Causality from fMRI?

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Grenoble Brain Connectivity Course

Yes!

- **Experiments (from 2003 on)**
  - Friston et al., NeuroImage, 2003 (DCM)
  - Goebel et al., Magn Reson Imaging, 2003 (GCM)
  - Roebroeck et al., NeuroImage, 2005 (GCM)
  - David et al., PLoS Biol, 2008 (DCM)
  - Ge et al., PLoS Comp Biol, 2009 (GCM)
  - Reyt et al., NeuroImage, 2010 (DCM)
  - Zhou et al., Magn Reson Imaging, 2011 (GCM)
  - Etc.

- **Simulations (from 2010 on)**
  - Kim and Horwitz, NeuroImage, 2009 (SEM)
  - Deshpande et al., NeuroImage, 2010 (GCM)
  - Havlicek et al., NeuroImage, 2010 (GCM)
  - Rogers et al., Magn Reson Imaging, 2010 (GCM)
  - Ryali et al., NeuroImage, 2011 (Multivariate Dynamical Systems)
  - Sato et al., NeuroImage, 2010 (GCM)
  - Schippers et al., NeuroImage, 2011 (GCM)
  - Smith et al., NeuroImage, 2011 (many methods)
  - Etc.

No!

- “**The limitations of fMRI are not related to physics** or poor engineering, and are unlikely to be resolved by increasing the sophistication and power of the scanners; **they are instead due to the circuitry and functional organization of the brain**, as well as to inappropriate experimental protocols that ignore this organization. **The fMRI signal cannot easily differentiate between function-specific processing and neuromodulation**, between bottom-up and top-down signals, and it may potentially confuse excitation and inhibition. **The magnitude of the fMRI signal cannot be quantified to reflect accurately differences between brain regions, or between tasks within the same region**. The origin of the latter problem is not due to our current inability to estimate accurately cerebral metabolic rate of oxygen (CMRO2) from the BOLD signal, but to the fact that **haemodynamic responses are sensitive to the size of the activated population, which may change as the sparsity of neural representations varies spatially and temporally**.”

Logothetis, Nature, 2008

Problems for causal inference from fMRI

- **Problem 1: searching over models**
  - Computational cost
- **Problem 2: indirect measurements**
  - Measured variables / Latent variables
- **Problem 3: modeling causal structure across individuals**
  - Intersubject variability / ROI selection
- **Problem 4: distinct but overlapping variable sets**
  - Subset selection over the group
- **Problem 5: varying delays in BOLD response**
  - Intrasubject hemodynamic variability
- **Problem 6: equilibrium or transients?**
  - Resting state / Exogeneous inputs

