Linearity of the BOLD Response

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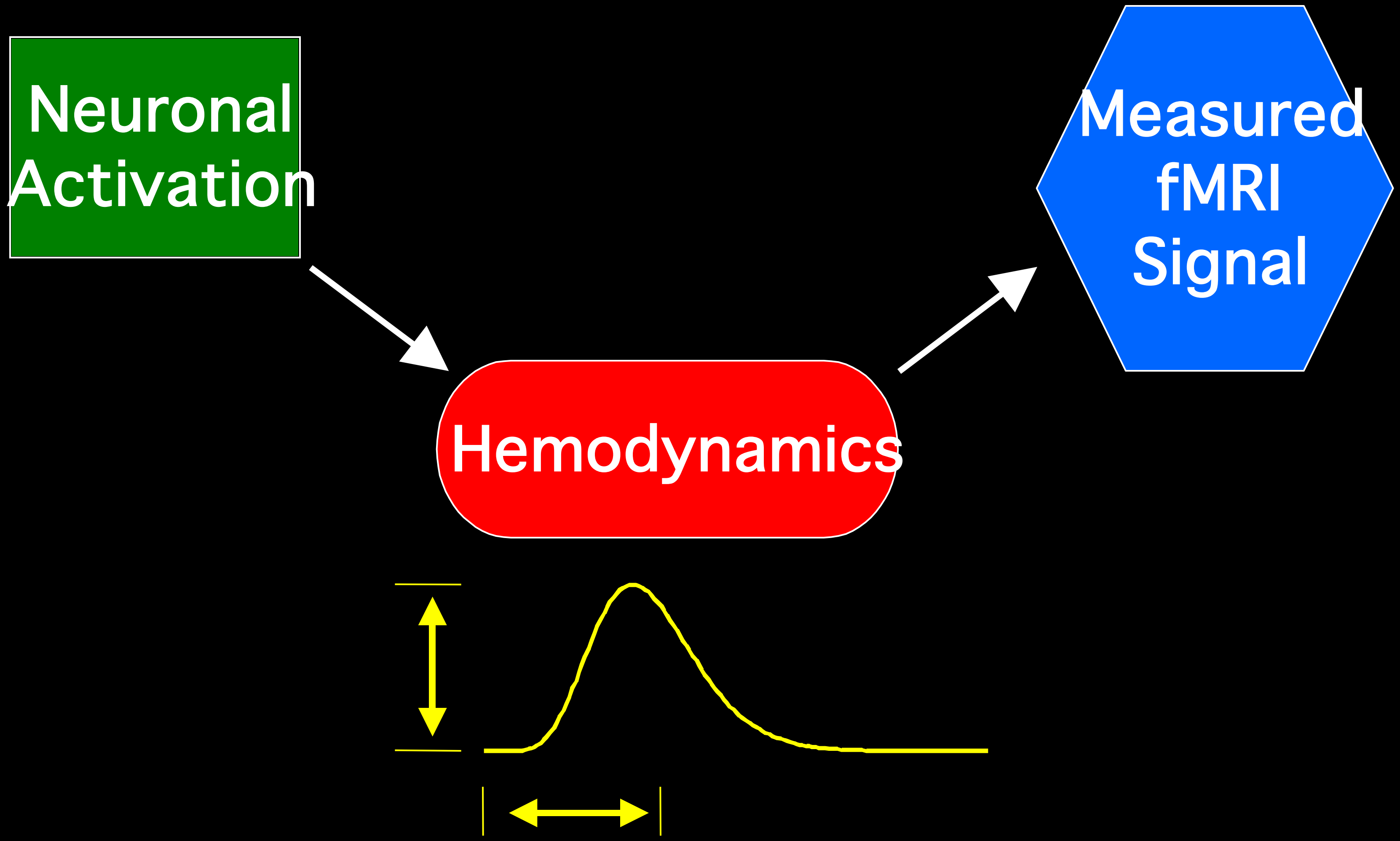
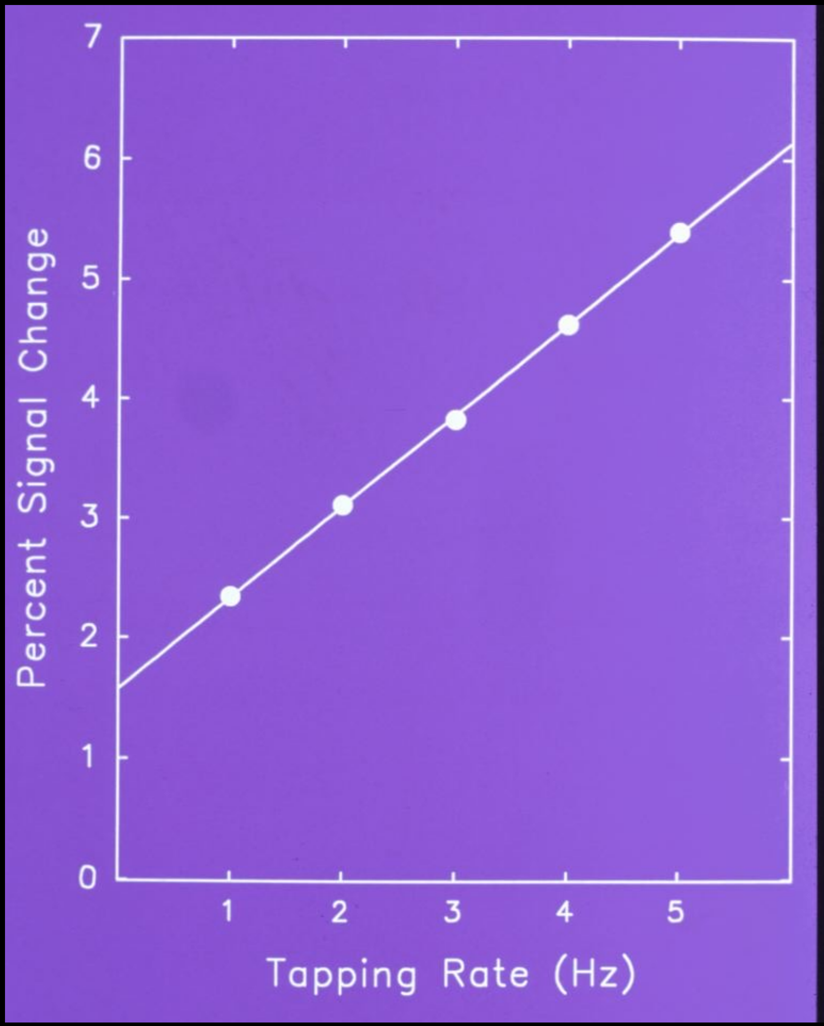
Hemodynamic Transfer Function

