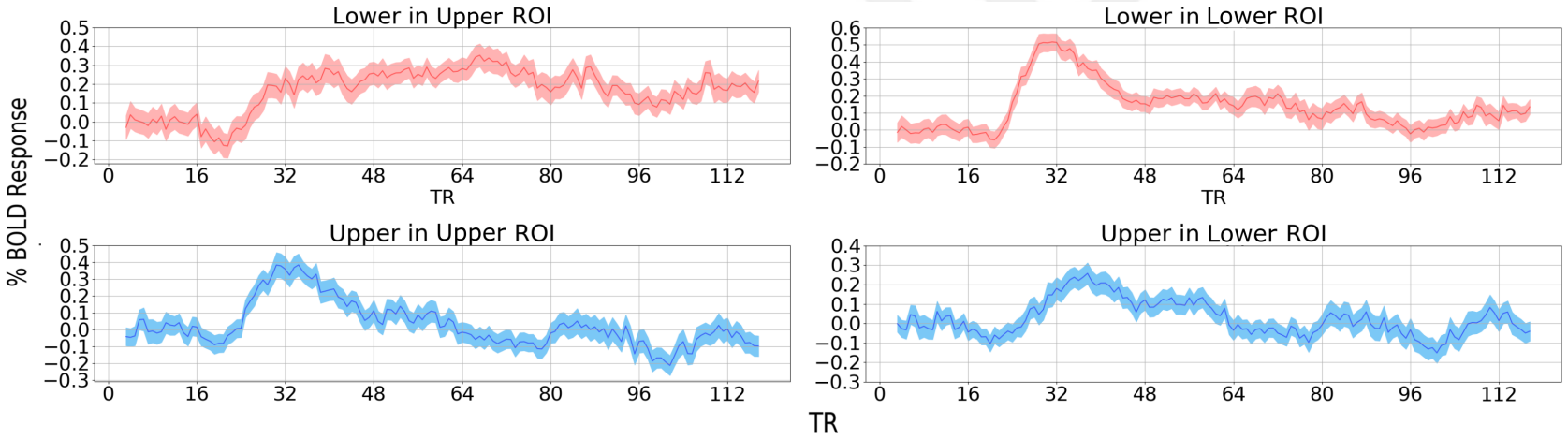

Figure 3.40: BOLD responses to 1 s stimulation (Longer Pulse Upp-Low SIRF). Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

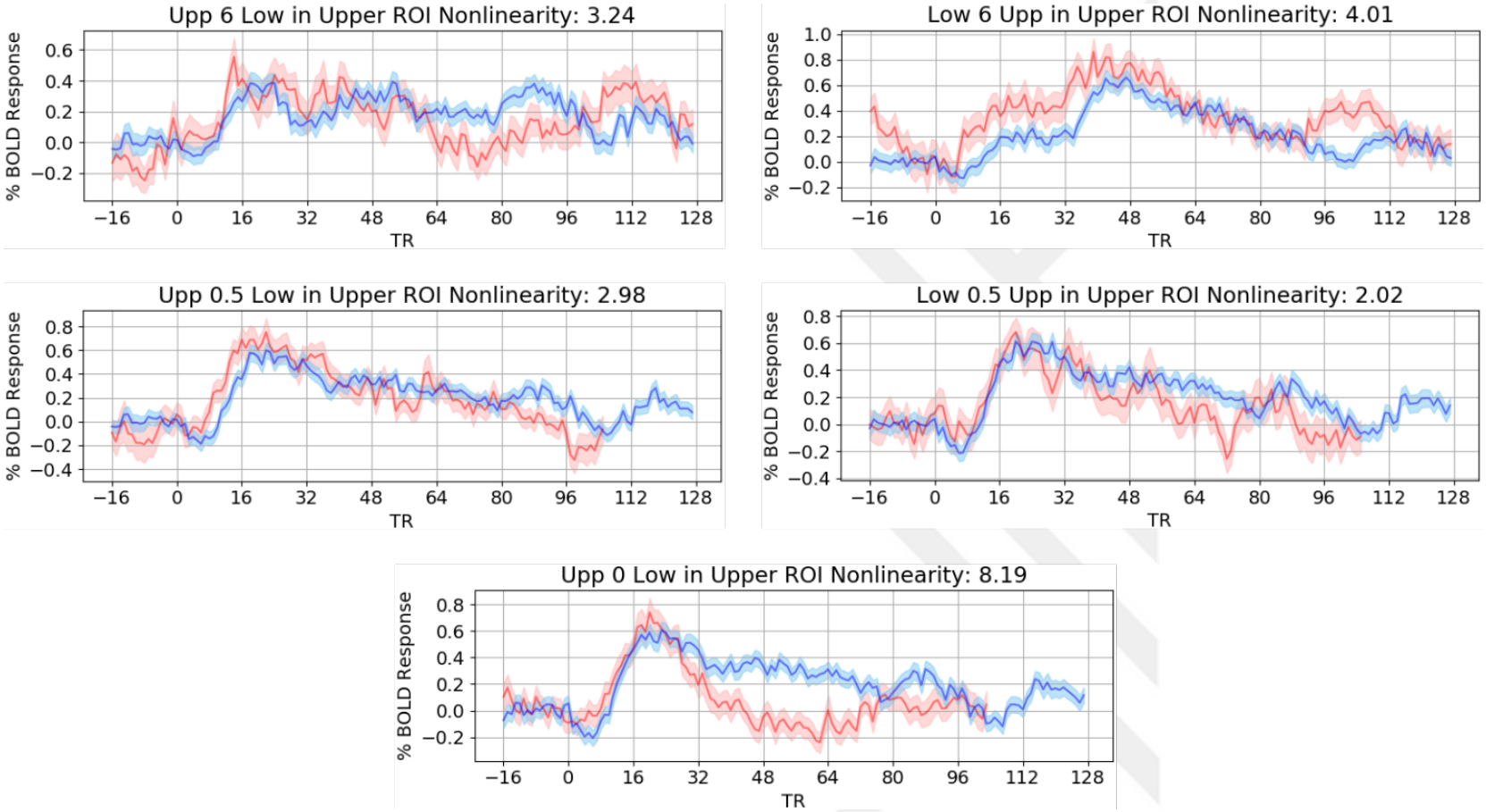

Figure 3.41: Longer Pulse Upp-Low SIRF vs. SOA in Upper ROI. Blue is the predicted response. Red is the observed response. The nonlinearity represents the difference between the predicted and observed responses and was calculated based on the residual formula for all TRs. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

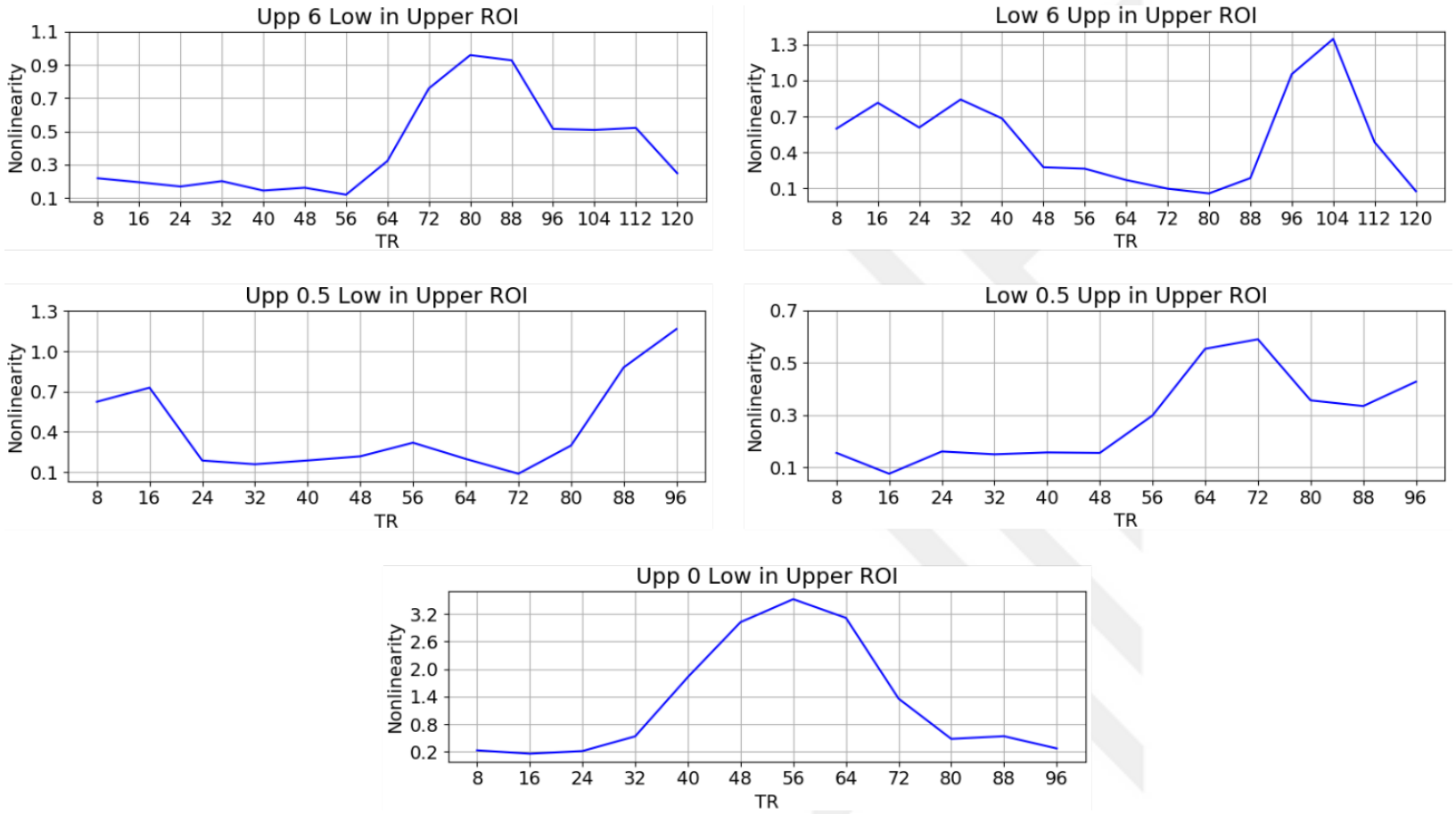

Figure 3.42: Longer Pulse Upp-Low in Upper ROI. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

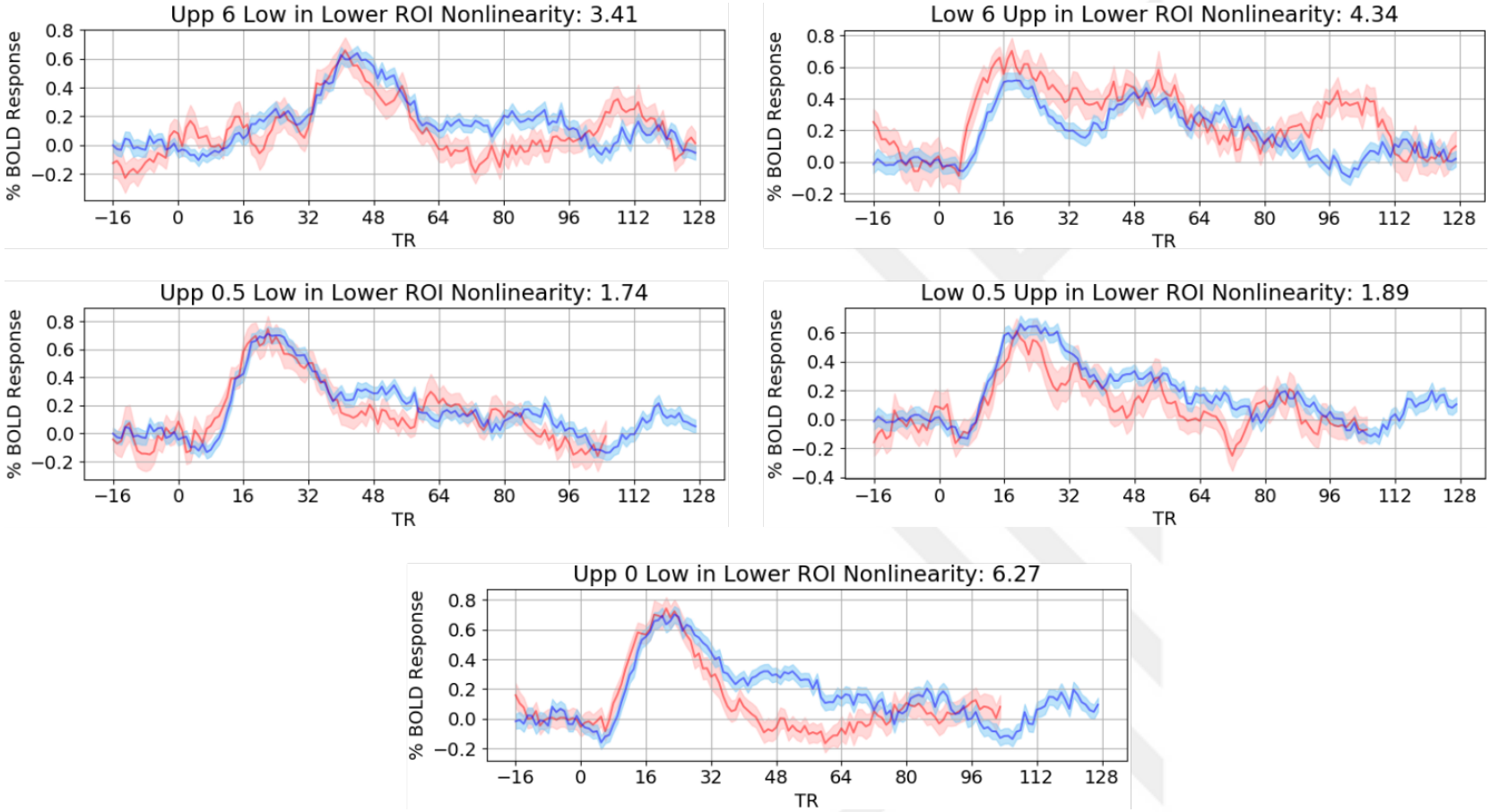

Figure 3.43: Longer Pulse Upp-Low SIRF vs. SOA in Lower ROI. Blue is the predicted response. Red is the observed response. The nonlinearity represents the difference between the predicted and observed responses and was calculated based on the residual formula for all TRs. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

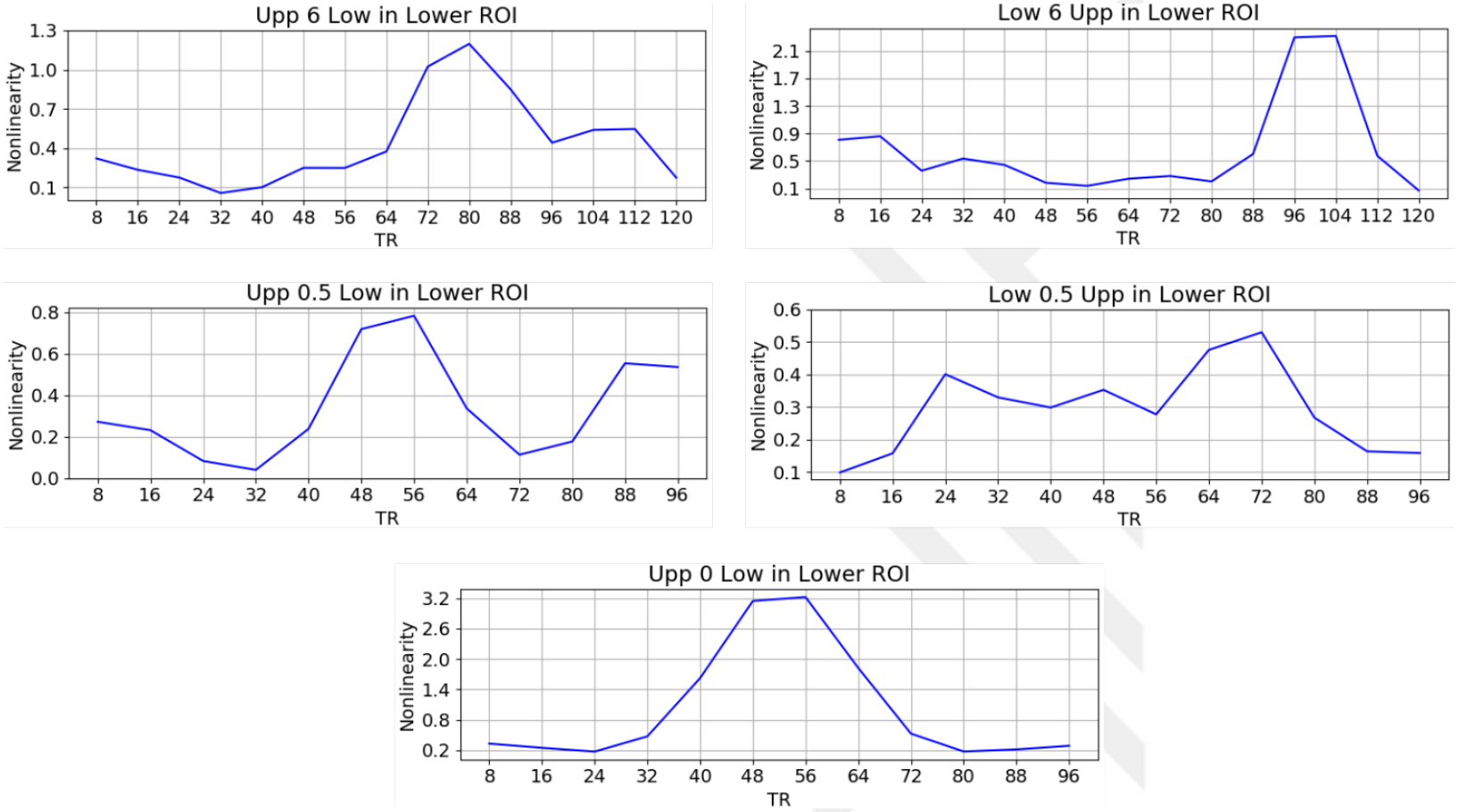

Figure 3.44: Longer Pulse Upp-Low in Lower ROI. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

3.2.2.5 Statistical Results

We performed 3-way ANOVA and Tukey's post-hoc test. The dependent variable was the nonlinearity index and the independent variables were TR, SOA, and flickering duration. Statistical significance between levels of an independent variable were found in all of the independent variables ($F_{TR} = 4.1, p < 0.001$), $F_{SOA} = 9.7, p < 0.001$, $F_{FlickDur} = 8.6, p < 0.005$). Besides, there were statistically significant two-way interactions between SOA and TR (F = 3.9, p $<$ 0.001), between SOA and flickering duration (F = 25, p $<$ 0.001), and between TR and flickering duration (F = 2.3, p $<$ 0.01). In addition, there was a statistically significant three-way interaction between TR, SOA, and flickering duration (F = 3.8, p $<$ 0.001).

3.2.2.5.1 Flickering Duration Comparison

We grouped all conditions within a spatial group (e.g., vertically adjacent spatial locations in the same hemifield) by their flickering durations (see section 2.1.8.1 for more details). Figure 3.45 compares the flickering durations (impulse and longer pulse) in the conditions of adjacent spatial locations in the same hemifield along y-axis. The nonlinearity in the longer pulse conditions is statistically bigger than the impulse conditions (p $<$ 0.01).

3.2.2.5.2 SOA Duration Comparison

We grouped all conditions within a spatial group (e.g., vertically adjacent spatial locations in the same hemifield along y-axis) by their SOA durations (see section 2.1.8.1 for more details). Figure 3.46 compares the SOA durations (0 s, 0.5 s, and 6 s) in the conditions of vertically adjacent spatial locations in the same hemifield along y-axis. Nonlinearity in SOA 0 is significantly bigger than nonlinearity SOA 0.5 (p $<$ 0.005) and nonlinearity in SOA 6 (p $<$ 0.001). However, no significant difference between SOA 0.5 and SOA 6 was observed although nonlinearity in SOA 0.5 is slightly bigger than nonlinearity SOA 6. Therefore, as it was the case

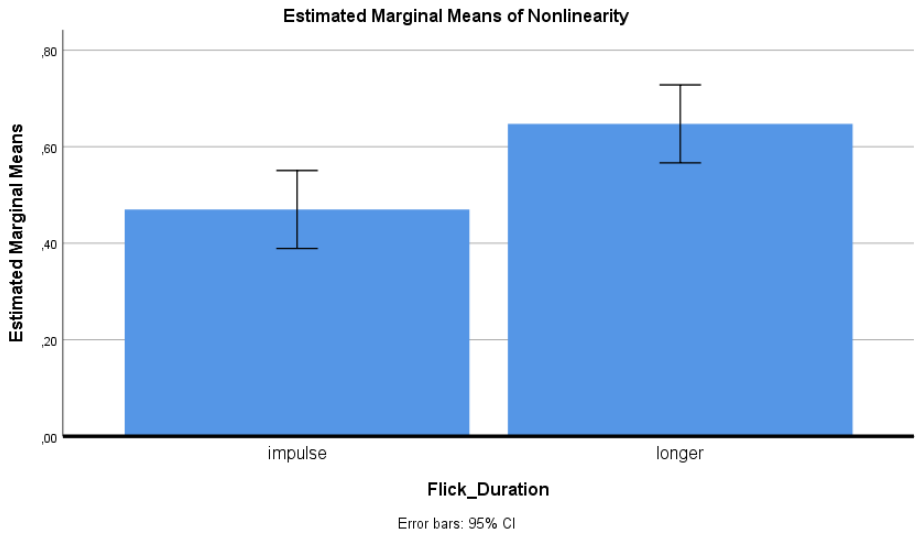

Figure 3.45: Nonlinearity as a variable of flickering duration between vertically adjacent visual fields in the same hemifield. The difference between impulse and longer pulse is statistically significant ($p < 0.01$).

in the experiment Inner-Outer, the nonlinearity increased as the SOA duration decreased.

3.2.3 Intermediate Discussion

3.2.3.1 Impulse SIRF

As expected, we saw positive responses for Upper stimulus in Upper ROI and Lower stimulus in Lower ROI due to the retinotopic organization of brain [52]. However, we also saw weaker but still positive responses in Upper stimulus in Lower ROI and Lower stimulus in Upper ROI. Possible explanations for the positive responses in the surrounding regions was mentioned in the section 3.1.3.1.

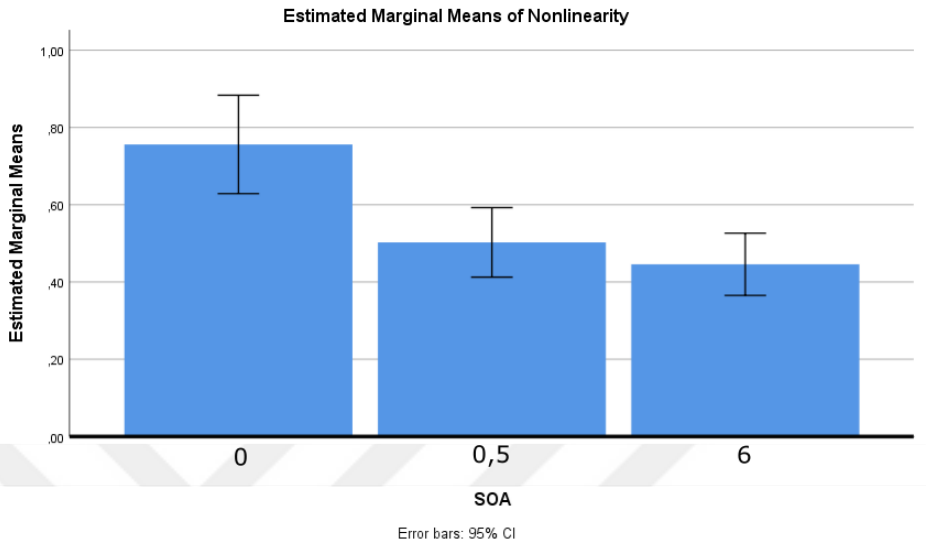

Figure 3.46: Nonlinearity as a variable of SOA duration between vertically adjacent visual fields in the same hemifield along y-axis. The difference between SOA 0 and SOA 0.5 is statistically significant ($p < 0.005$). The difference between SOA 0 and SOA 6 is statistically significant ($p < 0.001$). The difference between SOA 0.5 and SOA 6 is not significant.

3.2.3.2 Impulse SIRF vs. SOA Nonlinearity Comparison

Upp 0.5 Low in Lower ROI was the most nonlinear condition. In addition, Upp 0 Low in Lower ROI, Low 0.5 Upp in Lower ROI, Upp 0.5 Low in Upper ROI and Low 0.5 Upp in Upper ROI had small nonlinearities. Therefore, the results are very similar to the longer pulse results in the experiment Inner-Outer. No substantial nonlinearity was detected except Upp 0.5 Low in Lower ROI.

The same mechanism (i.e., mutual suppression) can be the underlying reasons for the emerging nonlinearities (see section 3.1.3.2 for more details).

3.2.3.3 Longer Pulse SIRF

As expected, we saw positive responses for Upper stimulus in Upper ROI and Lower stimulus in Lower ROI due to the retinotopic organization of brain [52]. However, we also saw smaller but still positive responses in Upper stimulus in

Lower ROI and Lower stimulus in Upper ROI. Positive activations in the surrounding regions are more severe than they were in the impulse results of the experiment. This could be due to the fact that stimulus duration (i.e., strength of stimulus) was longer in the longer pulse than impulse flickering duration because stronger stimuli typically evoke stronger BOLD response [11, 34]. Possible explanations for the positive responses in the surrounding regions was mentioned in the section 3.1.3.1.

3.2.3.4 Longer Pulse SIRF vs. SOA Nonlinearity Comparison

All conditions in both Upper and Lower ROIs (except the nonlinearity in Upp 0 Low in Upper and Lower ROIs) had small nonlinearities. Upp 0 Low in Upper and Lower ROIs had nonlinearity in its post-stimulus undershoot. [57] found that post-stimulus undershoot can be neuronal in origin. It is correlated with a signal in EEG that is associated with the cortical inhibition [57]. Post-stimulus undershoot also correlates with cerebral metabolic rate of oxygen (i.e., CMRO2) [57]. An increase in CMRO2 accompanies with a larger increase in CBF, resulting positive BOLD response [57]. If cortical inhibition takes place, CMRO2 decreases which results in post-stimulus undershoot [57]. The nonlinearity in Upp 0 Low in Upper and Lower ROIs may represent the existence of a cortical inhibition in Upp 0 Low. Therefore, the same mechanism (i.e., mutual suppression) can be the underlying reasons for the emerging nonlinearities (see section 3.1.3.2 for more details).

3.2.3.5 Impulse SIRF vs. Longer Pulse SIRF

Main (i.e., Upper stimulus Upper ROI, Lower stimulus in Lower ROI) and surrounding activations (i.e., Upper stimulus in Lower ROI, Lower stimulus in Upper ROI) in longer pulse are very roughly two times bigger in amplitude than the main and surrounding activations in impulse. This could be due to the fact that stimulus duration (i.e., strength of stimulus) was longer in the longer pulse than it was in the impulse because stronger stimuli typically evoke stronger BOLD

response [11, 34]. However, if the BOLD response holds the scaling property, longer pulse responses would have been much bigger in amplitude than twice the impulse responses since the longer pulse duration is much bigger than twice the impulse duration. Therefore, there is nonlinearity of BOLD response with respect to stimulus duration.

Table 3.2: Amplitudes of main and surrounding activations in Upper-Lower SIRF

Duration	**Main**	**Surrounding**	**ROI**
Impulse	0.4	0.1	Lower ROI
Impulse	0.15	0.3	Upper ROI
Longer	0.5	0.25	Lower ROI
Longer	0.4	0.3	Upper ROI

3.2.3.6 Flickering Duration Comparison

Figures 3.36, 3.38, 3.41, and 3.43 shows impulse are more nonlinear especially in Lower ROI than longer pulse if the figures are visually judged. In addition, the number of impulse conditions are bigger than the number of longer pulse conditions. From this perspective, the results are similar to the experiment Inner-Outer results. Therefore, the same mechanisms may be involved (see section 3.1.3.6 for more details). However, the quantitative result (see Figure 3.45) shows that the nonlinearity in longer pulse is significantly bigger than nonlinearity in impulse ($p < 0.005$). As it was the case in the experiment Inner-Outer (see section 3.1.3.6), there seems to be a mismatch between visually judgment and quantitative results. The possible reasons regarding the mismatch were explained in section 3.1.3.6.

3.2.3.7 SOA Duration Comparison

There were nonlinear conditions in both flickering durations. Upp 0.5 Low and Low 0.5 Upp in Upper and Lower ROIs and Upp 0 Low in Upper ROI were the nonlinear conditions in impulse flickering duration, while Upp 0 Low in Upper and

Lower ROIs were nonlinear in longer pulse flickering duration. Both impulse and longer pulse results show that there are nonlinearities at shorter SOAs (0 s and 0.5 s). In fact, Figure 3.46 shows that, in both impulse and longer pulse conditions, the nonlinearity in SOA 0 is significantly bigger than the nonlinearity SOA 0.5 and the nonlinearity in SOA 0.5 is bigger than the nonlinearity in SOA 6, although the difference between S0A 0.5 and SOA 6 is not significant. Nevertheless, one can conclude that the nonlinearity increases as the SOA duration decreases, which is consistent with the studies in the literature (see section 1.1.3).

Chapter 4

Comparisons of The Interactions with respect to Temporal Duration, And Spatial Distance

In this chapter, we analyzed the three experiments together.

4.1 Statistical Results

We performed 4-way ANOVA and Tukey's post-hoc test. The dependent variable was the nonlinearity index and the independent variables were TR, SOA, flickering duration, and spatial configuration. Statistical significance were found in all of the independent variables ($F_{TR} = 4.5, p < 0.001$), $F_{SOA} = 45.9, p < 0.001$, $F_{space} = 46.7, p < 0.001$, $F_{FlickDur} = 3.9, p < 0.05$). Besides, all two-way, three-way and four-way interactions were significant ($p < 0.001$).

4.1.1 Spatial Configuration

Figure 4.1 shows nonlinearity differences as a variable of spatial distance (i.e., the distance between the two wedges stimuli). The experiments had four different spatial configurations: between hemifields, vertically adjacent locations in the same hemifield, horizontally adjacent locations in the same hemifield, and the same location. The spatial distance between wedges in the same location is the least because wedges are located at the same location. Spatial distance in the configuration of adjacent locations in the same hemifield is bigger than the spatial distance of same location because wedges are located at nearby locations in the same hemifield. On the other hand, between hemifields is the spatial configuration in which the distance between the stimuli is the biggest because the wedges are located at separate hemifields. Therefore, spatial distance increases from the same location to the between hemifields.

Figure 4.1 shows that nonlinearity increases as the spatial distance between the wedges decreases. For example, nonlinearity in same location is significantly bigger than nonlinearity between hemifield ($p < 0.001$). Likewise, nonlinearities in horizontally and vertically adjacent locations are significantly bigger than nonlinearity between hemifield ($p < 0.001$, $p < 0.005$). Surprisingly, nonlinearity in horizontally adjacent location is also significantly bigger than nonlinearity in vertically adjacent location, although their spatial distances are roughly equal ($p < 0.001$).

We separately analyzed the impulse and longer pulse experiments as well. Both impulse and longer pulse experiments show the similar results, which are illustrated in Figures 4.2 and 4.3.

4.1.1.1 Intermediate Discussion

Figure 4.1 showed that the nonlinearity increased as the spatial distance decreased. This is expected because two activated brain regions start to get closer to

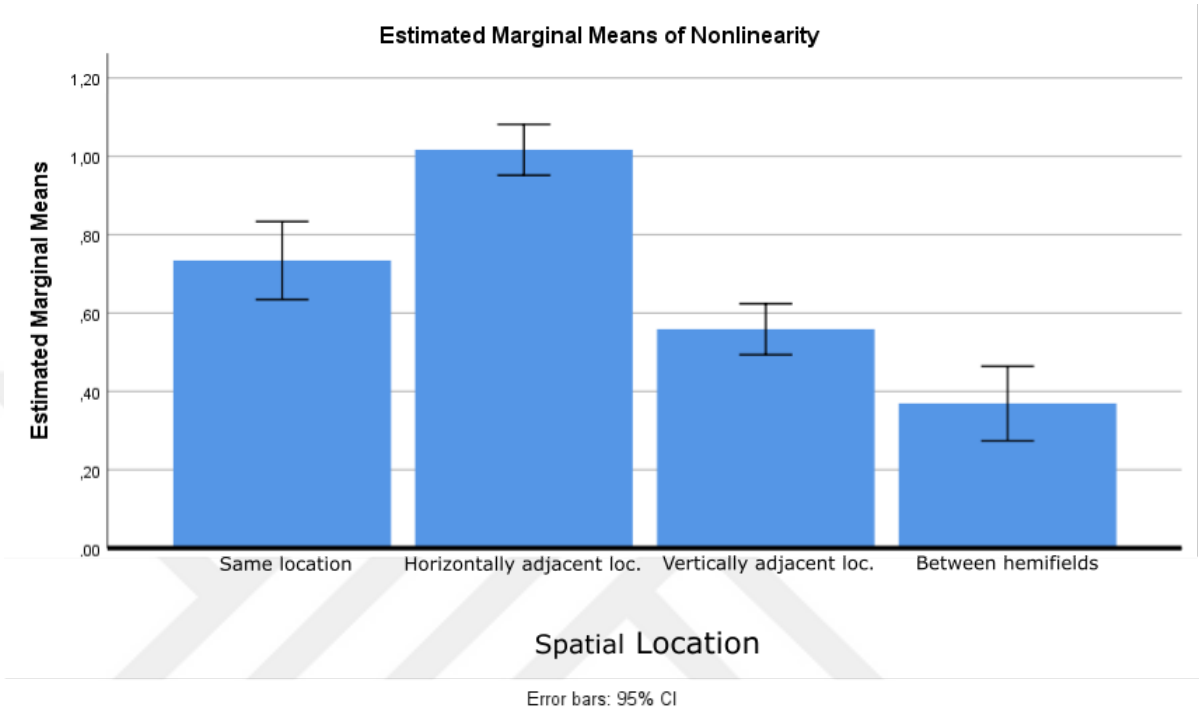

Figure 4.1: Nonlinearity with respect to spatial distance in impulse and longer pulse flickering. The difference between same location and between hemifields is statistically significant ($p < 0.001$). The difference between horizontally adjacent location and between hemifields is statistically significant ($p < 0.001$). The difference between vertically adjacent location and between hemifields is statistically significant ($p < 0.005$). The difference between same location and vertically adjacent location is statistically significant ($p < 0.005$). The difference between same location and horizontally adjacent location is statistically significant ($p < 0.005$).

each other as the spatial distance between the stimuli decreases. Spatially closer brain regions sharing the common vasculature structures gives rise to several inhibitory/facilitatory mechanisms such as refractory effect of vascular and neuronal responses, surround inhibition/facilitation, point spread function, and mutual suppression. Since point spread function, and surround inhibition/facilitation are the mechanisms that can occur in both SIRF and SOA results, they will not result in any deviation between SIRF and SOA results. On the contrary, mutual suppression and vascular and neuronal refractory effects may occur in SOA results but not in SIRF results. Since these two mechanisms have inhibitory effects, they may result in nonlinearities (i.e., deviations) between predicted and

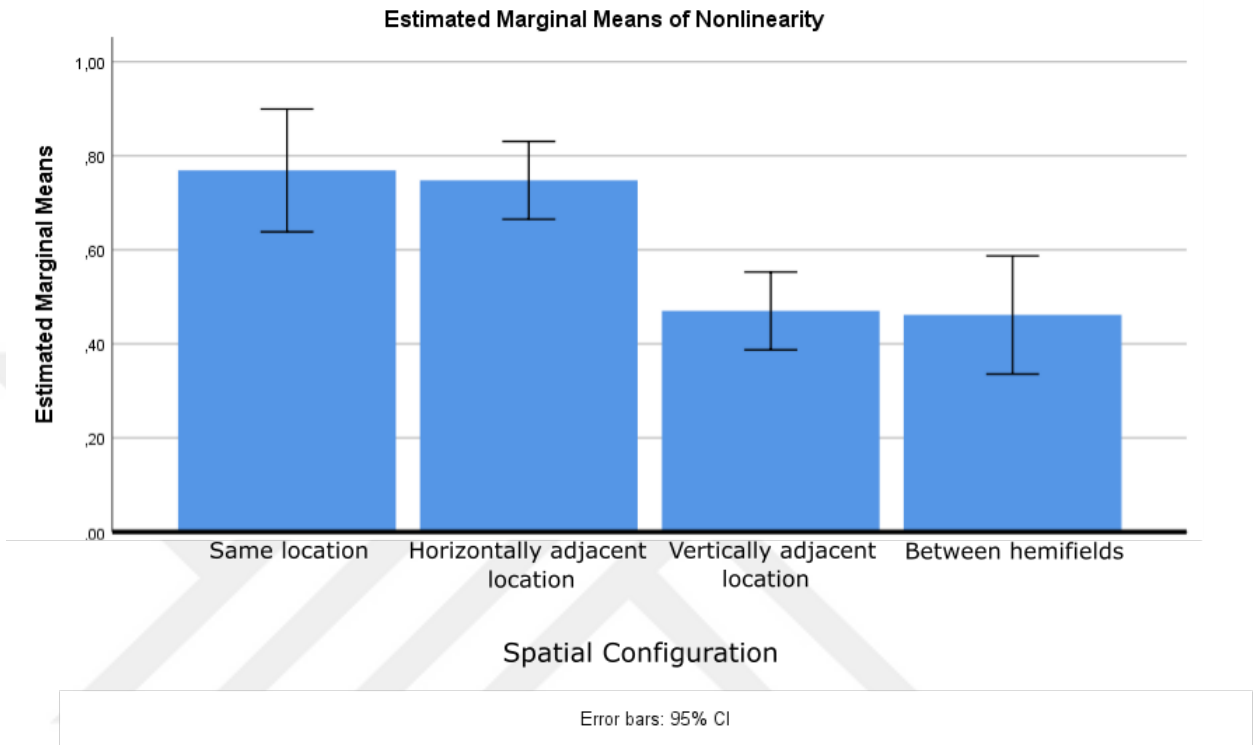

Figure 4.2: Nonlinearity with respect to spatial distance in impulse flickering. Nonlinearities in same location and horizontally adjacent location are significantly bigger than vertically adjacent location and between hemifields ($p < 0.001$). No significant difference was found between same location and horizontally adjacent location, and between vertically adjacent location and between hemifields.

observed responses. The strength of the mechanisms increased as the spatial distance decreased since they started to share the common vasculature structure. Besides, it seems that nonlinearity is not only related to spatial distance but also spatial configuration. For example, the experiment Inner-Outer have higher nonlinearities than the experiment Upper-Lower, although they share the same spatial distance. This might implies that suppressive mechanisms are stronger in Inner-Outer configuration than it is in Upper-Lower configuration. We also showed that neuronal modulations between hemifields through interhemispheric connections may also play a role in cortical inhibition.

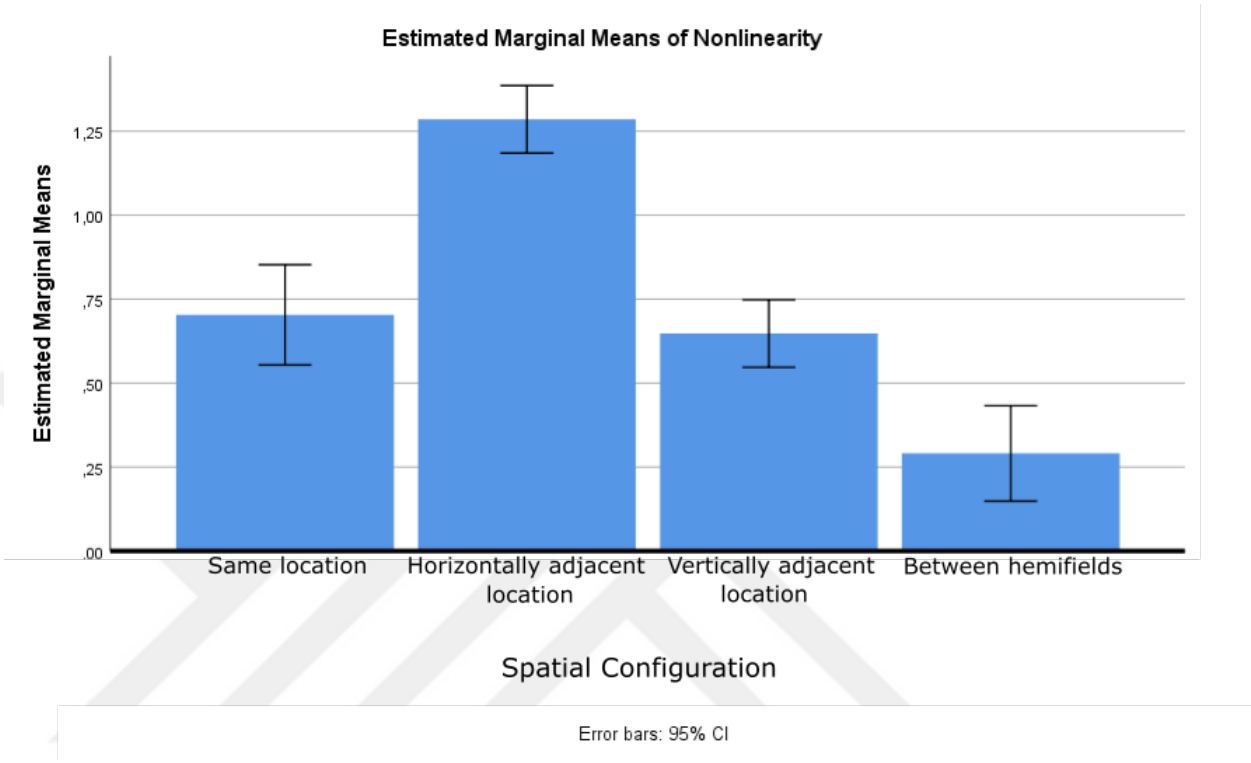

Figure 4.3: Nonlinearity with respect to spatial distance in longer pulse flickering. Nonlinearity between hemifields is statistically lower than the other spatial configurations ($p < 0.001$).

4.1.2 Temporal Duration

Figure 4.4 shows nonlinearity differences between different SOAs (0 s, 0.5 s, 1.5 s, 6 s). Both SOA 0 and SOA 6 groups include impulse and longer pulse conditions. However, SOA 0.5 includes impulse, and SOA 1.5 includes longer pulse conditions only. To compare all SOA groups equally, we grouped SOA 0.5 and SOA 1.5 and illustrated as the SOA 0.5 - 1.5 s group in Figure 4.4 so that the new group includes both impulse and longer pulse conditions together. Figure 4.4 shows that nonlinearity decreases as SOA increases. For example, nonlinearity in SOA 0 is significantly higher than nonlinearity in SOA 0.5 - 1.5 ($p < 0.05$). Likewise, nonlinearity in SOA 0.5 - 1.5 is significantly higher than nonlinearity in SOA 6 ($p < 0.001$).

We separately analyzed the impulse and longer pulse experiments as well.

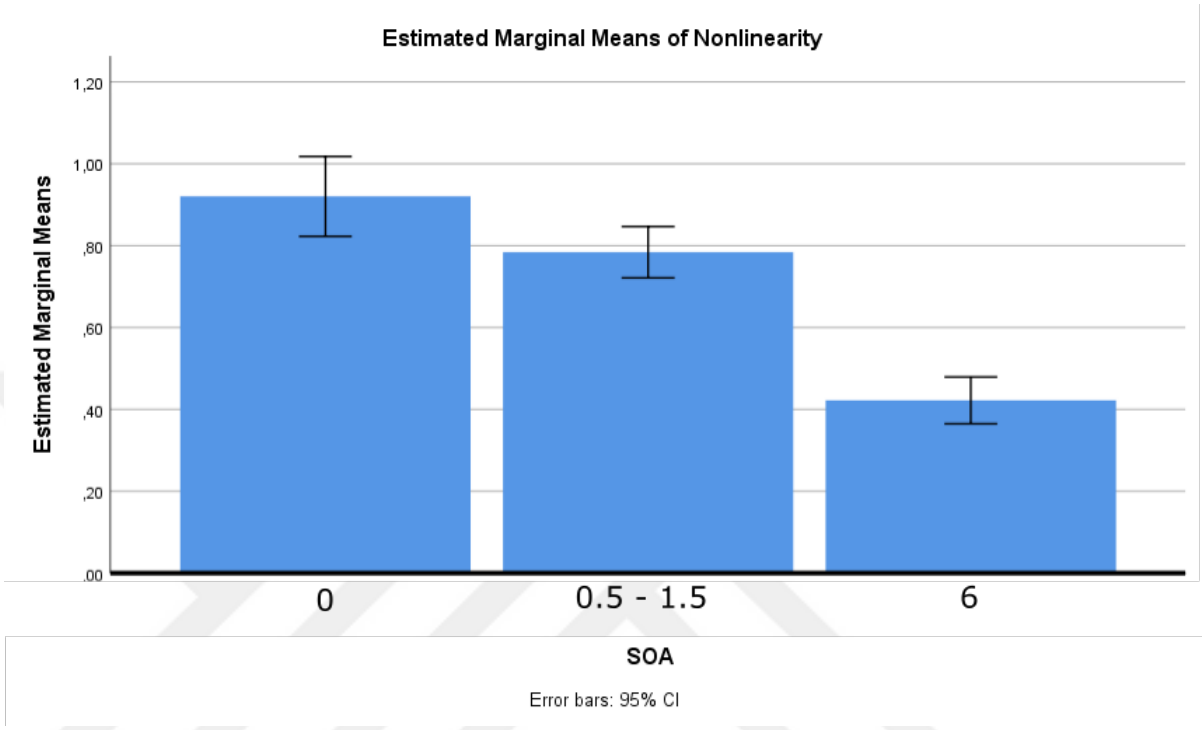

Figure 4.4: Nonlinearity with respect to temporal duration (SOA) in impulse and longer pulse flickering. The difference between SOA 0 and SOA 0.5 - 1.5 is statistically significant ($p < 0.05$). The difference between SOA 0 and SOA 6 is statistically significant ($p < 0.001$). The difference between SOA 0.5 - 1.5 and SOA 6 is statistically significant ($p < 0.001$).