Ramsey et al., NeuroImage, 2010

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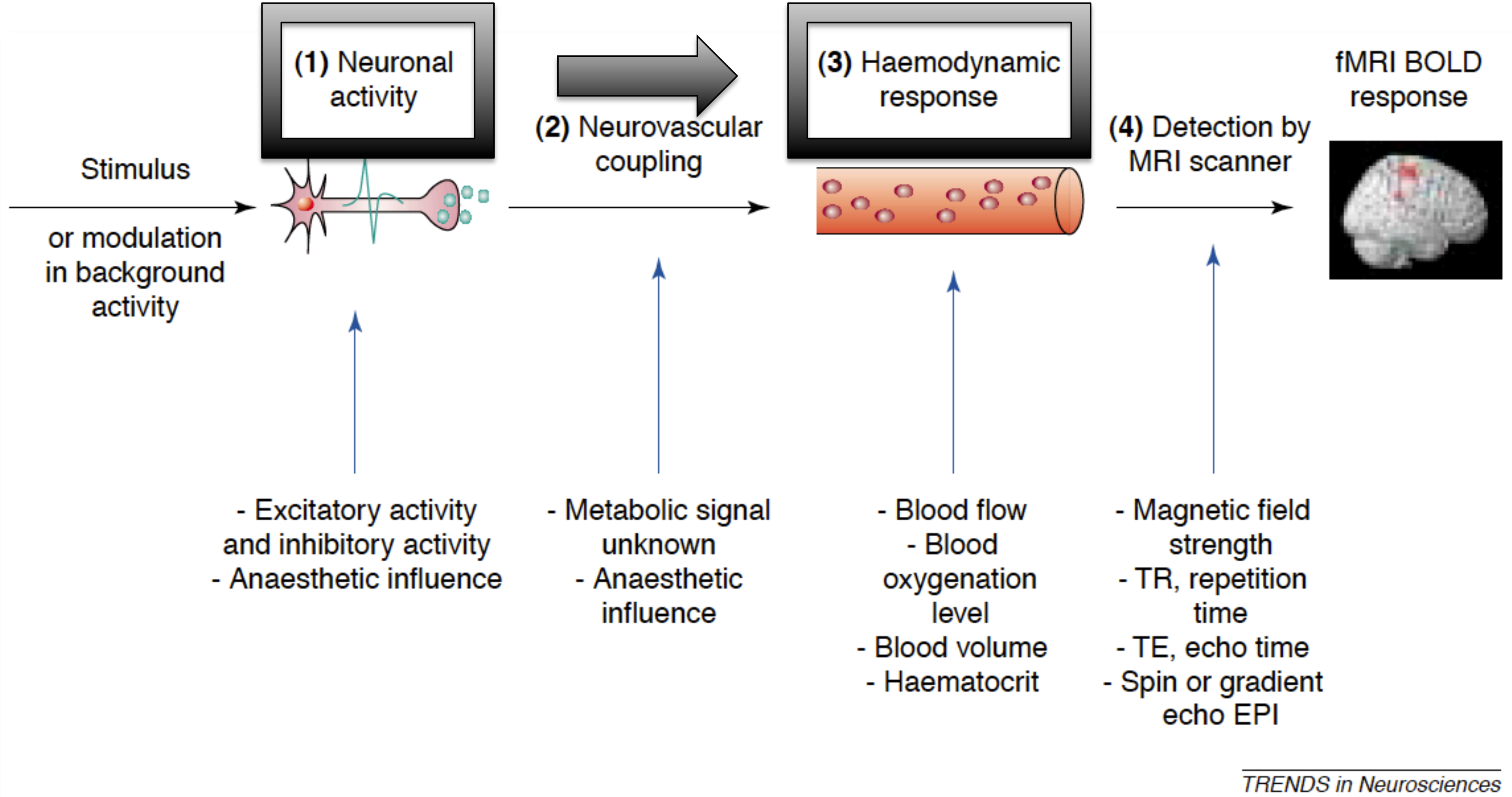
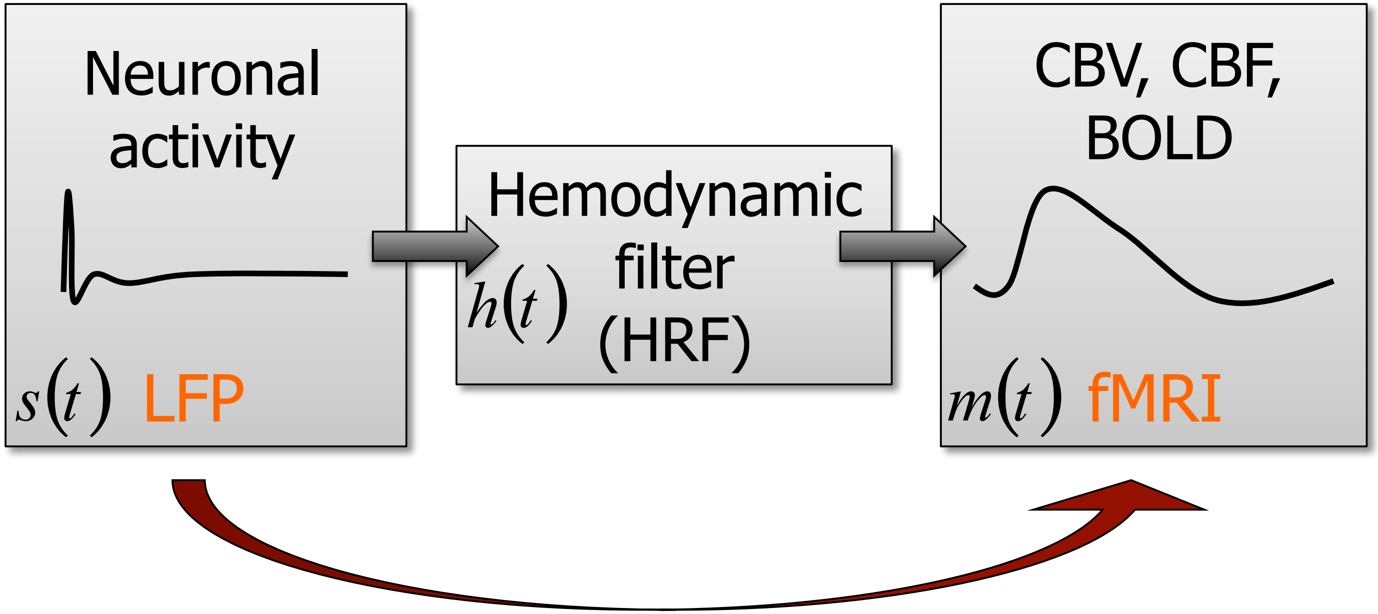
➡ **Biophysical models of fMRI signals and of brain function**