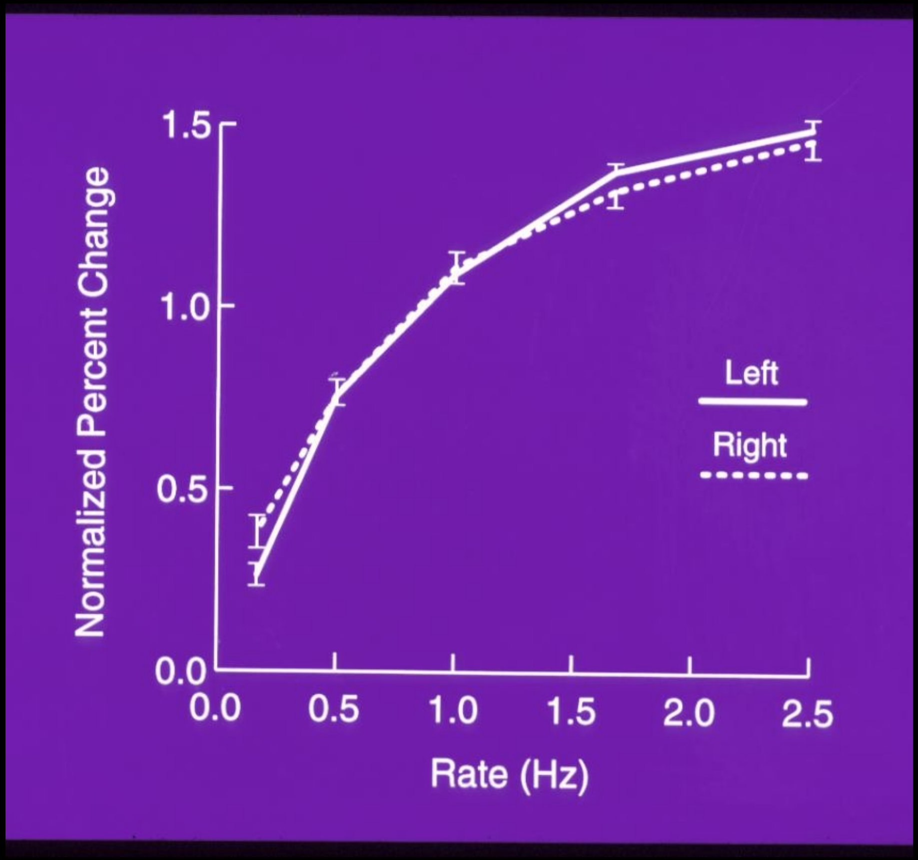


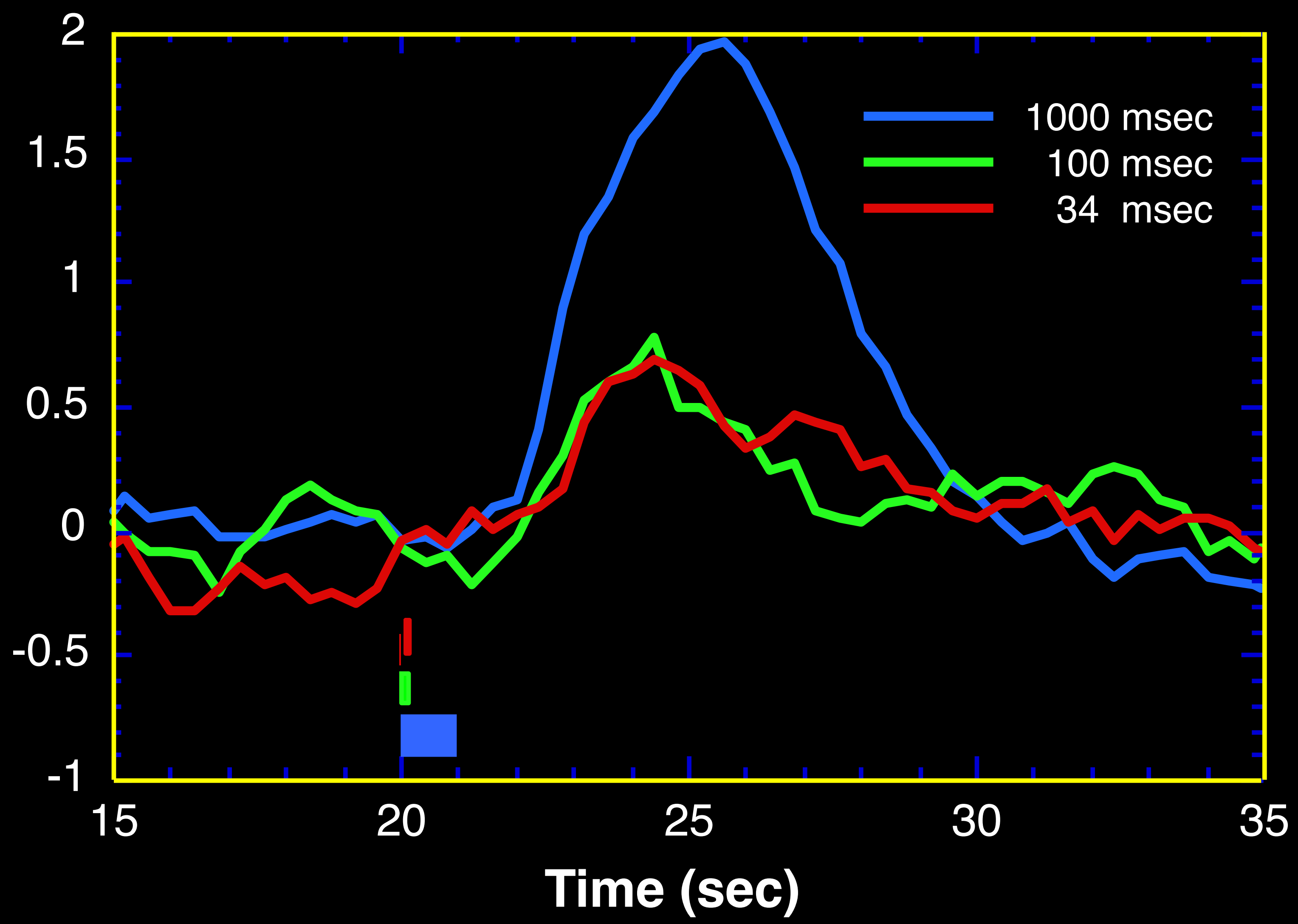
Physiolologic Factors

Motor Cortex

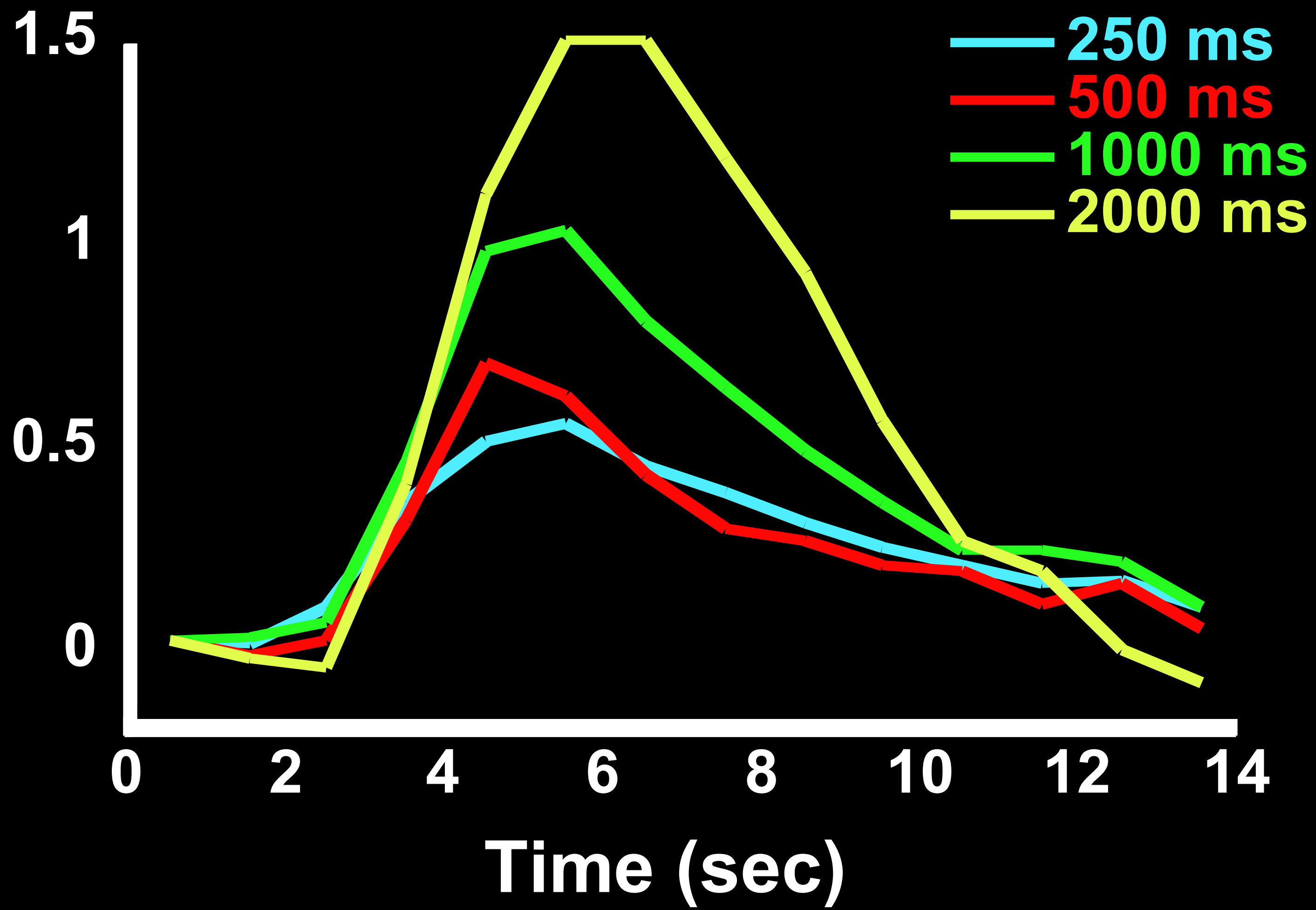


Auditory Cortex



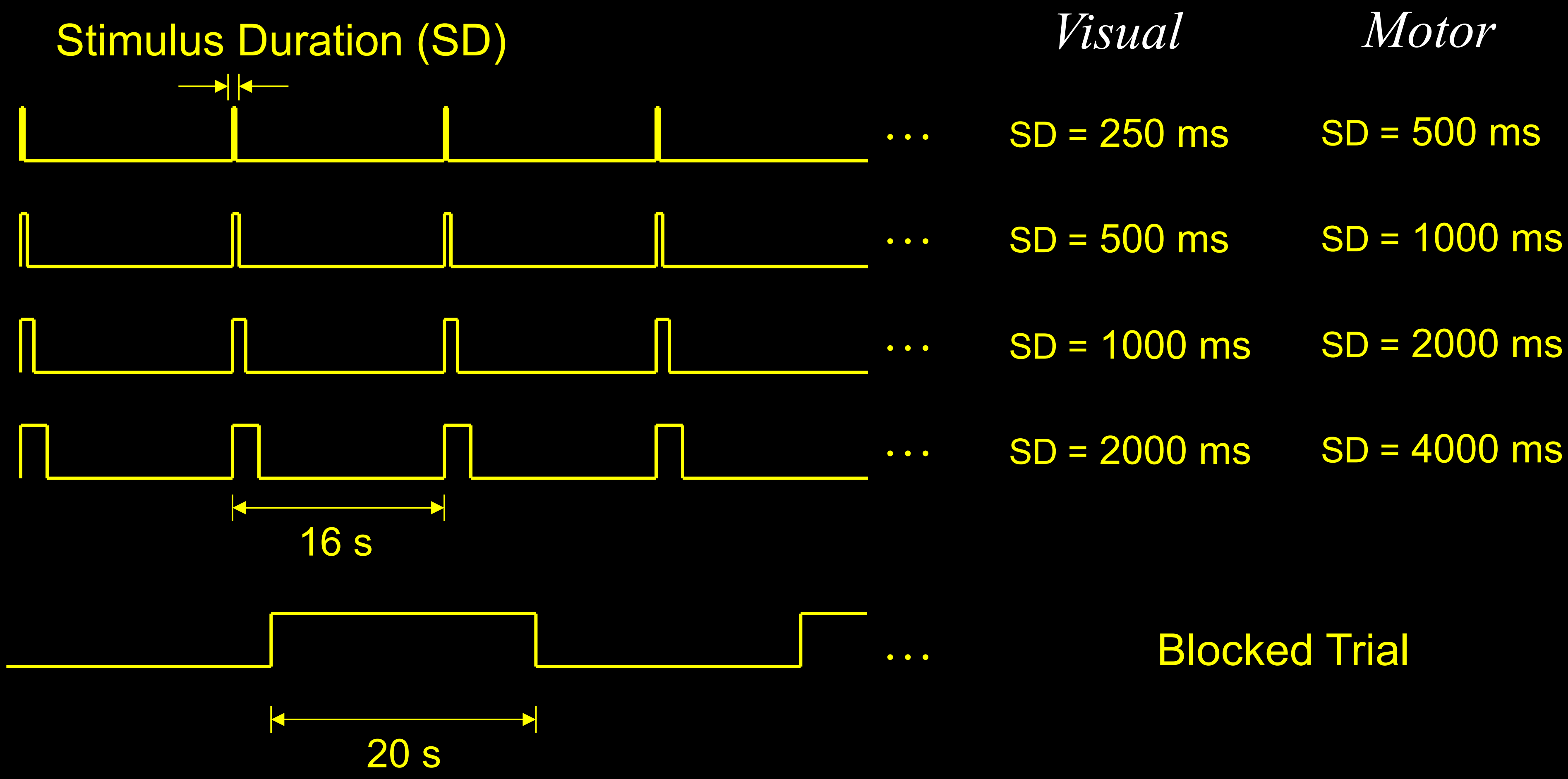


Savoy et al.



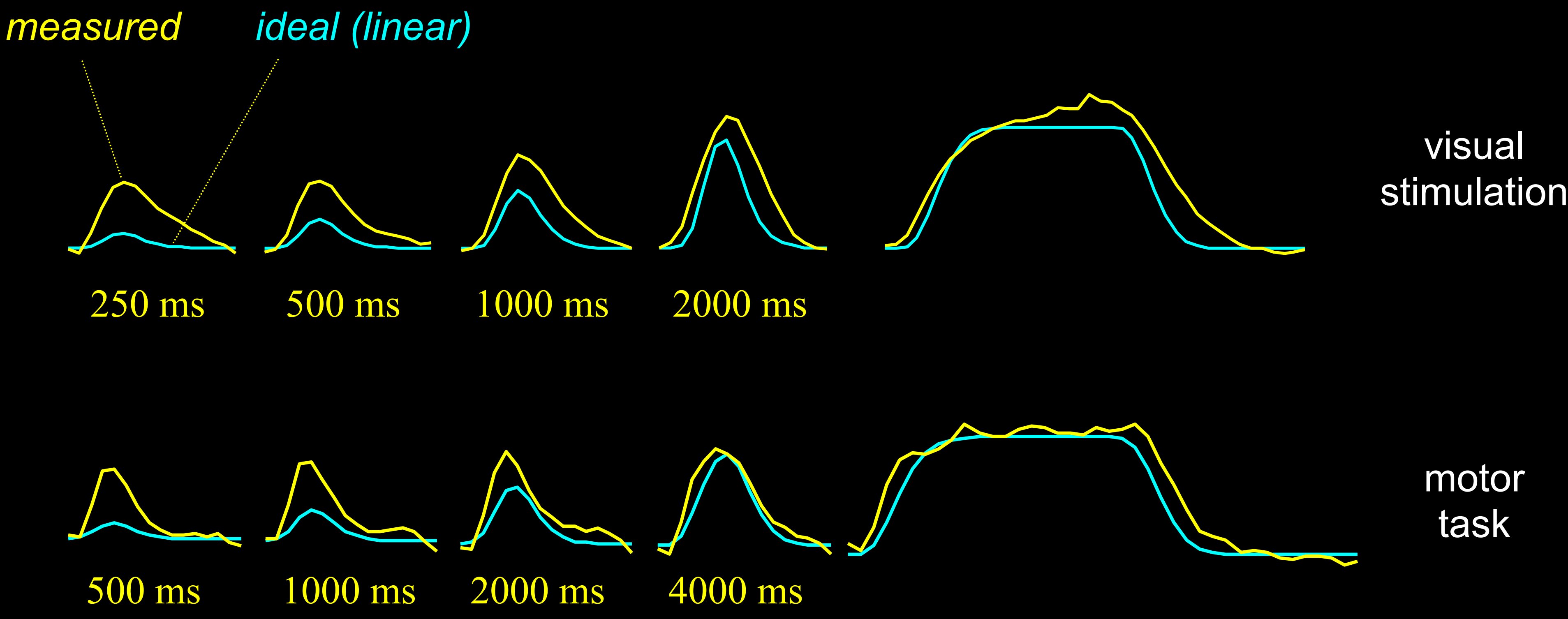
1.5
1
0.5
0
0
2
4
6
8
10
12
14
Time (sec)
250 ms
500 ms
1000 ms
2000 ms