Both impulse and longer pulse experiments show the similar results, which are illustrated in Figures 4.5 and 4.6.

4.1.2.1 Intermediate Discussion

The results summarize that shorter SOAs caused higher nonlinearities. Many studies showed that nonlinearity exists in V1 due to neuronal or vascular refractory effects and mutual suppression when two visual stimuli are close in time to each other. The strength of these inhibitory effects decreases as the SOA duration increases (see section 1.1.3). We also observed the similar pattern in spatial configuration (see section 4.1.1).

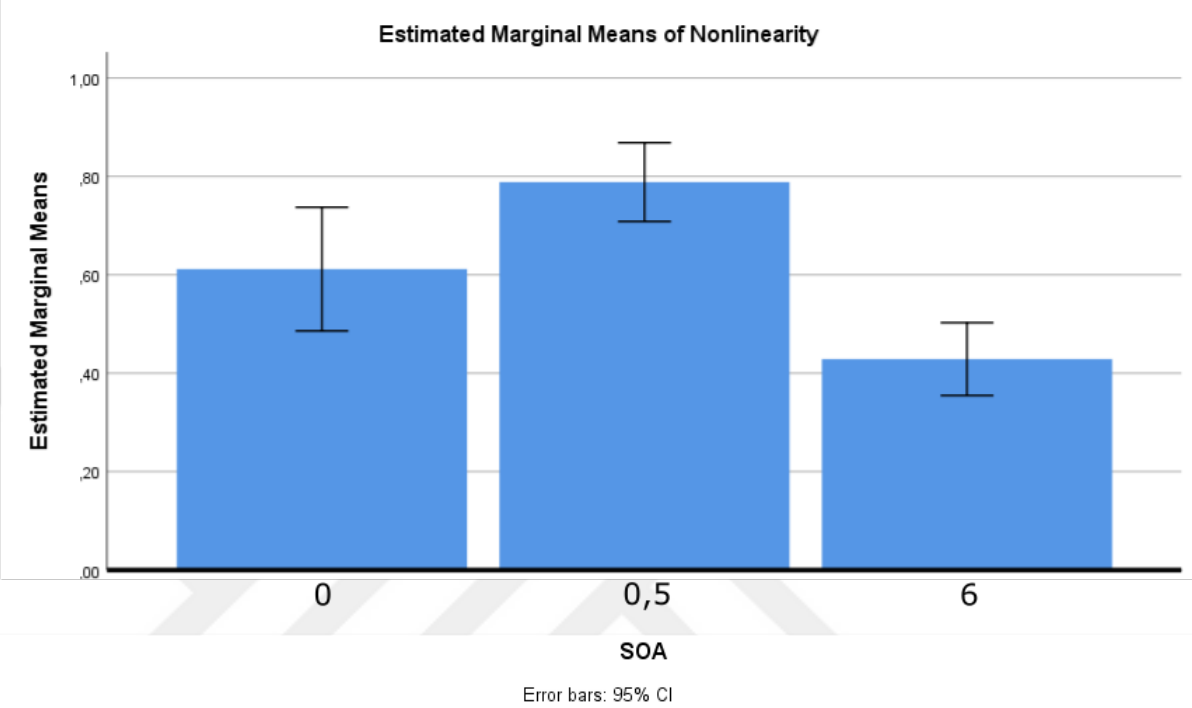

Figure 4.5: Nonlinearity with respect to temporal duration (SOA) in impulse flickering. Nonlinearity in SOA 6 is significantly lower than nonlinearities in SOA 0, 0.5, and 1.5 ($p < 0.001$).

4.1.3 Flickering Duration

Figure 4.7 shows that nonlinearity in longer pulse flickering duration is significantly higher than nonlinearity in impulse flickering duration ($p < 0.005$).

4.1.3.1 Intermediate Discussion

In all the experiments, we visually observed that the impulse flickering duration results were more nonlinear than the longer pulse flickering duration results. However, the quantitative result (see Figure 4.7) showed that the longer pulse results were more nonlinear than impulse results. The reasons of the mismatch between these two types of results were explained in section 3.1.3.6). However, in any case, one can conclude that different mechanisms took place in brain in

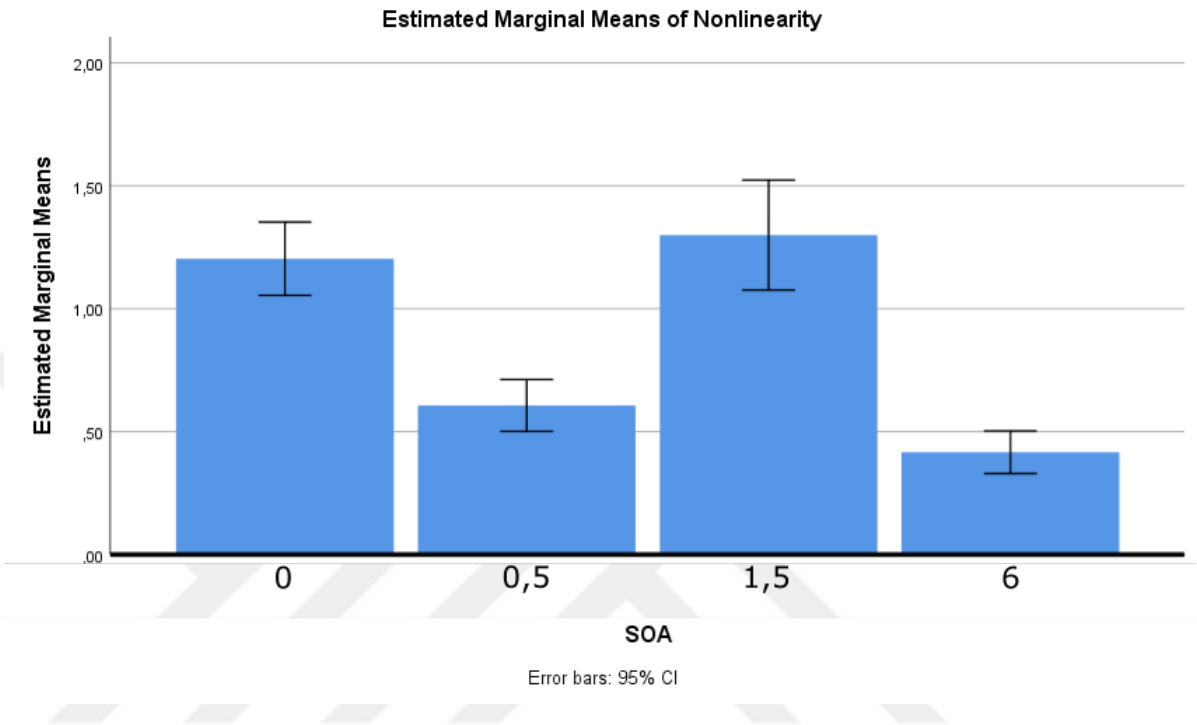

Figure 4.6: Nonlinearity with respect to temporal duration (SOA) in longer pulse flickering. Nonlinearity in SOA 6 is significantly lower than nonlinearities in SOA 0, 0.5, and 1.5 ($p < 0.05$).

impulse and longer pulse flickering durations. Selective attention and increased strength of stimulus can be the underlying reasons of this difference. The following paragraphs explains the underlying reasons by accepting the finding of the visual judgment (i.e., impulse is more nonlinear than longer pulse).

Selective attention reduces strength of mutual suppression [66, 45, 67, 50, 68, 51, 69]. Therefore, when selective attention is involved, the effect of mutual suppression may be reduced, resulting the disapperance of mutual suppressive effects. In our case, selective attention mechanism may be involved in longer pulse but not in impulse flickering duration to modulate V1. It is possible that selective attention is not able to modulate V1 in impulse since the impulse flickering duration is nearly instantaneous. Therefore it will not able to reduce the effect of mutual suppression in V1 for impulse at the short SOAs. Consequently, the effect of mutual suppression can be stronger in impulse than it was in longer flickering durations, which results in more nonlinearities in impulse.

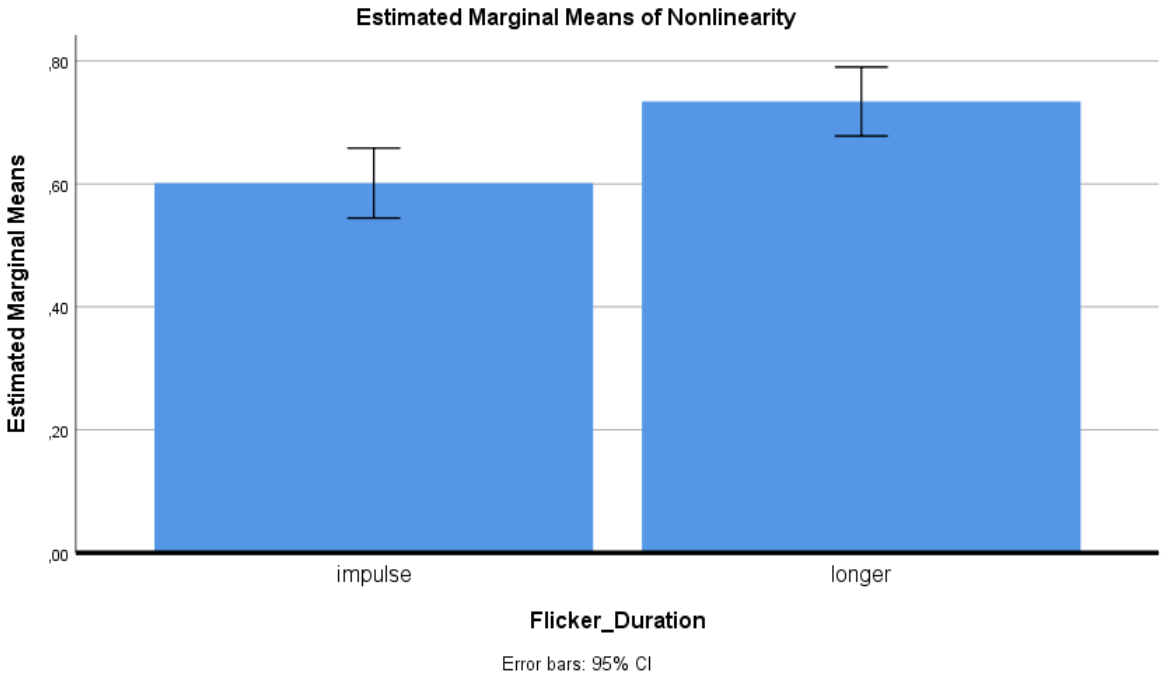

Figure 4.7: Nonlinearity with respect to flickering duration. The difference between impulse and longer pulse is statistically significant ($p < 0.005$).

As another explanation, it was previously shown that high contrast and 3 s flickering checkerboard visual stimuli showed spatial linearity at SOA 0 in V1 [36]. Similarly, in our study, the increase in stimulus duration decreased the nonlinearity (longer pulse vs. impulse). Therefore, one may conclude that increased strength of stimulus accompanying with larger BOLD response may reduce the suppressive effects. On the other hand, when strength of stimulus increases, effects of excitatory mechanisms increase more than effects of inhibitory mechanisms, resulting larger BOLD response. Since BOLD response is sum of responses of both excitatory and inhibitory mechanisms, excitatory mechanisms will be more dominant and determinant compared to inhibitory mechanisms as the strength of stimulus and the resulting BOLD response increase. Therefore, inhibitory effects may become less effective in modulating BOLD response and as a result less visible in BOLD response as strength of stimulus increases. For this reason, the authors in the study [36] might not be able to detect the inhibitory effects in BOLD response to stronger stimulus. The fact that degree of nonlinearity decreases as the contrast level increases was also demonstrated in [49].

Chapter 5

General Discussion

Our study examined interactions between space and time in V1 in response to the two flickering wedge stimuli. Our conditions were grouped in four different spatial configurations (i.e., between hemifields, horizontally and vertically adjacent locations in the same hemifield, and the same location), in four different SOAs (i.e., 0 s, 0.5 s, and 6 for impulse; 0 s, 0.5 s, 1.5 s and 6 s for longer pulse), and in two different flickering durations (i.e. impulse, and longer pulse). We observed that nonlinearity of BOLD response increased as the spatial distance and temporal duration (i.e., SOA) between the stimuli decreased in both flickering durations.

In Experiment 1, we examined two spatial distances (i.e., between hemifields, and the same location). It was found that the conditions of between hemifields had nonlinearities at shorter SOAs (0 s, and 0.5 s) in impulse flickering duration. The strength of nonlinearity was reduced in longer pulse flickering duration although small nonlinearities still exist at the shorter SOAs. Since, the interactions between hemifields cannot be vascular but neuronal in origin, this study showed that there are inhibitory neuronal interactions between hemifields at the shorter SOAs. It has been reported that there are interhemispheric connections between V1 neurons in the left and right hemifields through corpus callosum [56]. The effect of nonlinearity in impulse flickering duration was found more severe than the nonlinearity in longer pulse flickering duration. In the same experiment, we

examined conditions of the same location, too. The findings showed that the nonlinearity in conditions of the same location was stronger than the nonlinearity of between hemifields. We found that the conditions of the same location had very strong nonlinearities at SOAs (0.5 s in impulse, 1.5 s in longer pulse). Nonlinearities were observed even at SOA 6 s for the conditions of the same location. One can conclude that nonlinearity of BOLD response increases as the spatial distance decreases. Therefore, the results showed that spatial distance modulated nonlinearity of BOLD response. Inhibitory mechanisms such as mutual suppression [54, 55, 51, 45, 47] and the refractory effect [34] account for the spatial-dependent nonlinearity of BOLD response.

In Experiment 2 (Inner-Outer), we examined one type of the spatial distances (i.e., horizontally adjacent locations in the same hemifield along x-axis) as a variable of SOA and flickering duration. We found that the conditions show strong nonlinearities at shorter SOAs (0 s, 0.5 s) in impulse flickering duration and at SOA 0.5 s in longer pulse flickering duration. These results show that there are interactions at shorter SOAs between horizontally adjacent visual fields located at along x-axis in the same hemisphere for both flickering durations. The observed suppressive effects in the surrounding regions could be due to mutual suppression mechanism and the vascular refractory effect [45, 46, 47, 62, 70]. Besides, we found that the nonlinearities in impulse are more extreme in amplitude than the nonlinearities in longer pulse. One of the possible explanations is that top-down selective attention mechanism may be involved in longer pulse but may not sufficiently involved in impulse flickering duration to modulate V1 since the impulse duration is nearly instantaneous. It was shown that selective attention mechanism eliminates the effect of mutual suppression [66, 45, 67, 50, 68, 51, 69].

In Experiment 3 (Upper-Lower), we examined one type of the spatial distances (i.e., vertically adjacent locations in the same hemifield along y-axis) as a variable of SOA and flickering duration. We discovered that the conditions showed strong nonlinearities at SOAs 0 s and 0.5 s in impulse flickering duration and at SOAs 0 s in longer pulse flickering duration. These results show that there are interactions at the shorter SOAs (0 s, 0.5 s) between vertically adjacent visual fields located along the y-axis in the same hemisphere for both flickering duration. The results

found in the experiment Upper-Lower are similar to the results in the experiment Inner-Outer. Therefore, the same mechanisms such as mutual suppression and the vascular refractory effect driving the interactions between horizontally adjacent spatial locations along the x-axis (i.e. Inner-Outer spatial configuration) may also drive the interactions between vertically adjacent spatial locations along the y-axis (i.e., in Upper-Lower spatial configuration).

To sum up, we observed that nonlinearity of BOLD response increased as the spatial distance between the stimuli decreased. For example, nonlinearities in the same location and adjacent locations in the same hemisphere are significantly stronger than the nonlinearity in between hemifields (see Figure 4.1). In addition, BOLD responses to the stimuli separated by SOA 0 s, 0.5 s and 1.5 s are significantly more nonlinear than the BOLD response at SOA 6 s as seen in Figure 4.4. Therefore, we showed that spatial summation did not work when two visual stimuli were at the same location or the adjacent locations in the same hemifield of brain at the shorter SOAs (0 s, 0.5 s, and 1.5 s) for both flickering duration. The similar results were also found in [45, 46, 47, 62].

However, there are specific stimulus configurations that support spatial summation in V1 [36]. They used much higher contrast level in their 3 s flickering checkerboard stimuli than the level of 40% Michelson contrast used in our study. Longer stimulus duration and the increase in level of contrast with accompanying increase in BOLD response might have reduced the strengths of mutual and surround suppression mechanisms. On the other hand, as strength of stimulus increases, effects of excitatory mechanisms increase more than effects of inhibitory mechanisms, resulting larger BOLD response to stronger stimulus. Since BOLD response is sum of responses of both excitatory and inhibitory mechanisms, excitatory mechanisms will be more dominant and determinant compared to inhibitory mechanisms as the strength of stimulus and the resulting BOLD response increase. Therefore, inhibitory effects may become less effective in modulating BOLD response and as a result less visible in BOLD response, as strength of stimulus increases. The fact that degree of nonlinearity decreases as the contrast level increases was also demonstrated in [49]. The same phenomenon was also

observed between our impulse and longer pulse results. Our longer pulse stimulus duration results, activating stronger BOLD response, showed less nonlinearity than the impulse results based on the visual judgment, which is consistent with the studies [36, 49], although our quantitative result showed the opposite (see section 3.1.3.6). Nonlinearity difference found between our impulse and longer flickering duration results might be explained by this mechanism. Another reason for the nonlinearity difference between impulse and longer pulse results could be top-down selective attention mechanism. It was found that selective attention reduces the effect of mutual suppression [66, 45, 67, 50, 68, 51, 69]. Since impulse flickering duration is nearly instantaneous unlike longer pulse flickering duration, selective attention mechanism may not be able to modulate impulse results as strong as it modulates longer pulse results. Consequently, the mechanism cannot be able to reduce the effect of mutual suppression in impulse results, while it can do in longer pulse results.

In conclusion, assuming BOLD response is linear and time invariant is not always true. A care should be taken in applying methods and analyses that assume BOLD response is a linear and time-invariant system with respect to stimulus.

5.1 Limitations

First of all, we showed that nonlinearities as variables of SOA and spatial distance depend on stimulus duration. The temporal and spatial variations could have been investigated in a wider sets of flickering duration. However, in our study, we only used two different stimulus durations, although they are the most commonly used flickering durations used in many event-related designs. Nevertheless, another stimulus duration which could be larger than 1 s can also be investigated to check if a different mechanism may play a role in nonlinearity in longer stimulus duration ($>$ 1 s). For example, it is known that stronger suppressive effects can be expected in longer duration, since longer stimulus duration

activate more neurons in time. Likewise, instead of using a constant level of contrast, contrast could be another variable that can be investigated to investigate its interactions with respect to SOA and spatial distance.

Secondly, this work is only limited to the primary visual cortex and the findings may not be correct or as accurate as for the other visual areas and for the other regions of brain. In fact, characteristics of the refractory effect are changed from region to region [39].

Thirdly, these results were found when presented wedges stimuli with black-and-white flickering checkerboard pattern at 8 Hz in 40% Michelson contrast. Different stimulus configuration may elicit different responses in V1, which may affect the linearity of V1. Therefore, it would not be appropriate to assume that every visual stimulus will evoke similar degree of linearity/nonlinearity in V1.

Fourthly, we investigated nonlinearity in the same location, in the horizontally and vertically adjacent locations, and in the different hemifields but not diagonally adjacent locations.

Fifthly, results substantially varied by subjects especially in impulse flickering duration of all the experiments.

Lastly, degree of nonlinearity significantly changes by magnetic field strength [38]. This work is limited to 3 Tesla. At 3 Tesla, fMRI BOLD response mostly depends on the contributions of large veins [78], resulting in deterioration in the spatial correlation between the BOLD response and the underlying neuronal activity (i.e. lower BOLD specificity)[79]. It would be better to investigate the spatial and temporal nonlinearities of the BOLD response at higher magnetic fields, where BOLD response is a more robust predictor of the underlying neuronal activity [80].

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Appendix A

Data

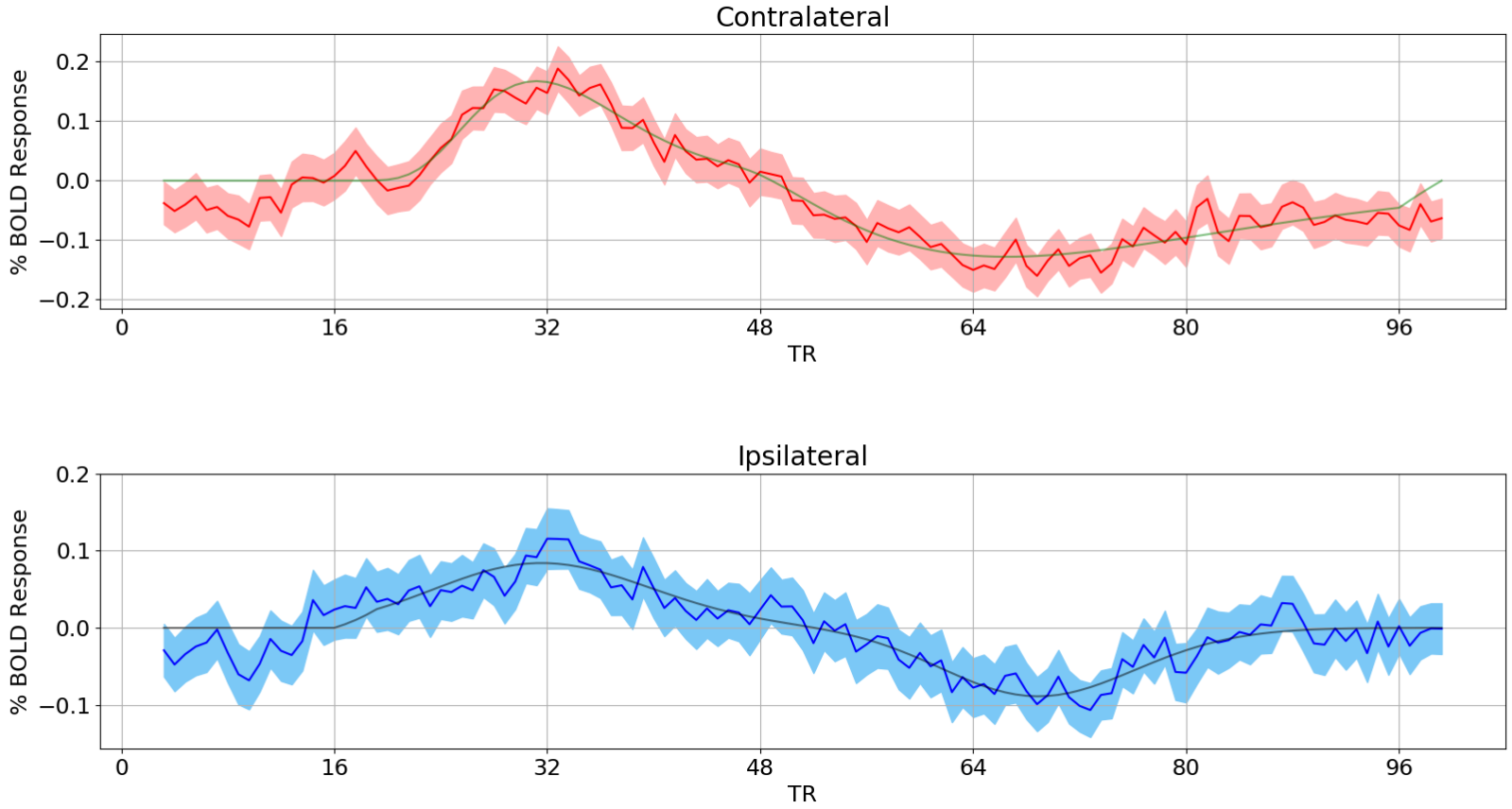

Figure A.1: BOLD responses to impulse stimulation (Impulse Experiment 1 SIRF) in LT 05. Green is the SIRF model. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR = 250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

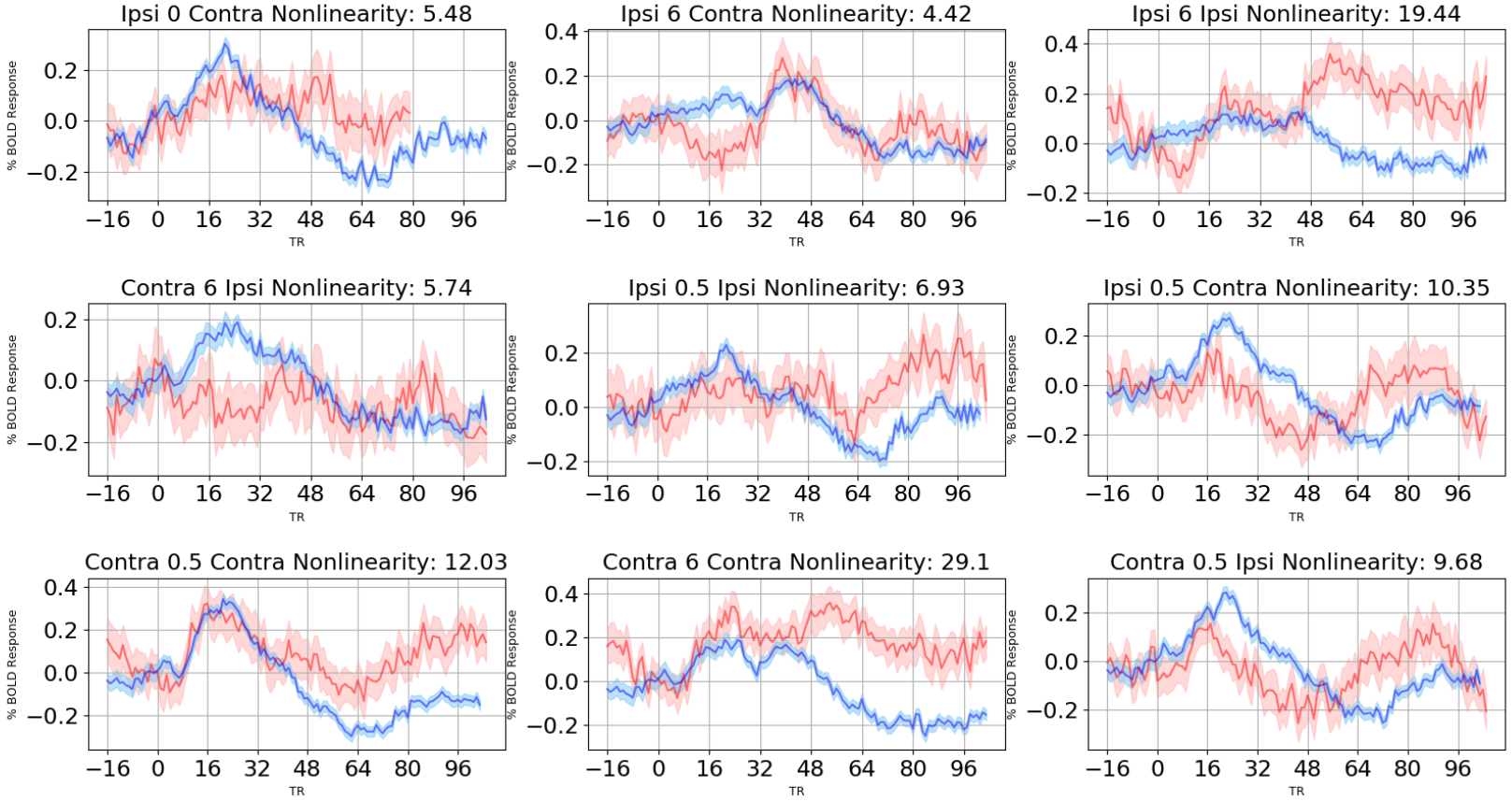

Figure A.2: Impulse Experiment 1 SIRF vs. SOA in LT 05. Blue is the predicted response. Red is the observed response. The nonlinearity index measures the degree of the difference between the predicted and observed responses and was calculated based on the residual (nonlinearity) formula for all TRs. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

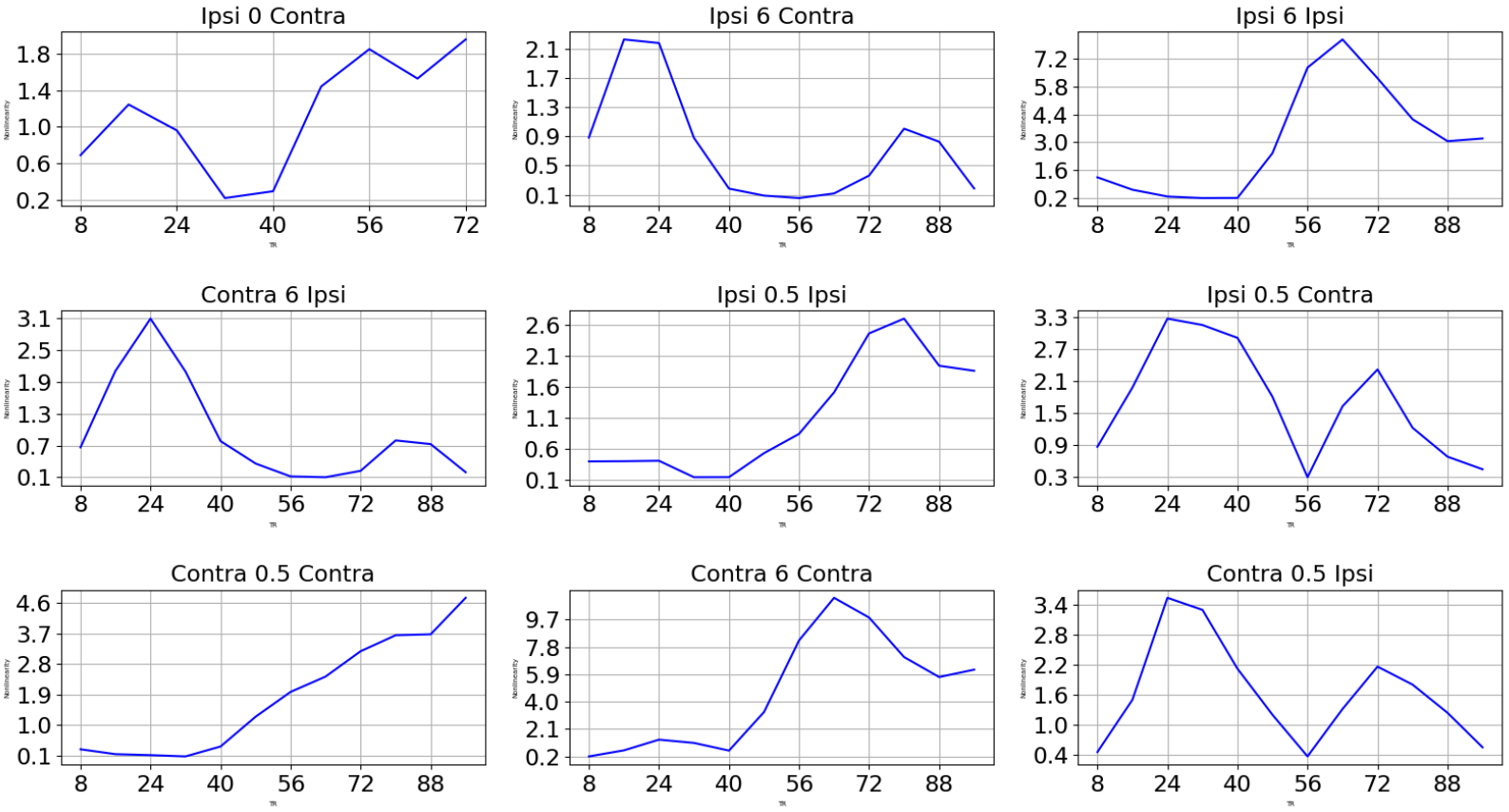

Figure A.3: Impulse Experiment 1 in LT 05. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

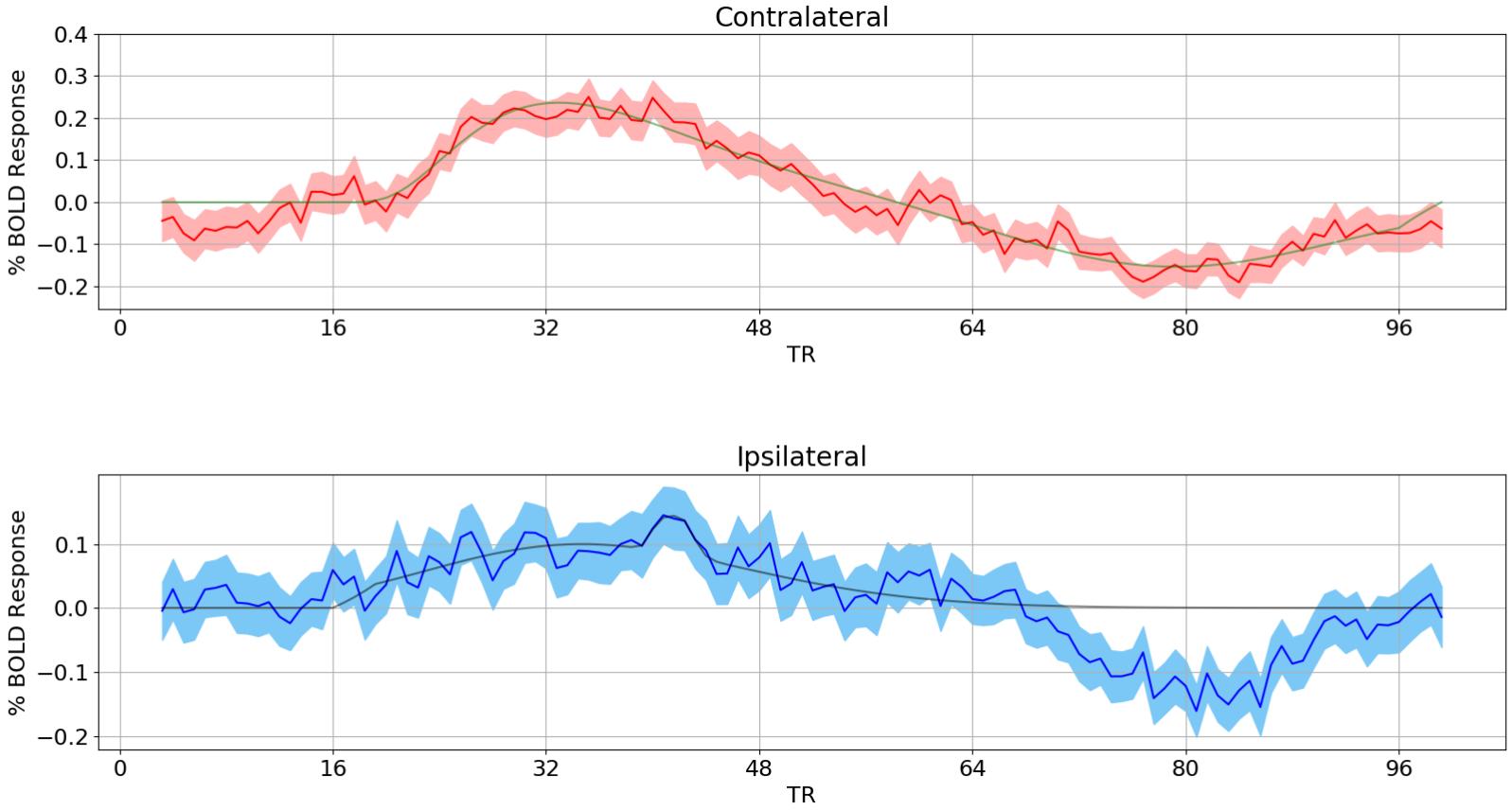

Figure A.4: BOLD responses to impulse stimulation (Impulse Experiment 1 SIRF) in LT 06. Green is the SIRF model. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR = 250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

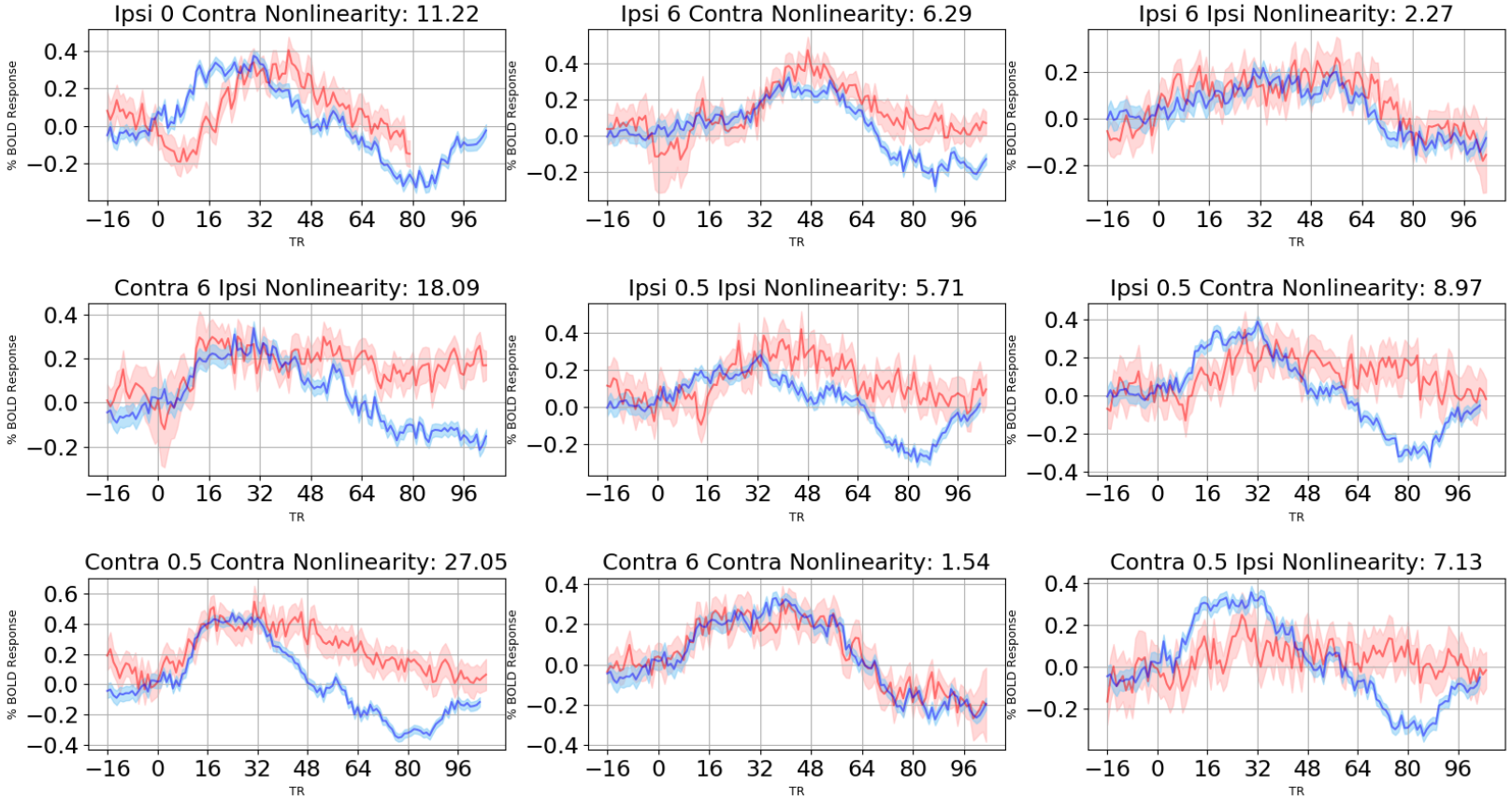

Figure A.5: Impulse Experiment 1 SIRF vs. SOA in LT 06. Blue is the predicted response. Red is the observed response. The nonlinearity index measures the degree of the difference between the predicted and observed responses and was calculated based on the residual (nonlinearity) formula for all TRs. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

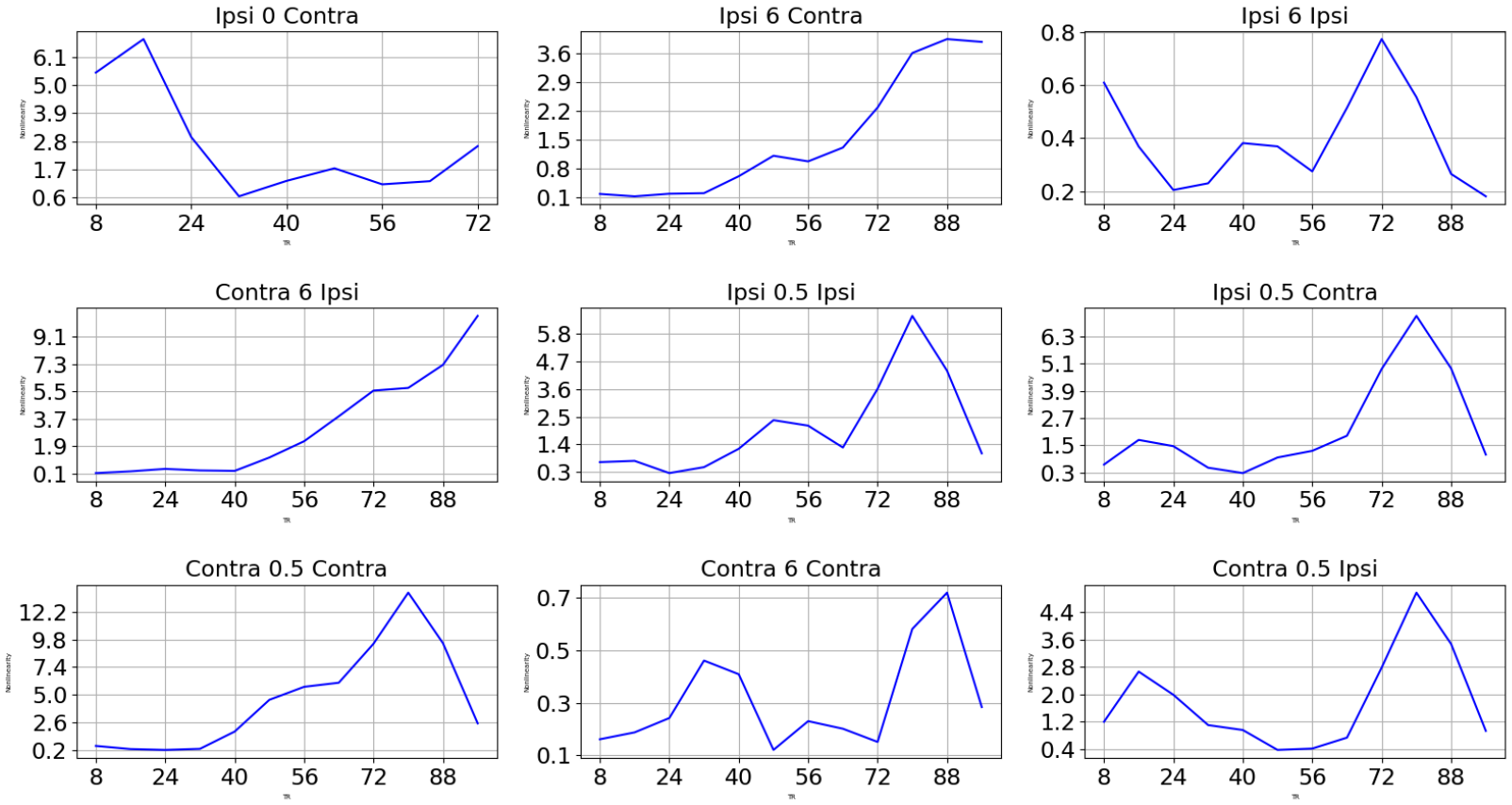

Figure A.6: Impulse Experiment 1 in LT 06. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