Methods

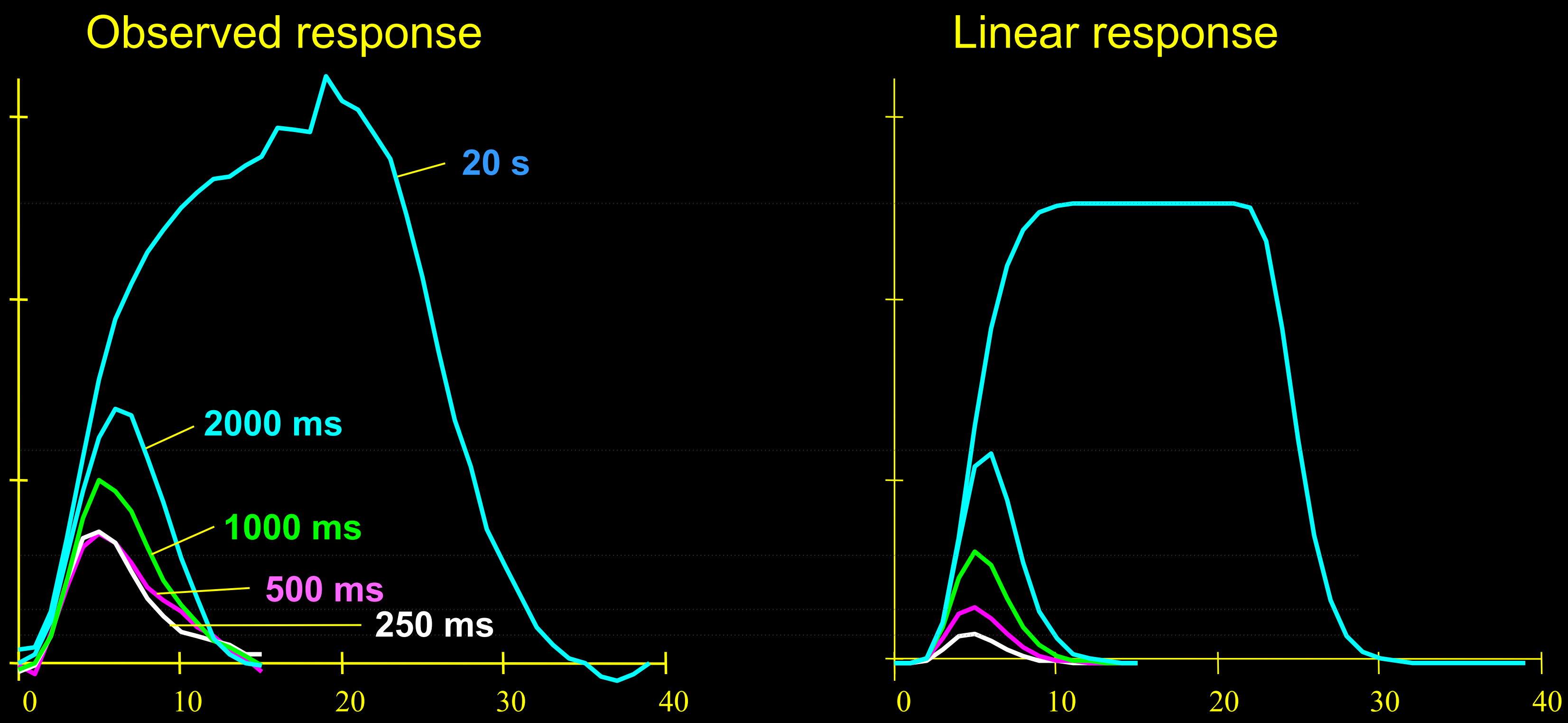


Stimulus Duration (SD)
Visual
Motor
SD = 250 ms
SD = 500 ms
SD = 500 ms
SD = 1000 ms
SD = 1000 ms
SD = 2000 ms
SD = 2000 ms
SD = 4000 ms
16 s
Blocked Trial
20 s

Observed Responses

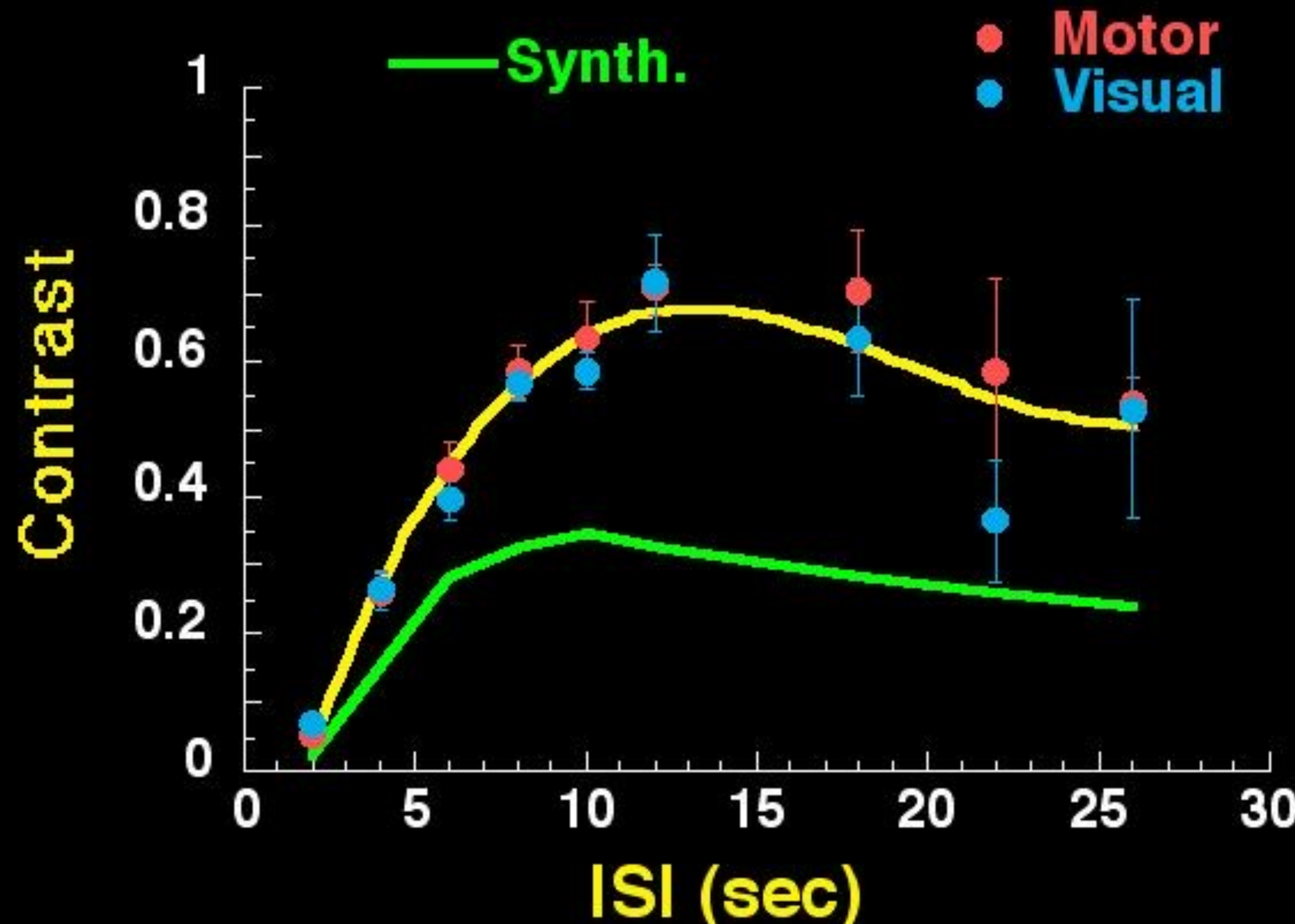


BOLD response is nonlinear



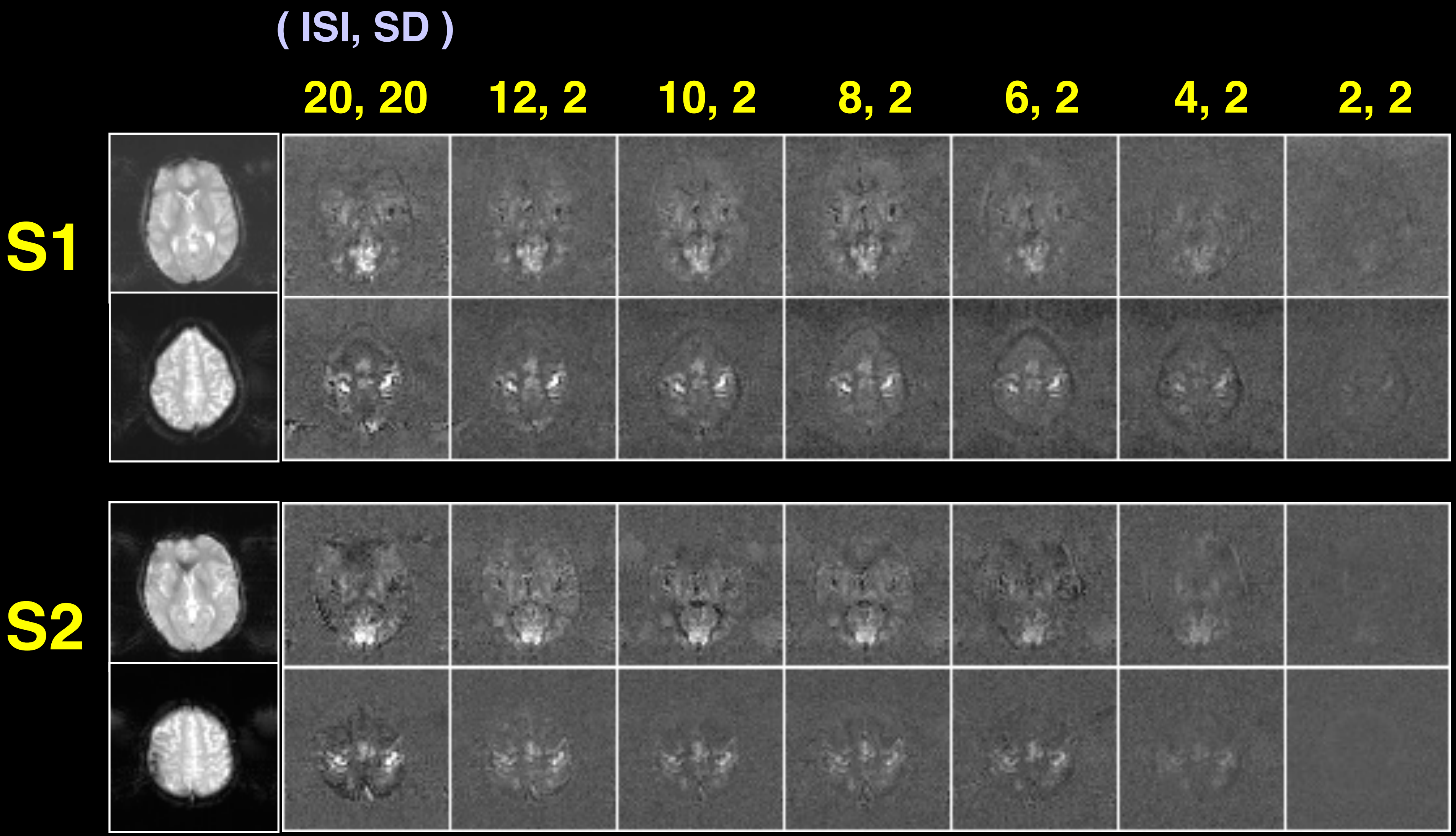
Short duration stimuli produce larger responses than expected

Functional Contrast



(Block design = 1)

Contrast to Noise Images



Source of the Nonlinearity

Neuronal

Hemodynamic

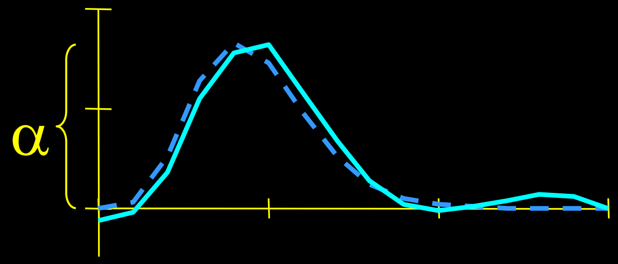
Miller et al. 1998 – Flow is linear, BOLD is nonlinear

Friston et al. 2000 – hemodynamics can explain nonlinearity

If nonlinearity is hemodynamic in origin, a measure of this nonlinearity will reflect any spatial variation of the vasculature

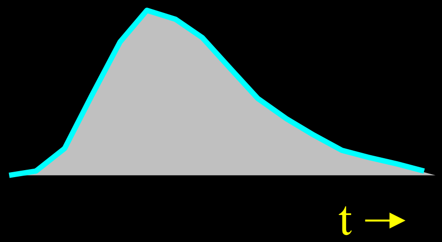
Compute nonlinearity *(for each voxel)*

- Amplitude of Response



Fit ideal (linear) to response

- Area under response / Stimulus Duration



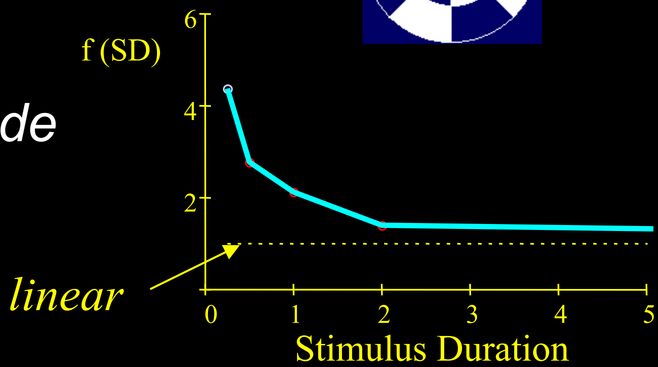
Output Area / Input Area

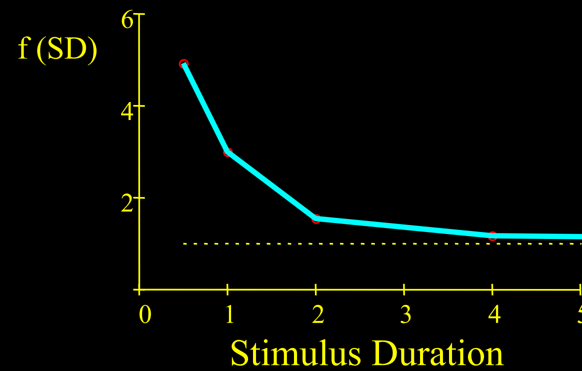
Nonlinearity

Visual

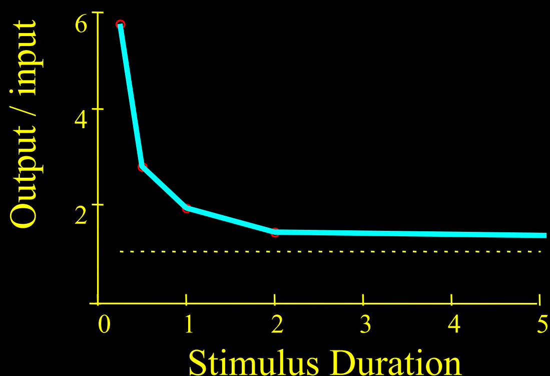
Motor

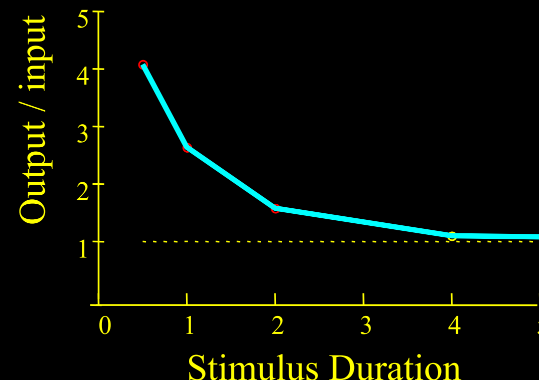
Magnitude





Area



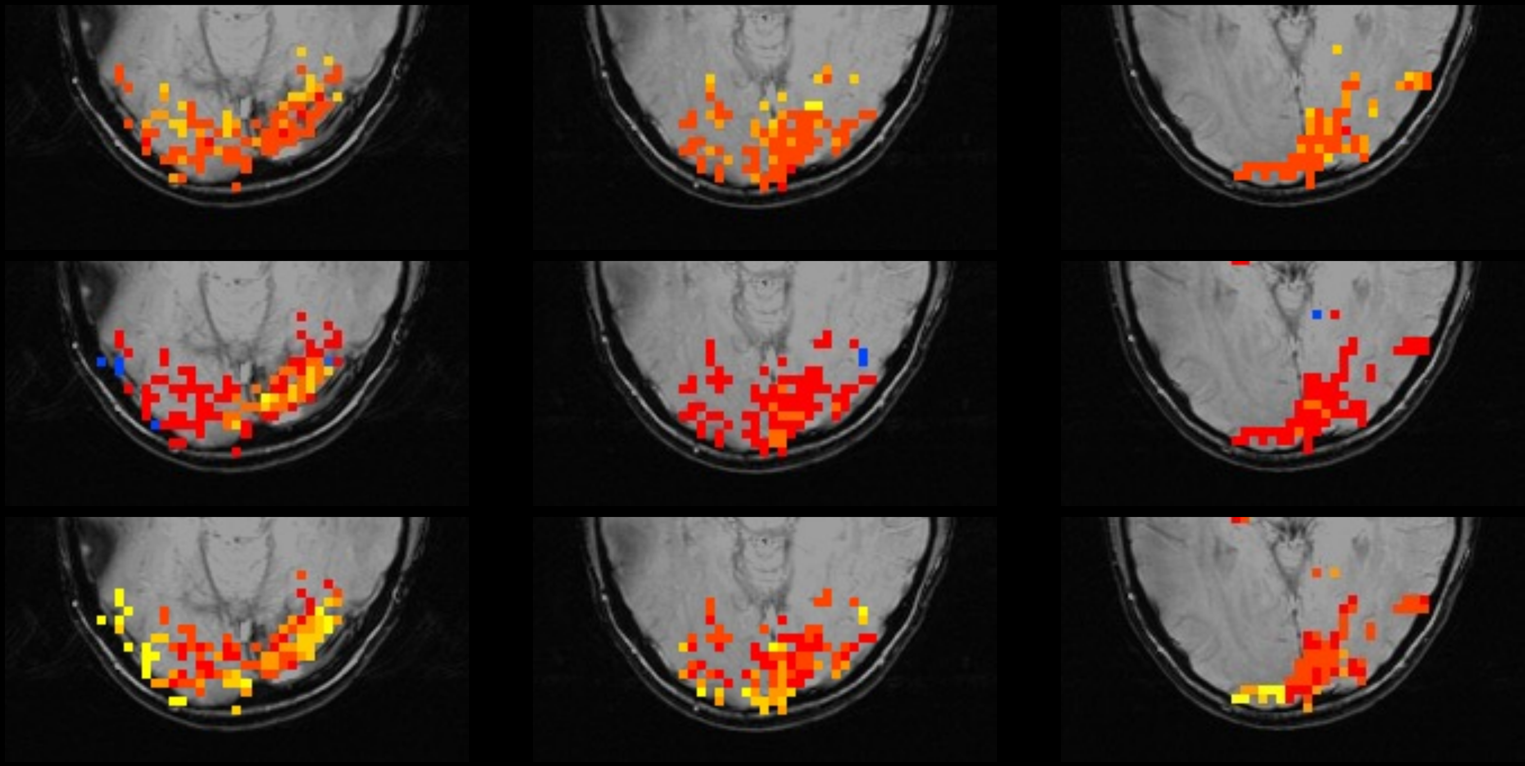


Results – visual task

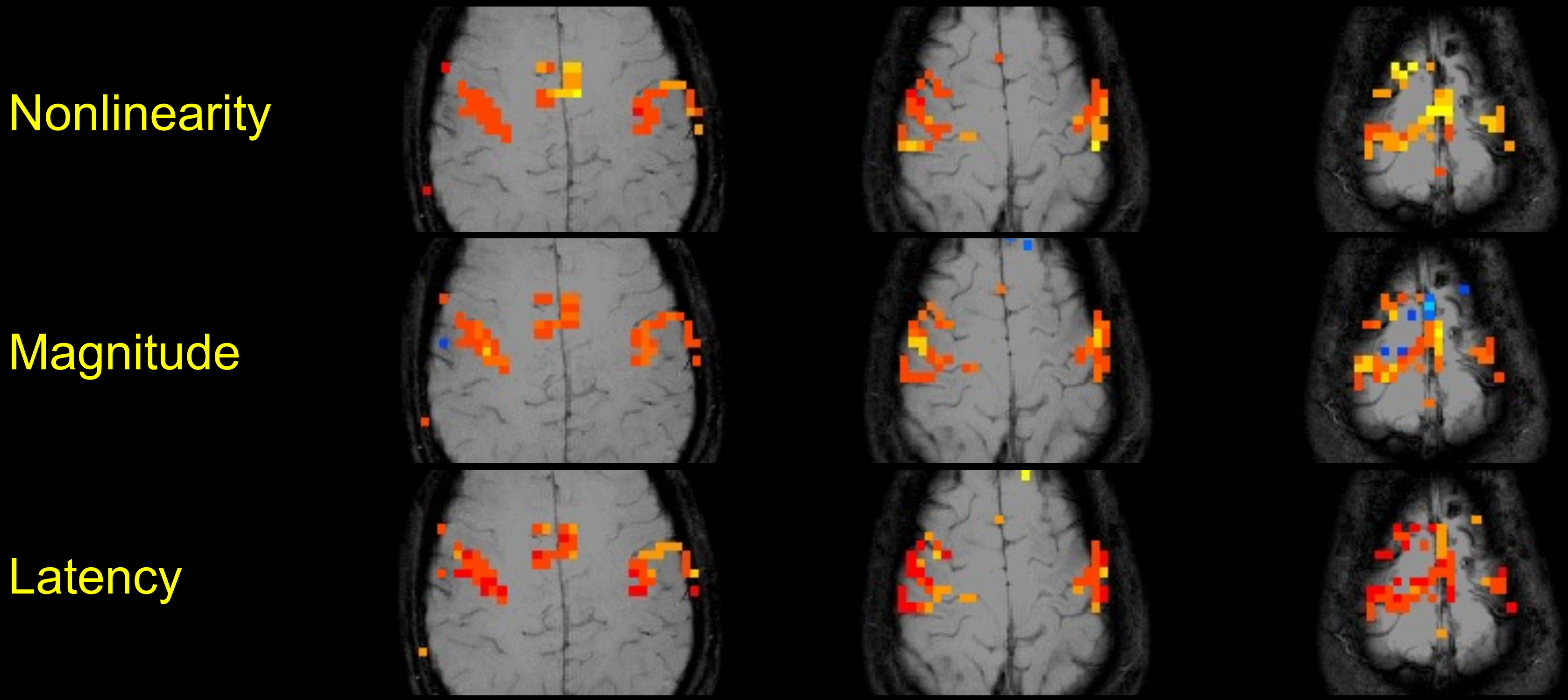
Nonlinearity

Magnitude

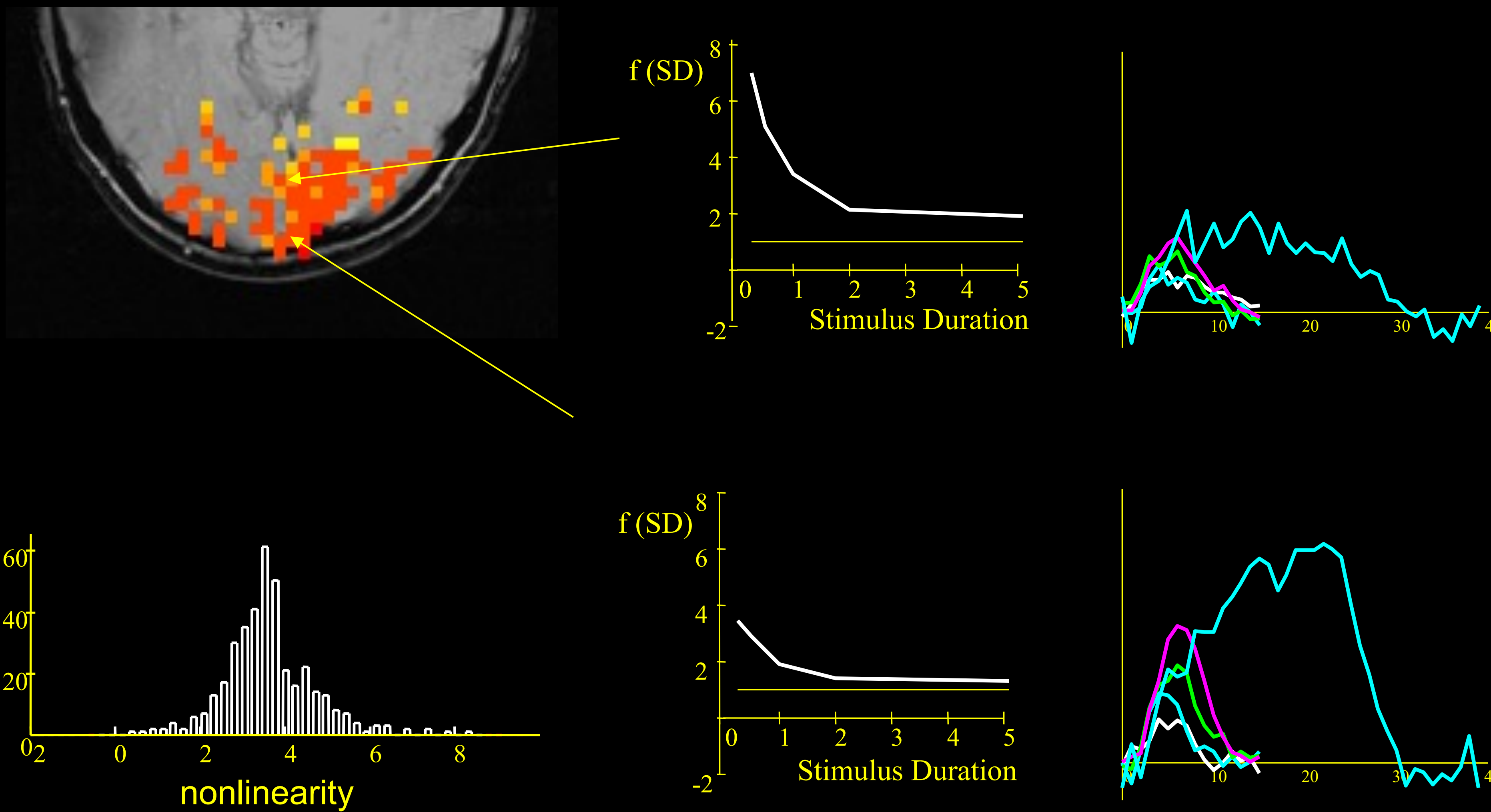
Latency



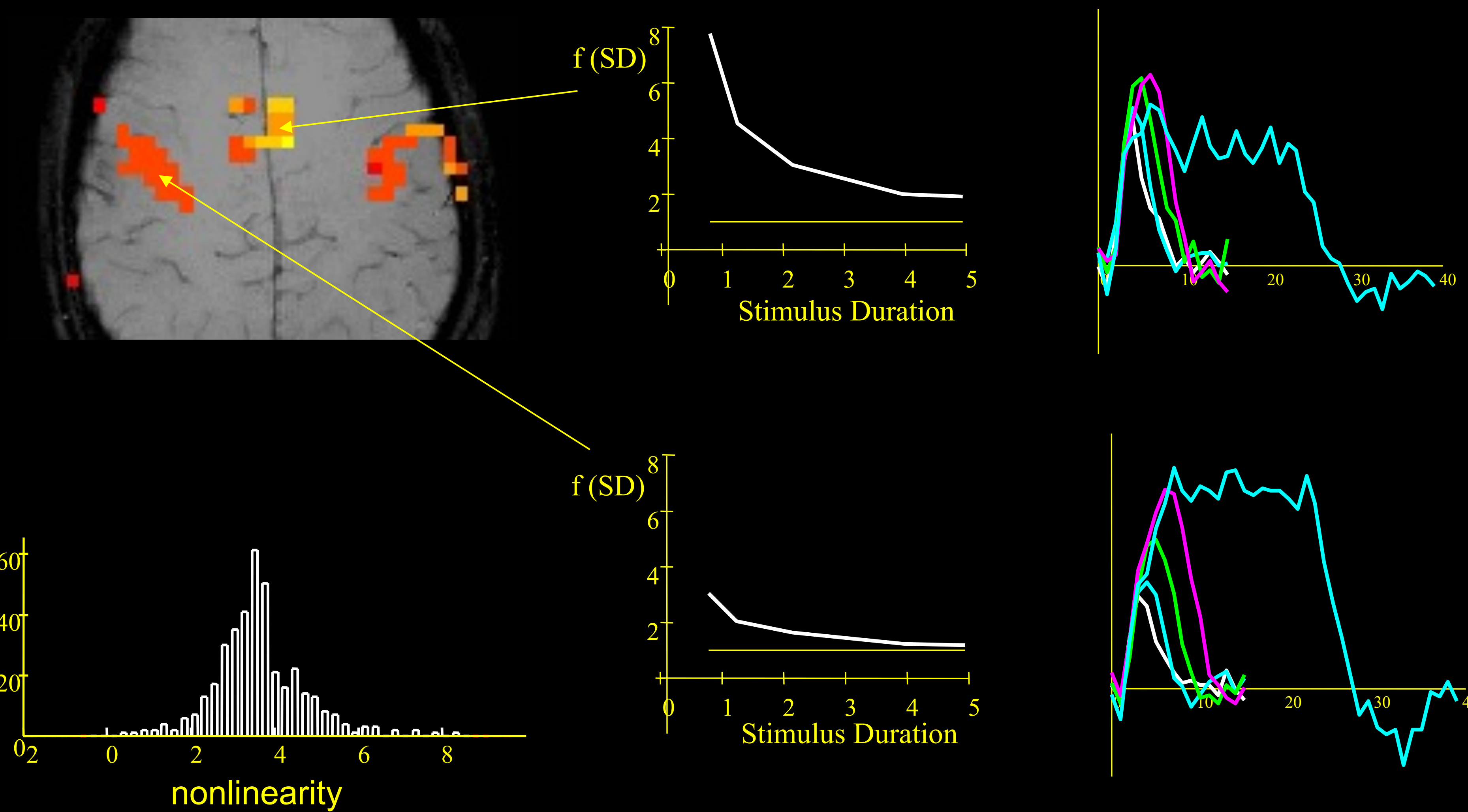
Results – motor task