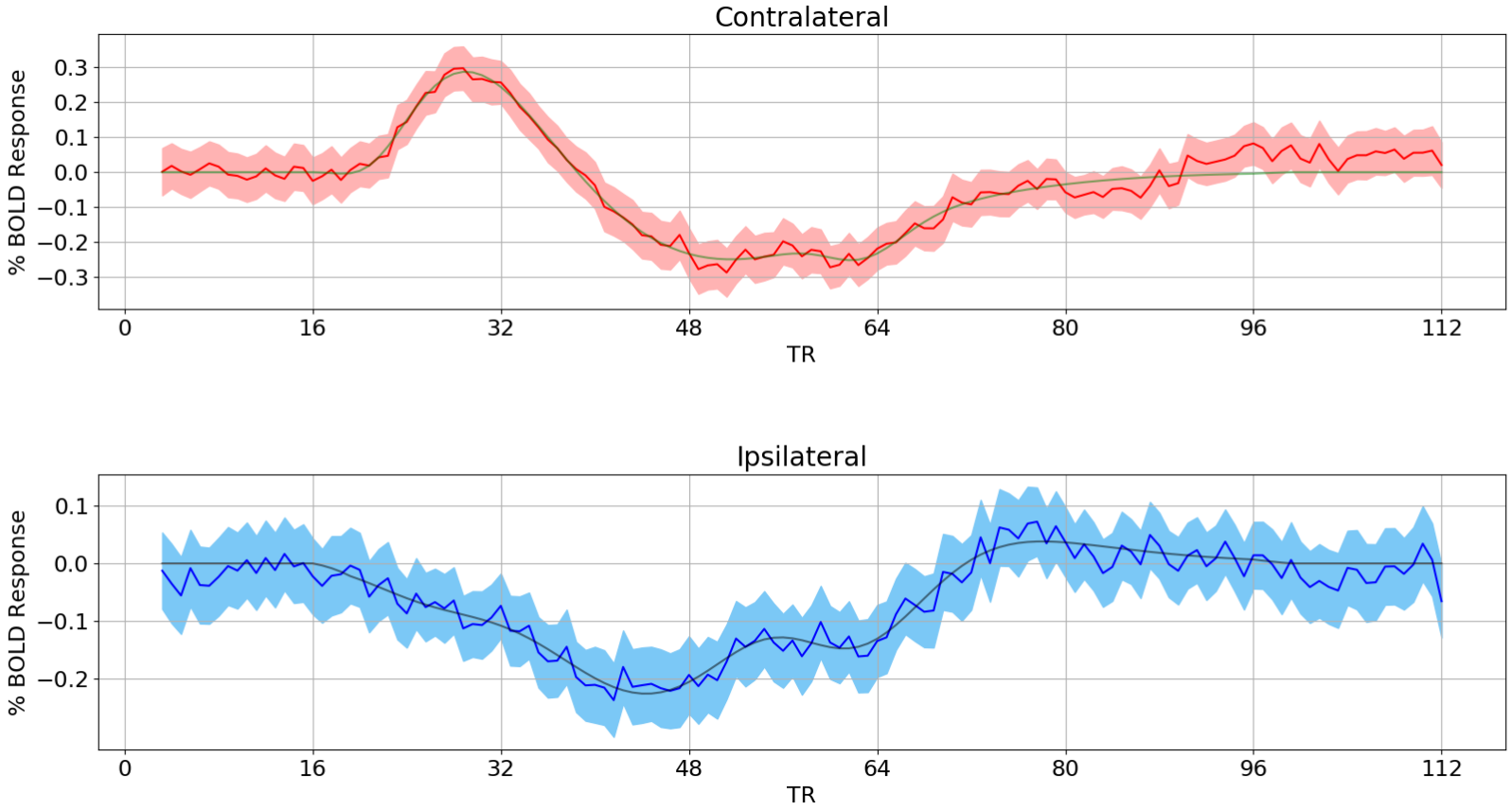

Figure A.7: BOLD responses to impulse stimulation (Impulse Experiment 1 SIRF) in LT 07. Green is the SIRF model. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR = 250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

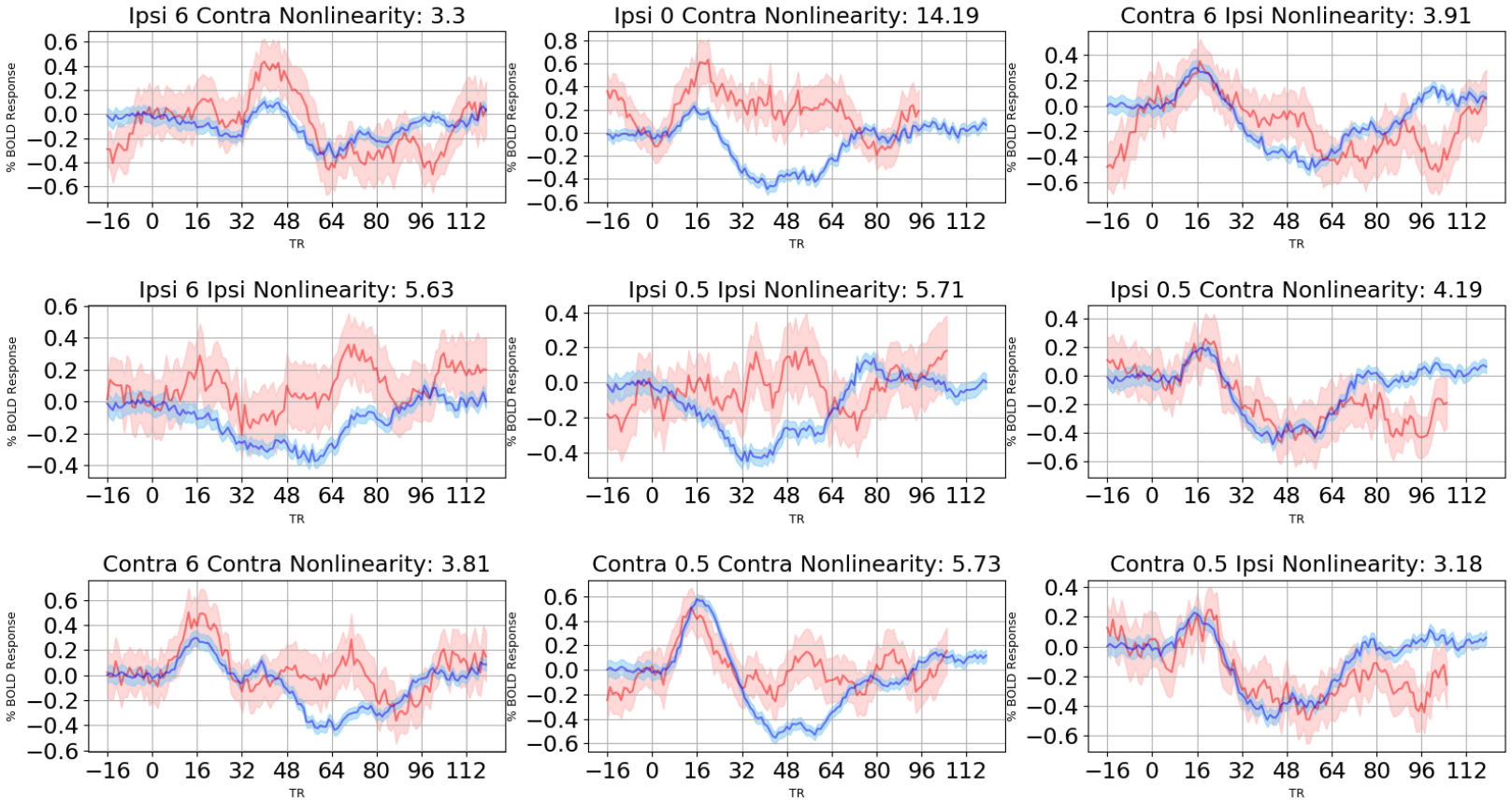

Figure A.8: Impulse Experiment 1 SIRF vs. SOA in LT 07. Blue is the predicted response. Red is the observed response. The nonlinearity index measures the degree of the difference between the predicted and observed responses and was calculated based on the residual (nonlinearity) formula for all TRs. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

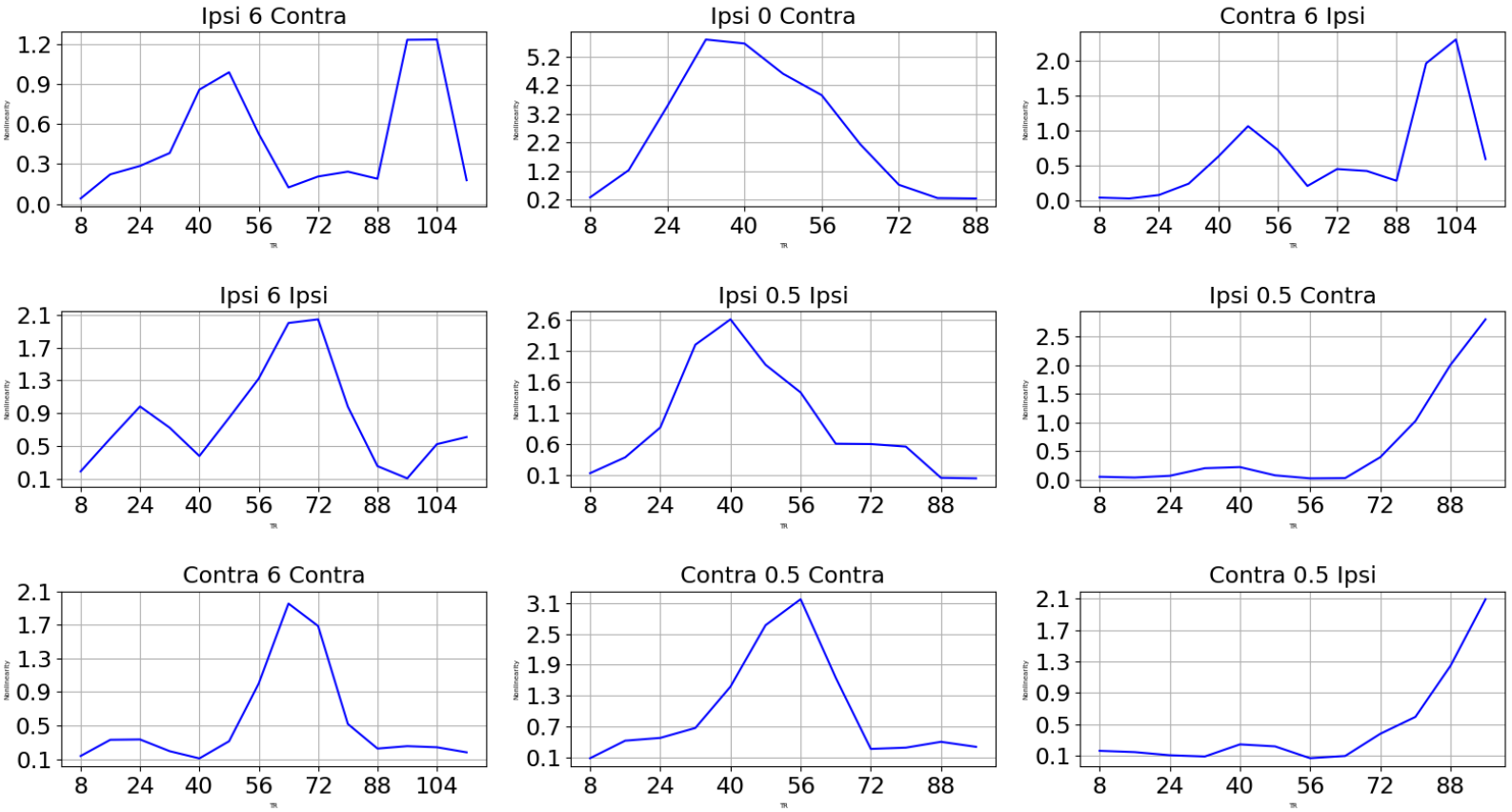

Figure A.9: Impulse Experiment 1 in LT 07. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

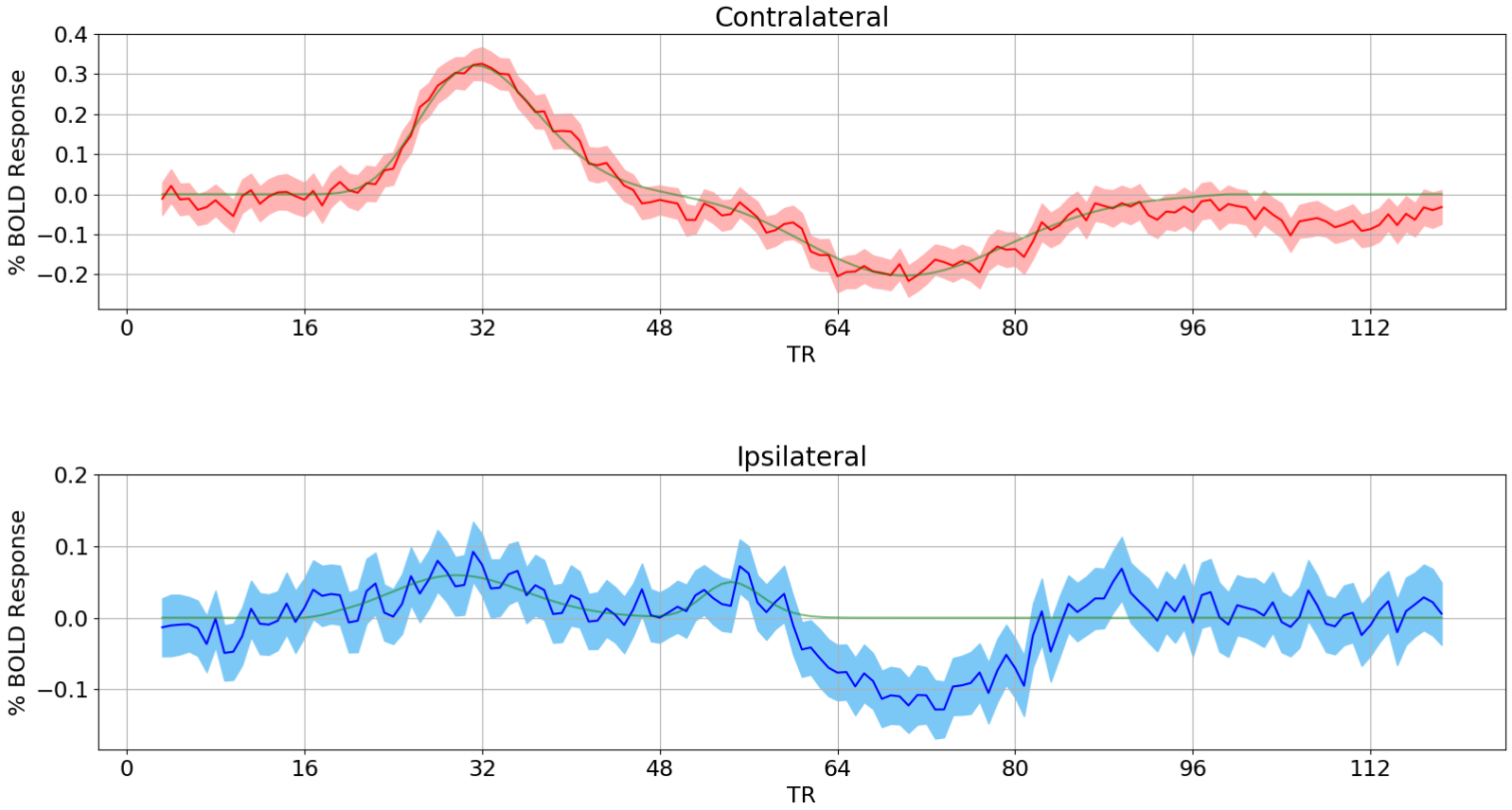

Figure A.10: BOLD responses to 1 s stimulation (Longer Pulse Experiment 1 SIRF) in LT 05. Green is the SIRF model. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR = 250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

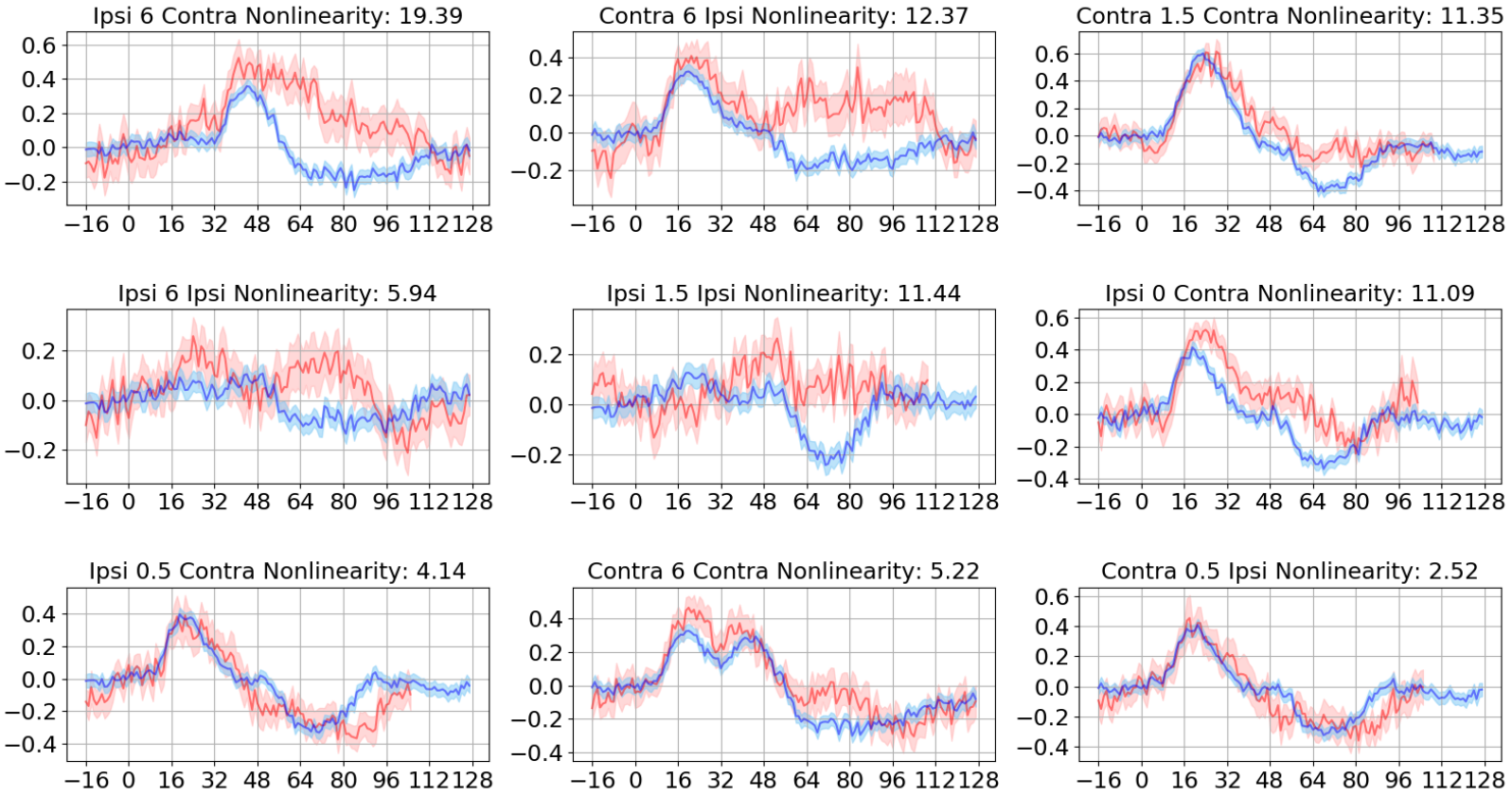

Figure A.11: Longer Pulse Experiment 1 SIRF vs. SOA in LT 05. Blue is the predicted response. Red is the observed response. The nonlinearity index measures the degree of the difference between the predicted and observed responses and was calculated based on the residual (nonlinearity) formula for all TRs. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

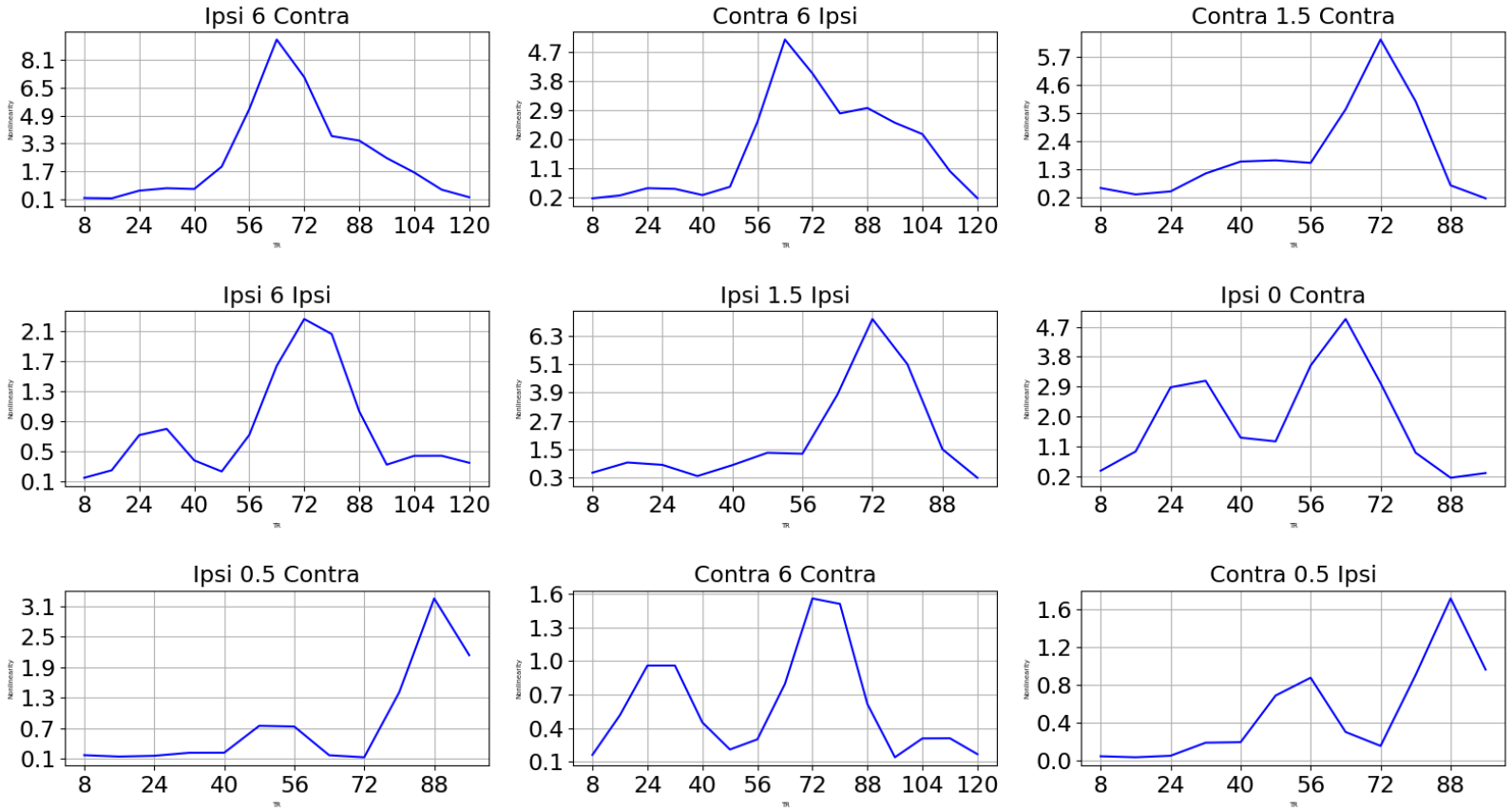

Figure A.12: Longer Pulse Experiment 1 in LT 05. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

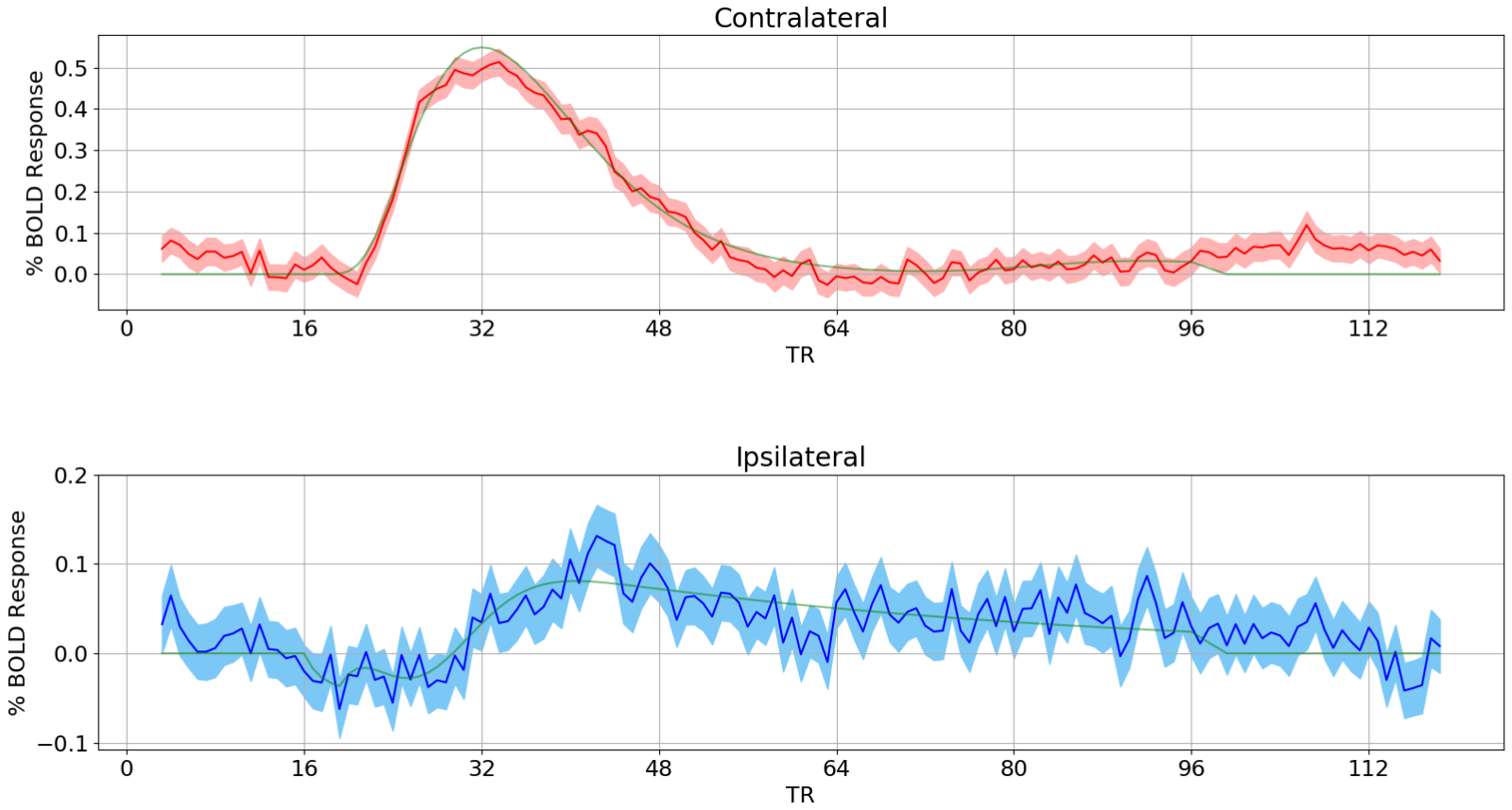

Figure A.13: BOLD responses to 1 s stimulation (Longer Pulse Experiment 1 SIRF) in LT 06. Green is the SIRF model. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR = 250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

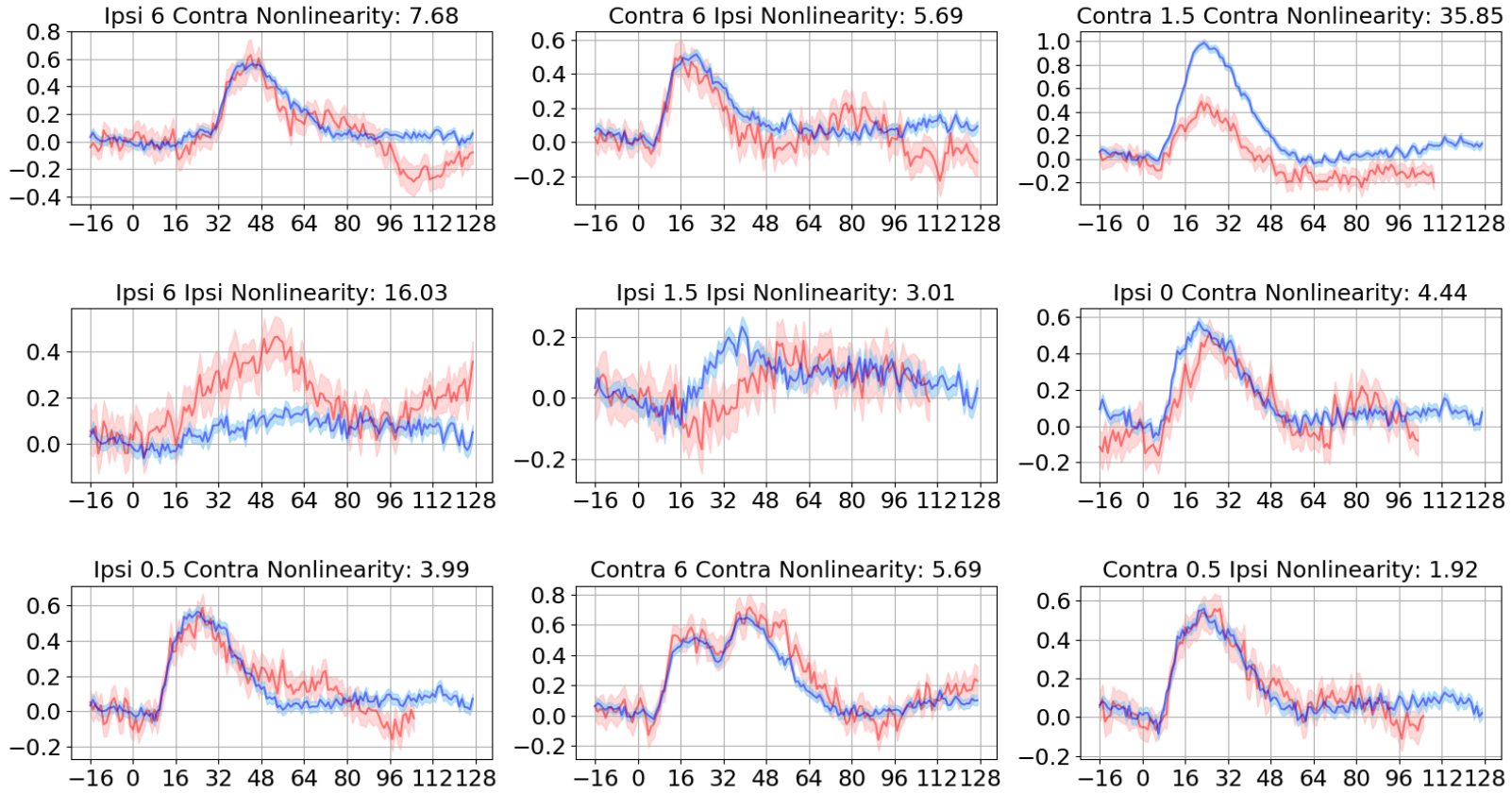

Figure A.14: Longer Pulse Experiment 1 SIRF vs. SOA in LT 06. Blue is the predicted response. Red is the observed response. The nonlinearity index measures the degree of the difference between the predicted and observed responses and was calculated based on the residual (nonlinearity) formula for all TRs. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

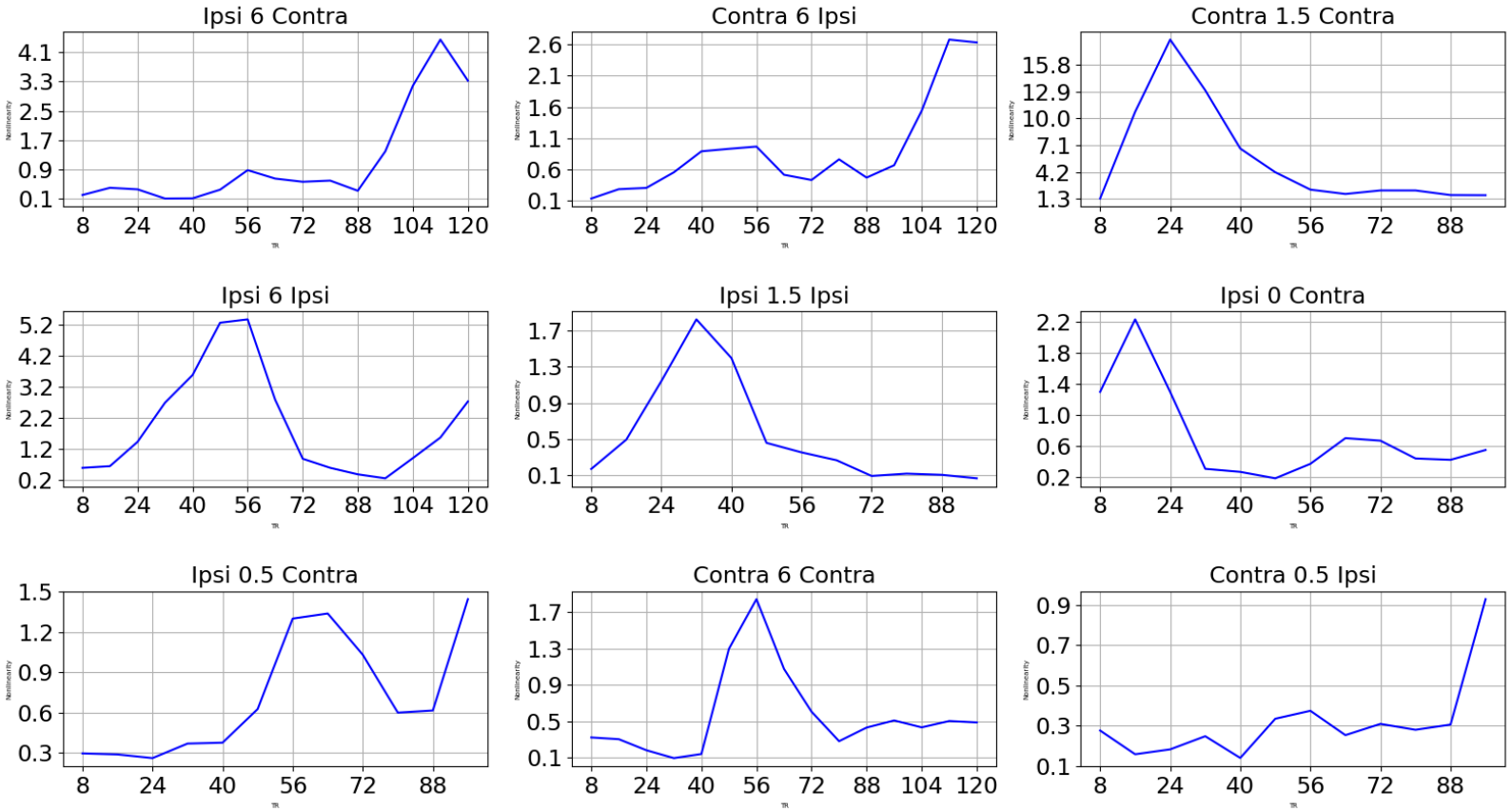

Figure A.15: Longer Pulse Experiment 1 in LT 06. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

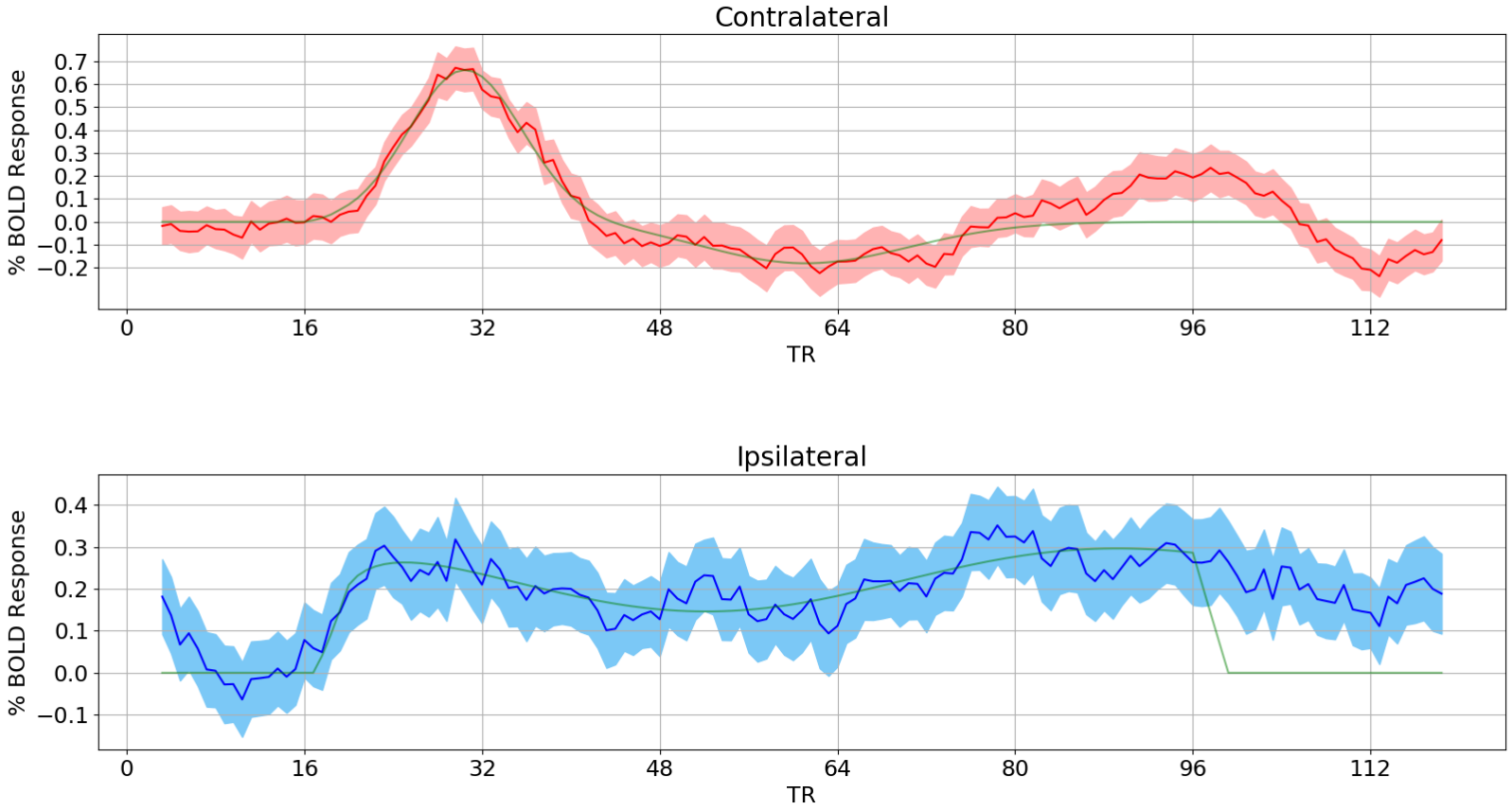

Figure A.16: BOLD responses to 1 s stimulation (Longer Pulse Experiment 1 SIRF) in LT 07. Green is the SIRF model. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR = 250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

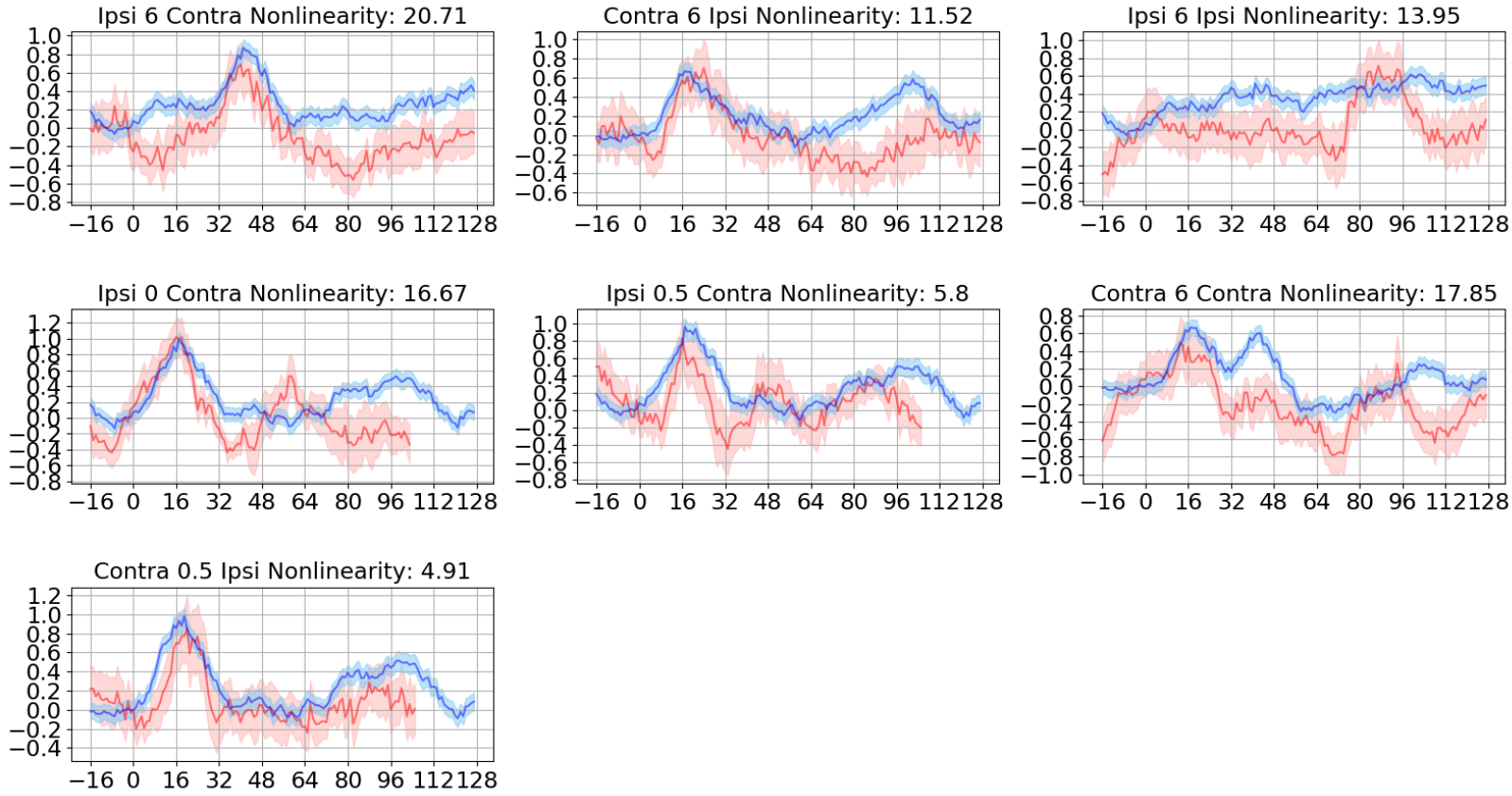

Figure A.17: Longer Pulse Experiment 1 SIRF vs. SOA in LT 07. Blue is the predicted response. Red is the observed response. The nonlinearity index measures the degree of the difference between the predicted and observed responses and was calculated based on the residual (nonlinearity) formula for all TRs. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

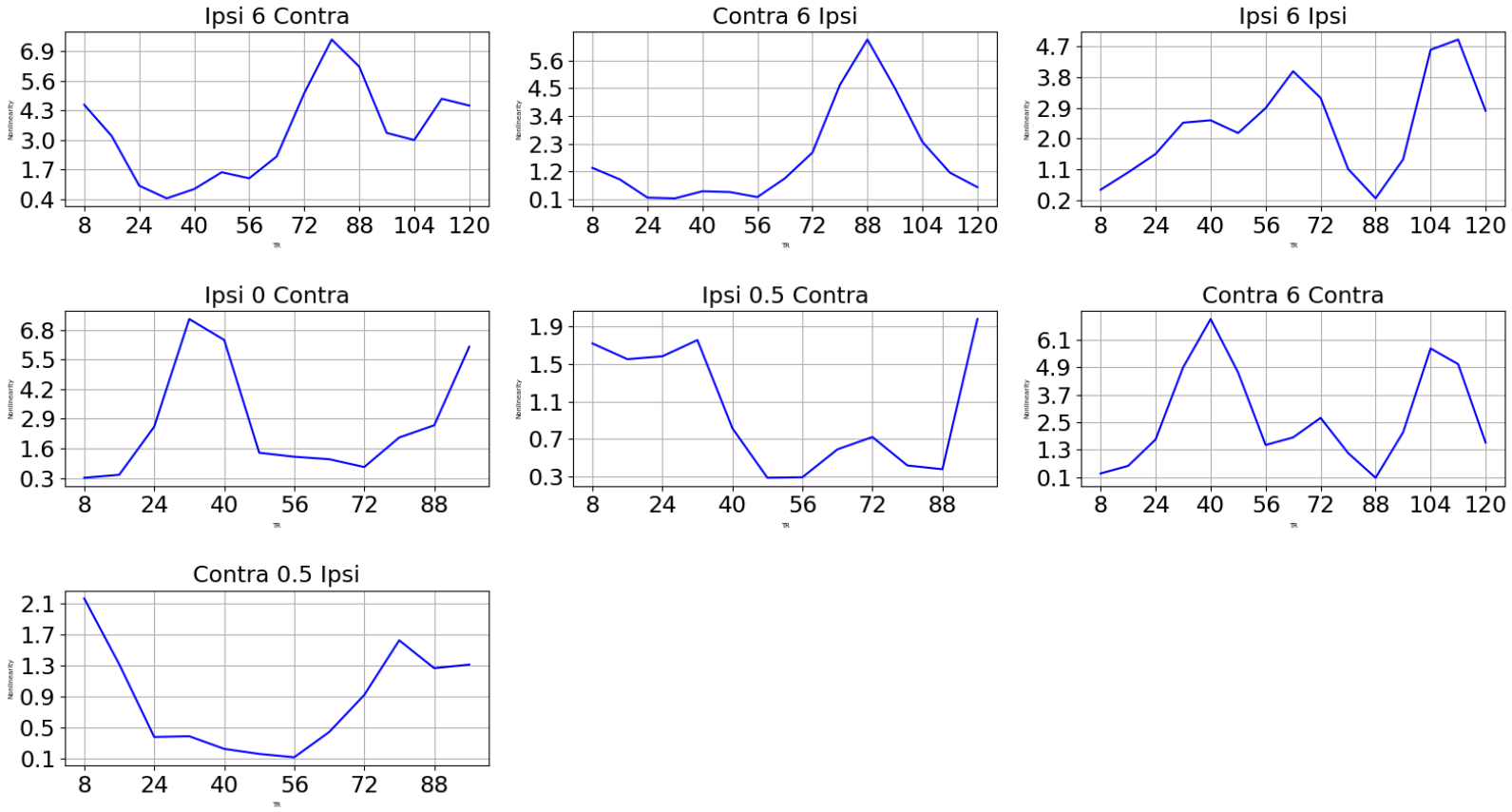

Figure A.18: Longer Pulse Experiment 1 in LT 07. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