Results – visual task

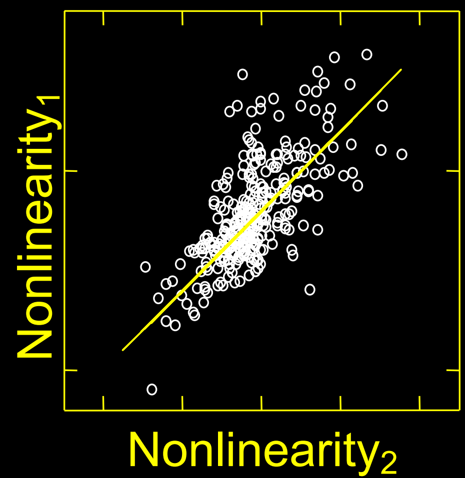


Results – motor task

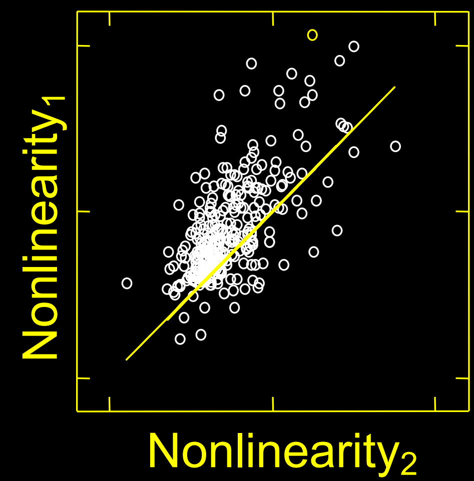


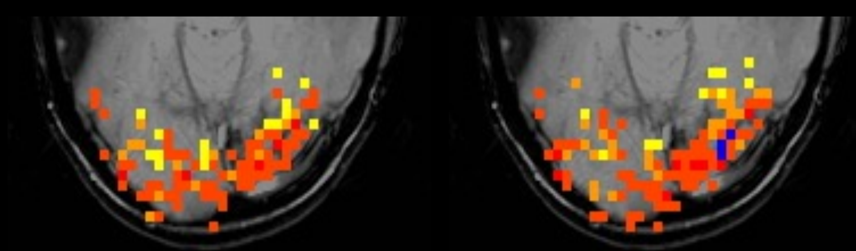
Reproducibility

Visual task

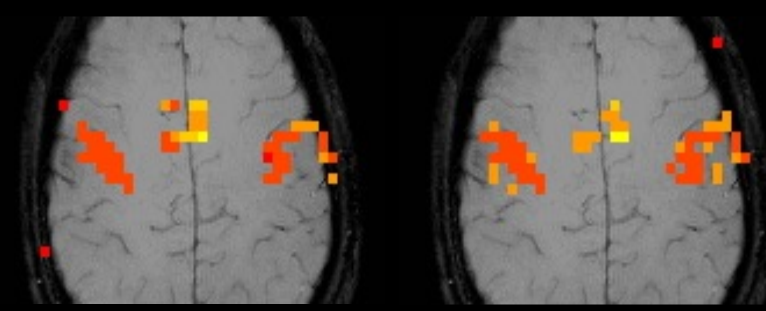


Motor task



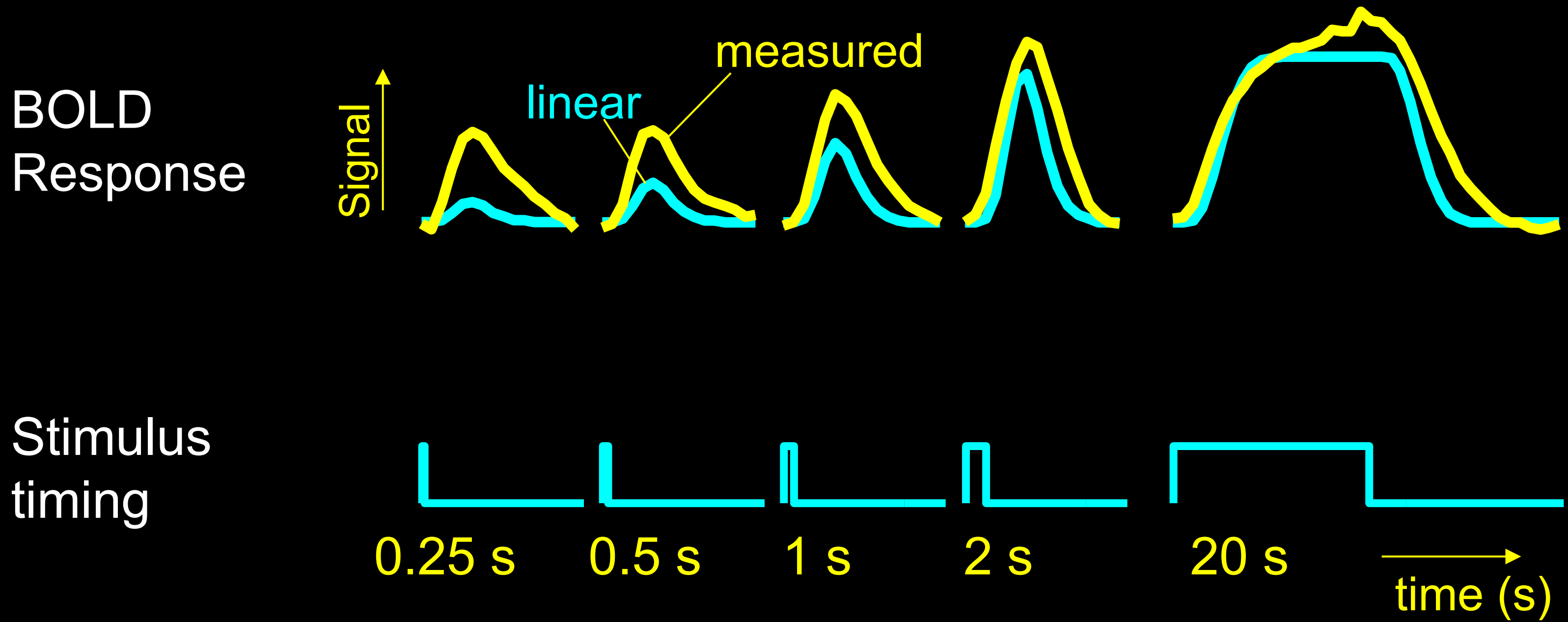


Experiment 1   Experiment 2



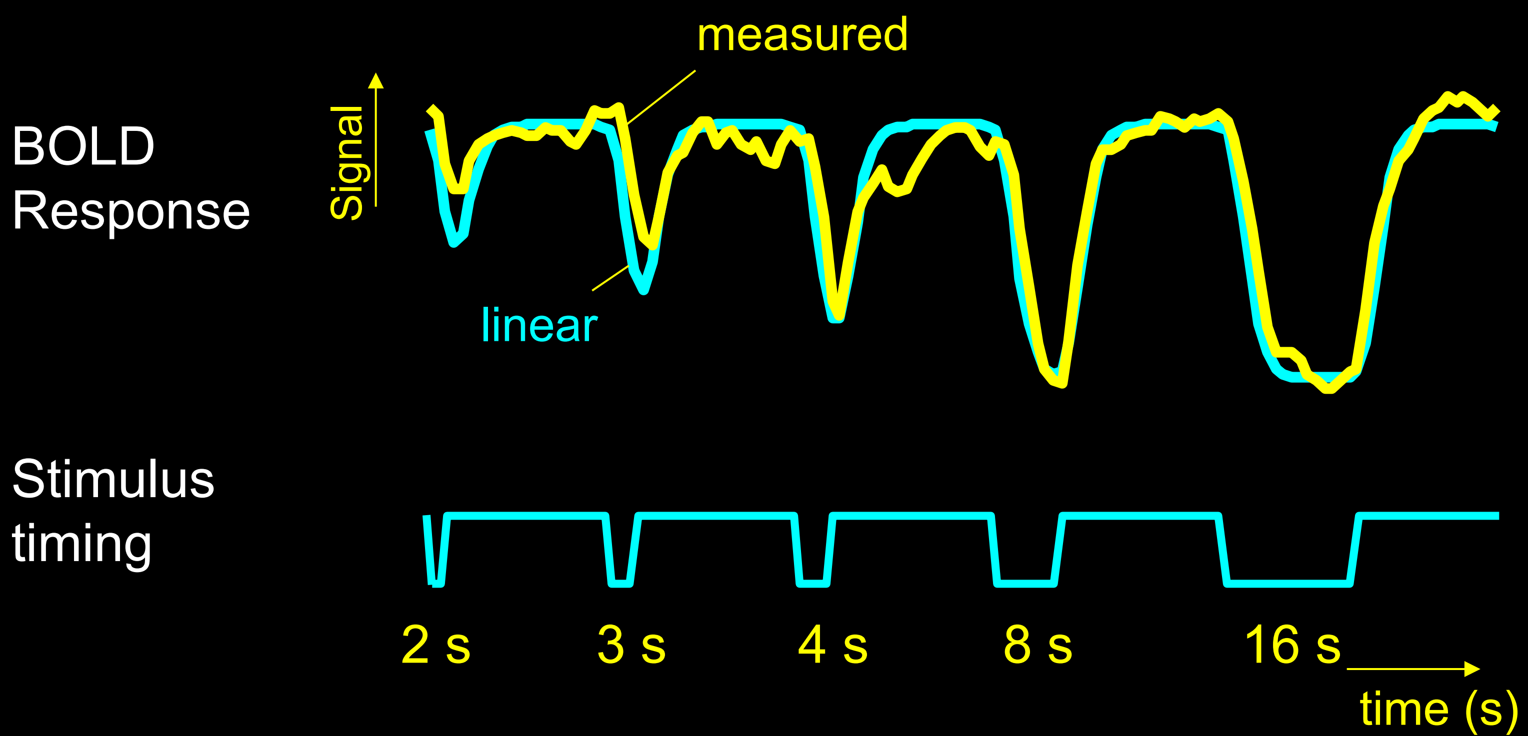
Experiment 1   Experiment 2

Different stimulus “ON” periods



Brief stimuli produce larger responses than expected

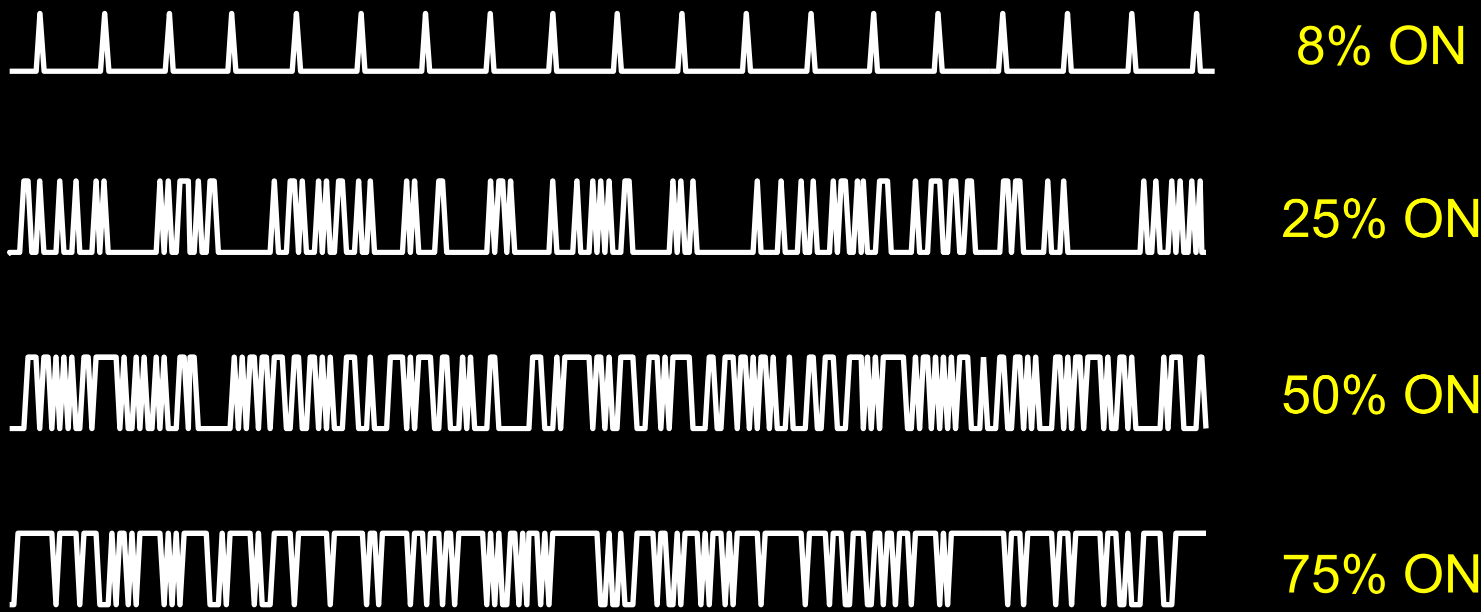
Different stimulus “ON” periods



Brief stimulus OFF periods produce smaller decreases than expecte

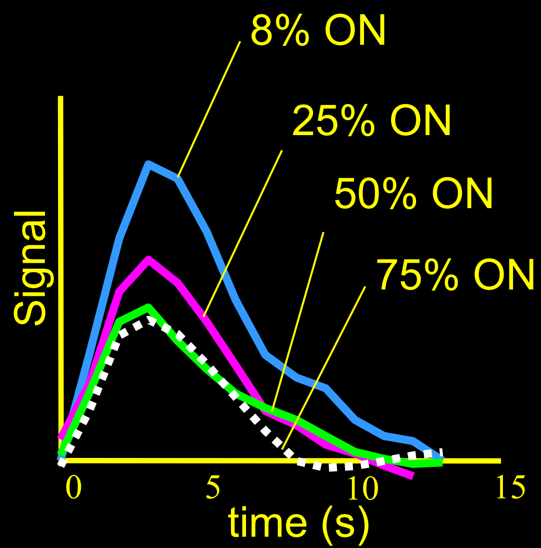
Varying "ON" and "OFF" periods

- *Rapid event-related design with varying ISI*

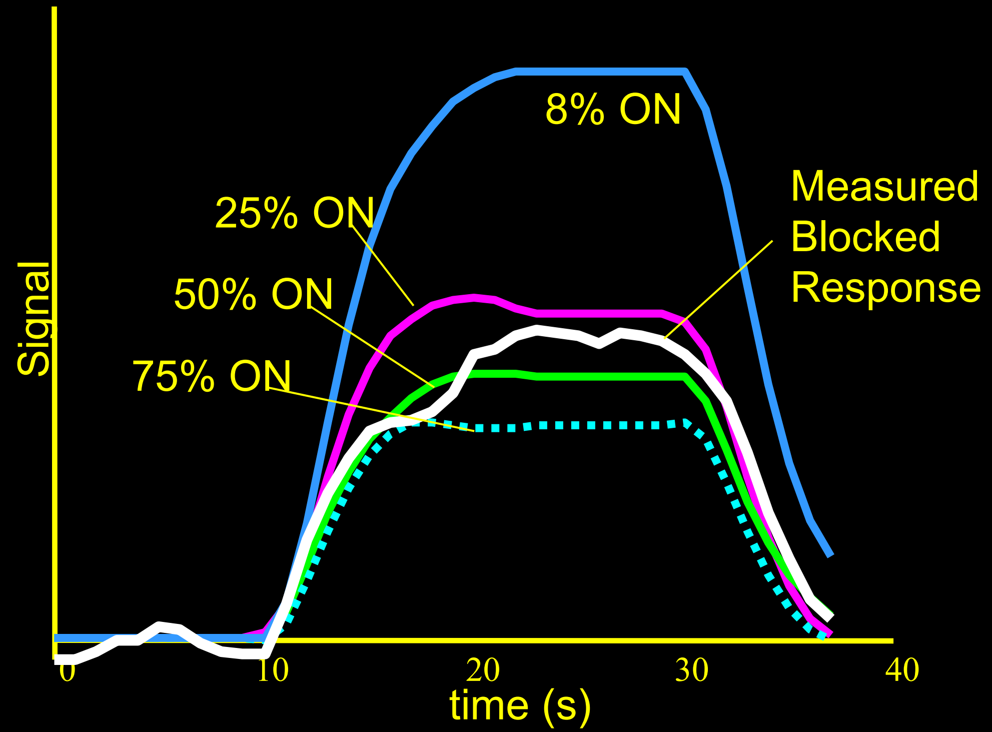


Varying “ON” and “OFF” periods

Estimated Impulse Response



Predicted Responses to 20 s stimulation

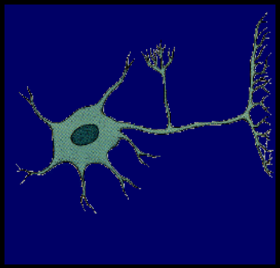


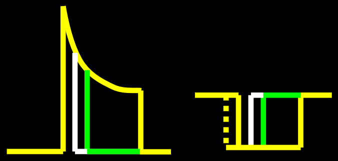
Conclusions

- For brief stimulus "ON" periods, signal increases are larger than expected. These nonlinearities show considerable yet reproducible spatial heterogeneity.
- For brief stimulus "OFF" periods, signal decreases are smaller than expected
- For varying "ON" and "OFF" periods, deconvolved impulse response depends on fraction of time in "ON" state.