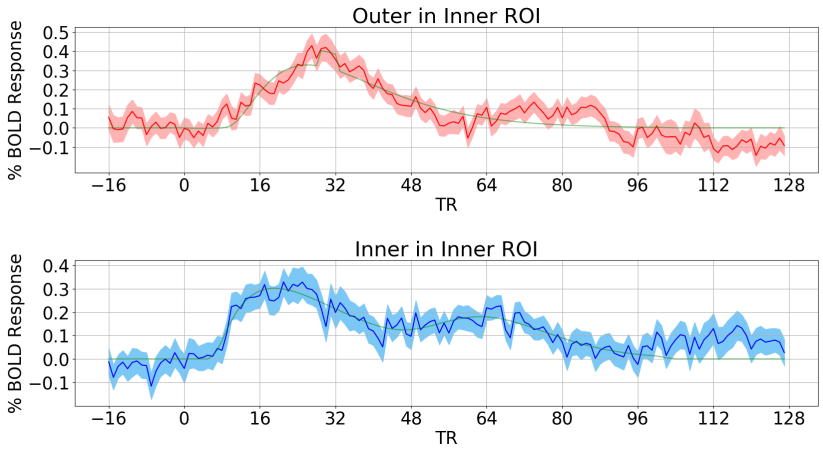

Figure A.19: BOLD responses to impulse stimulation (Impulse Inn-Out SIRF in Inner ROI) in LT 06. Green is the SIRF model. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR = 250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

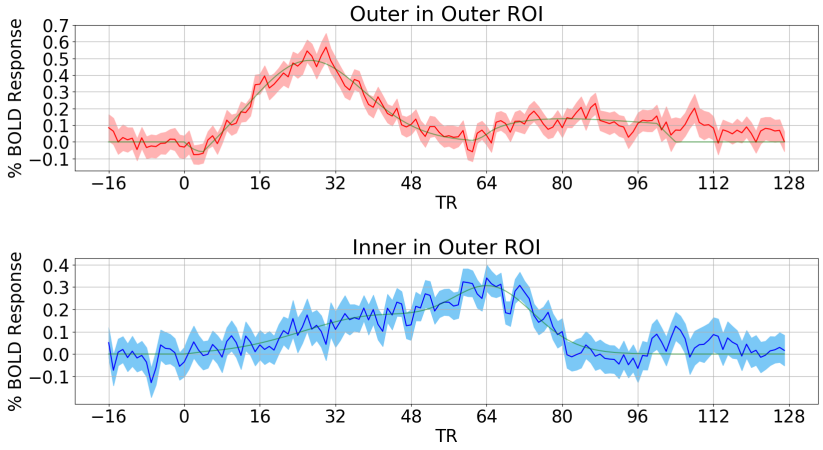

Figure A.20: BOLD responses to impulse stimulation (Impulse Inn-Out SIRF in Outer ROI) in LT 06. Green is the SIRF model. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR = 250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

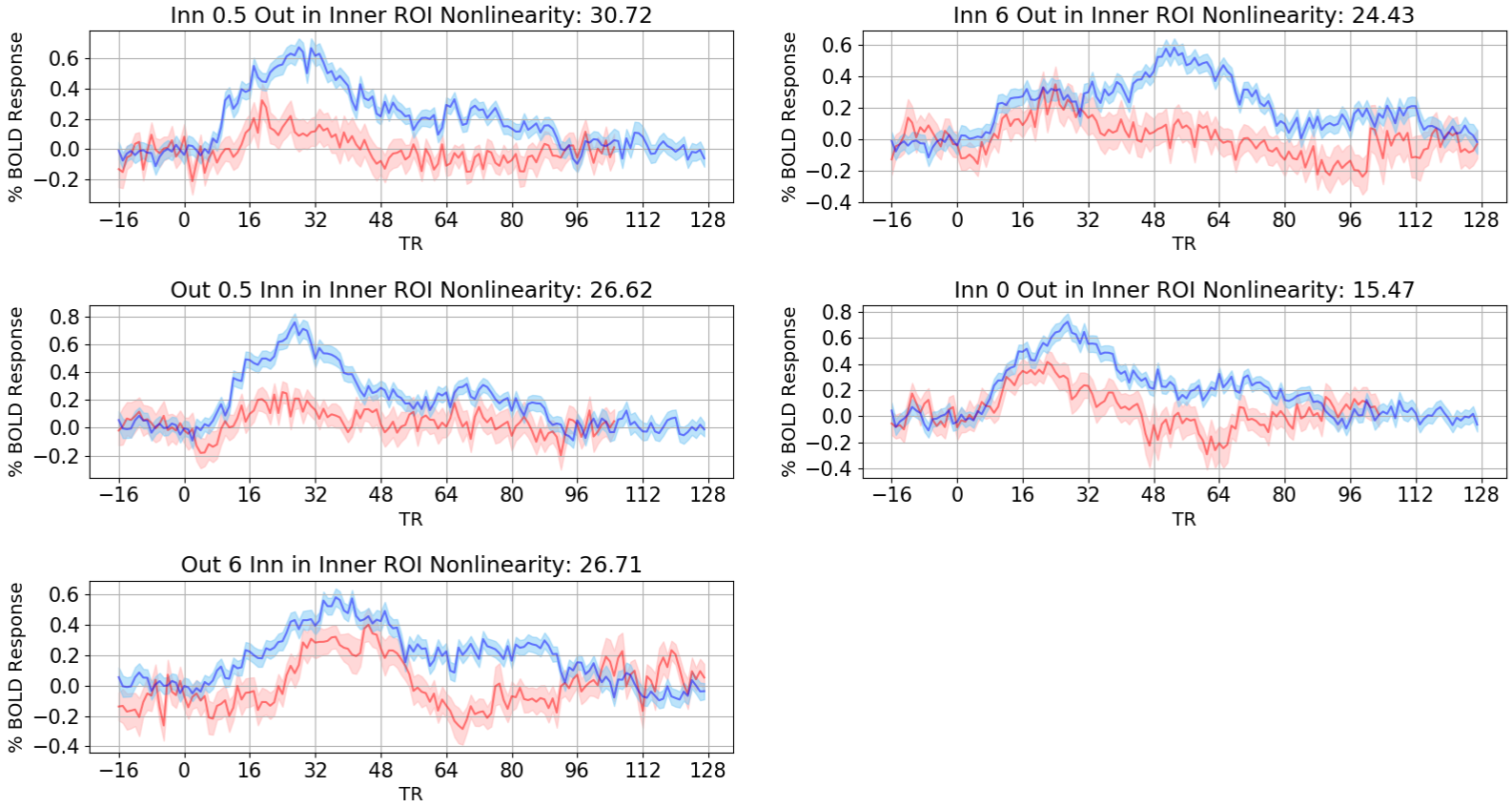

Figure A.21: Impulse Inn-Out SIRF vs. SOA in Inner ROI in LT 06. Blue is the predicted response. Red is the observed response. The nonlinearity represents the difference between the predicted and observed responses and was calculated based on the residual formula for all TRs. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

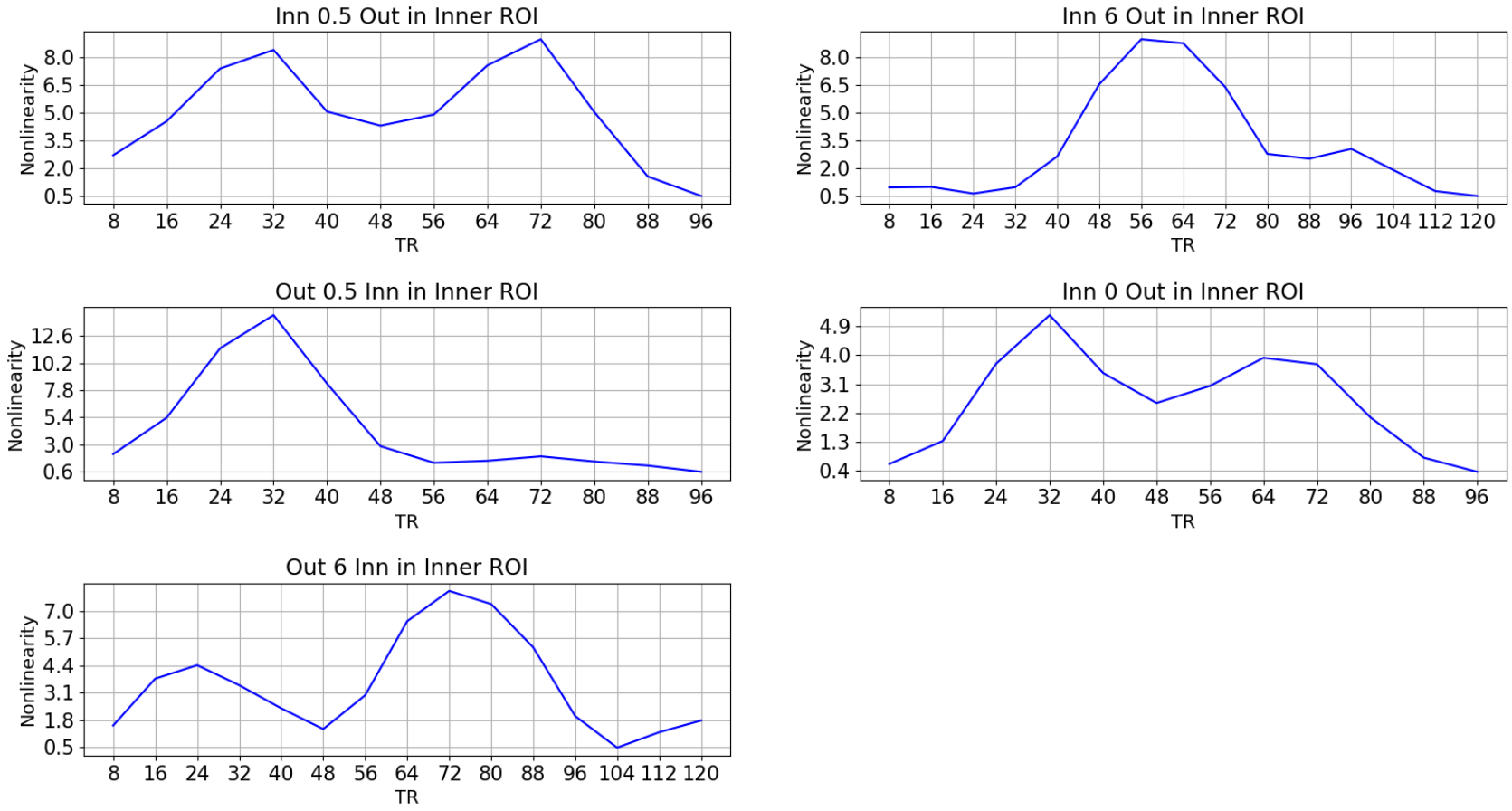

Figure A.22: Impulse Inn-Out in Inner ROI in LT 06. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

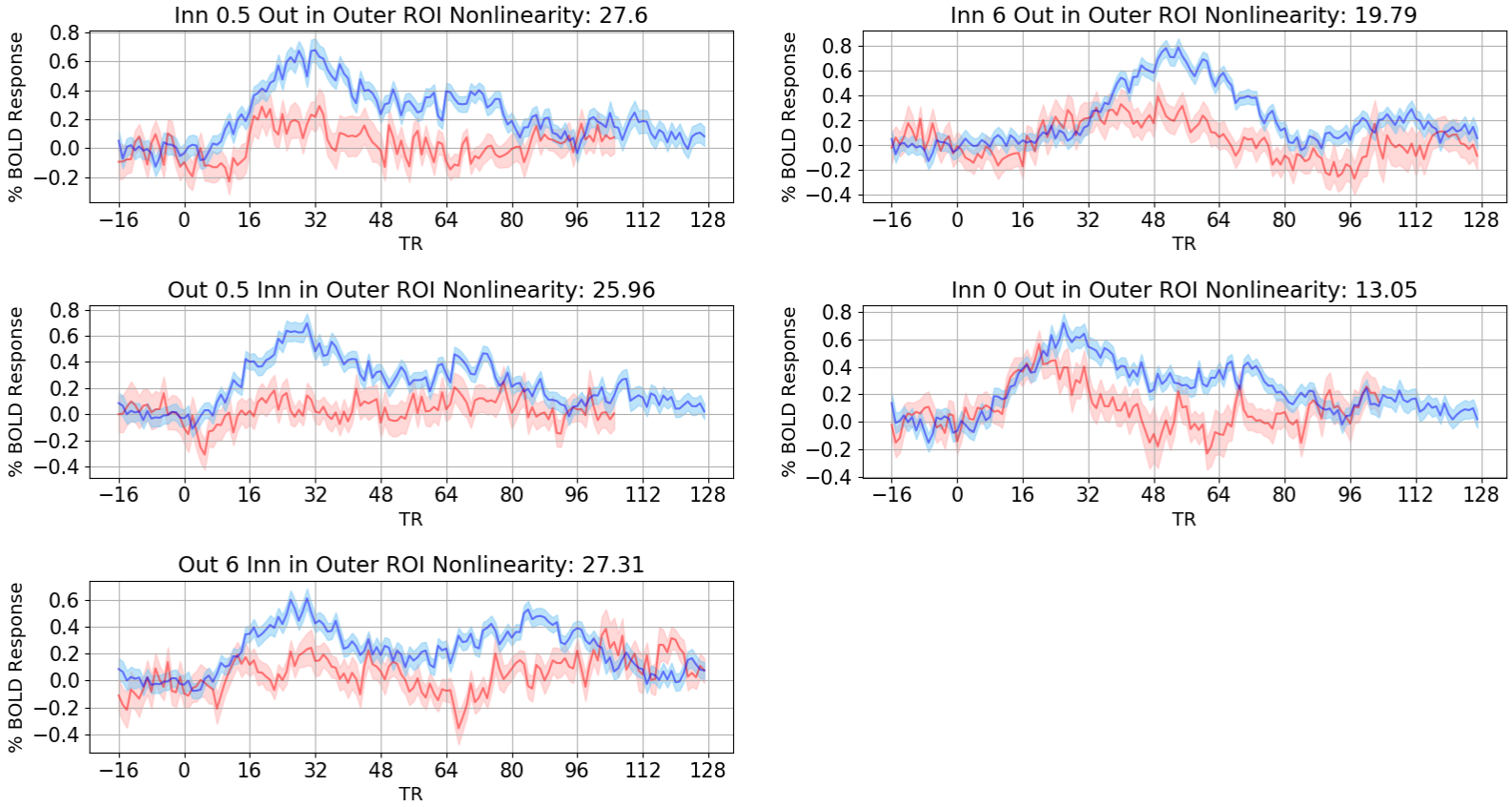

Figure A.23: Impulse Inn-Out SIRF vs. SOA in Outer ROI in LT 06. Blue is the predicted response. Red is the observed response. The nonlinearity represents the difference between the predicted and observed responses and was calculated based on the residual formula for all TRs. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

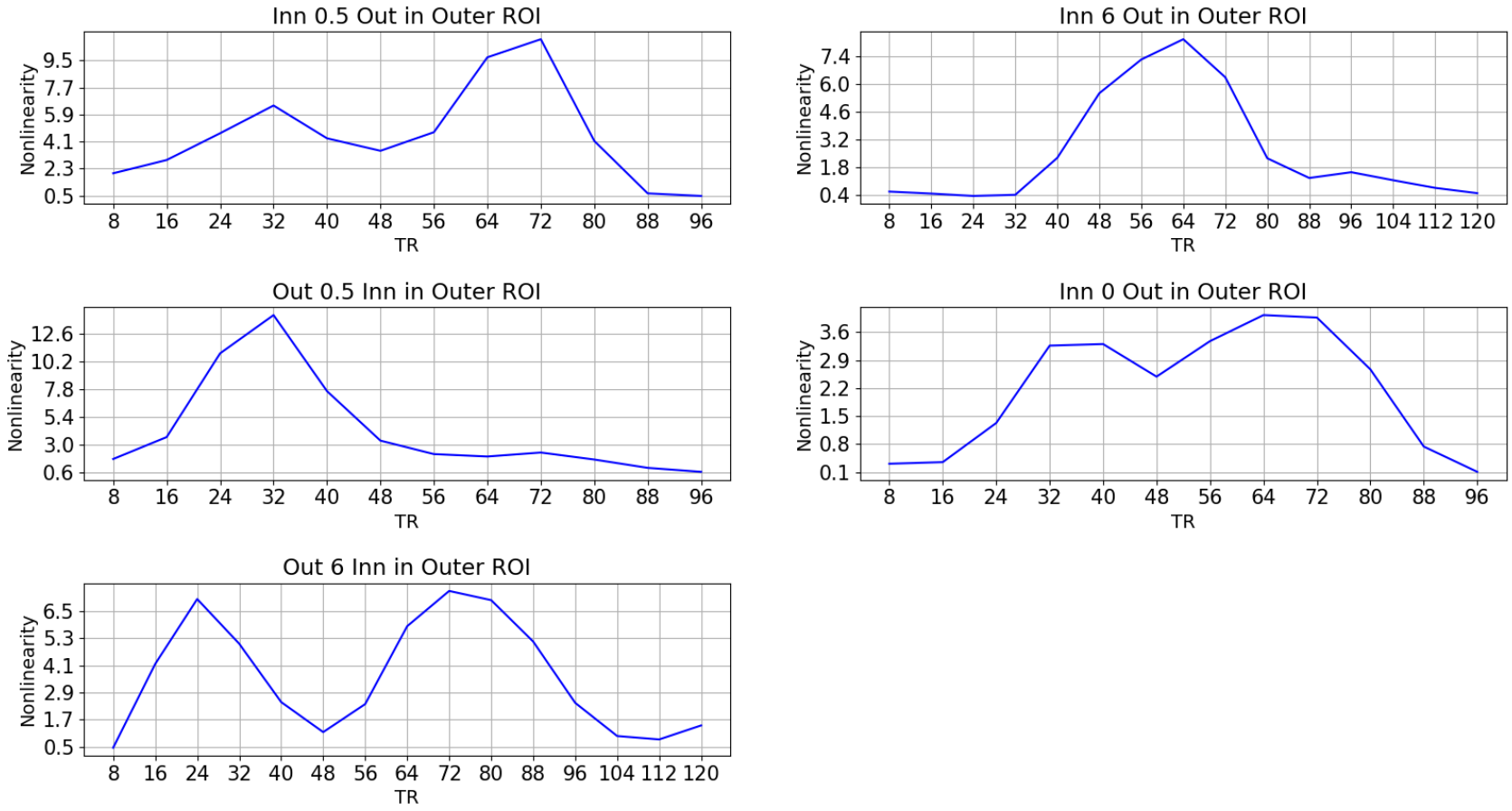

Figure A.24: Impulse Inn-Out in Outer ROI in LT 06. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

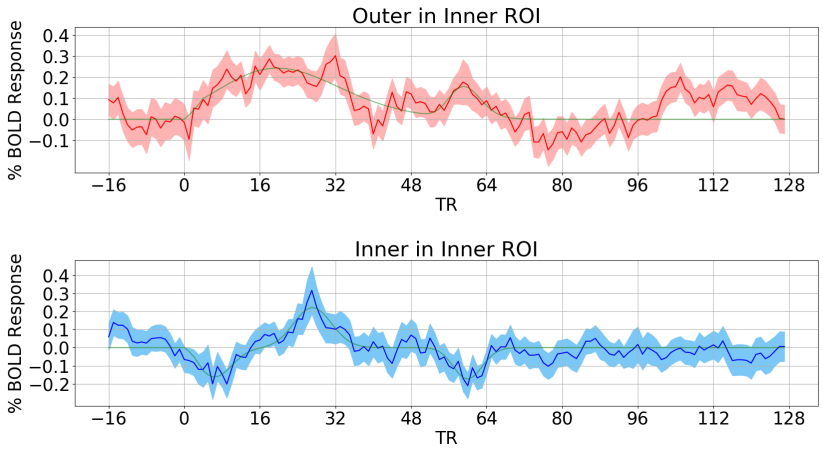

Figure A.25: BOLD responses to impulse stimulation (Impulse Inn-Out SIRF in Inner ROI) in LT 09. Green is the SIRF model. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR = 250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

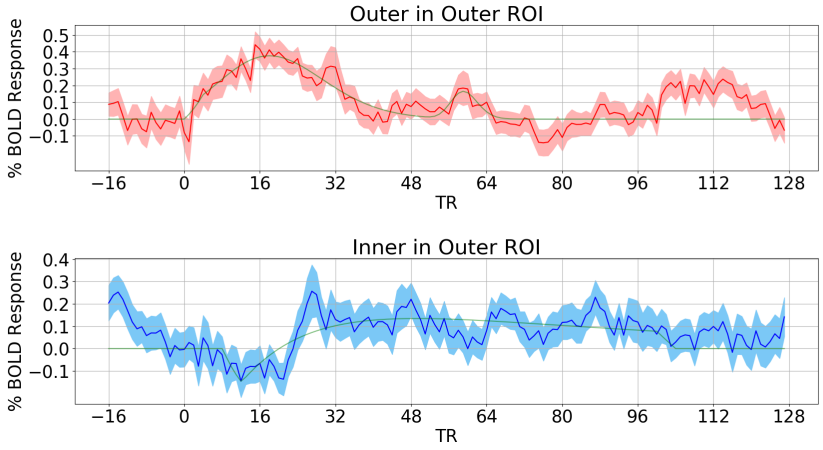

Figure A.26: BOLD responses to impulse stimulation (Impulse Inn-Out SIRF in Outer ROI) in LT 09. Green is the SIRF model. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR = 250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

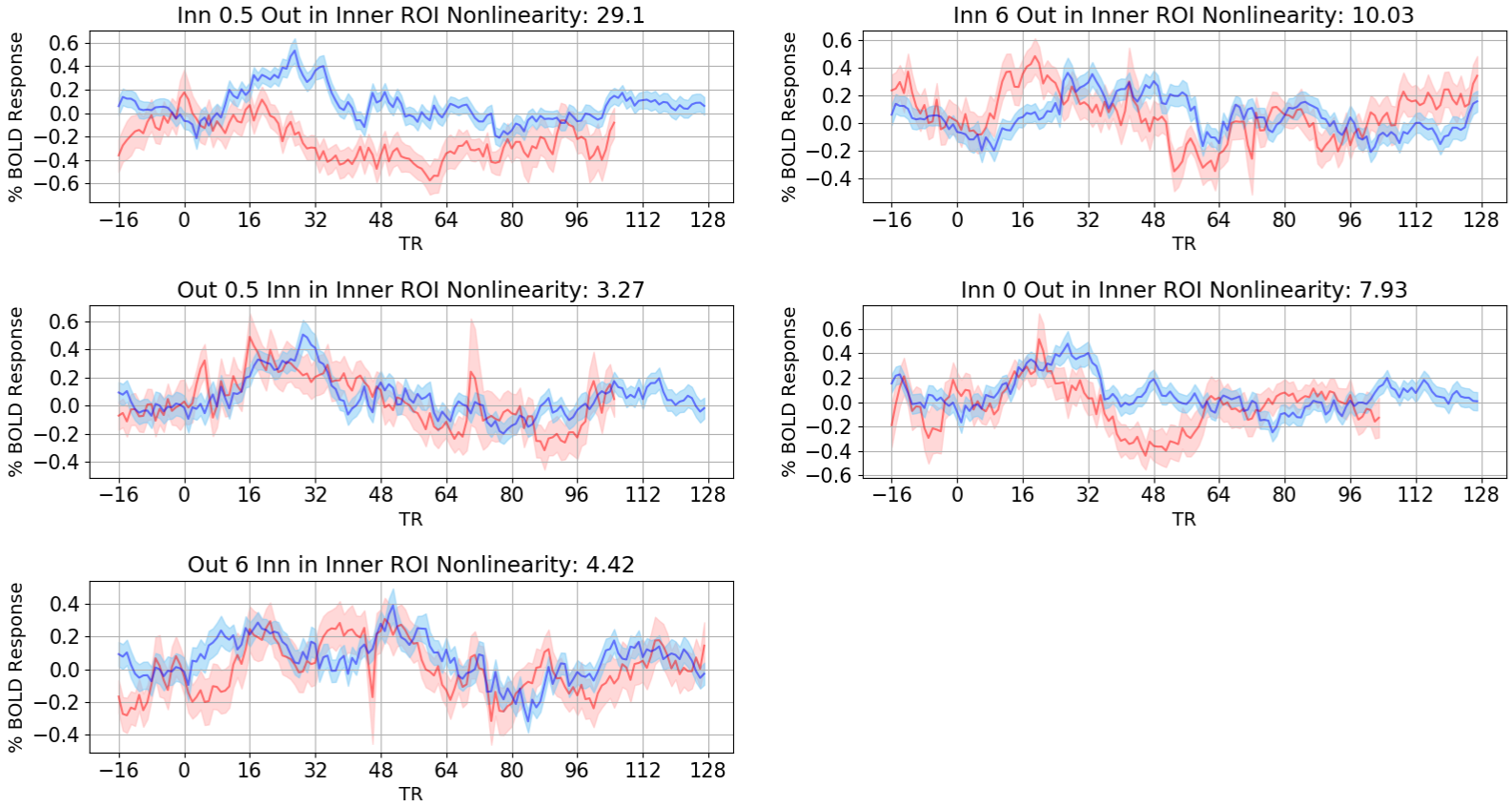

Figure A.27: Impulse Inn-Out SIRF vs. SOA in Inner ROI in LT 09. Blue is the predicted response. Red is the observed response. The nonlinearity represents the difference between the predicted and observed responses and was calculated based on the residual formula for all TRs. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

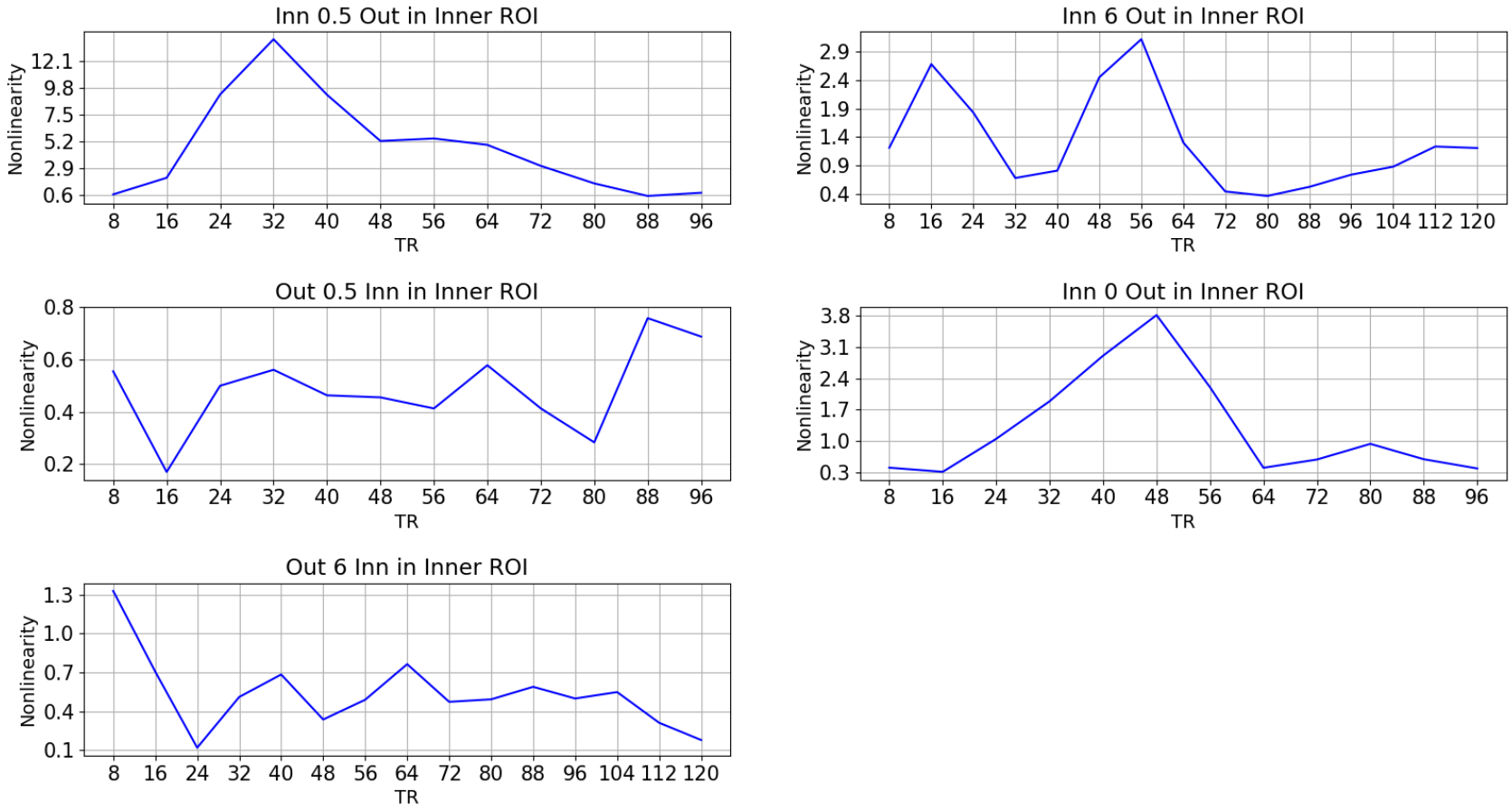

Figure A.28: Impulse Inn-Out in Inner ROI in LT 09. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

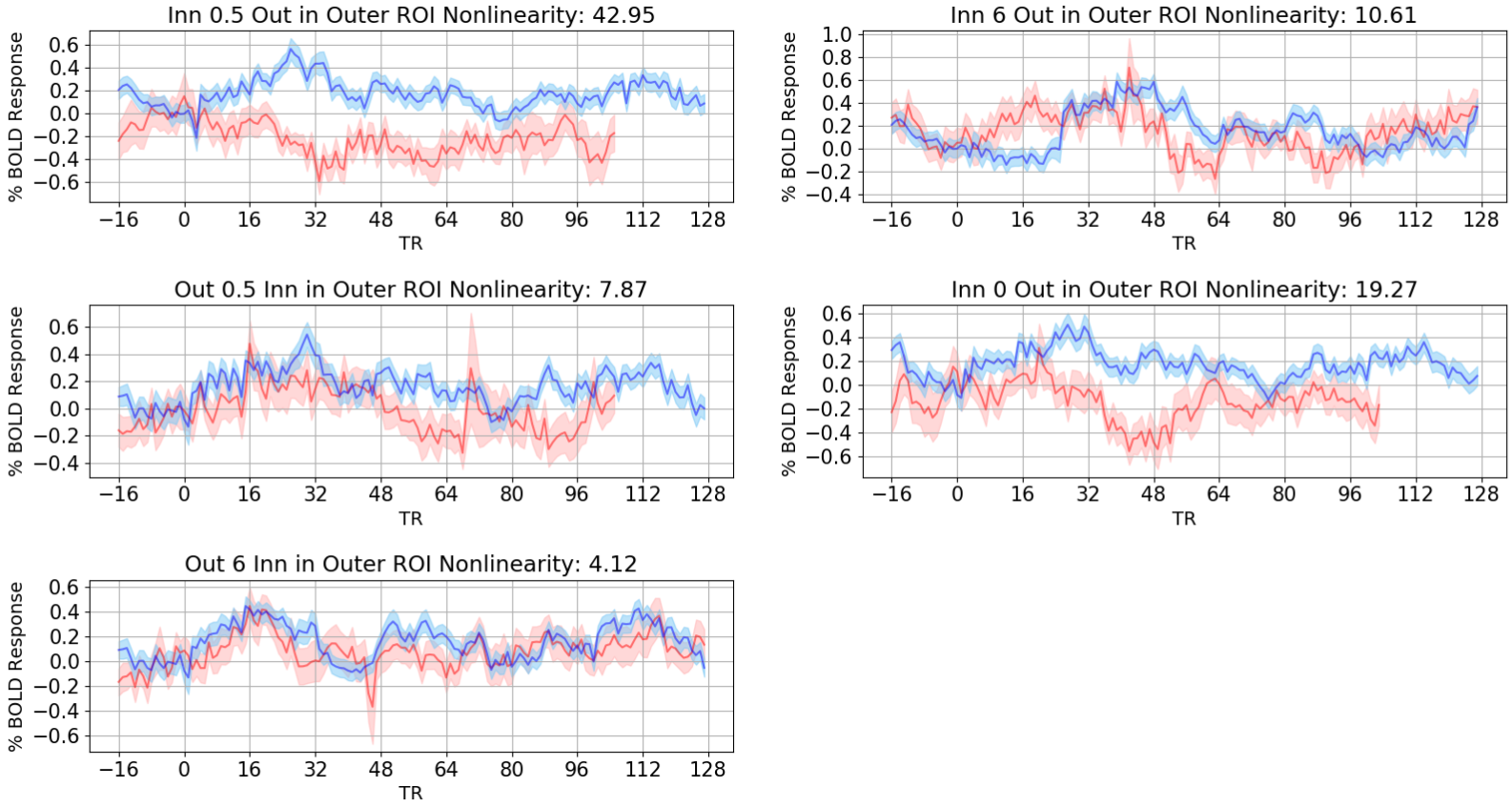

Figure A.29: Impulse Inn-Out SIRF vs. SOA in Outer ROI in LT 09. Blue is the observed SIRF data. Black is the SIRF model. Red is the observed SOA data. Green is the SOA model. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR = 250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

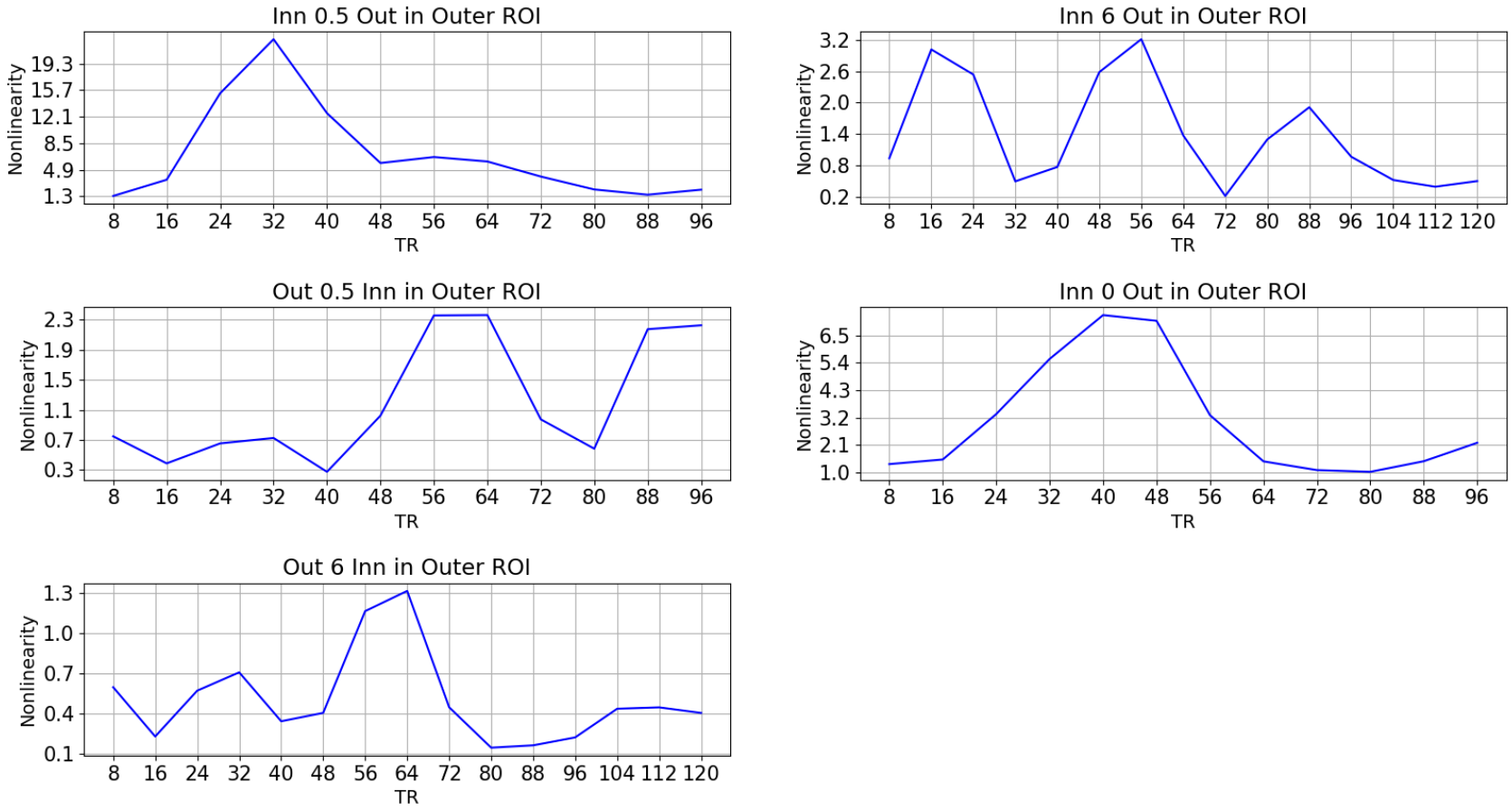

Figure A.30: Impulse Inn-Out in Outer ROI in LT 09. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

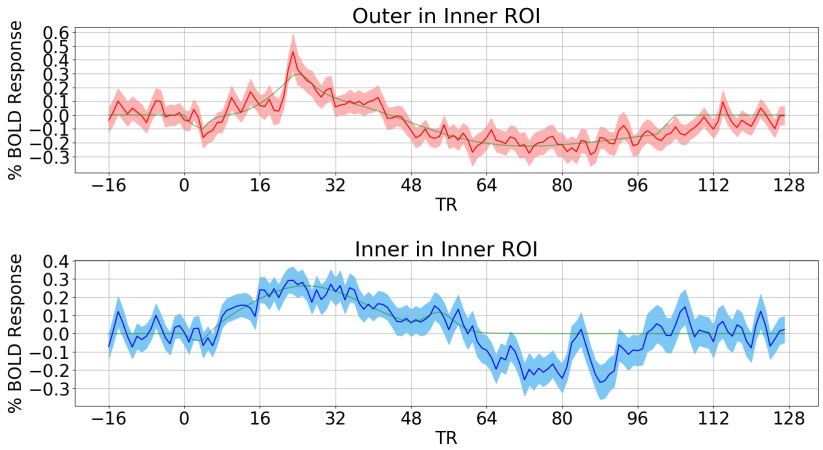

Figure A.31: BOLD responses to impulse stimulation (Impulse Inn-Out SIRF in Inner ROI) in LT 11. Green is the SIRF model. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR = 250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

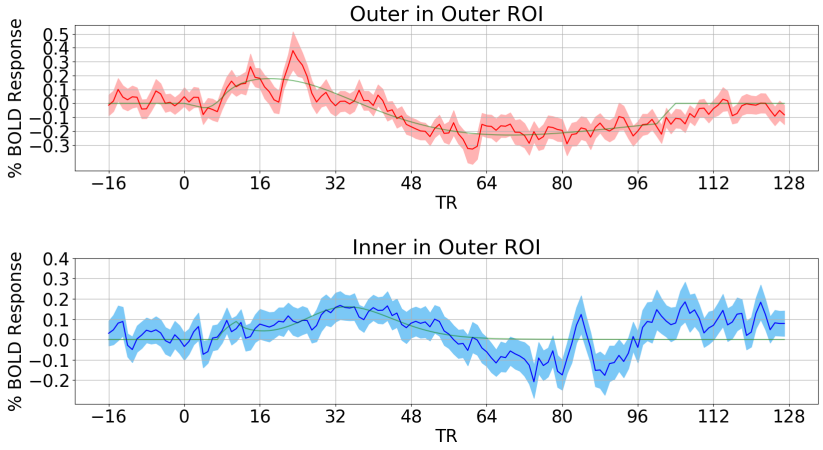

Figure A.32: BOLD responses to impulse stimulation (Impulse Inn-Out SIRF in Outer ROI) in LT 11. Green is the SIRF model. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR = 250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

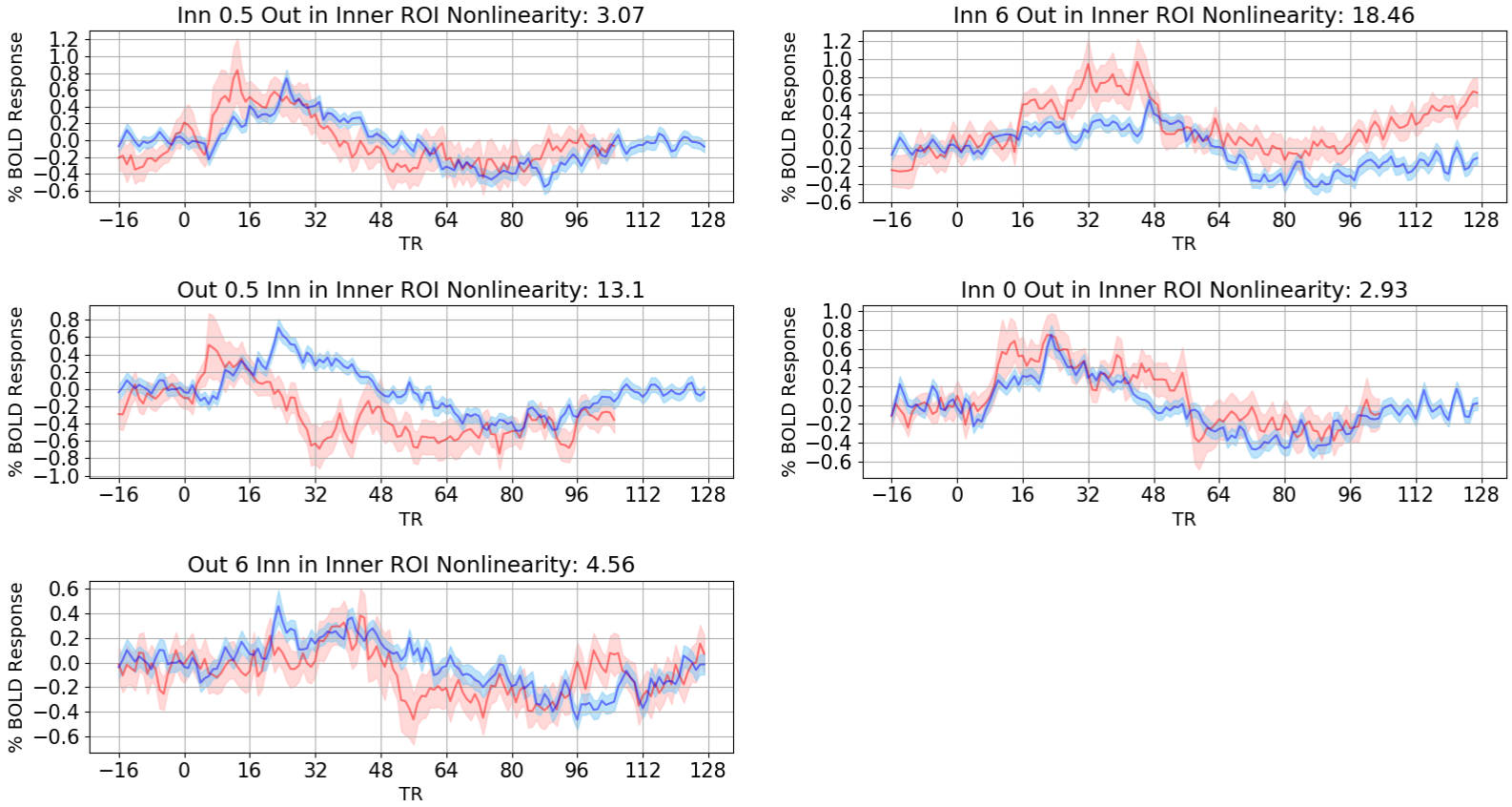

Figure A.33: Impulse Inn-Out SIRF vs. SOA in Inner ROI in LT 11. Blue is the predicted response. Red is the observed response. The nonlinearity represents the difference between the predicted and observed responses and was calculated based on the residual formula for all TRs. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

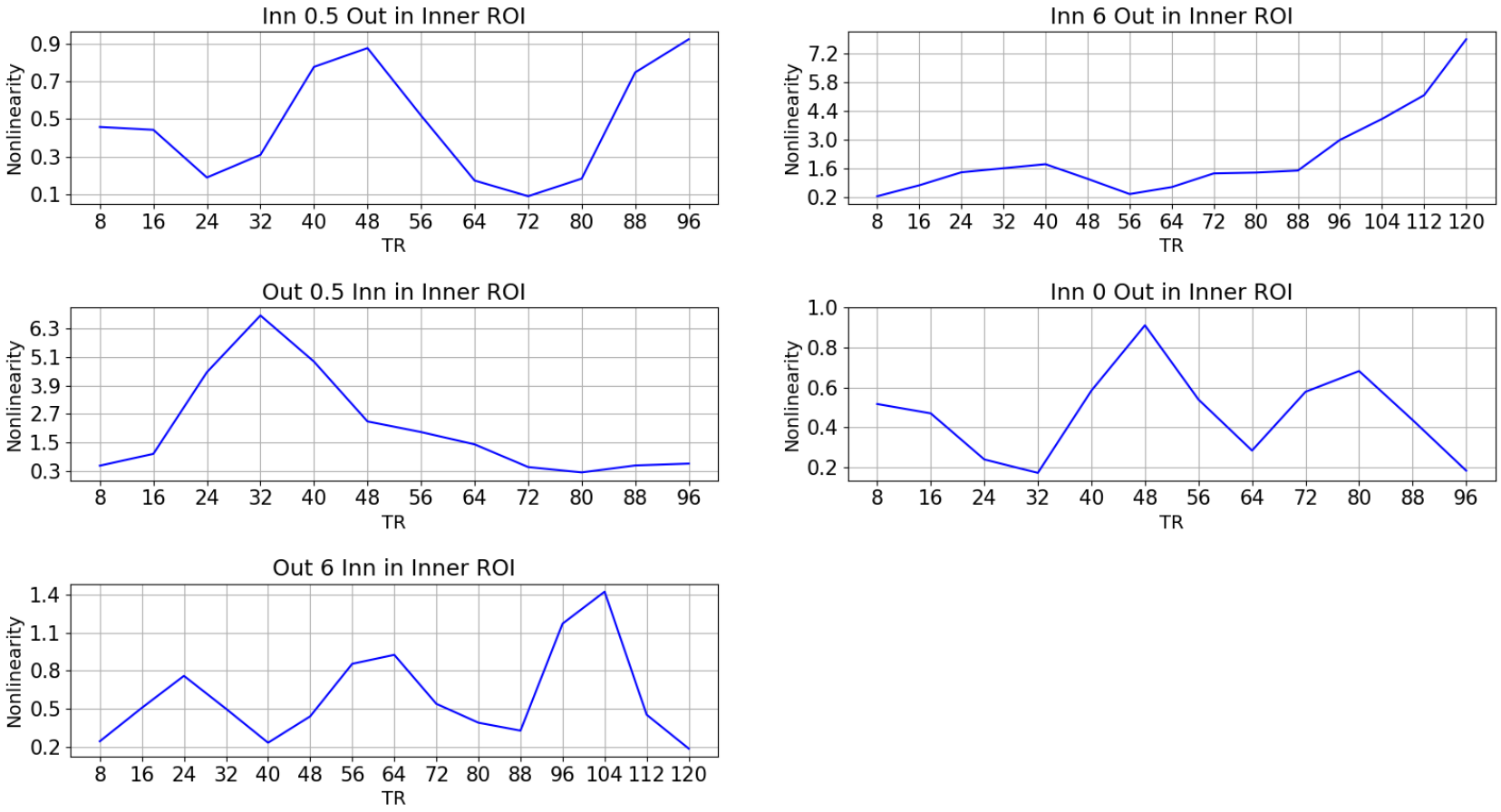

Figure A.34: Impulse Inn-Out in Inner ROI in LT 11. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

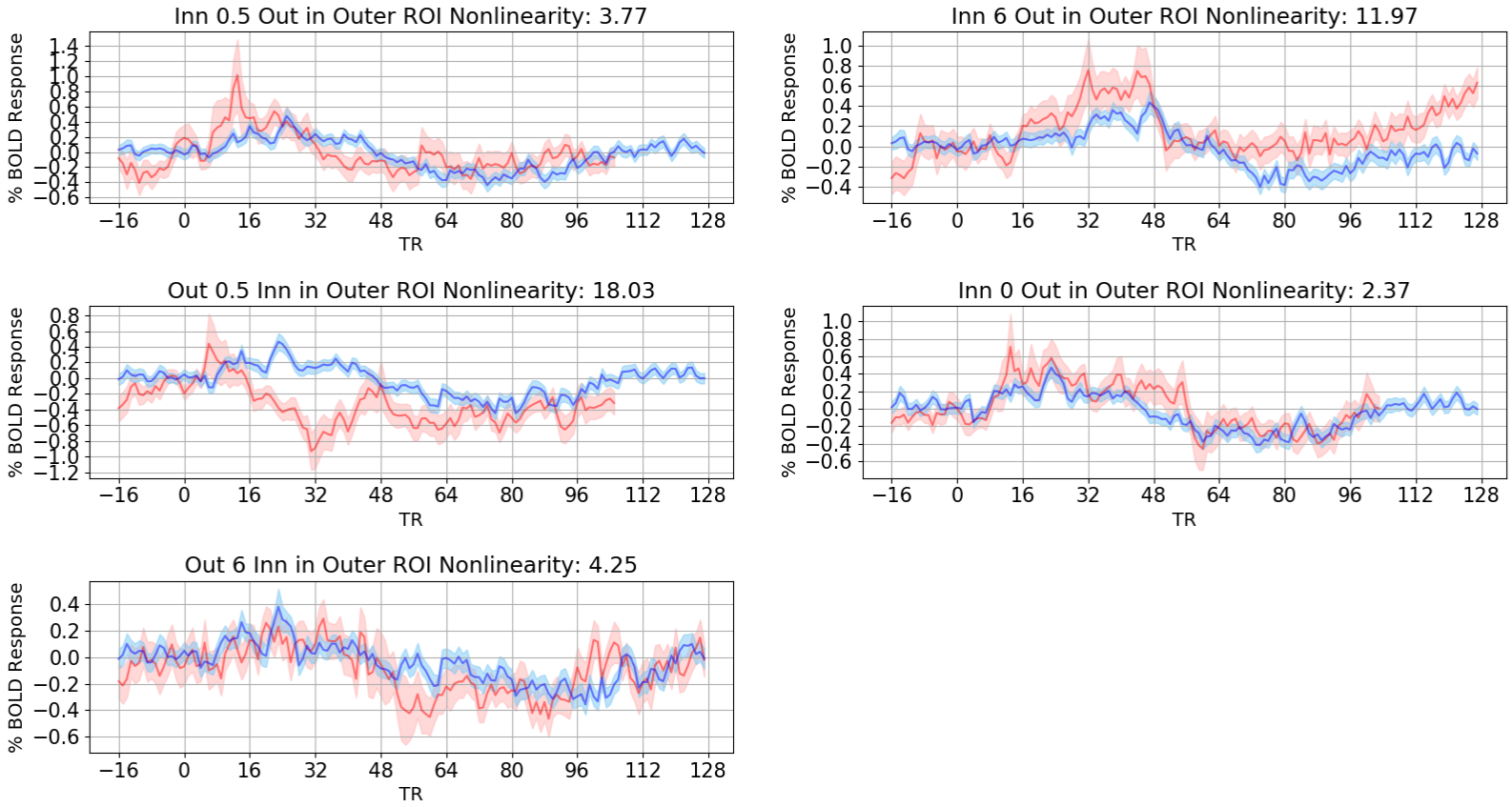

Figure A.35: Impulse Inn-Out SIRF vs. SOA in Outer ROI in LT 11. Blue is the predicted response. Red is the observed response. The nonlinearity represents the difference between the predicted and observed responses and was calculated based on the residual formula for all TRs. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

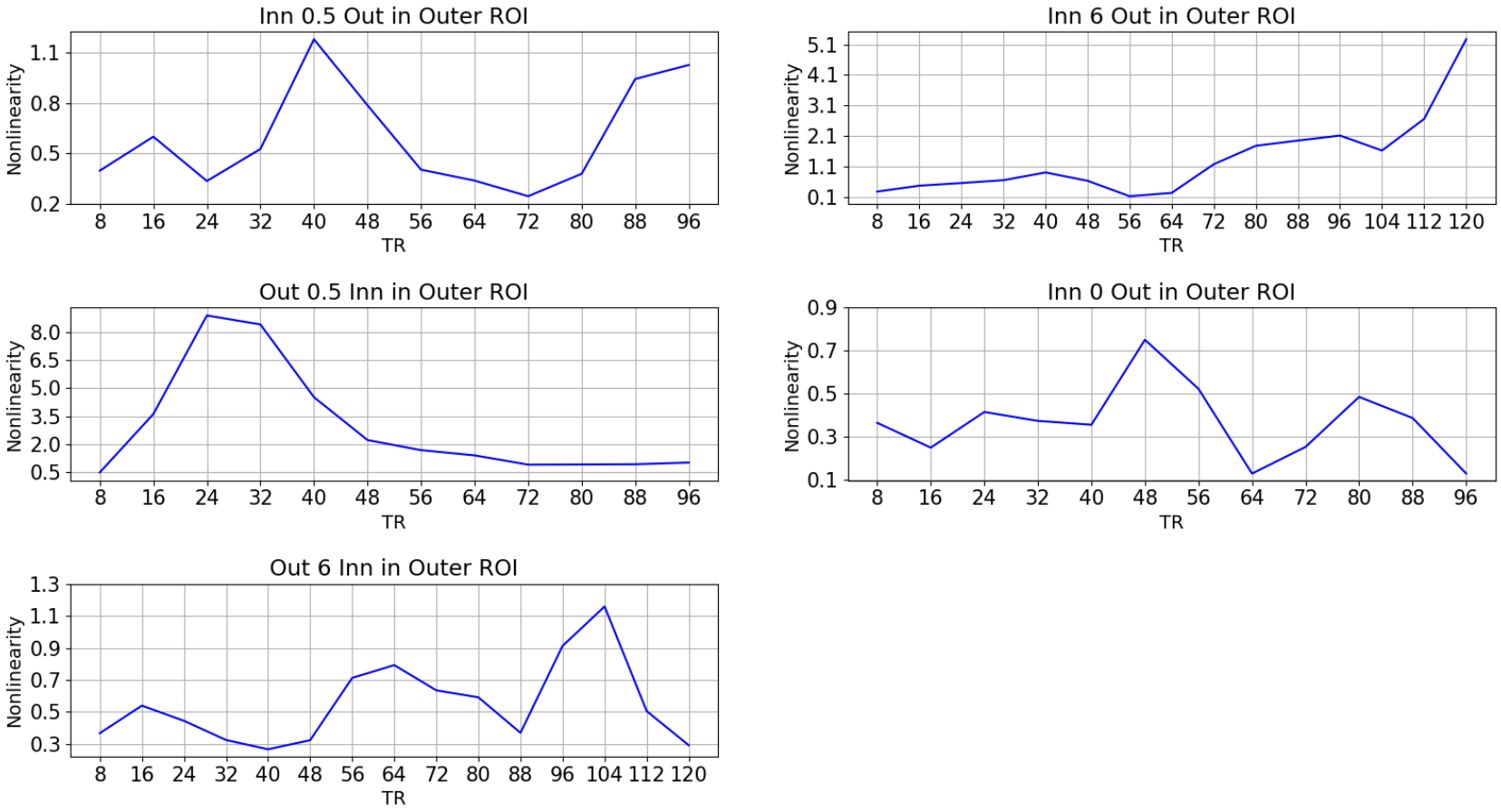

Figure A.36: Impulse Inn-Out in Outer ROI in LT 11. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

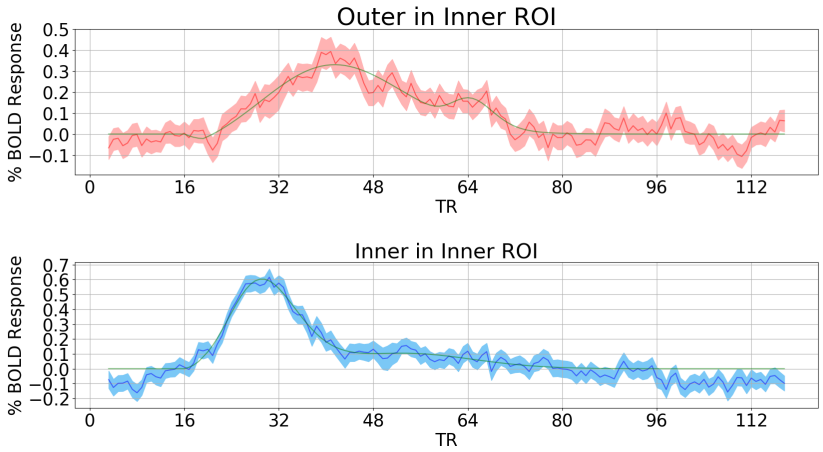

Figure A.37: BOLD responses to 1 s stimulation (Longer Pulse Inn-Out SIRF in Inner ROI) in LT 06. Green is the SIRF model. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR = 250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

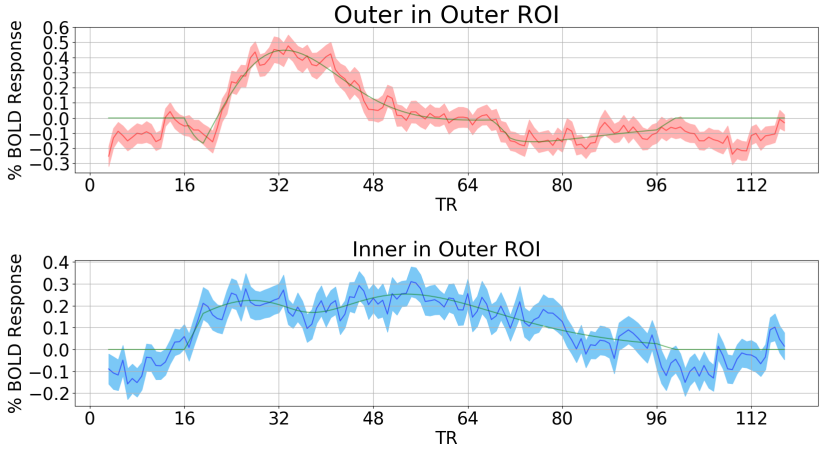

Figure A.38: BOLD responses to 1 s stimulation (Longer Pulse Inn-Out SIRF in Outer ROI) in LT 06. Green is the SIRF model. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR = 250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

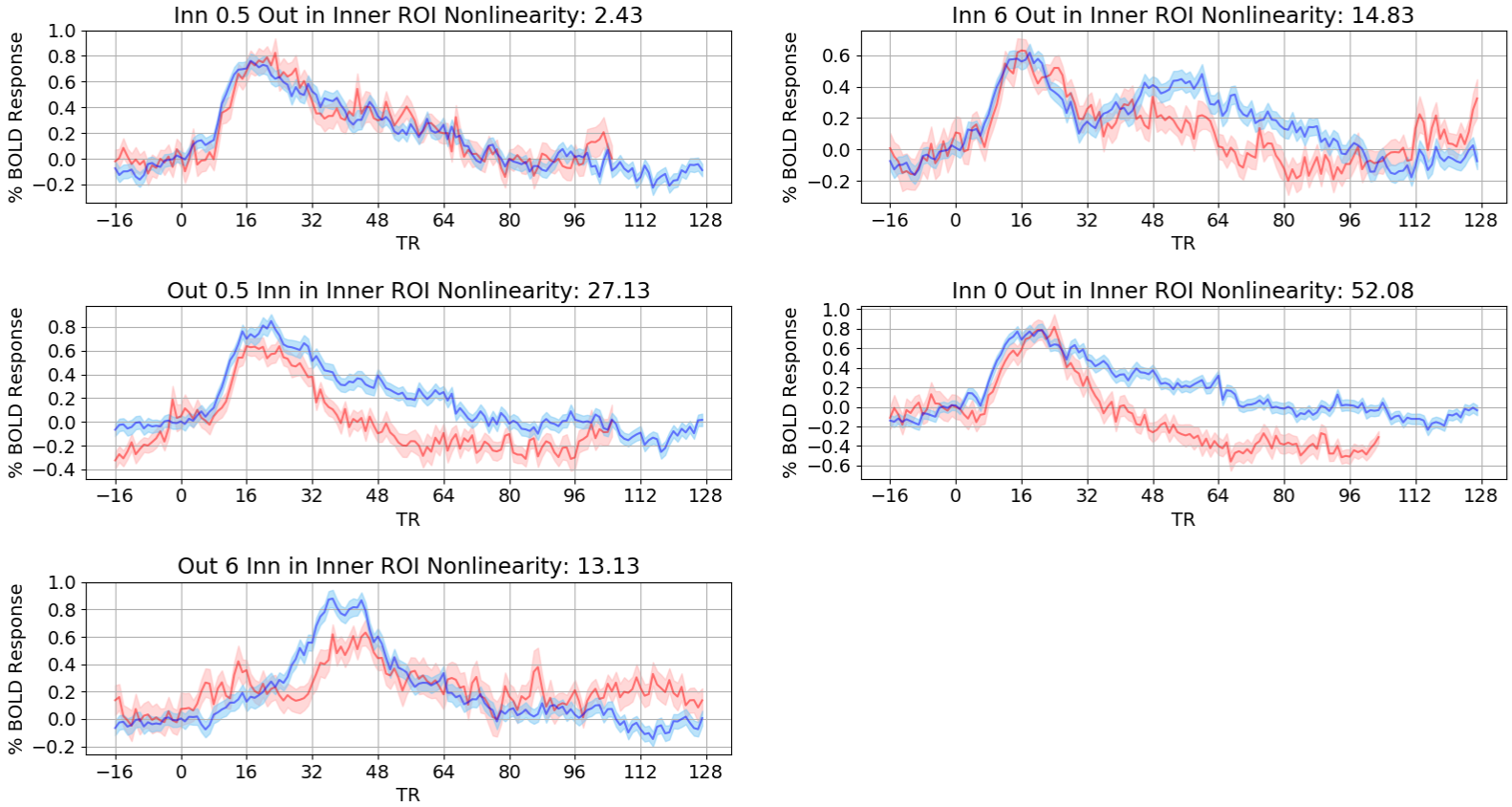

Figure A.39: Longer Pulse Inn-Out SIRF vs. SOA in Inner ROI in LT 06. Blue is the predicted response. Red is the observed response. The nonlinearity represents the difference between the predicted and observed responses and was calculated based on the residual formula for all TRs. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

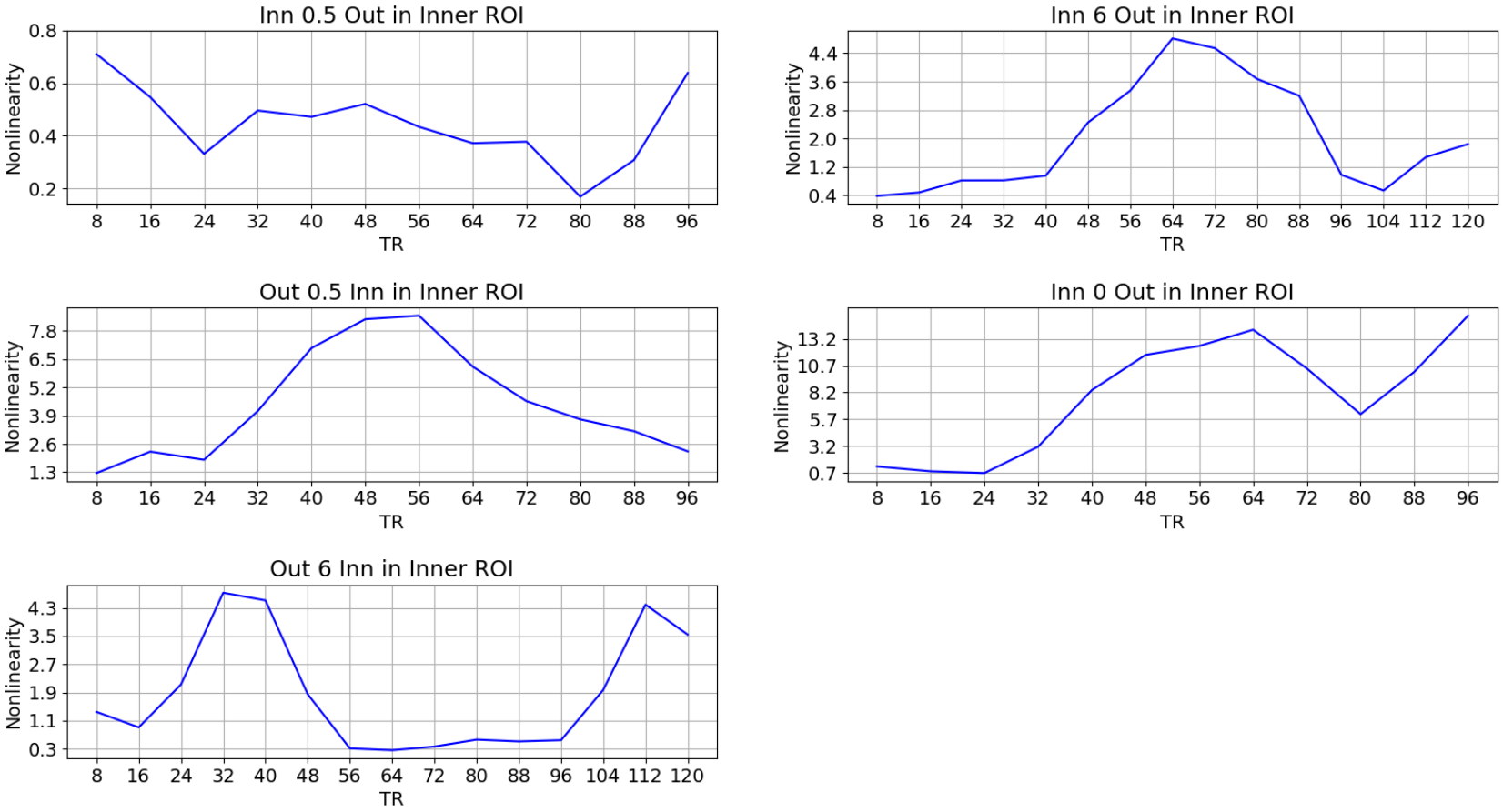

Figure A.40: Longer Pulse Inn-Out in Inner ROI in LT 06. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

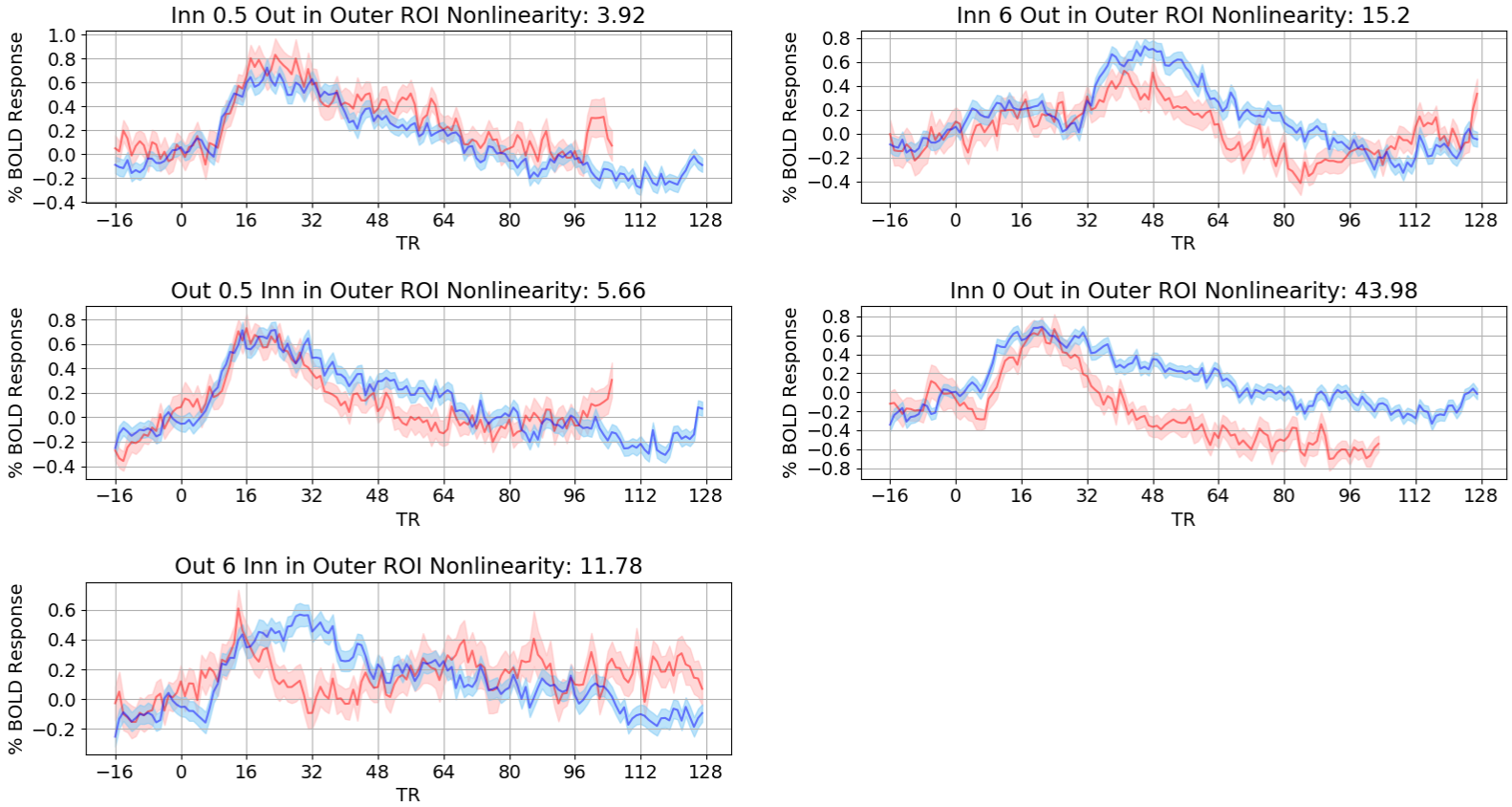

Figure A.41: Longer Pulse Inn-Out SIRF vs. SOA in Outer ROI in LT 06. Blue is the predicted response. Red is the observed response. The nonlinearity represents the difference between the predicted and observed responses and was calculated based on the residual formula for all TRs. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

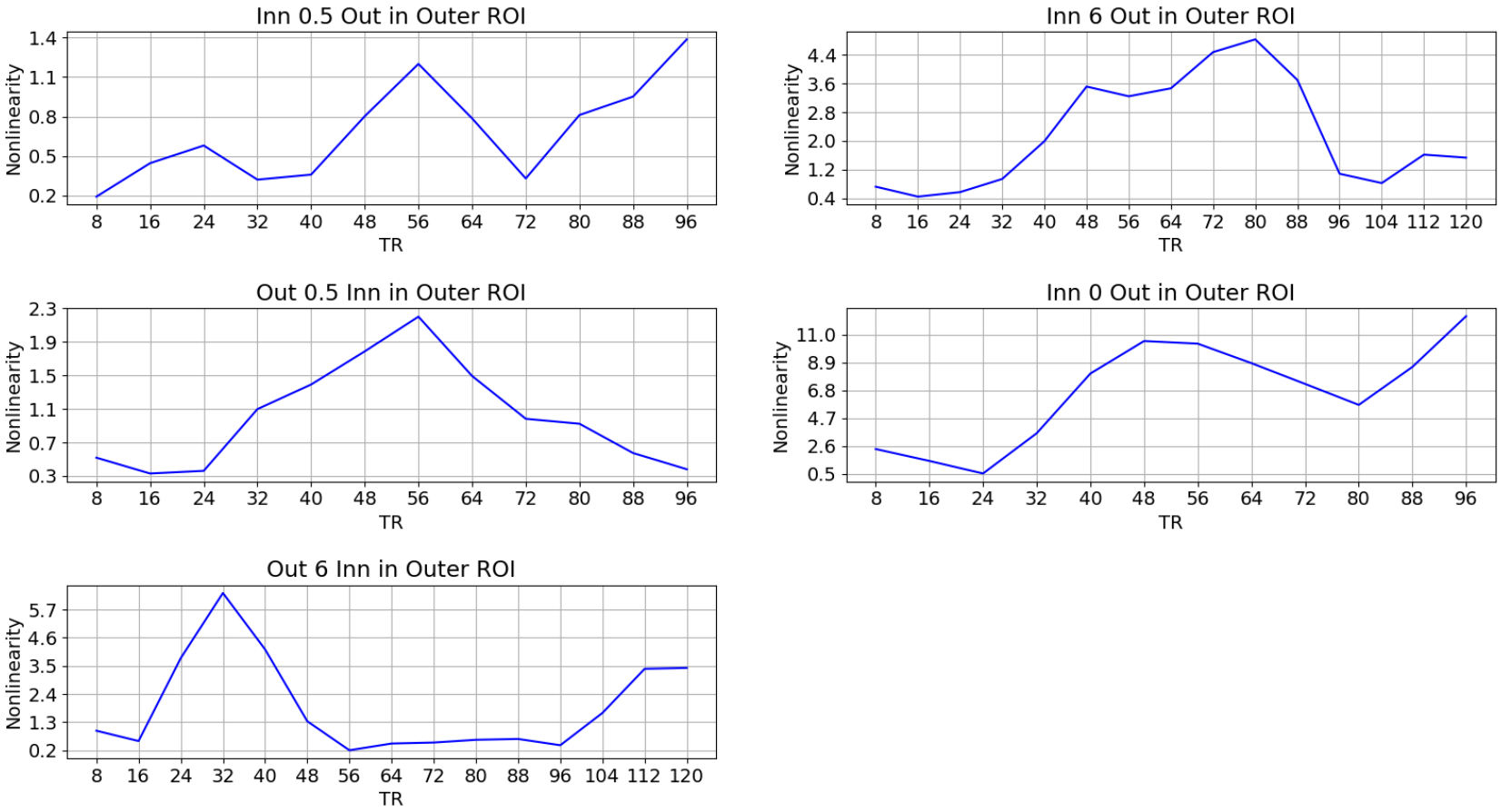

Figure A.42: Longer Pulse Inn-Out in Outer ROI in LT 06. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

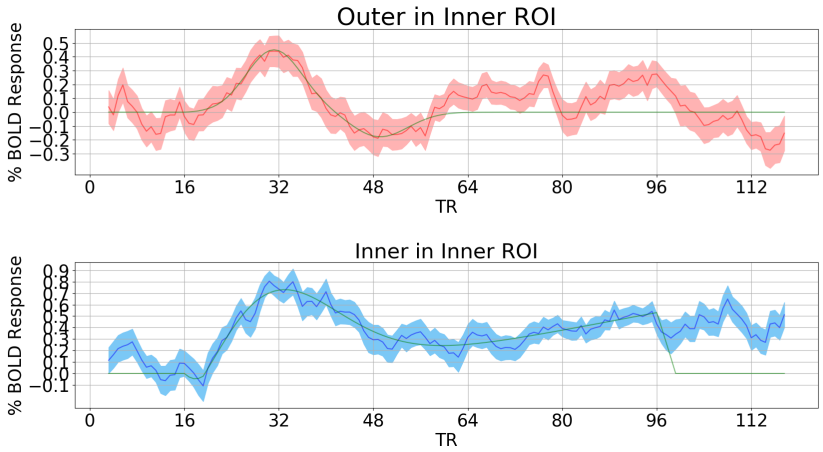

Figure A.43: BOLD responses to 1 s stimulation (Longer Pulse Inn-Out SIRF in Inner ROI) in LT 09. Green is the SIRF model. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR = 250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

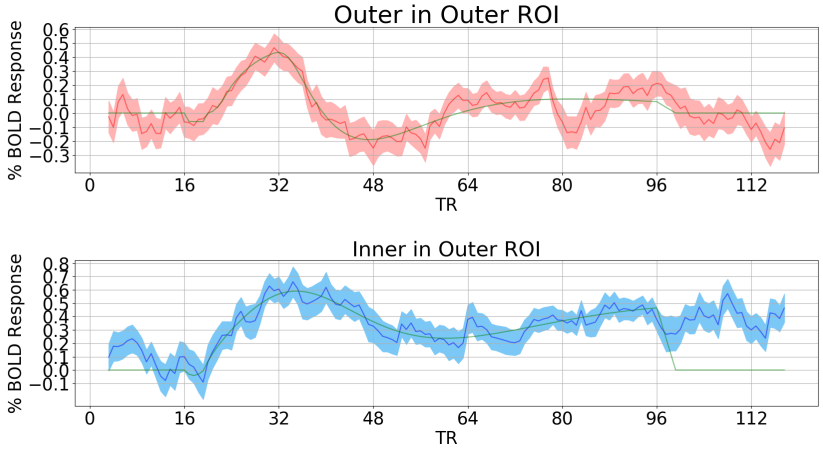

Figure A.44: BOLD responses to 1 s stimulation (Longer Pulse Inn-Out SIRF in Outer ROI) in LT 09. Green is the SIRF model. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR = 250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

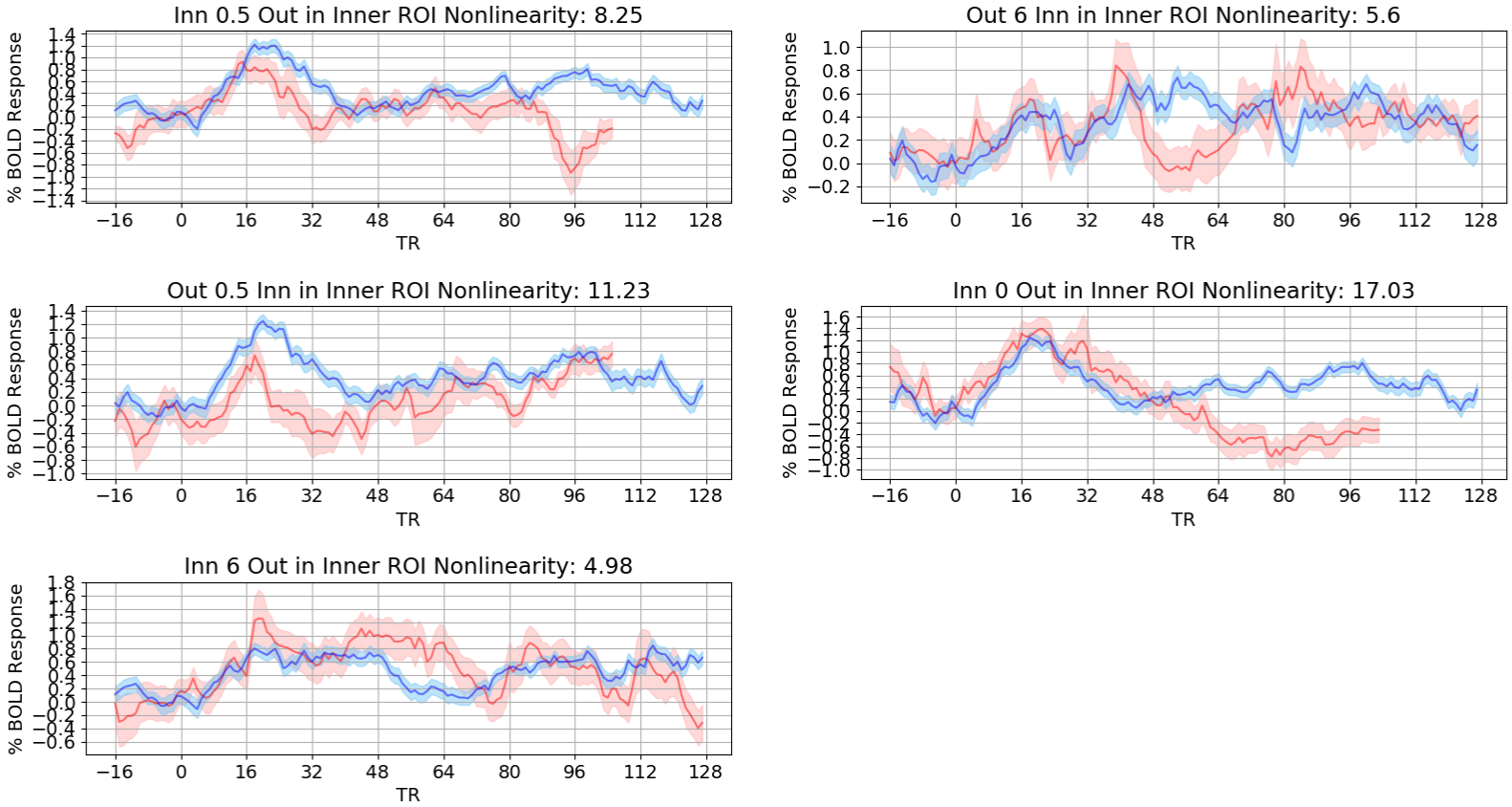

Figure A.45: Longer Pulse Inn-Out SIRF vs. SOA in Inner ROI in LT 09. Blue is the predicted response. Red is the observed response. The nonlinearity represents the difference between the predicted and observed responses and was calculated based on the residual formula for all TRs. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

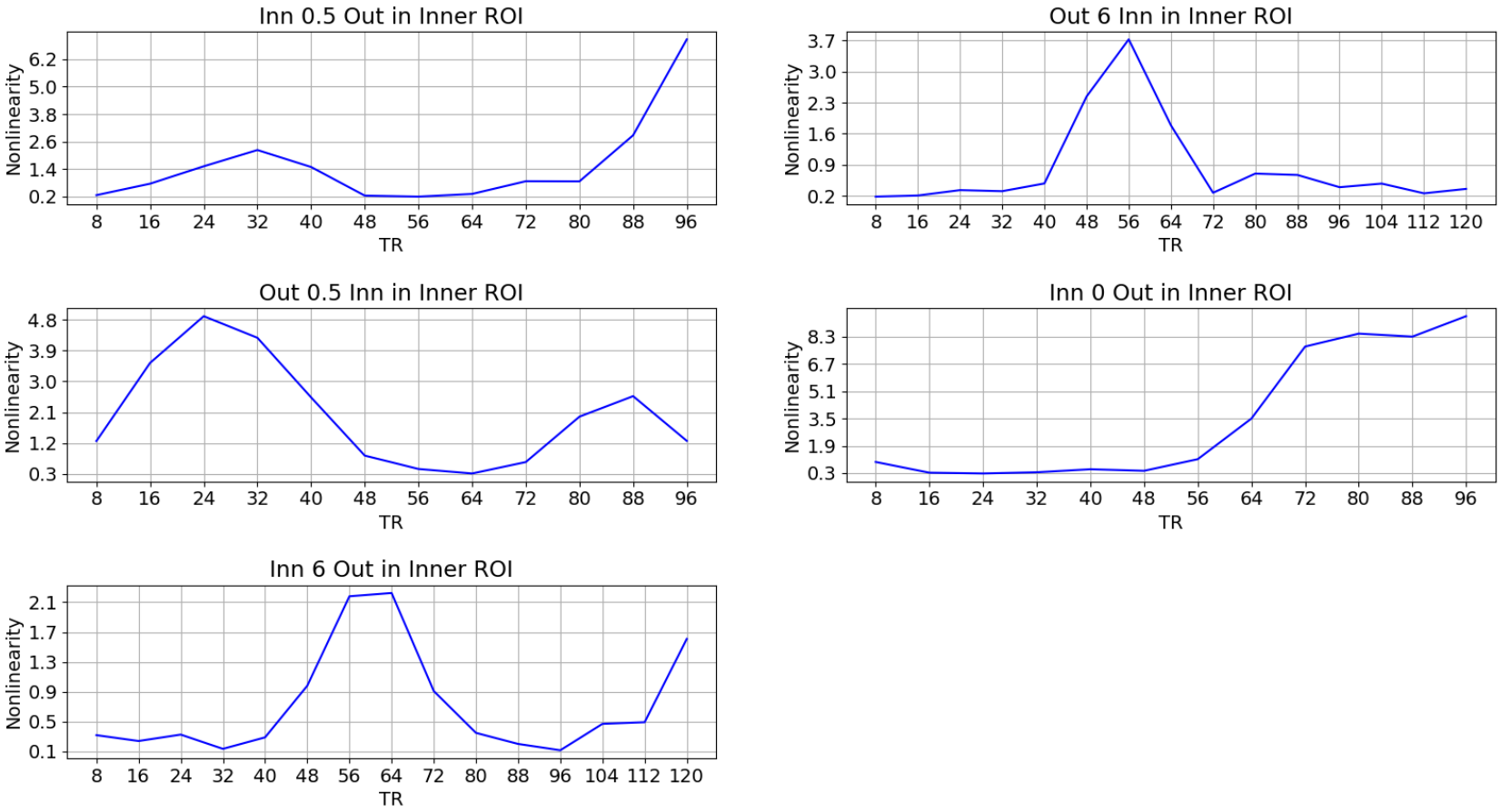

Figure A.46: Longer Pulse Inn-Out in Inner ROI in LT 09. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

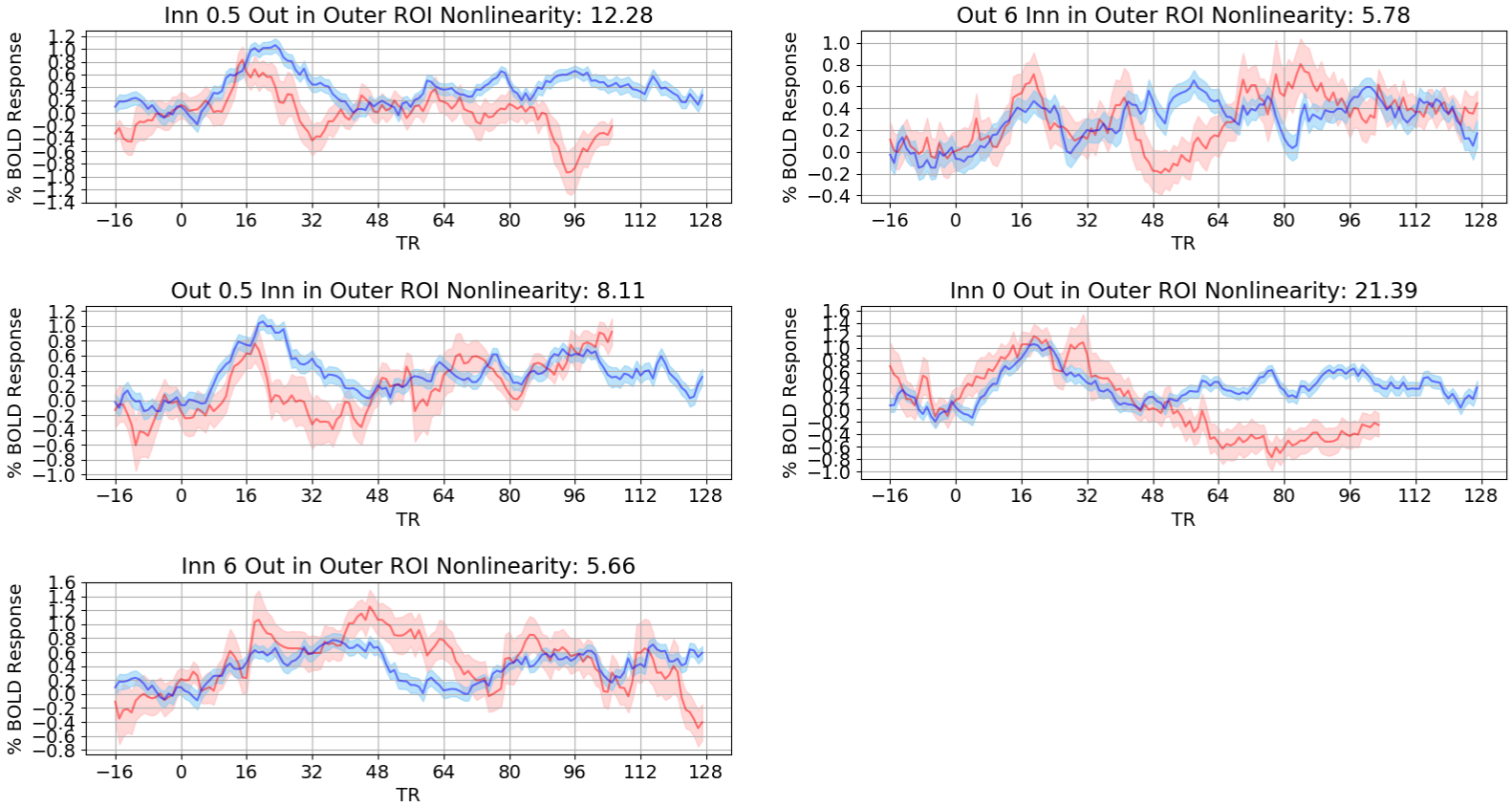

Figure A.47: Longer Pulse Inn-Out SIRF vs. SOA in Outer ROI in LT 09. Blue is the predicted response. Red is the observed response. The nonlinearity represents the difference between the predicted and observed responses and was calculated based on the residual formula for all TRs. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