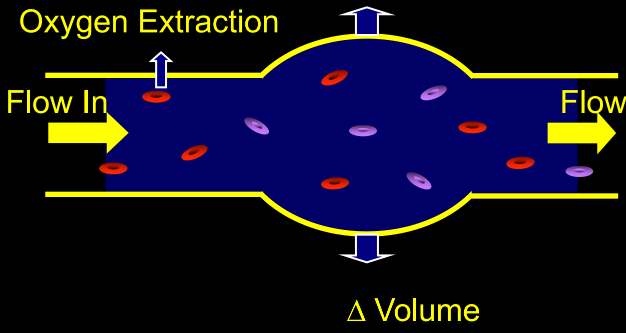
Sources of this Nonlinearity

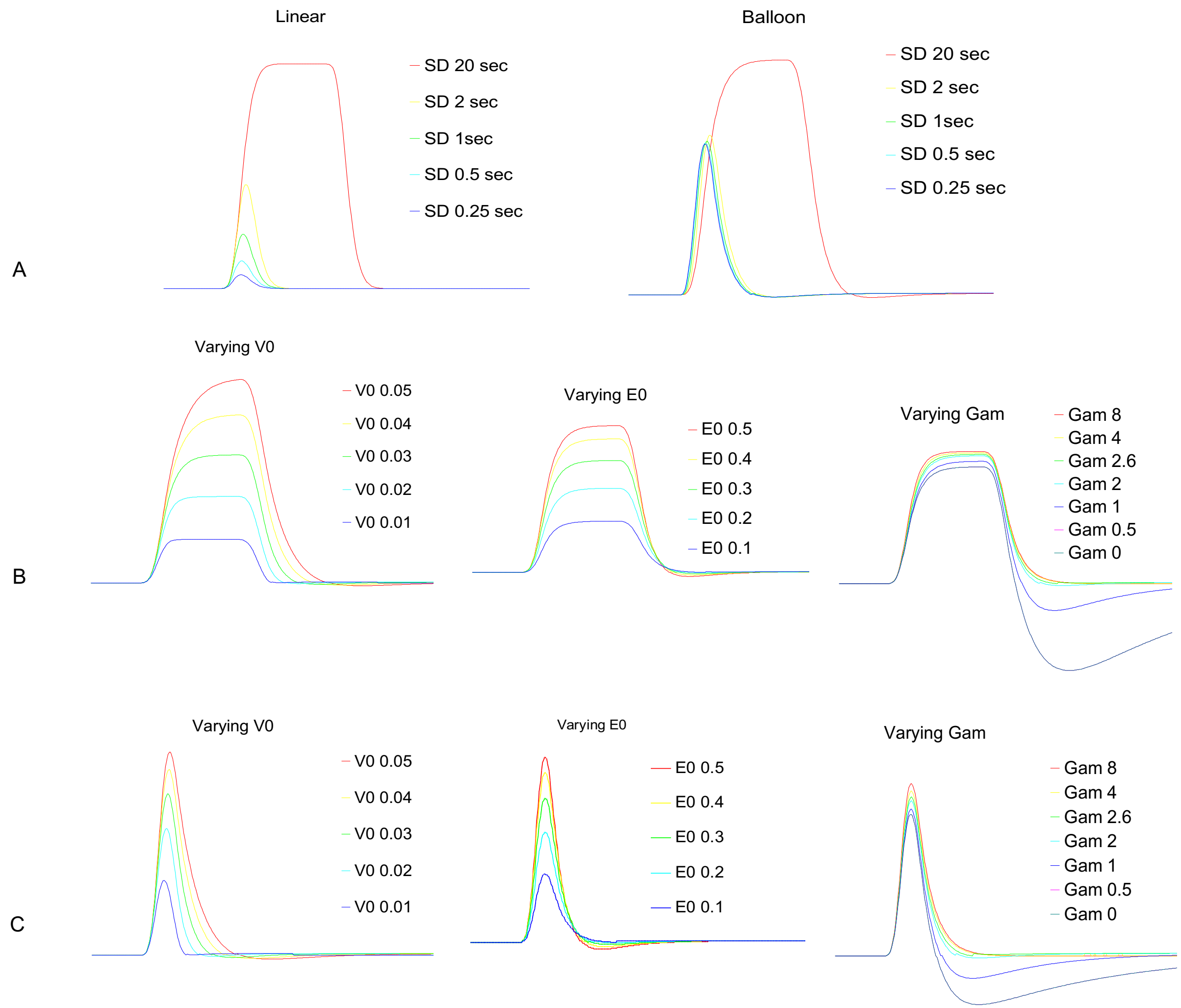
- Neuronal





- Hemodynamic
  - Oxygen extraction
  - Blood volume dynamics





BOLD Curves

A Linear and Nonlinear "Balloon" BOLD Curves for Varying SD 20,2,1,0.5, 0.25 sec

B Balloon Curves, SD = 20 sec: One parameter is varied at a time. When not varied they are set equal to V_0 = 0.03, E_0 = 0.3, and Gam = 2.6

C Balloon Curves, SD = 2 sec: One parameter is varied at a time. When not varied they are set equal to V_0 = 0.03, E_0 = 0.3, and Gam = 2.6

Balloon Model Parameters

For a given flow of blood into the venous compartment, the three Balloon parameters which control the hemodynamic contribution to the BOLD signal are thought to be E_0, V_0, and Gam.

E_0 represents the fraction of total hemoglobin not bound to O_2;

v(t) is the fraction of voxel volume filled with blood during the active state normalized to that at rest, **V_0**;

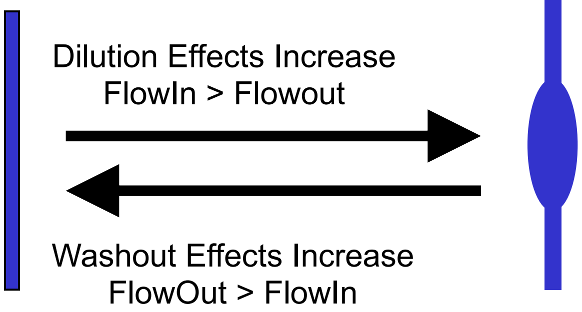
τ_o is the mean venous transit time of blood in the venous compartment and equals **V_0 / FlowOut(0)**;

Gam is the exponent defining the relationship between venous outflow and fractional blood volume;

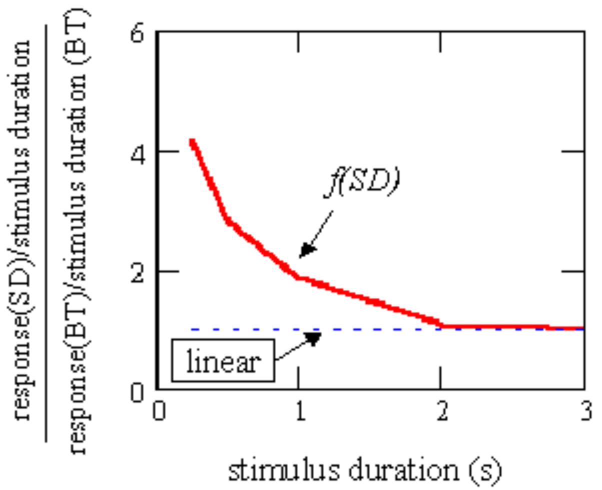
q(t) is the total voxel content of dHB during the active state normalized to that at rest;

viscos is a viscosity term that varies between viscup, during balloon inflation, and viscdown, during balloon deflation.

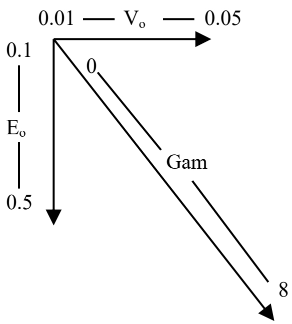
On a voxelwise basis, the stimulus waveform was smoothed (WAVrisetime), scaled (FLINamp), and phase shifted (FLINdelay) in order to generate an optimally fitting curve, ShiftedFlowIn(t), representing blood flow into the venous compartment.

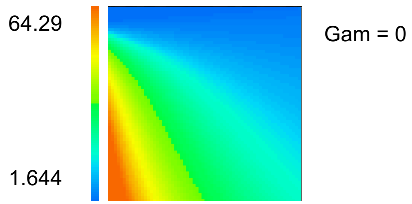


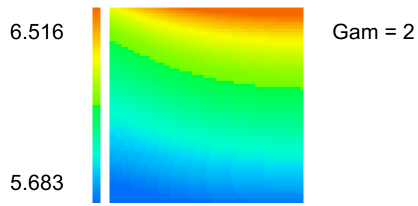
Nonlinearity = Area Under f(SD) greater than 1

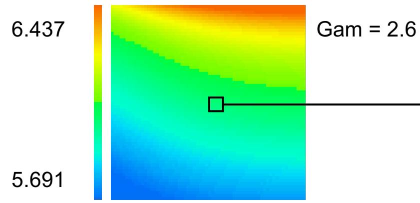


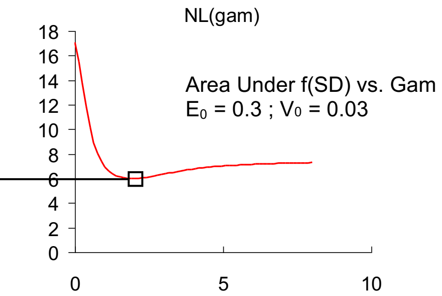
Balloon Model Nonlinearity Maps

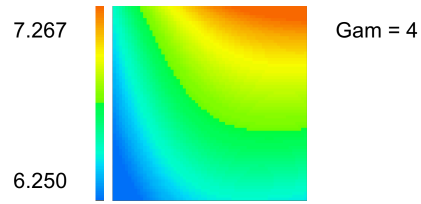


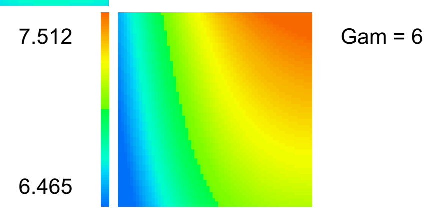


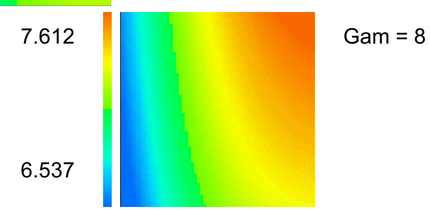












E_0, dHb fraction;
V_0, blood volume fraction at rest;
Gam, steady state venous outflow-volume relationship
τ_0 , the mean venous transit time of blood;

Physiological Parameter Contribution to NL

Gam << 2	Gam >> (τ_0 > E_0)
2 << Gam << 4	τ_0 >> (E_0 > Gam)
Gam ≈ 4	(τ_0 ≈ E_0) >> Gam
4<< Gam < 8	E_0 >> (τ_0 > Gam)

	Main NL dependence			
Gam << 2	v(t) and FlowOut(t)		NL Range >> 1	
			Larger NL	Smaller NL
		τ_0	Shorter	Longer
		E_0	Larger	Smaller
Gam >= 2	τ_0 and E_0		NL Range ≈ 1	
			Larger NL	Smaller NL
		τ_0	Longer	Shorter
		E_0	Smaller	Larger

For TE = 30ms

	1.5T	3.0T
k1	$5.2 * E_0$	$10.4 * E_0$
k2	$1.43 * E_0$	$0.5 * E_0$
k3	0.43	-0.5

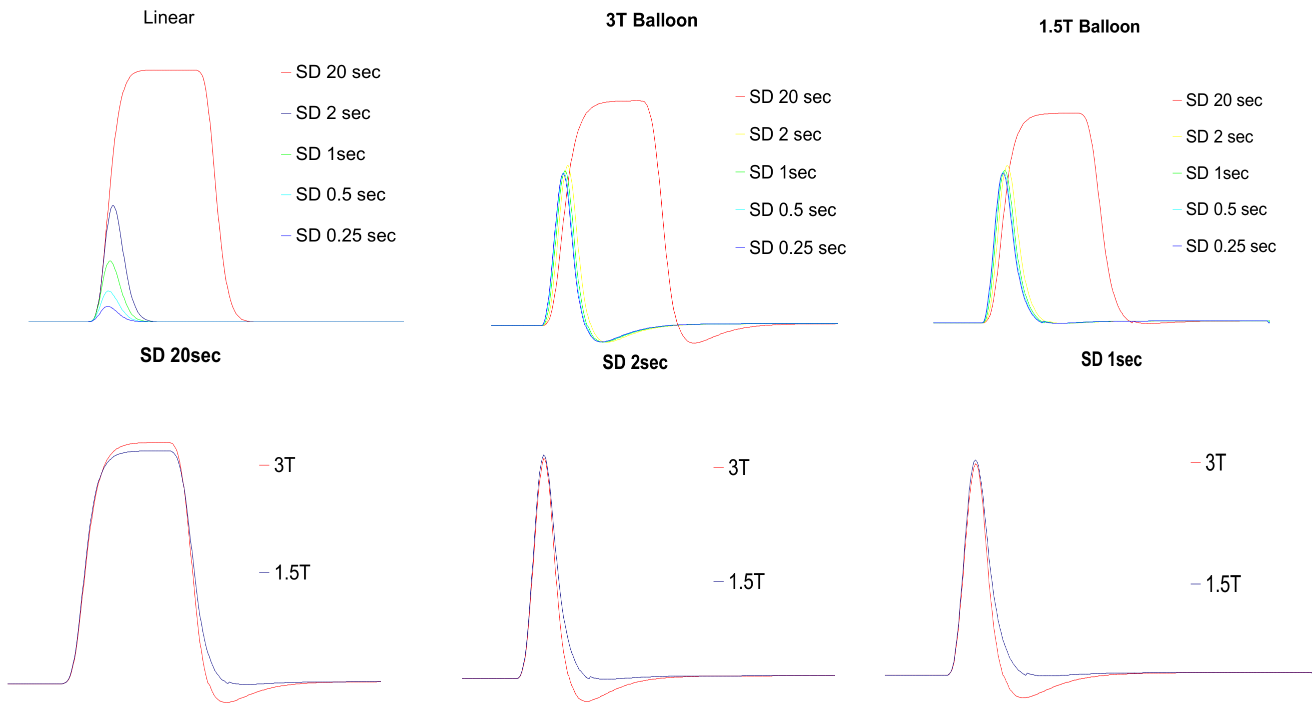


Figure 2:
Balloon Curves at different Tesla, SD = 20 sec.
V_0 = 0.03, E_0 = 0.3, and Gam = 2.6

Conclusions

When varied independently, E_0, V_0, and Gam each affect the BOLD signal in different ways. The interaction of these parameters produces BOLD curves that are nonlinear when compared to the linear results using the same SD.