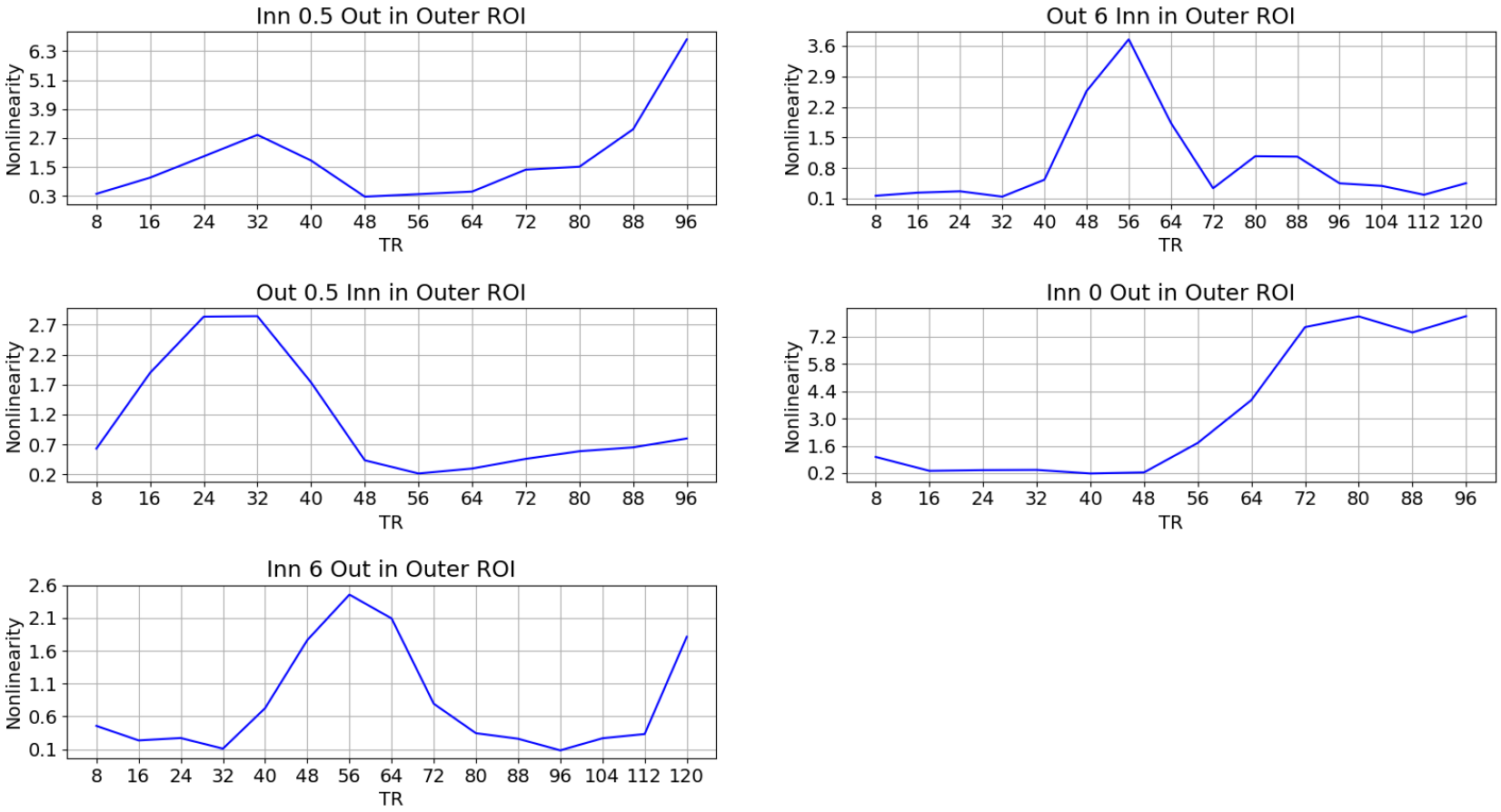

Figure A.48: Longer Pulse Inn-Out in Outer ROI in LT 09. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

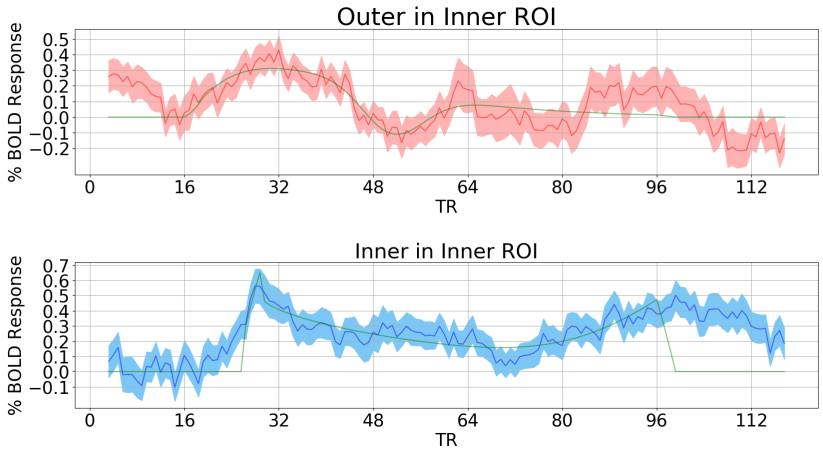

Figure A.49: BOLD responses to 1 s stimulation (Longer Pulse Inn-Out SIRF in Inner ROI) in LT 11. Green is the SIRF model. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR = 250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

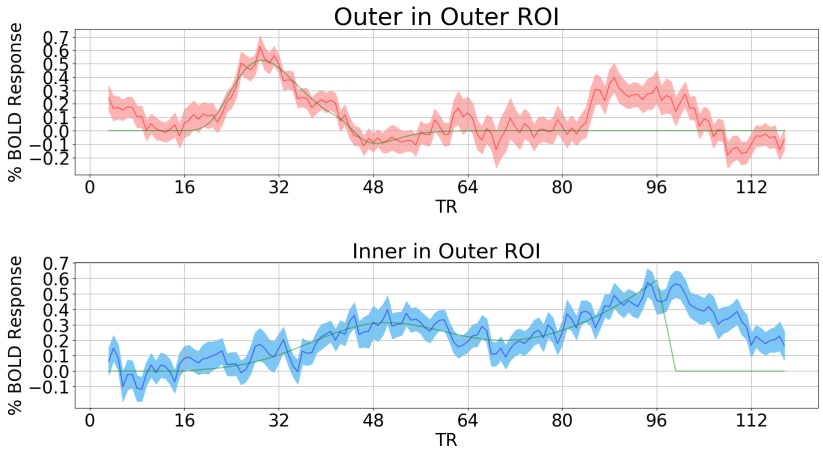

Figure A.50: BOLD responses to 1 s stimulation (Longer Pulse Inn-Out SIRF in Outer ROI) in LT 11. Green is the SIRF model. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR = 250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

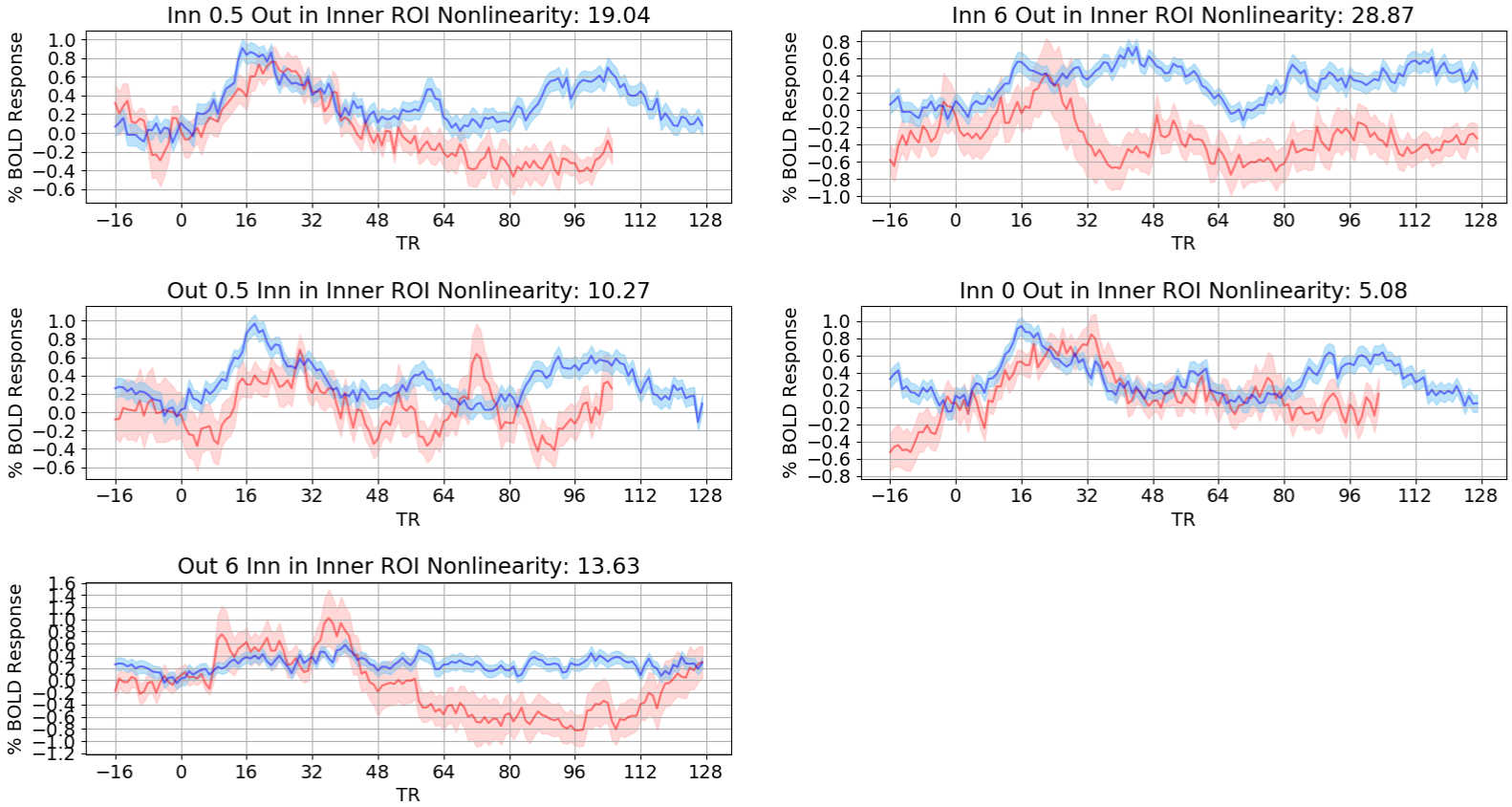

Figure A.51: Longer Pulse Inn-Out SIRF vs. SOA in Inner ROI in LT 11. Blue is the predicted response. Red is the observed response. The nonlinearity represents the difference between the predicted and observed responses and was calculated based on the residual formula for all TRs. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

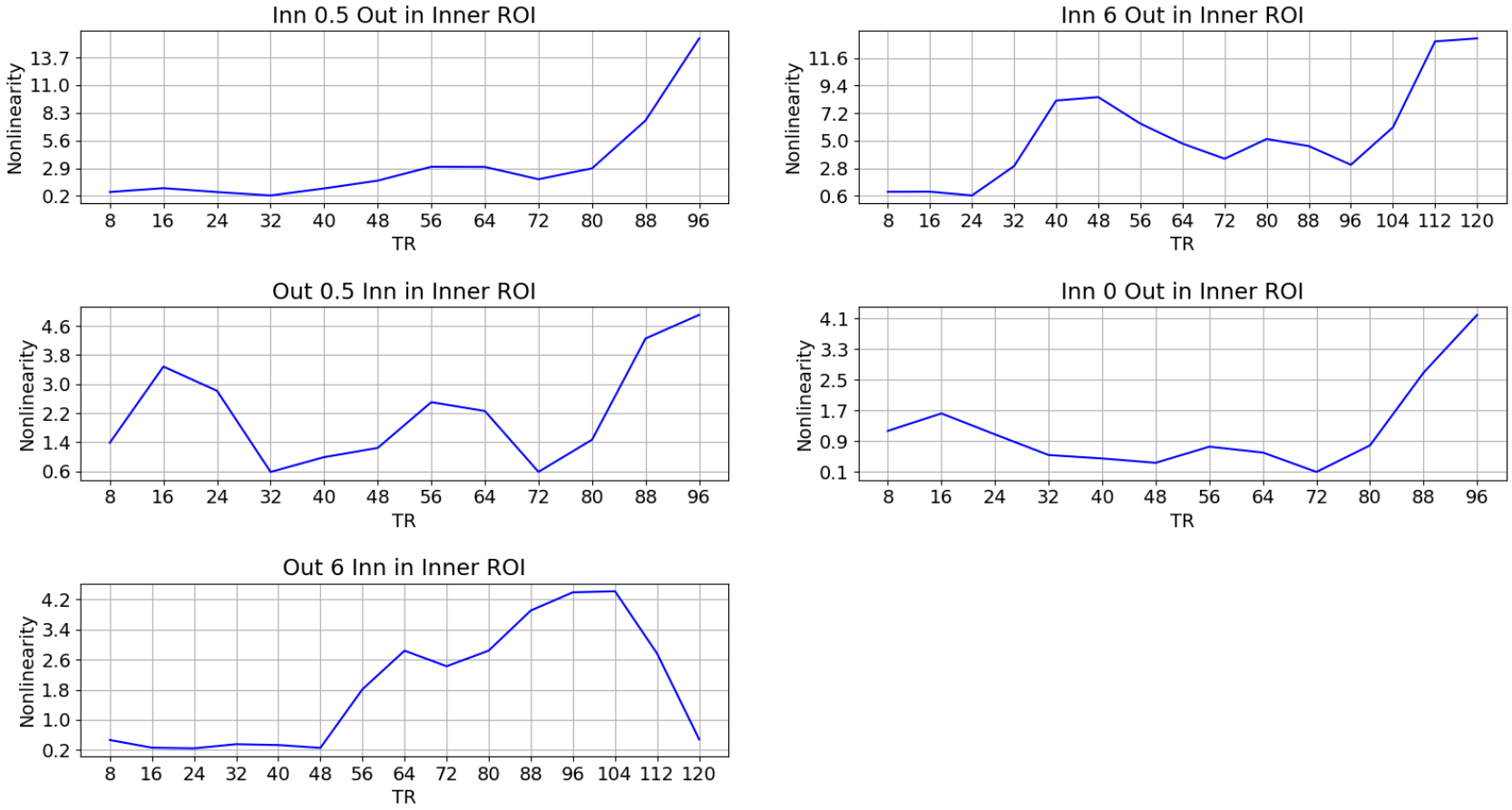

Figure A.52: Longer Pulse Inn-Out in Inner ROI in LT 11. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

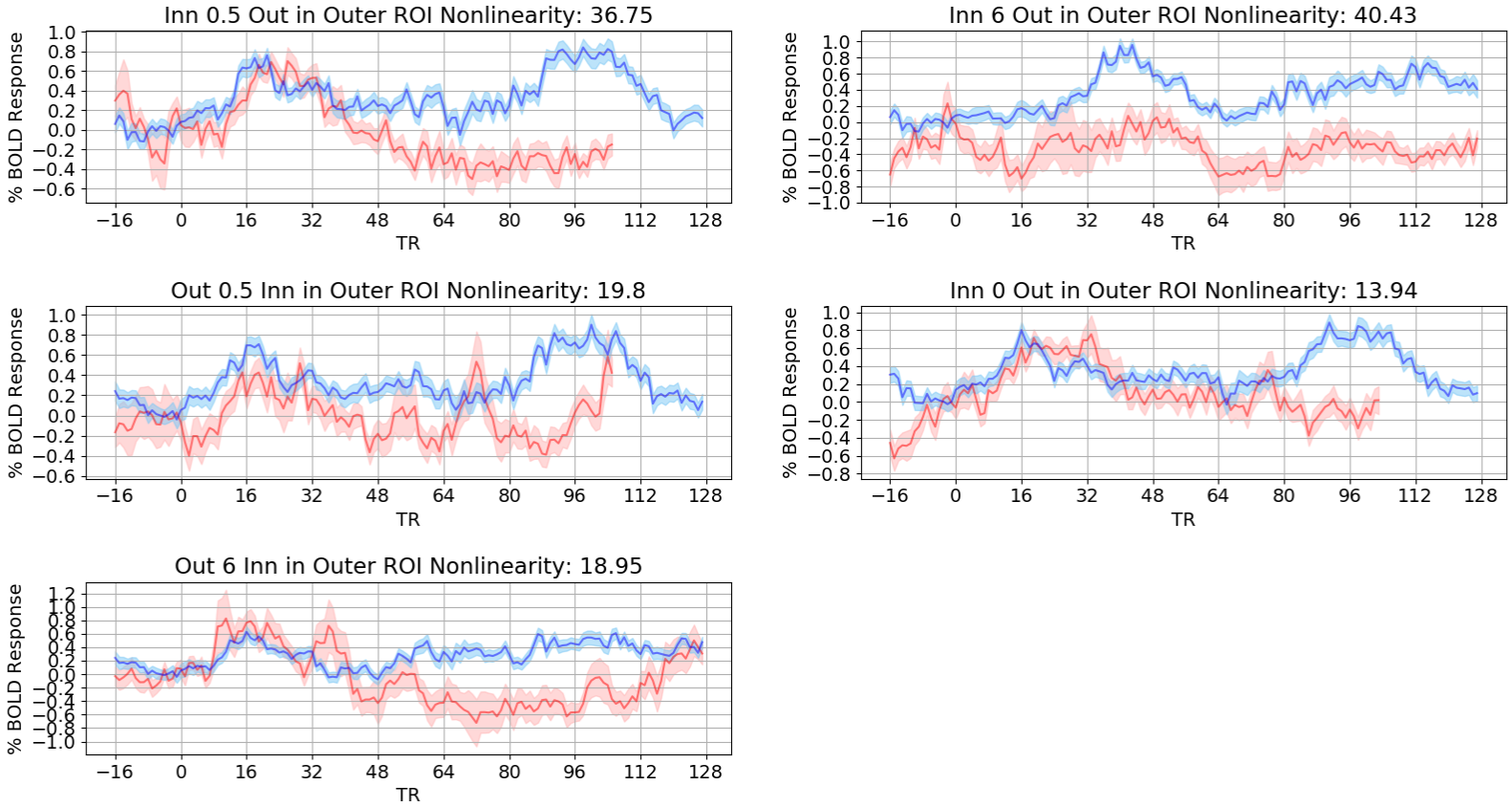

Figure A.53: Longer Pulse Inn-Out SIRF vs. SOA in Outer ROI in LT 11. Blue is the predicted response. Red is the observed response. The nonlinearity represents the difference between the predicted and observed responses and was calculated based on the residual formula for all TRs. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

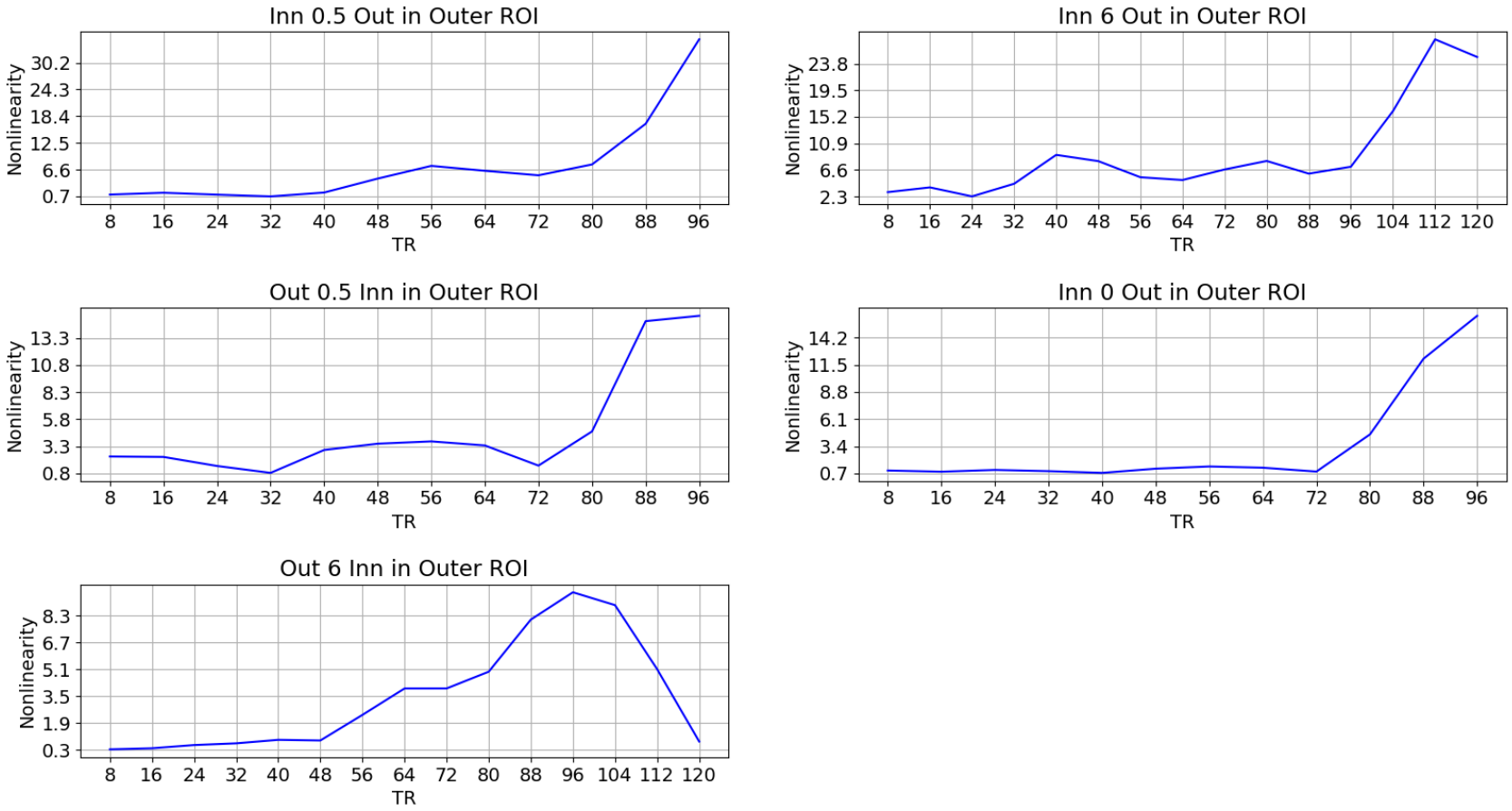

Figure A.54: Longer Pulse Inn-Out in Outer ROI in LT 11. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

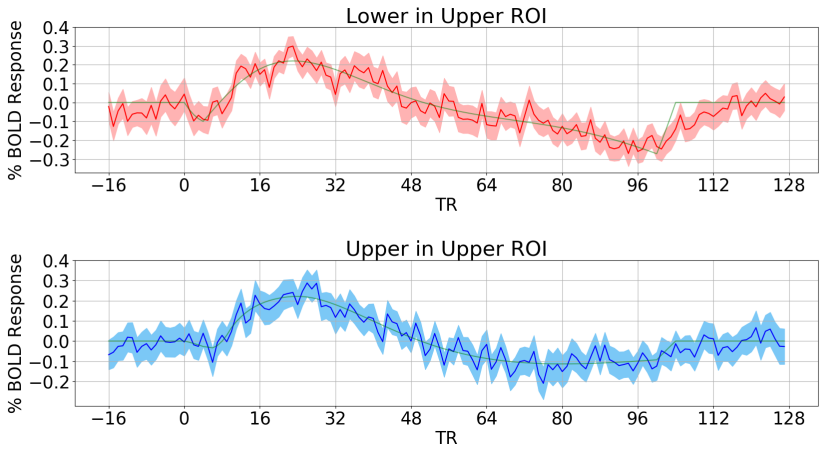

Figure A.55: BOLD responses to impulse stimulation (Impulse Upp-Low SIRF in Upper ROI) in LT 06. Green is the SIRF model. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR = 250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

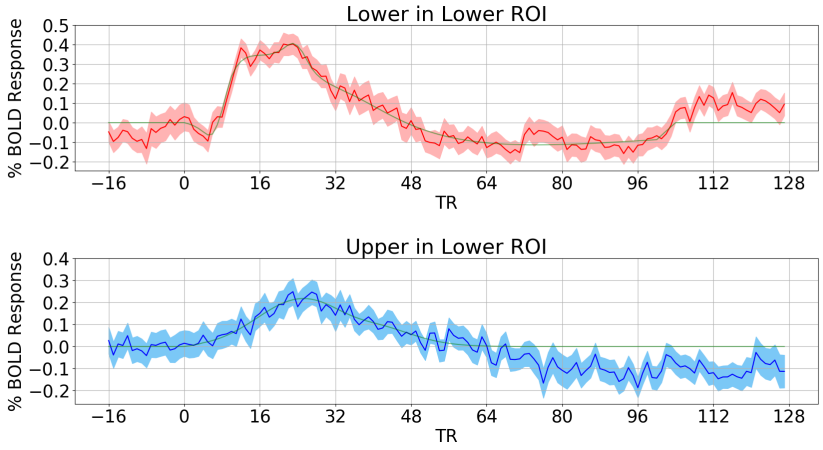

Figure A.56: BOLD responses to impulse stimulation (Impulse Upp-Low SIRF in Lower ROI) in LT 06. Green is the SIRF model. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR = 250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

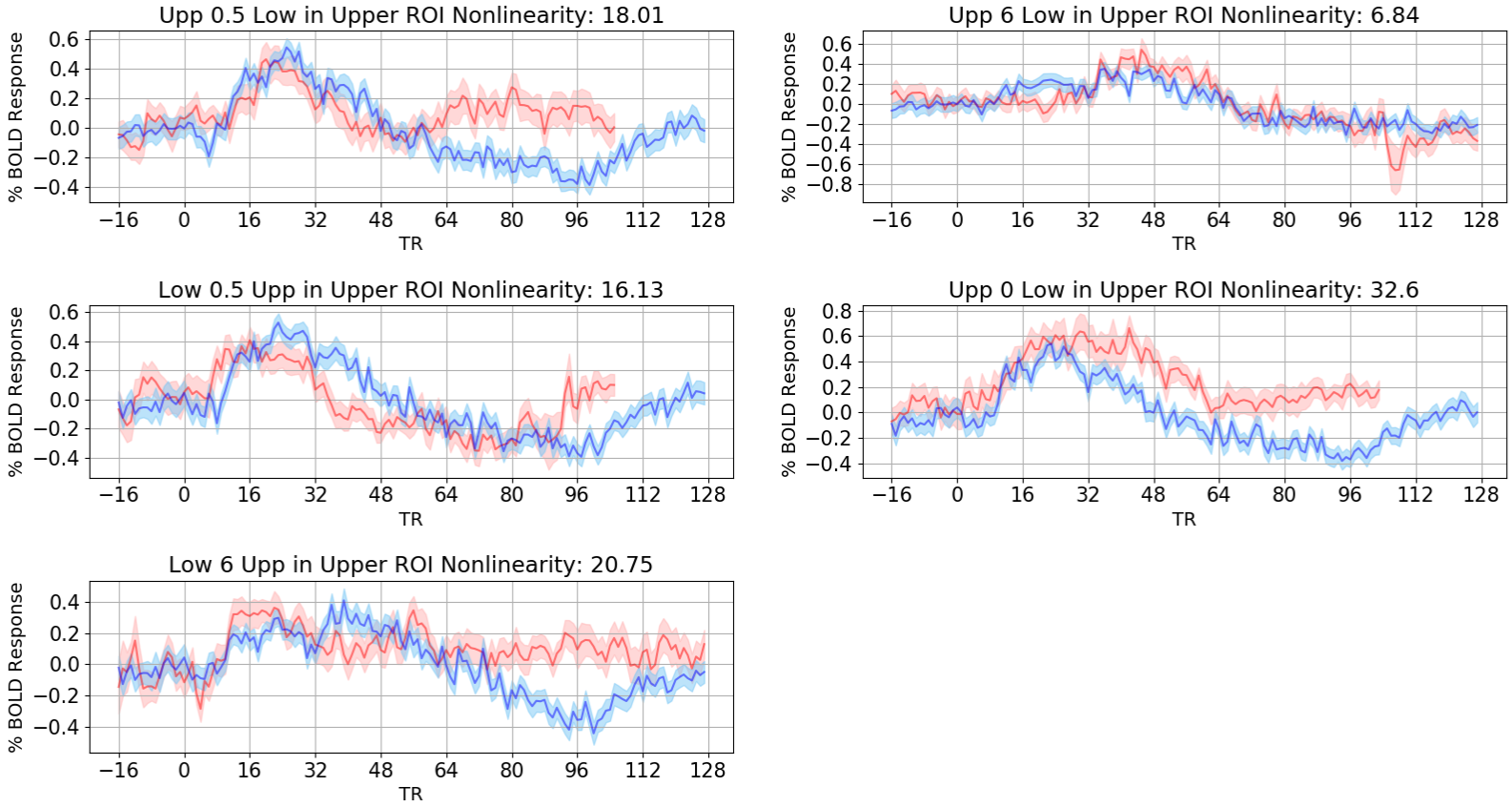

Figure A.57: Impulse Upp-Low SIRF vs. SOA in Upper ROI in LT 06. Blue is the predicted response. Red is the observed response. The nonlinearity represents the difference between the predicted and observed responses and was calculated based on the residual formula for all TRs. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

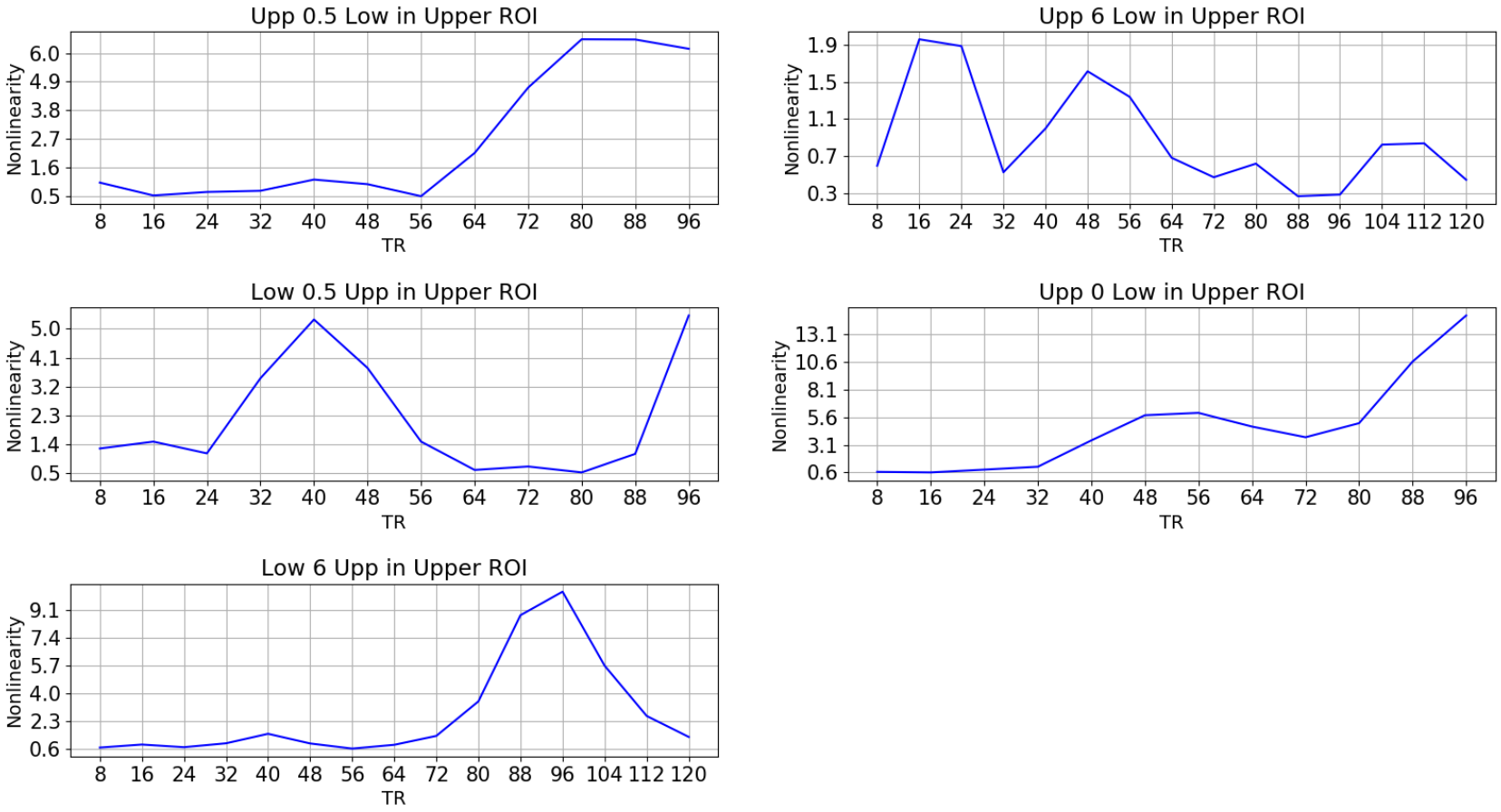

Figure A.58: Impulse Upp-Low in Upper ROI in LT 06. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

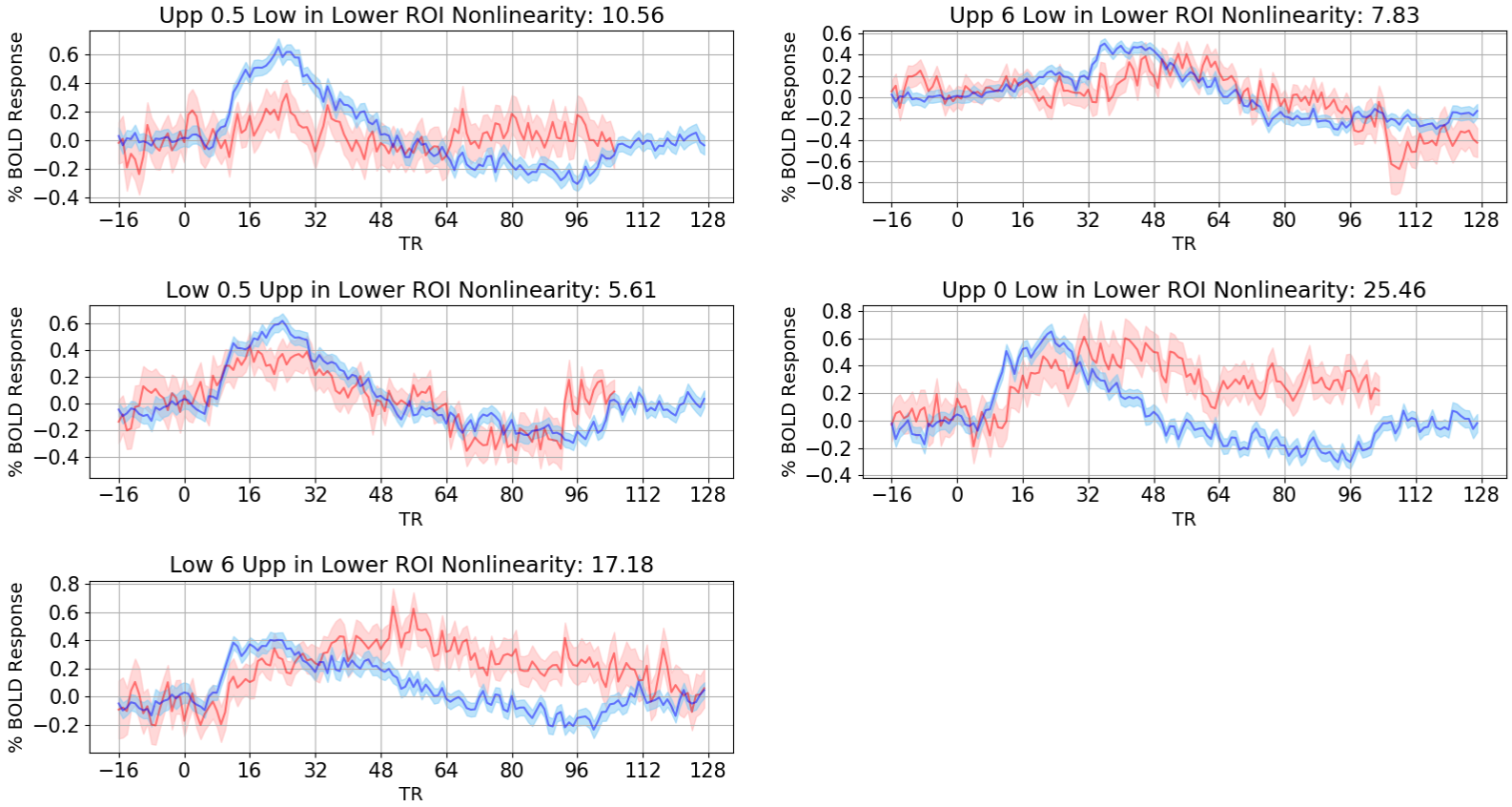

Figure A.59: Impulse Upp-Low SIRF vs. SOA in Lower ROI in LT 06. Blue is the predicted response. Red is the observed response. The nonlinearity represents the difference between the predicted and observed responses and was calculated based on the residual formula for all TRs. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

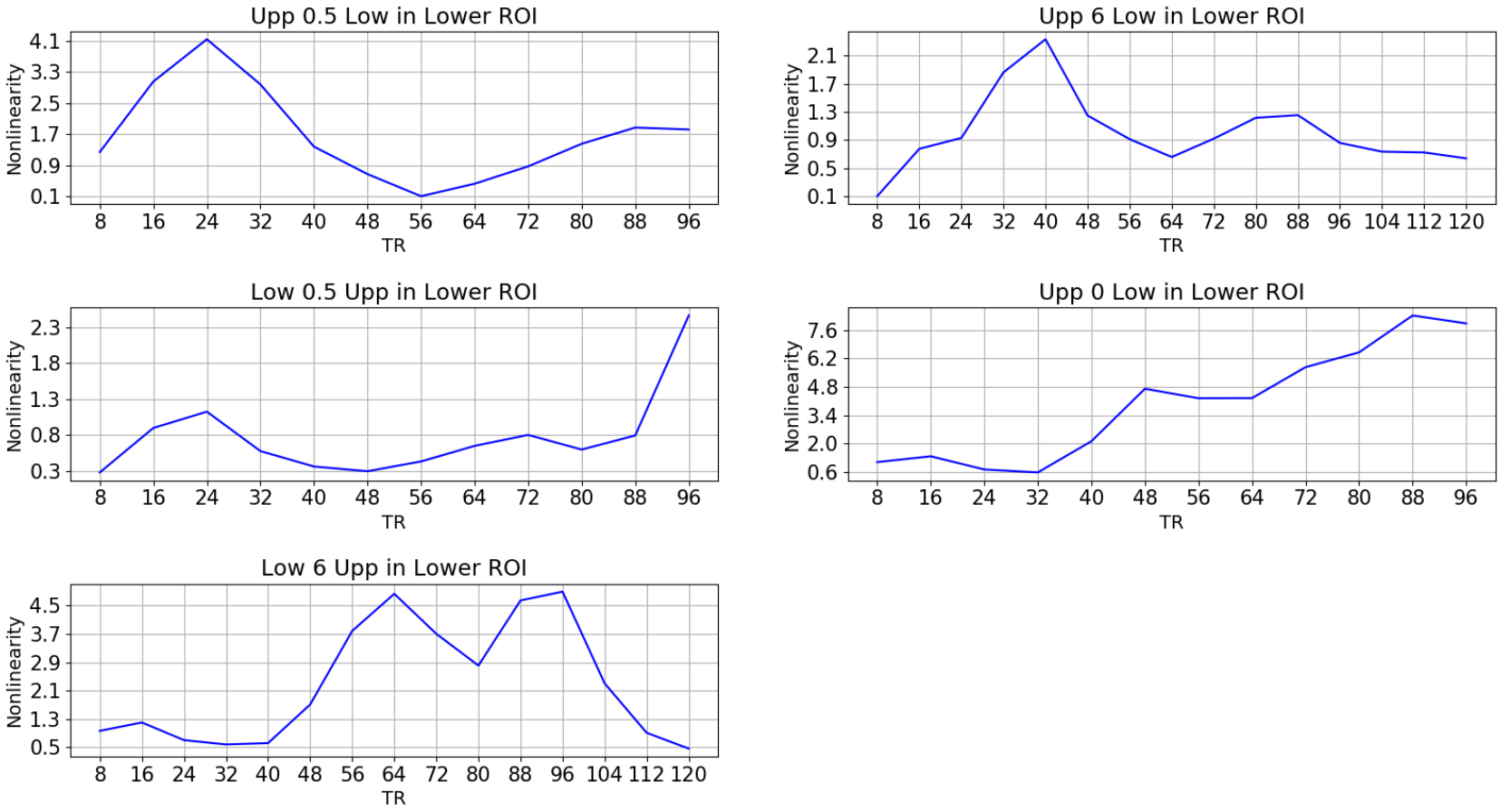

Figure A.60: Impulse Upp-Low in Lower ROI in LT 06. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

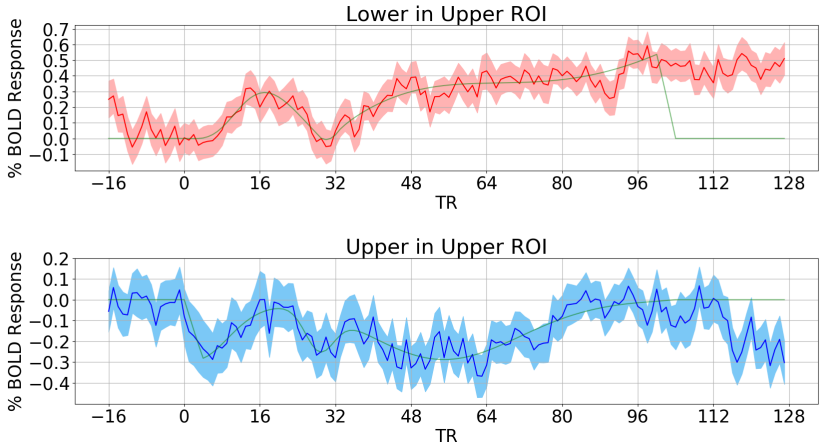

Figure A.61: BOLD responses to impulse stimulation (Impulse Upp-Low SIRF in Upper ROI) in LT 09. Green is the SIRF model. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR = 250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

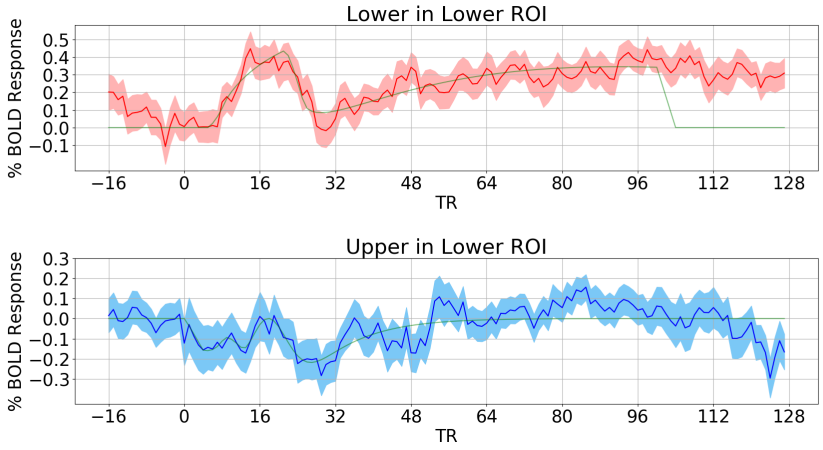

Figure A.62: BOLD responses to impulse stimulation (Impulse Upp-Low SIRF in Lower ROI) in LT 09. Green is the SIRF model. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR = 250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