For Gam values between 0 and 2, in which venous outflow is not laminar, small increases in Gam reduce nonlinearity (NL).

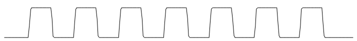
Nonlinearity is a function of several parameters, whose relative contributions to NL are determined by the value of each parameter.

For Gam values between 2.1 to 6.4 and with other parameters in physiological range, NL values ranged from 6.01 to 7.53.

By limiting the NL range to the range of NL obtained experimentally (NL between 5 and 10), the balloon model can be further constrained in our attempt to extract physiologic information from the BOLD response in humans. Further analysis is necessary to determine how varying the viscoelasticity of the venous compartment affects NL.

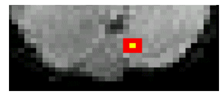
Overview

Balloon Input



ShiftedFlowIn(t)

Functional Dataset



Balloon Model Equations

$$\frac{\Delta S}{S} = V_0\left[(k1+k2)(1-q(t)) - (k2+k3)(1-v(t))\right]$$

$$\mathrm{Exfrac}(t) = 1-(1-E_0)^{\frac{1}{\mathrm{ShiftedFlowIn}(t)}}$$

$$\mathrm{CMRO}_2(t) = \mathrm{ShiftedFlowIn}(t) * \frac{\mathrm{Exfrac}(t)}{E_0}$$

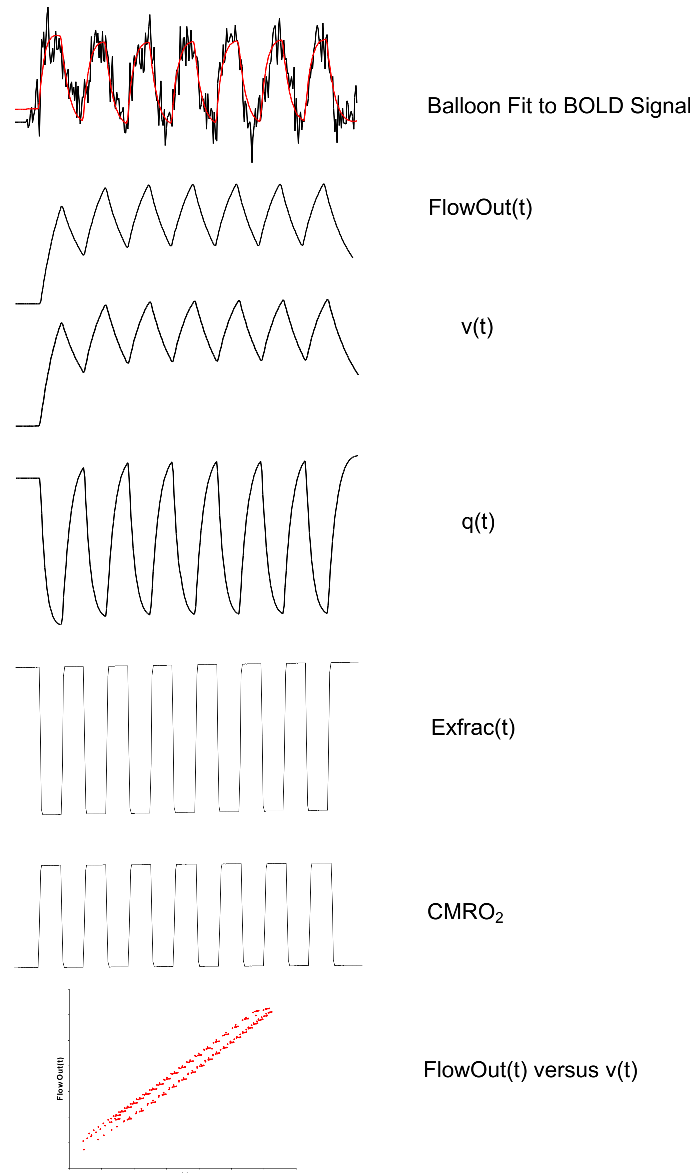
$$\mathrm{FlowOut}(t) = v(t)^{\mathrm{Gam}}; \quad \frac{df}{dv} = \mathrm{Gam}(v(t))^{(\mathrm{Gam}-1)}$$

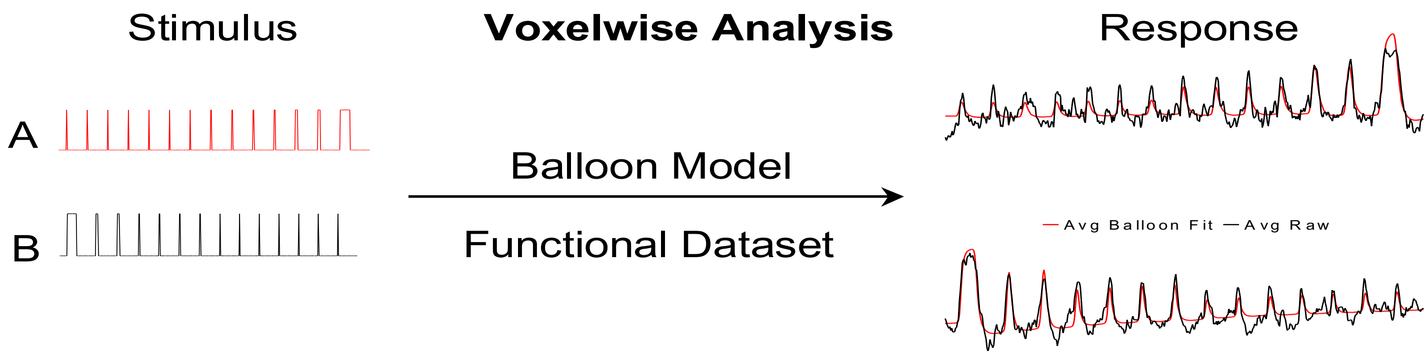
$$\tau_0 = \frac{V_0}{\mathrm{FlowOut}(0)}$$

$$q(t) = \frac{Q(t)}{Q_0}; \quad \frac{dq}{dt} = \frac{1}{\tau_0}\left[\mathrm{ShiftedFlowIn}(t)\frac{\mathrm{Exfrac}(t)}{E_0} - \mathrm{FlowOut}(t)\frac{q(t)}{v(t)}\right]$$

$$v(t) = \frac{V(t)}{V_0}; \quad \frac{dv}{dt} = \frac{1}{\tau_0}\left[\frac{\mathrm{ShiftedFlowIn}(t) - \mathrm{FlowOut}(t)}{1+0.5\left(\frac{dt}{\tau_0}\right)\left(\frac{df}{dv}\right)+\left(\frac{\mathrm{viscos}}{\sqrt{v(t)}}\right)}\right]$$

Optimized Balloon Output



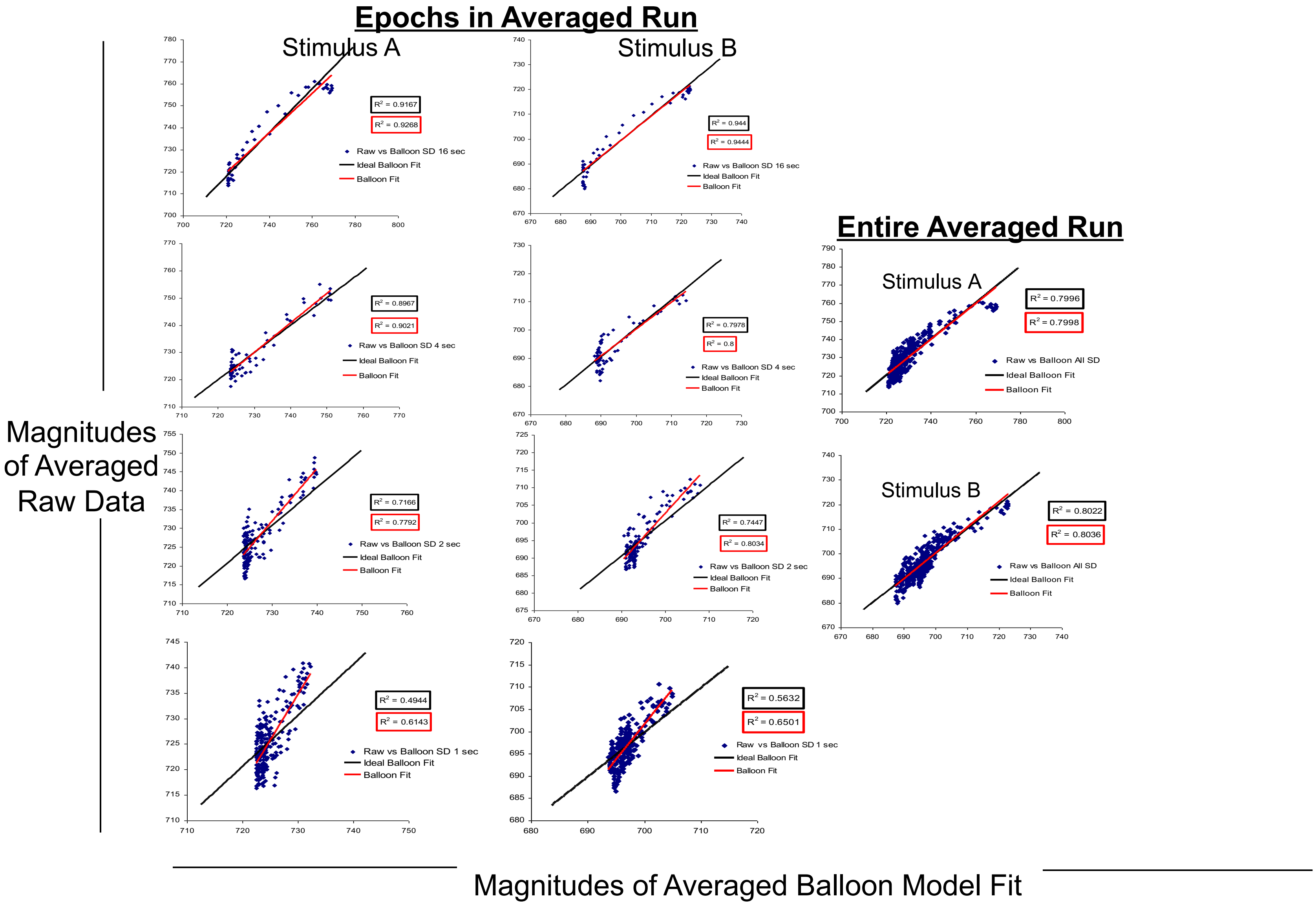


Relevant Physiologic Range

E_0	0.2 to 0.4
V_0	0.02 to 0.05
Gam	2.1 to 6.4

Balloon Model Parameter Estimation

	A1	A2	Mean	StdDev	%StdDev/Mean	B1	B2	Mean	StdDev	%StdDev/Mean
constant	726.422	719.873	723.148	4.631	0.640	687.650	695.451	691.551	5.516	0.798
linear	-0.008	0.029	0.011	0.026	241.779	0.023	0.005	0.014	0.013	94.457
FLINamp	0.598	0.491	0.545	0.076	13.938	0.582	0.603	0.592	0.015	2.498
FLINdelay	-0.794	-0.808	-0.801	0.010	-1.227	0.662	0.545	0.604	0.083	13.748
Vo	0.051	0.049	0.050	0.002	3.825	0.034	0.041	0.037	0.004	12.007
Eo	0.330	0.295	0.312	0.025	7.982	0.436	0.393	0.415	0.030	7.288
Gam	4.151	3.723	3.937	0.303	7.687	3.742	3.495	3.618	0.175	4.830
WAVrisetime	2.572	2.788	2.680	0.153	5.706	2.431	2.625	2.528	0.138	5.445
viscup	3.780	3.206	3.493	0.406	11.620	8.529	7.115	7.822	1.000	12.782
viscdown	8.870	11.086	9.978	1.567	15.704	9.945	10.250	10.098	0.215	2.133



Raw Experimental Data versus the Optimal Balloon Model Fit
The magnitudes for different stumuli (A and B), averaged across two runs, are plotted for epochs (16, 4, 2, 1 sec) within an averaged run and for all epochs in the averaged run).

Conclusions

Balloon model hemodynamics do not fully account for human BOLD signal NL.

Within a run for a given stimulus, epochs of longer stimulus duration are better characterized by the Balloon model than shorter stimulus durations.

As epoch durations become briefer, the Balloon model fits become more linear relative to experimental data.