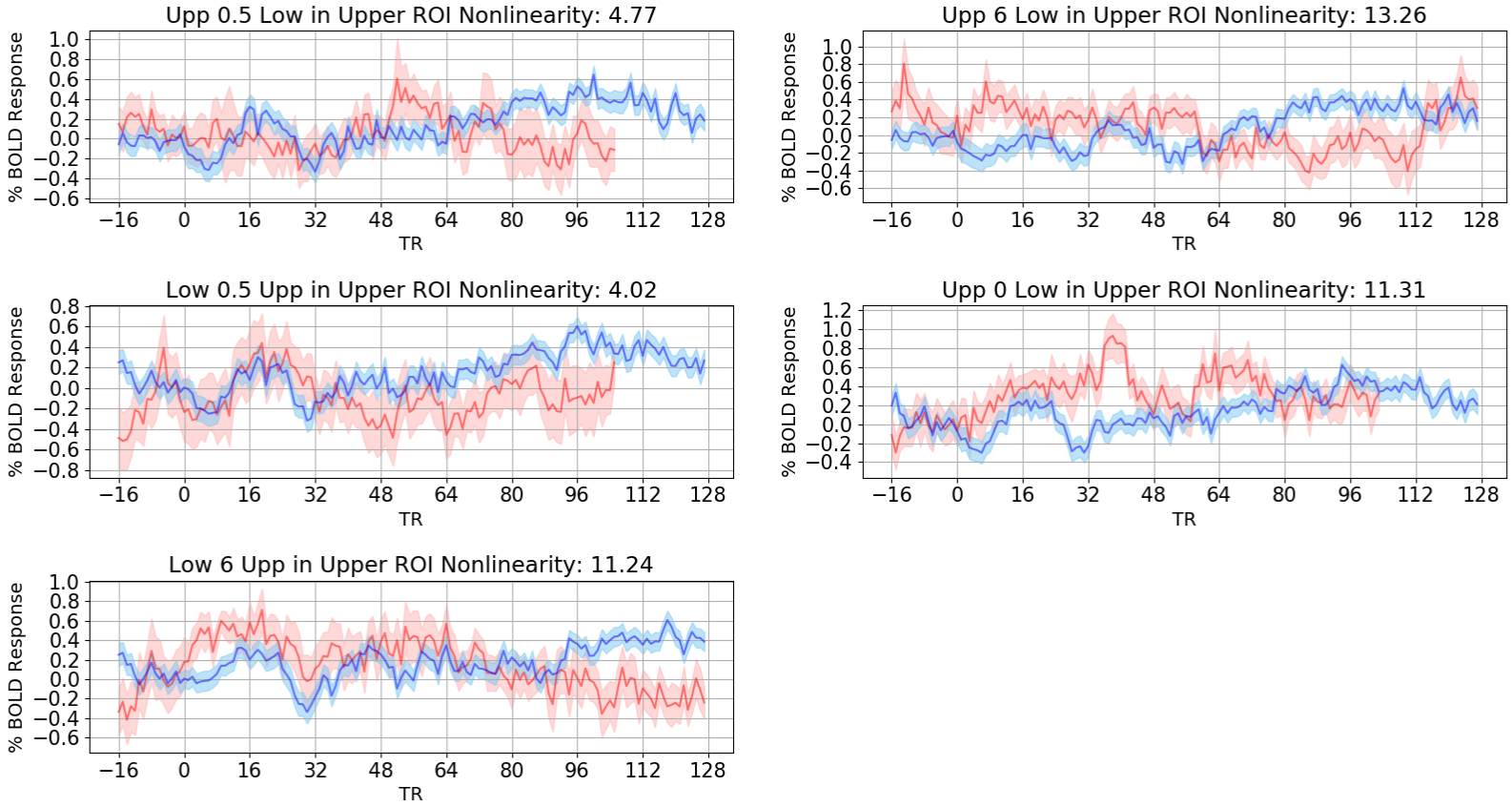

Figure A.63: Impulse Upp-Low SIRF vs. SOA in Upper ROI in LT 09. Blue is the predicted response. Red is the observed response. The nonlinearity represents the difference between the predicted and observed responses and was calculated based on the residual formula for all TRs. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

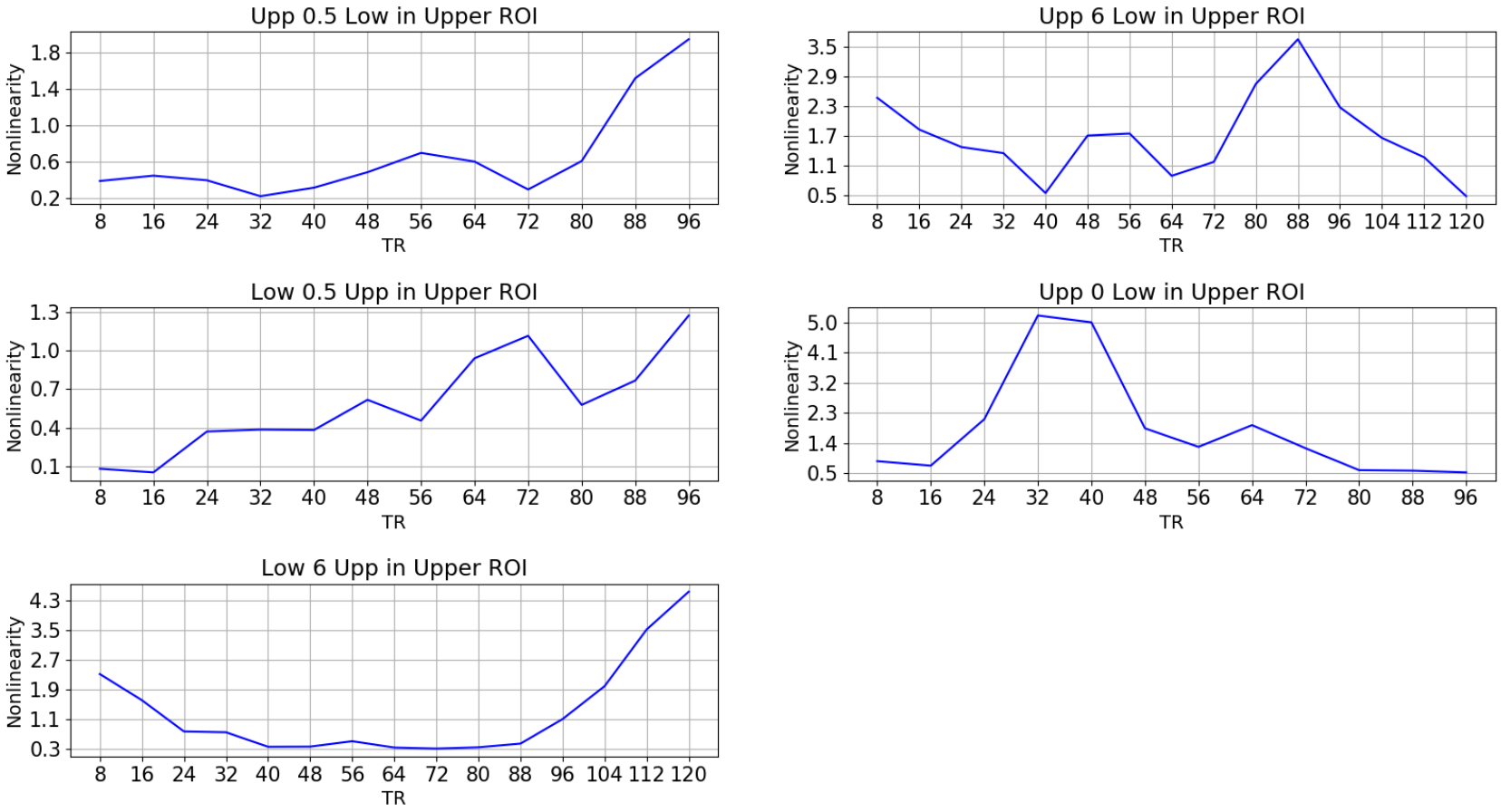

Figure A.64: Impulse Upp-Low in Upper ROI in LT 09. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

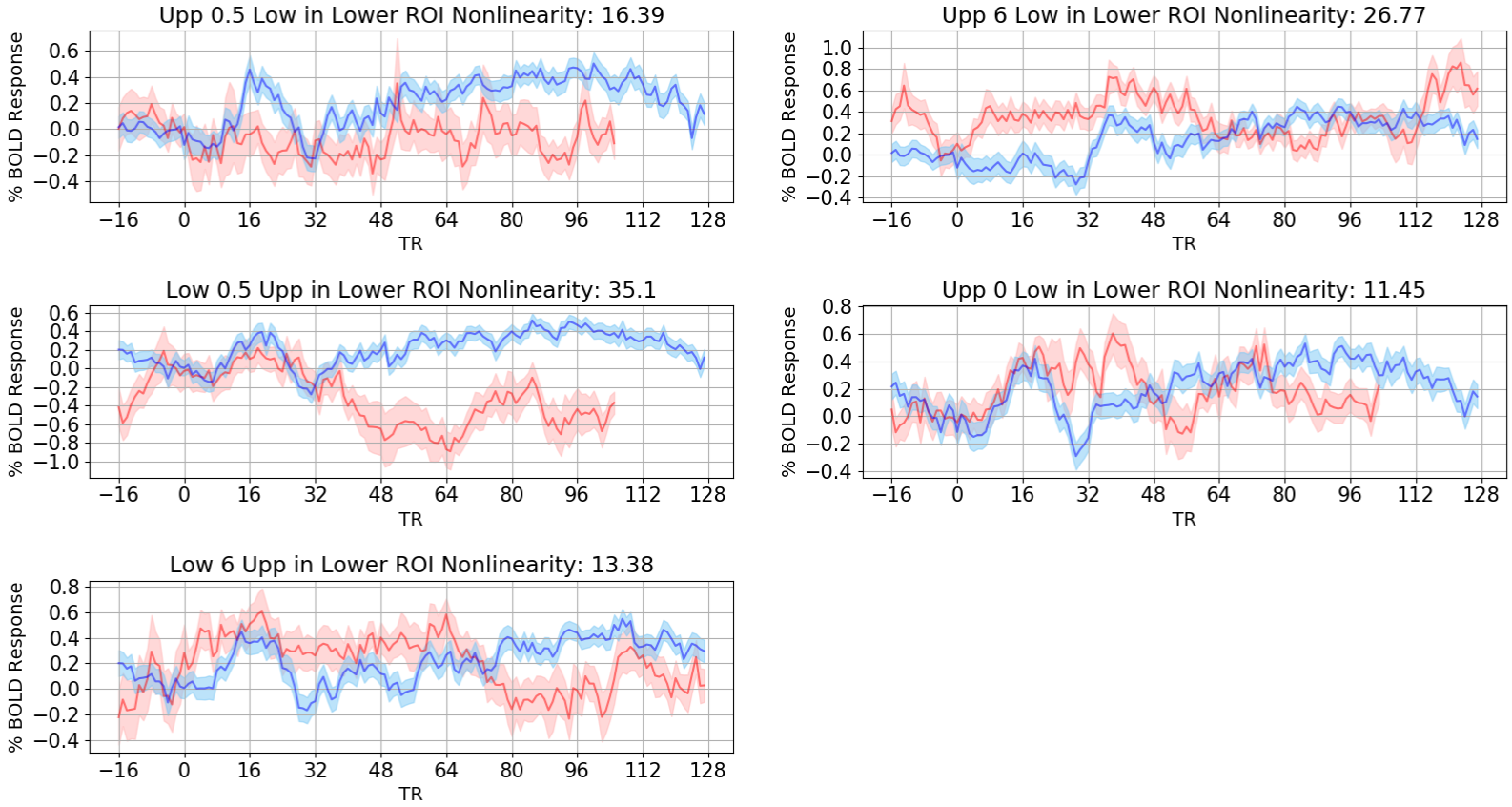

Figure A.65: Impulse Upp-Low SIRF vs. SOA in Lower ROI in LT 09. Blue is the predicted response. Red is the observed response. The nonlinearity represents the difference between the predicted and observed responses and was calculated based on the residual formula for all TRs. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

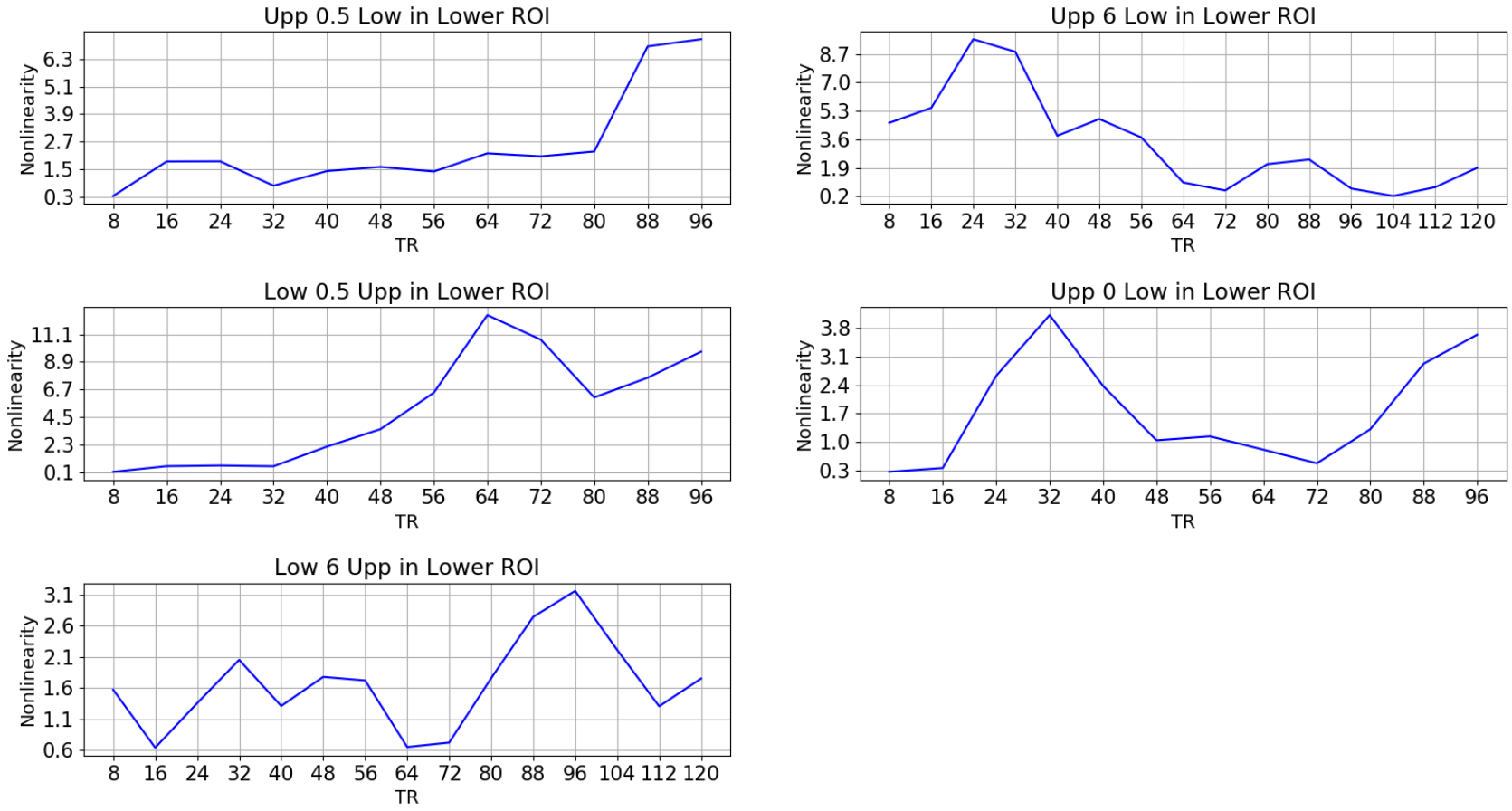

Figure A.66: Impulse Upp-Low in Lower ROI in LT 09. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

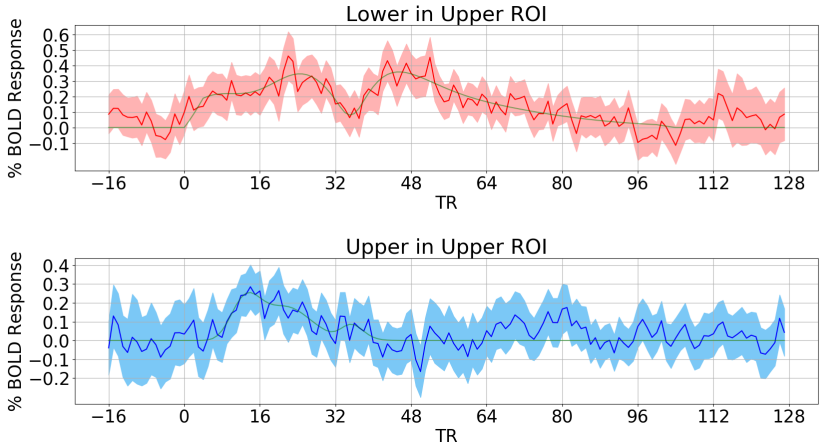

Figure A.67: BOLD responses to impulse stimulation (Impulse Upp-Low SIRF in Upper ROI) in LT 11. Green is the SIRF model. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR = 250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

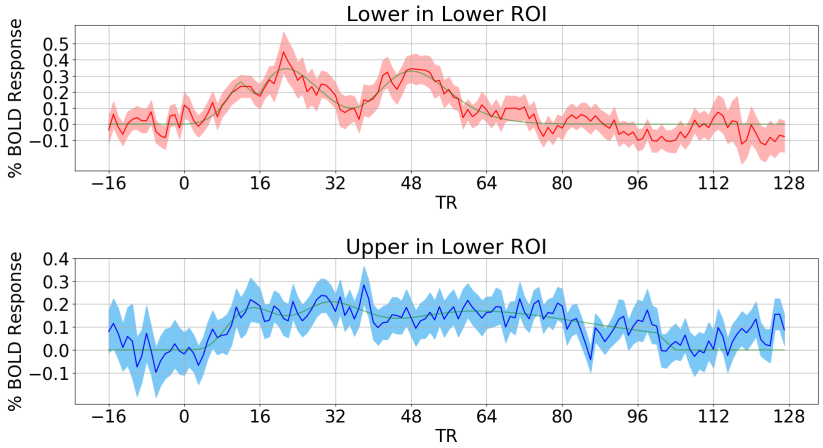

Figure A.68: BOLD responses to impulse stimulation (Impulse Upp-Low SIRF in Lower ROI) in LT 11. Green is the SIRF model. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR = 250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

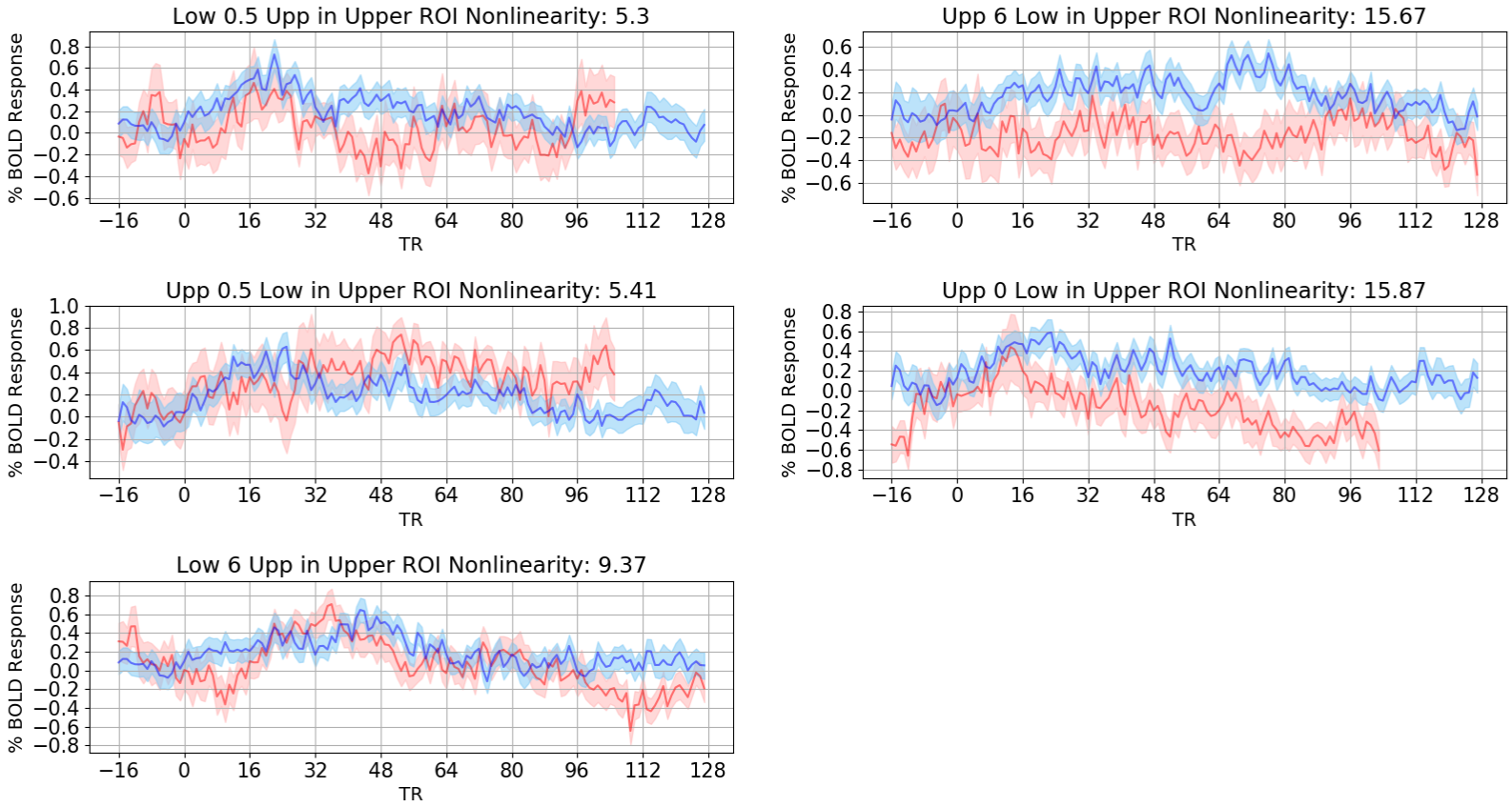

Figure A.69: Impulse Upp-Low SIRF vs. SOA in Upper ROI in LT 11. Blue is the predicted response. Red is the observed response. The nonlinearity represents the difference between the predicted and observed responses and was calculated based on the residual formula for all TRs. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

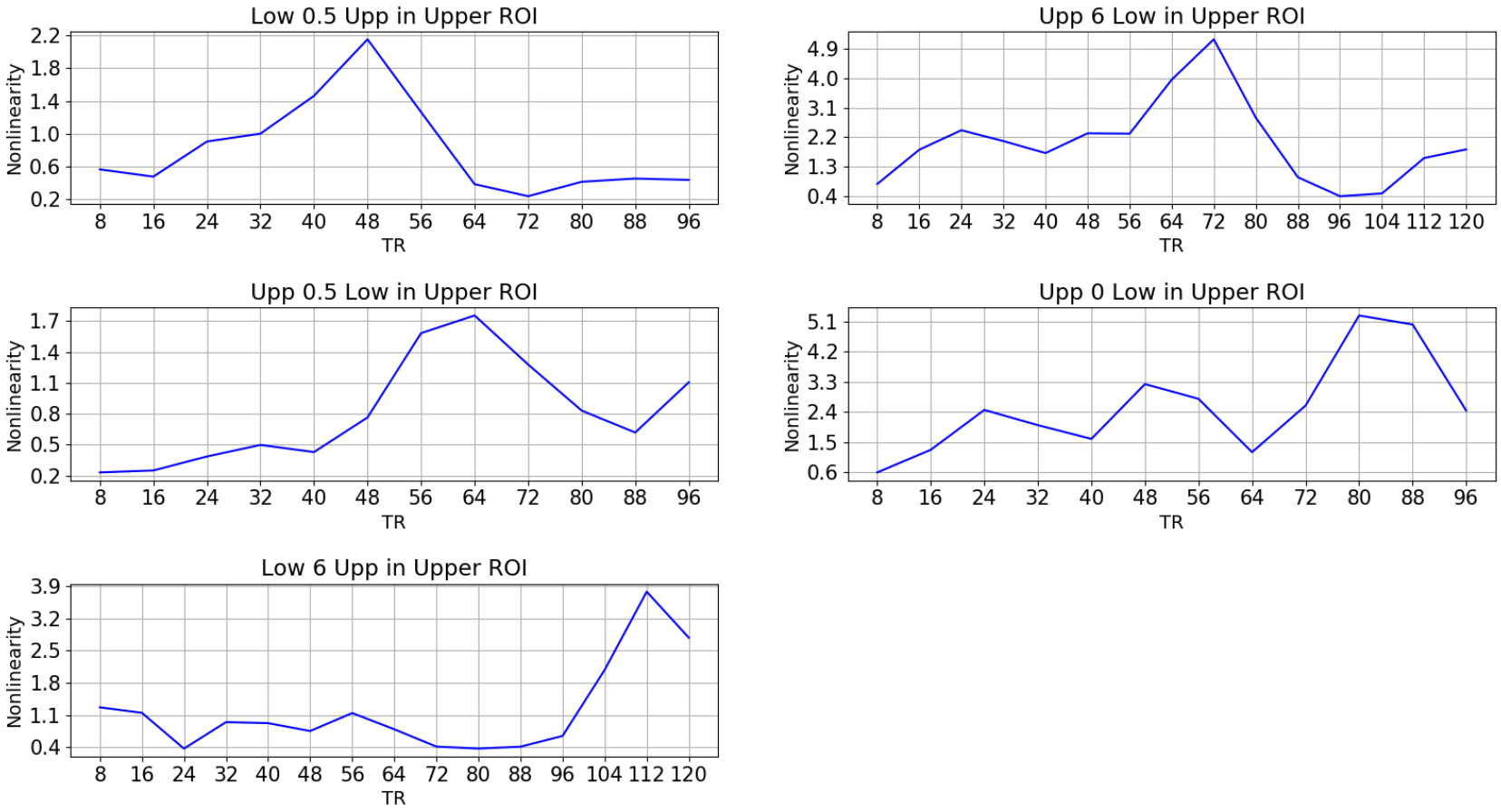

Figure A.70: Impulse Upp-Low in Upper ROI in LT 11. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

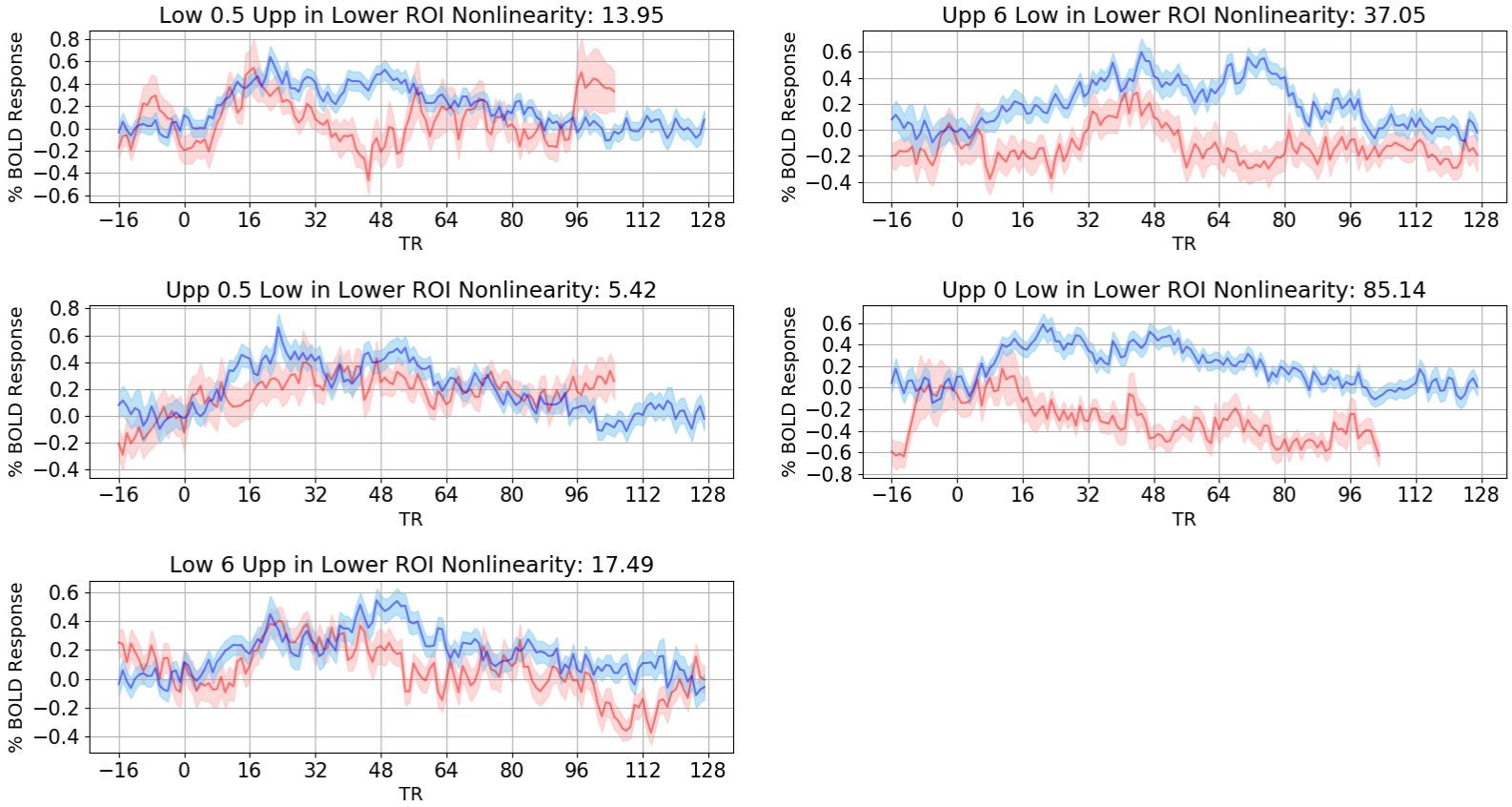

Figure A.71: Impulse Upp-Low SIRF vs. SOA in Lower ROI in LT 11. Blue is the predicted response. Red is the observed response. The nonlinearity represents the difference between the predicted and observed responses and was calculated based on the residual formula for all TRs. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

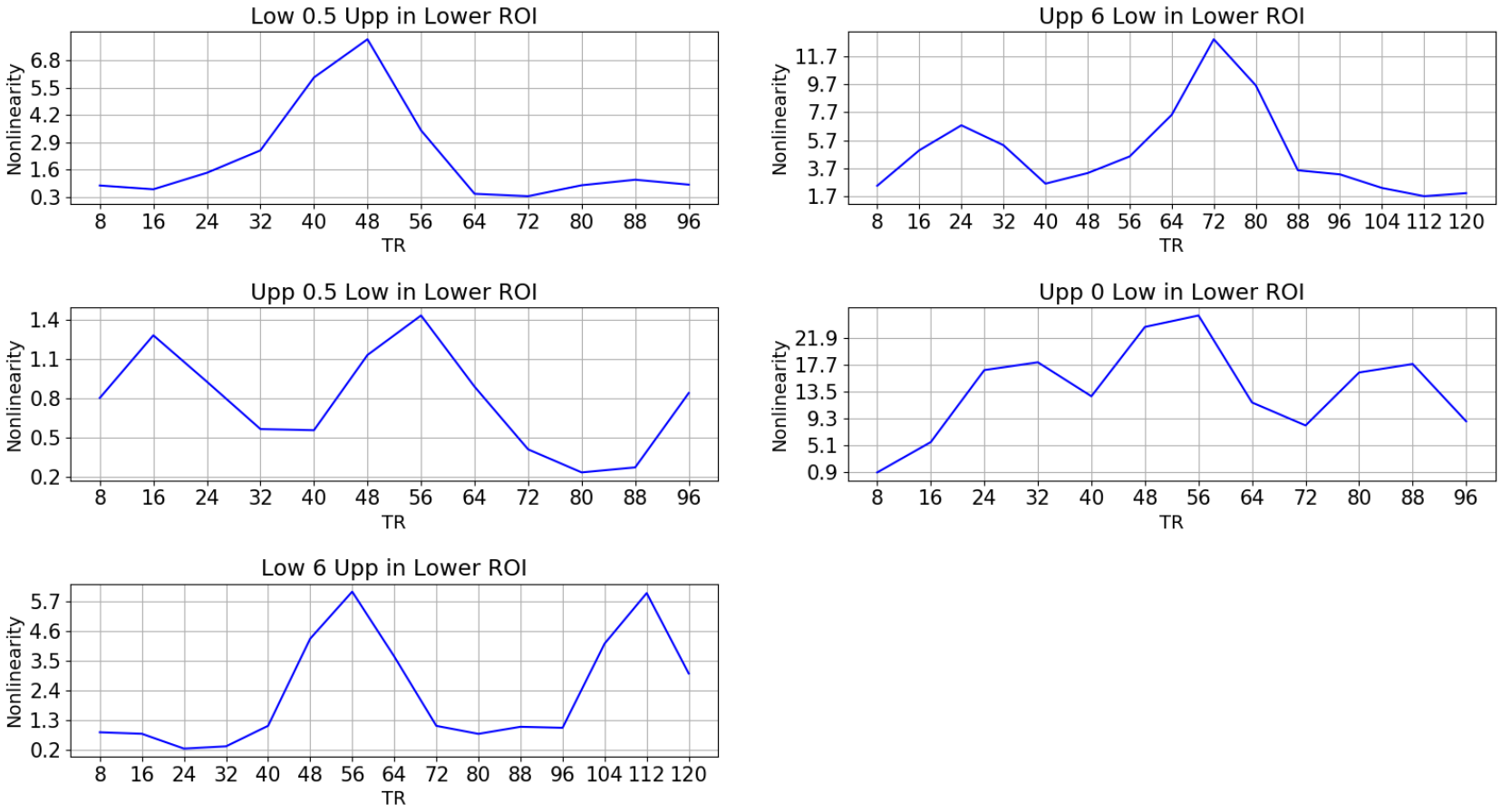

Figure A.72: Impulse Upp-Low in Lower ROI in LT 11. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

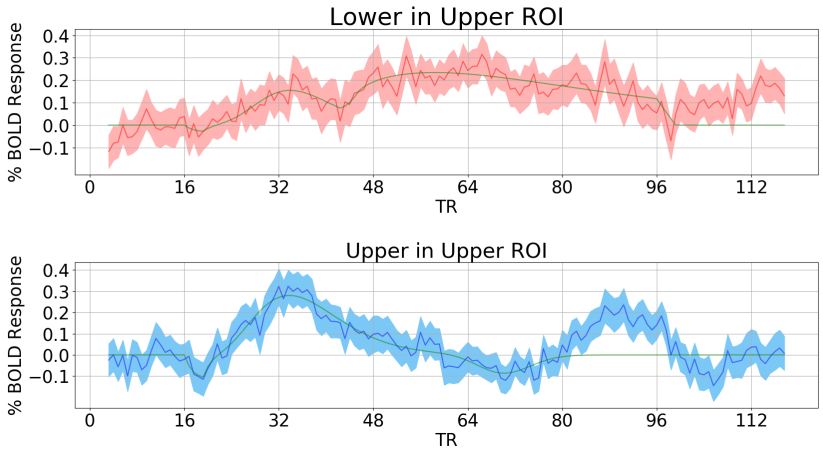

Figure A.73: BOLD responses to 1 s stimulation (Longer Pulse Upp-Low SIRF in Upper ROI) in LT 06. Green is the SIRF model. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR = 250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

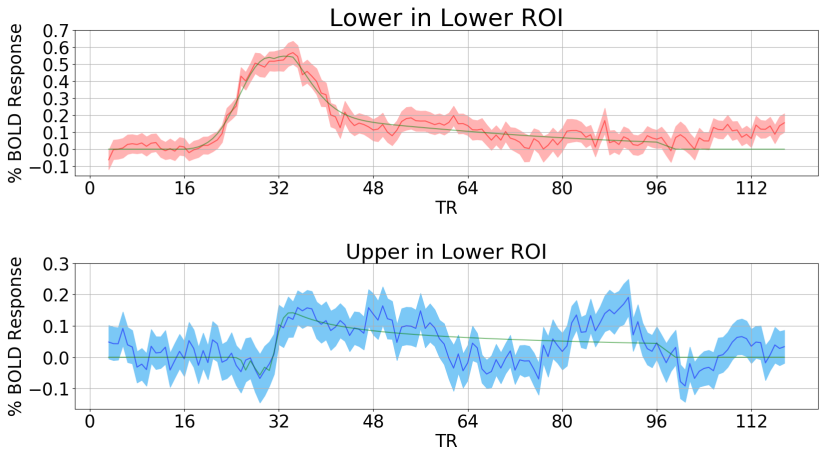

Figure A.74: BOLD responses to 1 s stimulation (Longer Pulse Upp-Low SIRF in Lower ROI) in LT 06. Green is the SIRF model. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR = 250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

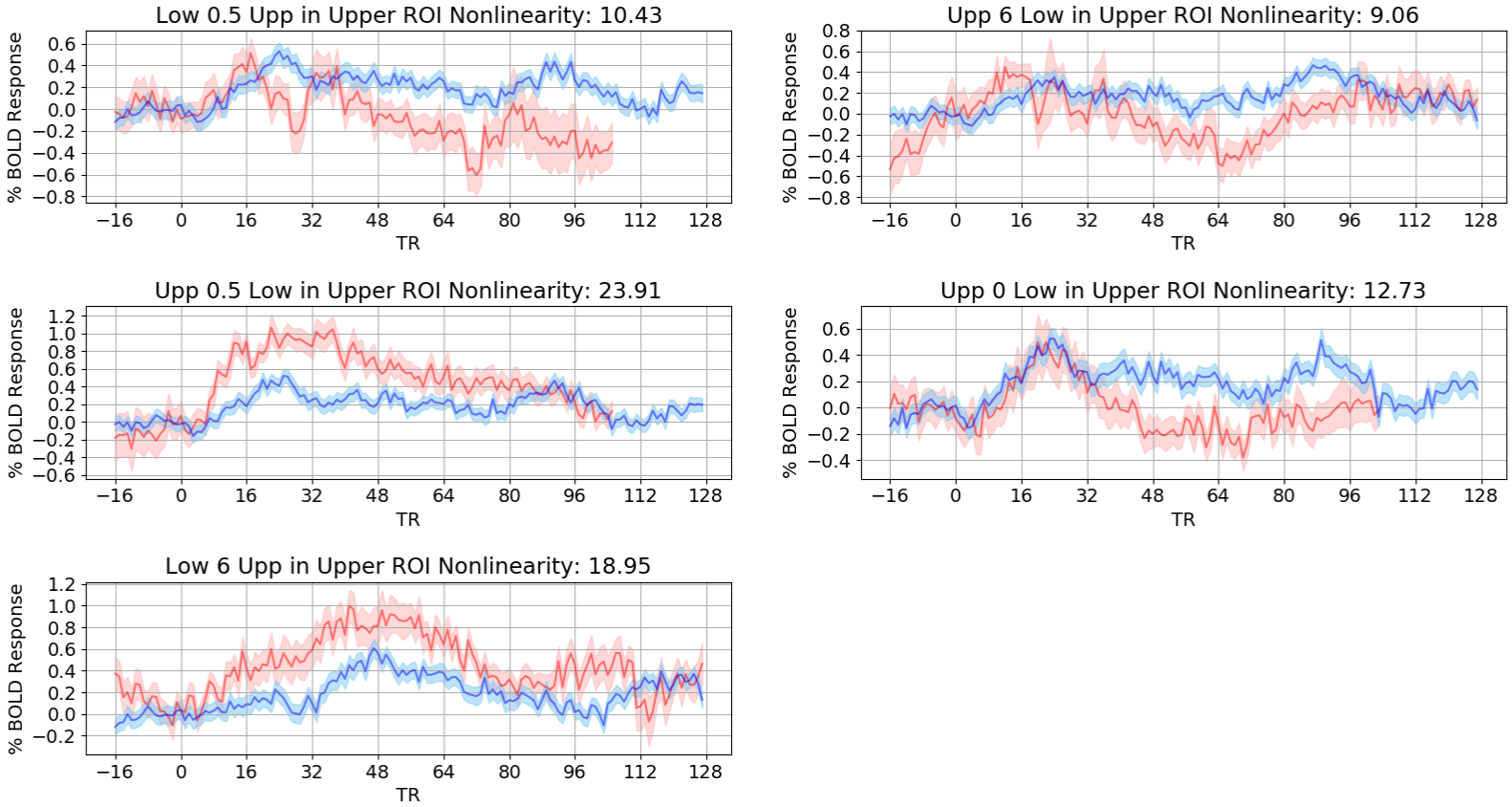

Figure A.75: Longer Pulse Upp-Low SIRF vs. SOA in Upper ROI in LT 06. Blue is the predicted response. Red is the observed response. The nonlinearity represents the difference between the predicted and observed responses and was calculated based on the residual formula for all TRs. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

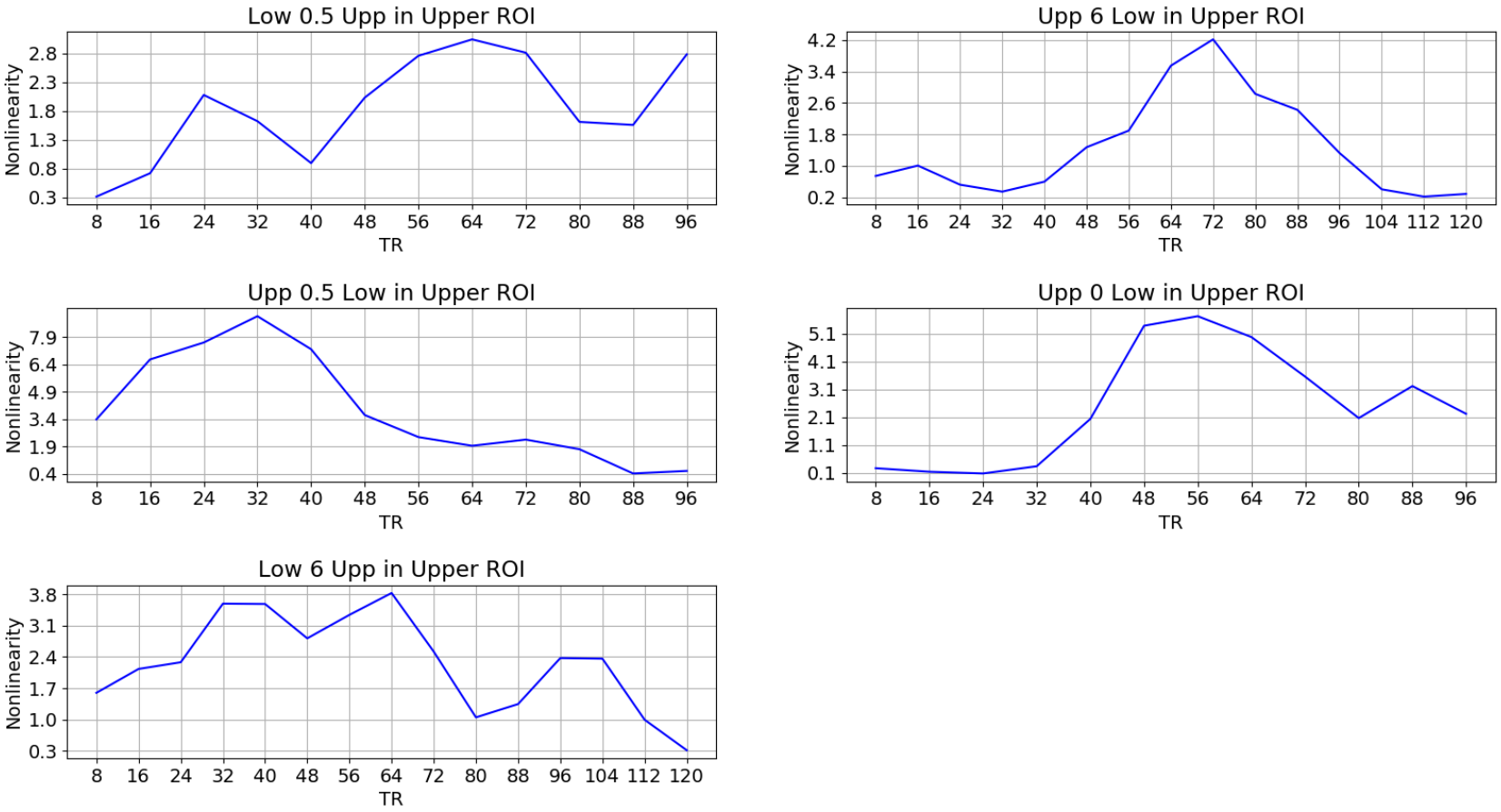

Figure A.76: Longer Pulse Upp-Low in Upper ROI in LT 06. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

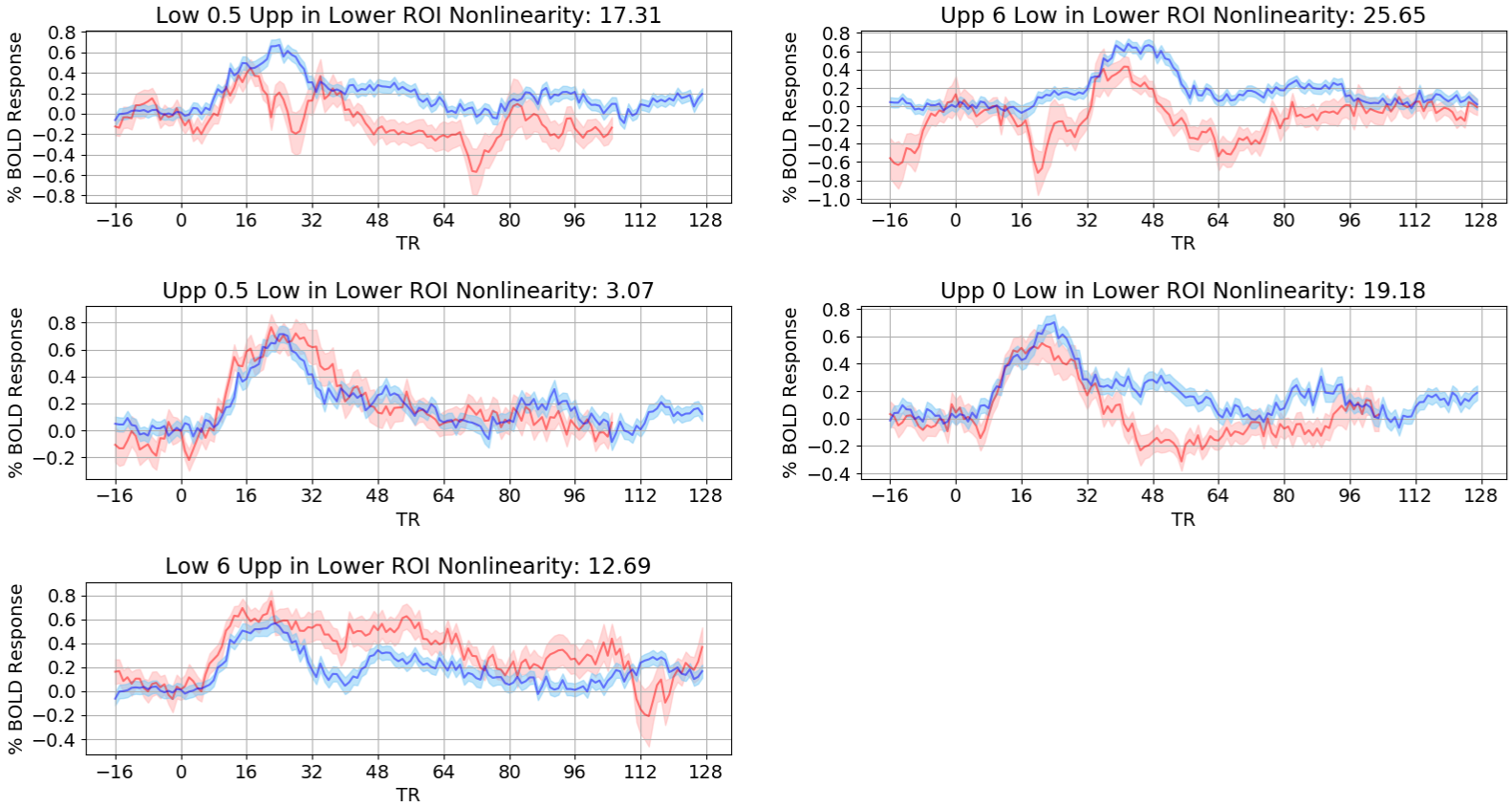

Figure A.77: Longer Pulse Upp-Low SIRF vs. SOA in Lower ROI in LT 06. Blue is the predicted response. Red is the observed response. The nonlinearity represents the difference between the predicted and observed responses and was calculated based on the residual formula for all TRs. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

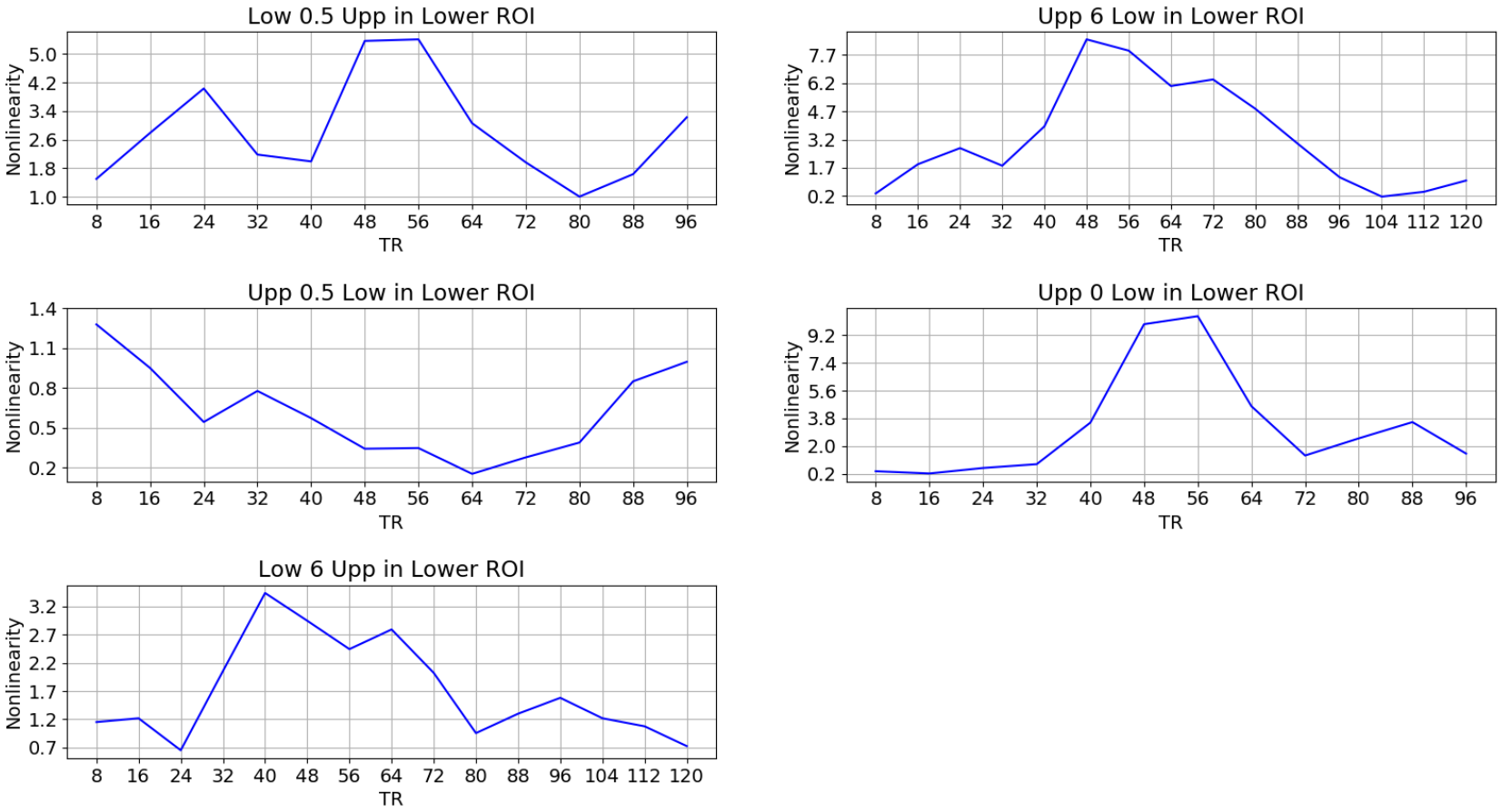

Figure A.78: Longer Pulse Upp-Low in Lower ROI in LT 06. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

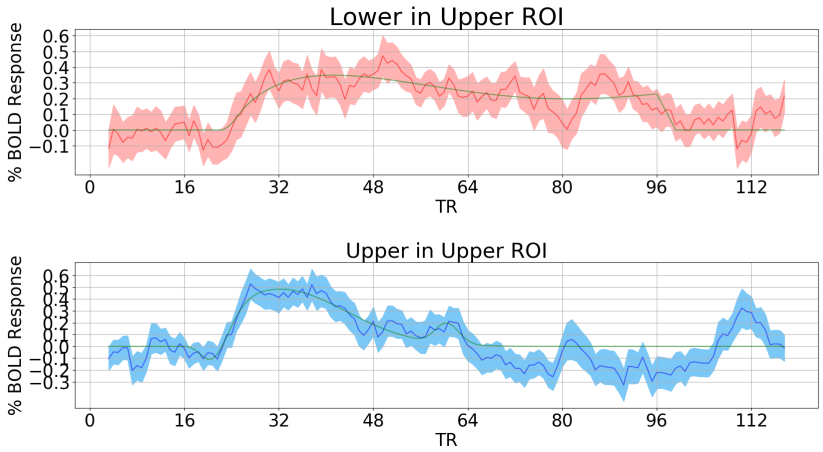

Figure A.79: BOLD responses to 1 s stimulation (Longer Pulse Upp-Low SIRF in Upper ROI) in LT 09. Green is the SIRF model. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR = 250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

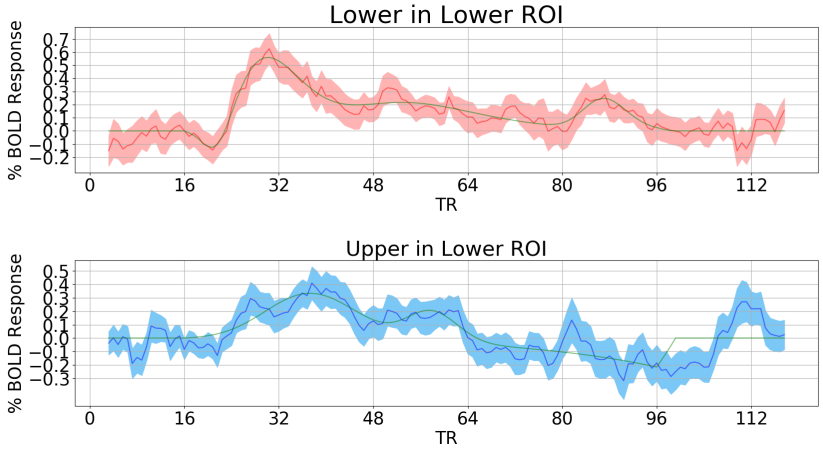

Figure A.80: BOLD responses to 1 s stimulation (Longer Pulse Upp-Low SIRF in Lower ROI) in LT 09. Green is the SIRF model. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR = 250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

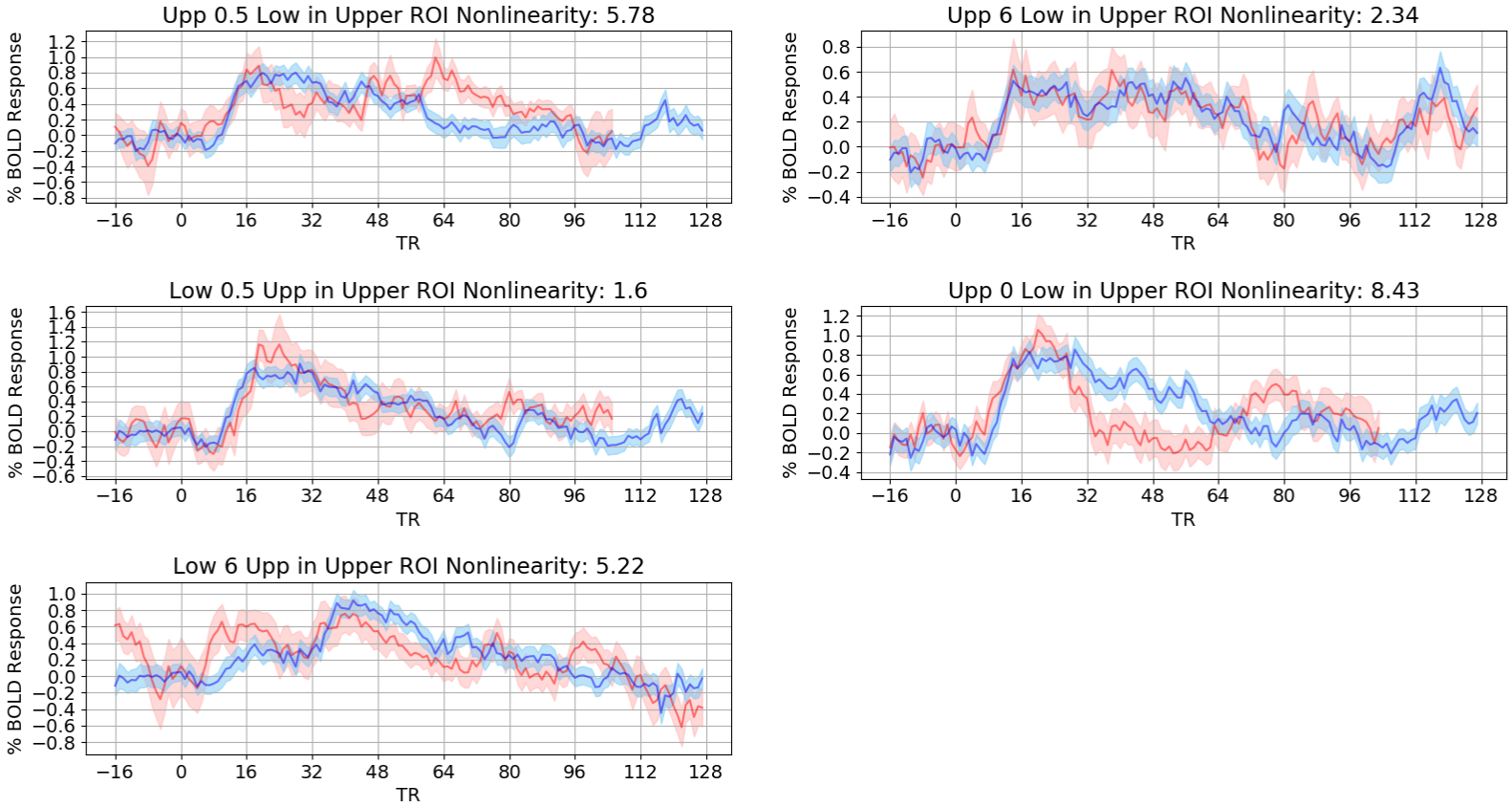

Figure A.81: Longer Pulse Upp-Low SIRF vs. SOA in Upper ROI in LT 09. Blue is the predicted response. Red is the observed response. The nonlinearity represents the difference between the predicted and observed responses and was calculated based on the residual formula for all TRs. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

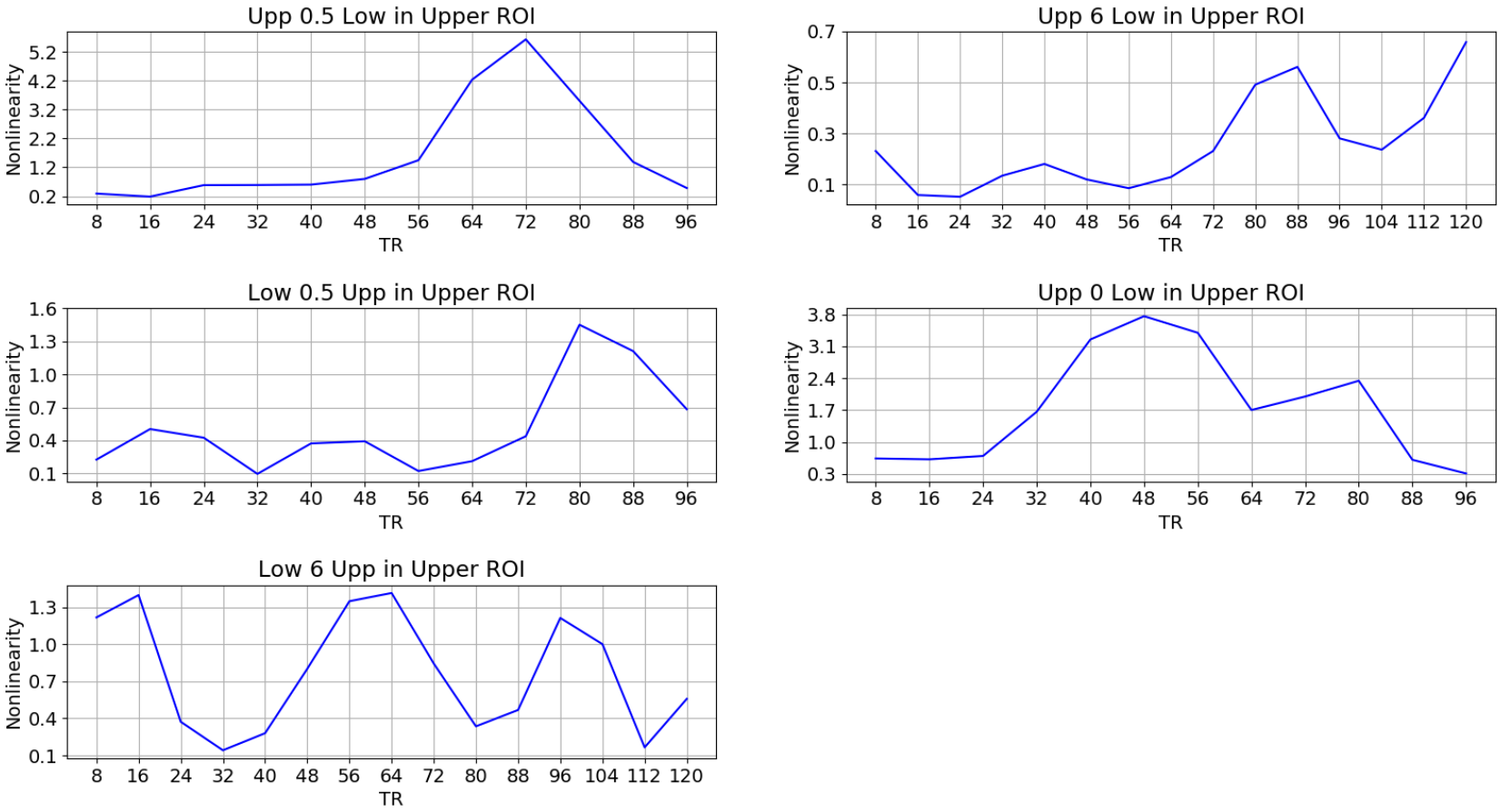

Figure A.82: Longer Pulse Upp-Low in Upper ROI in LT 09. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

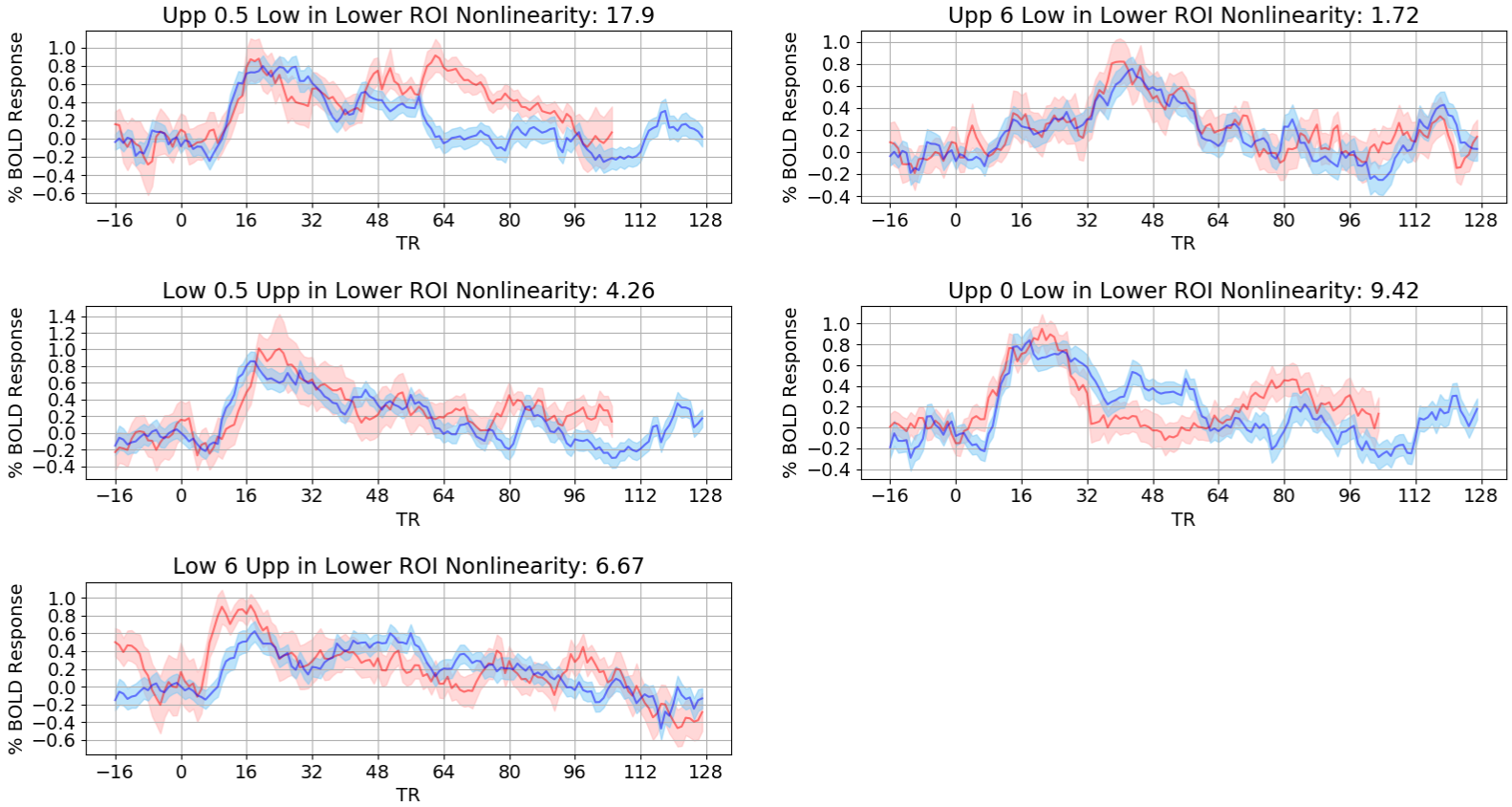

Figure A.83: Longer Pulse Upp-Low SIRF vs. SOA in Lower ROI in LT 09. Blue is the predicted response. Red is the observed response. The nonlinearity represents the difference between the predicted and observed responses and was calculated based on the residual formula for all TRs. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

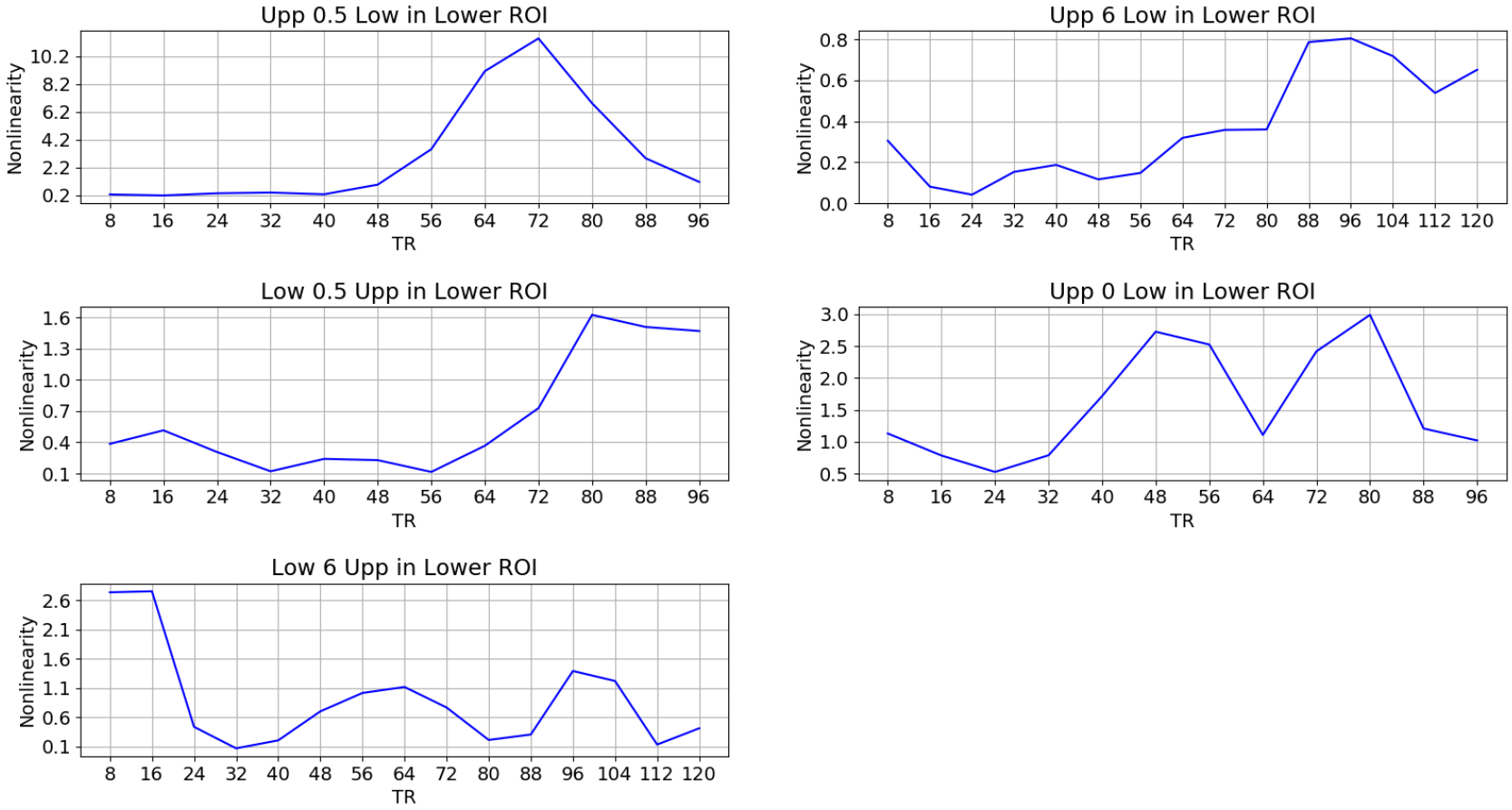

Figure A.84: Longer Pulse Upp-Low in Lower ROI in LT 09. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

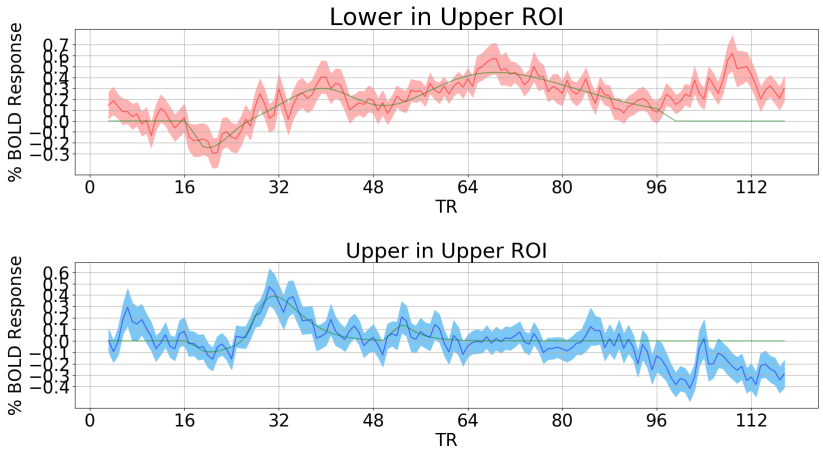

Figure A.85: BOLD responses to 1 s stimulation (Longer Pulse Upp-Low SIRF in Upper ROI) in LT 11. Green is the SIRF model. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR = 250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

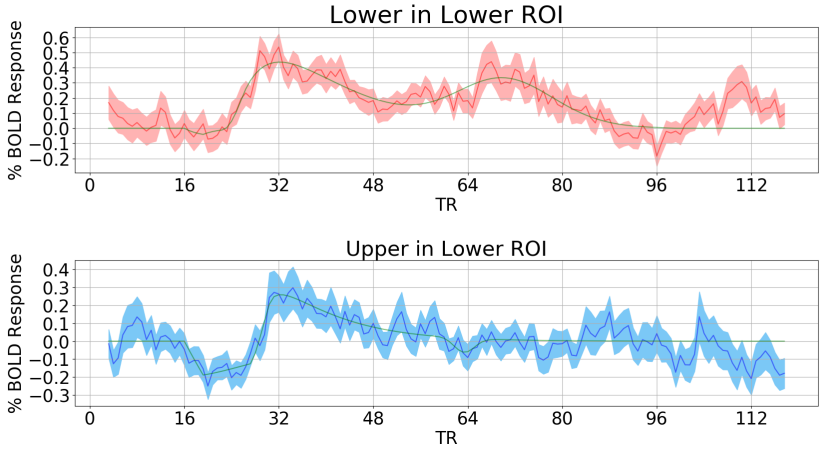

Figure A.86: BOLD responses to 1 s stimulation (Longer Pulse Upp-Low SIRF in Lower ROI) in LT 11. Green is the SIRF model. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR = 250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

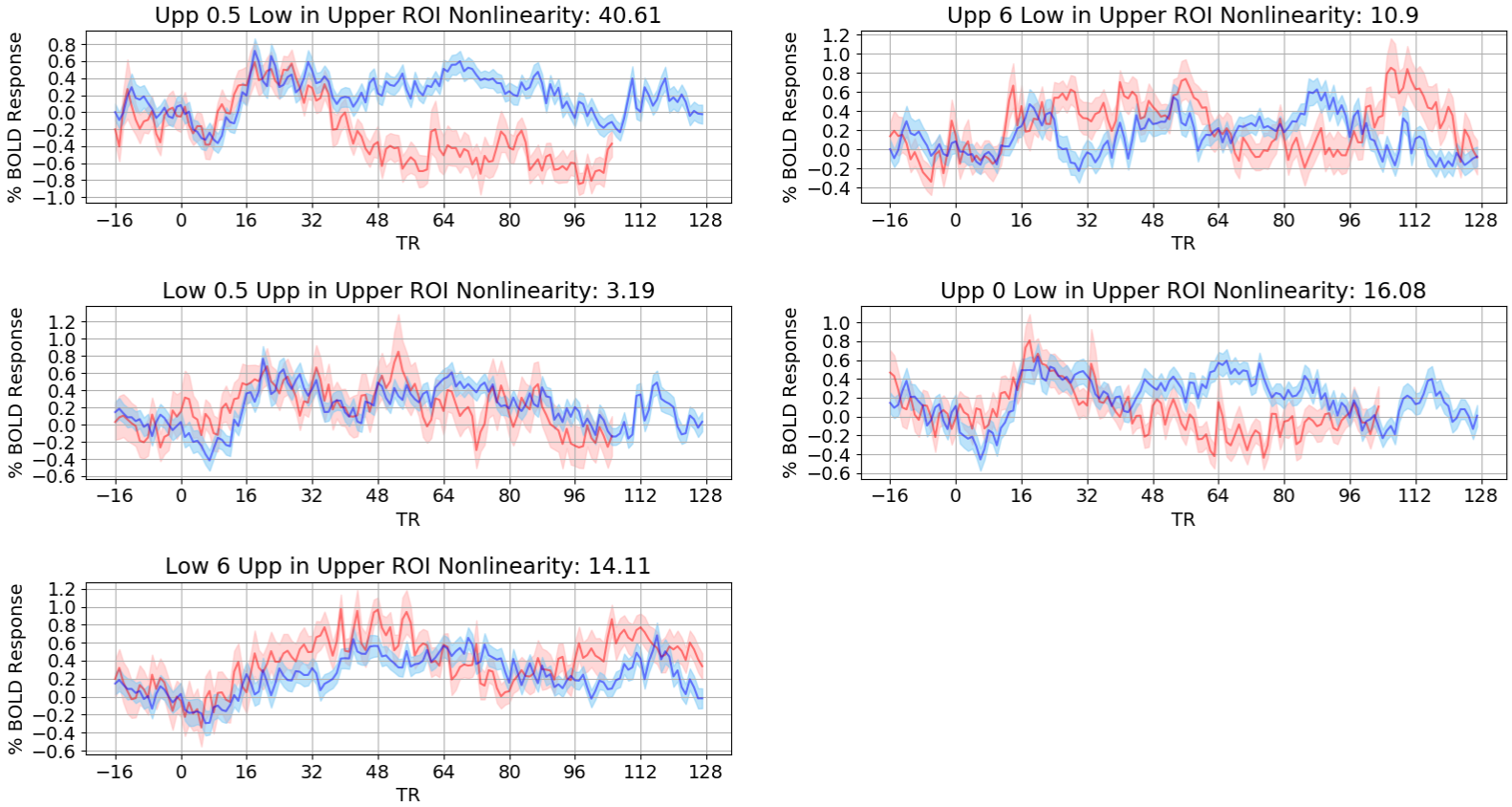

Figure A.87: Longer Pulse Upp-Low SIRF vs. SOA in Upper ROI in LT 11. Blue is the predicted response. Red is the observed response. The nonlinearity represents the difference between the predicted and observed responses and was calculated based on the residual formula for all TRs. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

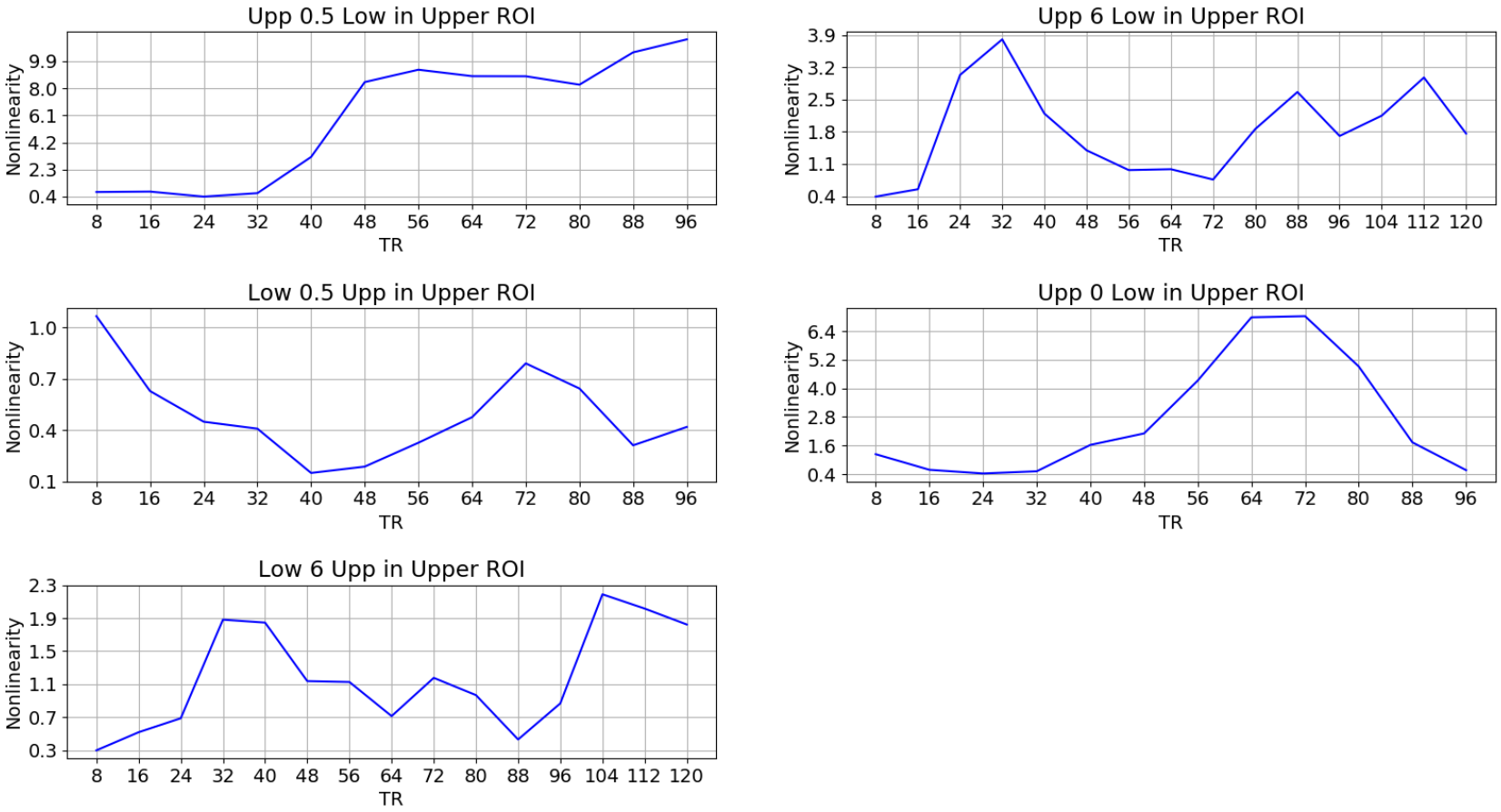

Figure A.88: Longer Pulse Upp-Low in Upper ROI in LT 11. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

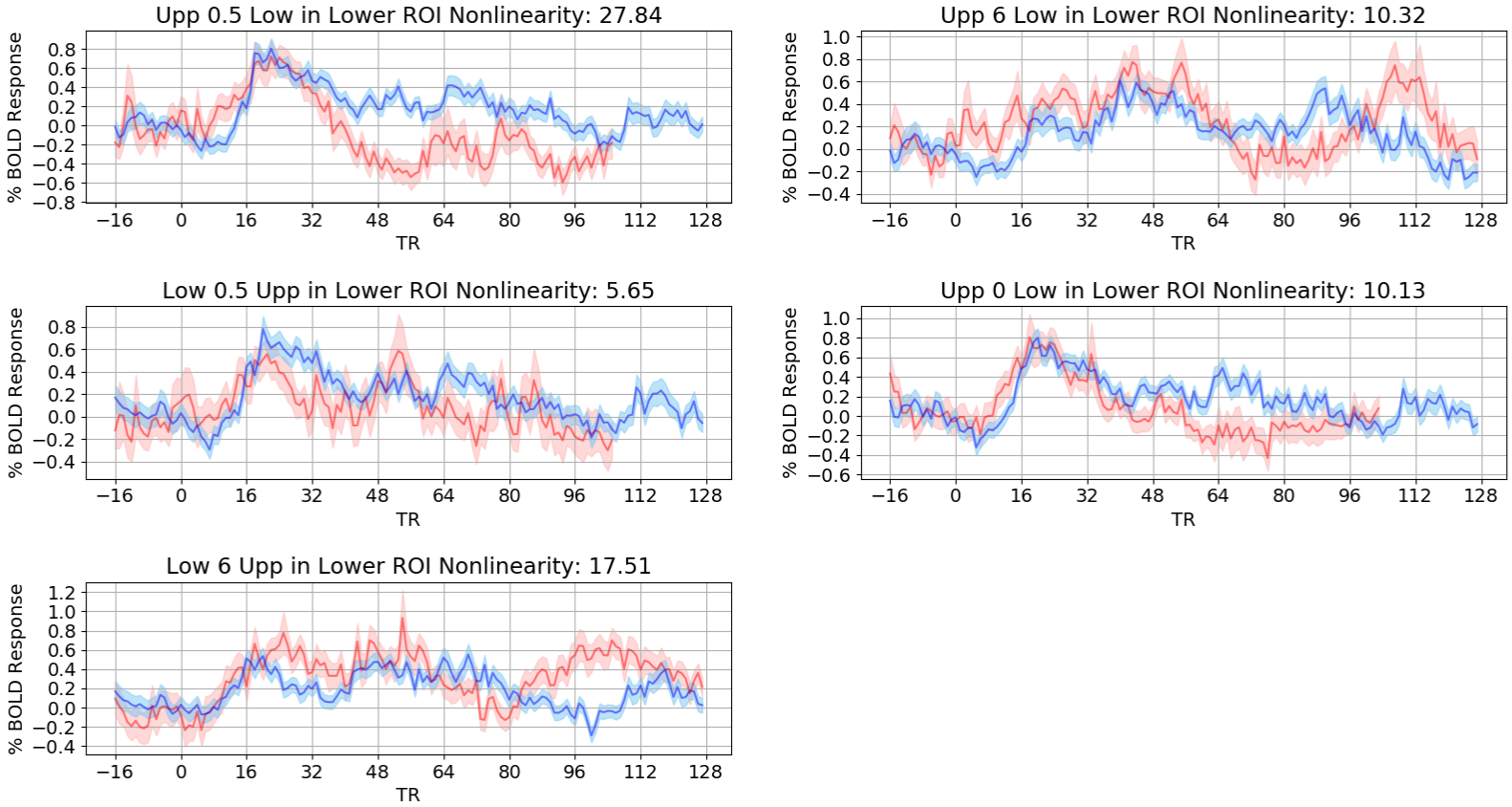

Figure A.89: Longer Pulse Upp-Low SIRF vs. SOA in Lower ROI in LT 11. Blue is the predicted response. Red is the observed response. The nonlinearity represents the difference between the predicted and observed responses and was calculated based on the residual formula for all TRs. Shaded regions represent standard error of the mean. X-axis and y-axis show time(s) in TR (TR=250 ms, e.g., 16 TR = 4 s), and percent change of BOLD response, respectively. TR 0 represents the onset of stimulus.

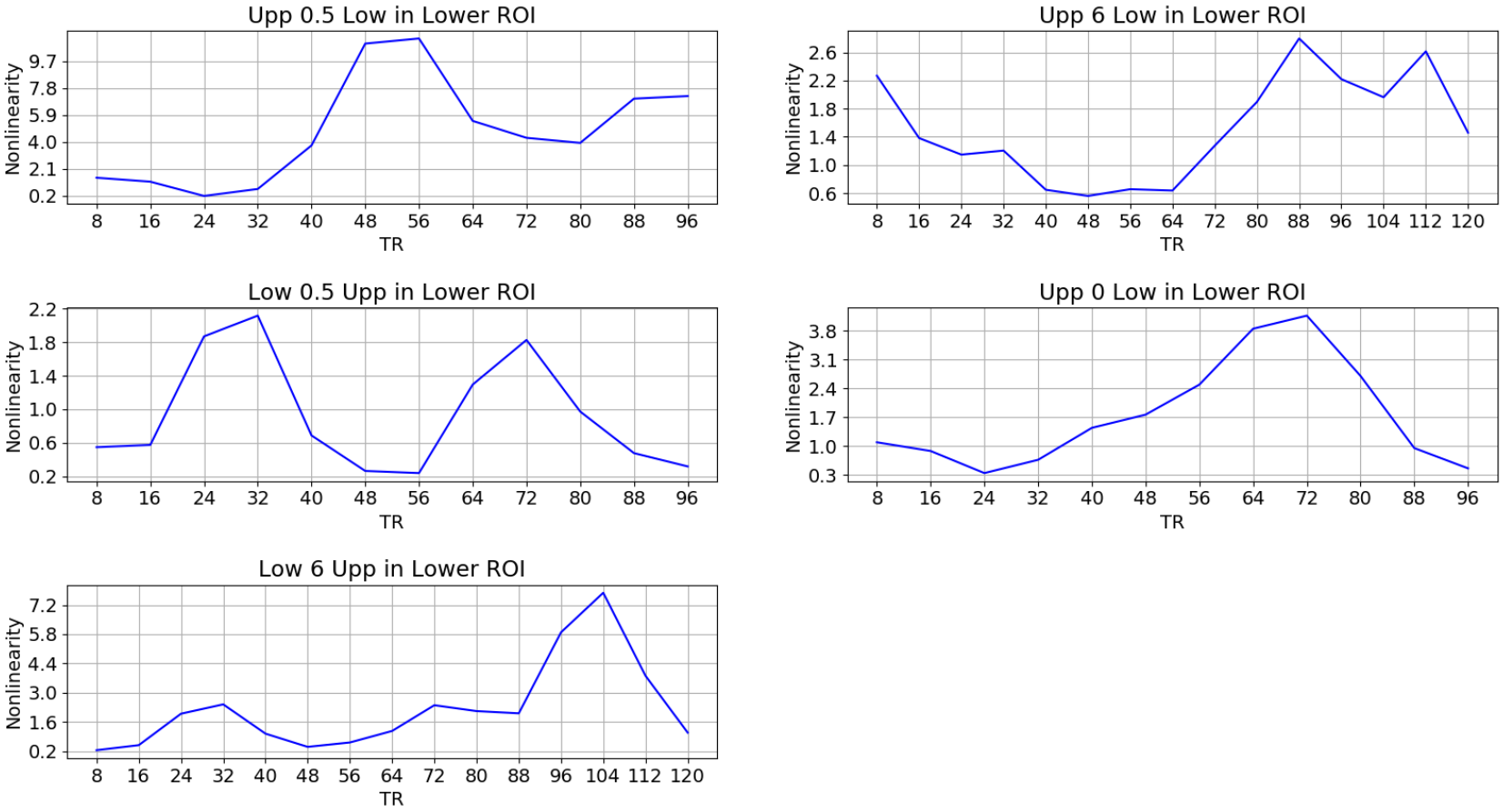

Figure A.90: Longer Pulse Upp-Low in Lower ROI in LT 11. Blue represents the difference between the predicted and observed responses. The difference between the predicted and observed responses was calculated based on the residual (nonlinearity) formula through sliding window procedure. Window size is 16 TRs and window step size is 8 TRs (TR=250 ms, e.g., 16 TR = 4 s).

Appendix B

Code

Code available upon request.