LFP/BOLD
Standard biophysical model



Arthurs & Boniface, TINS, 2000

LFP/BOLD
Standard biophysical model

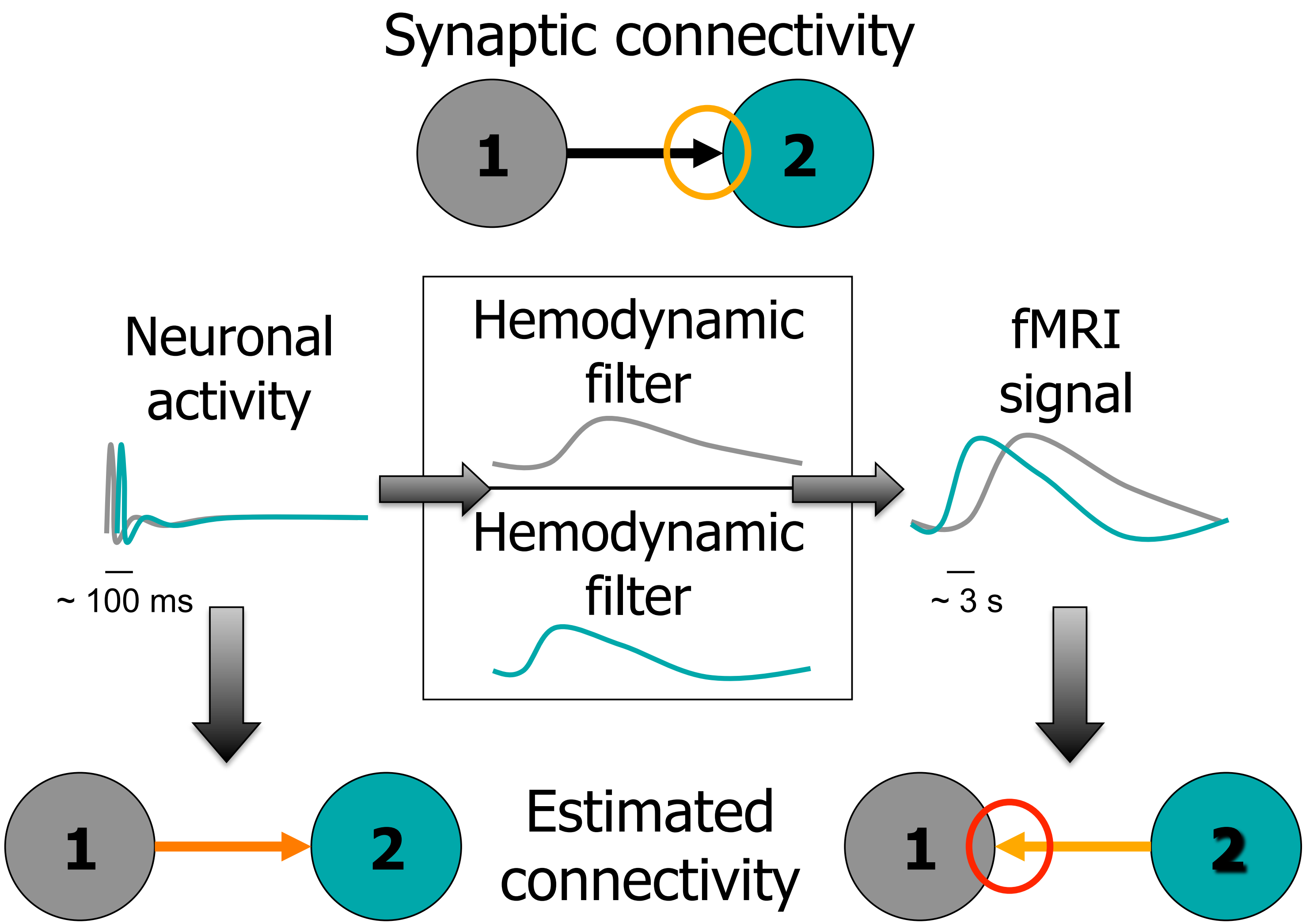


Prediction

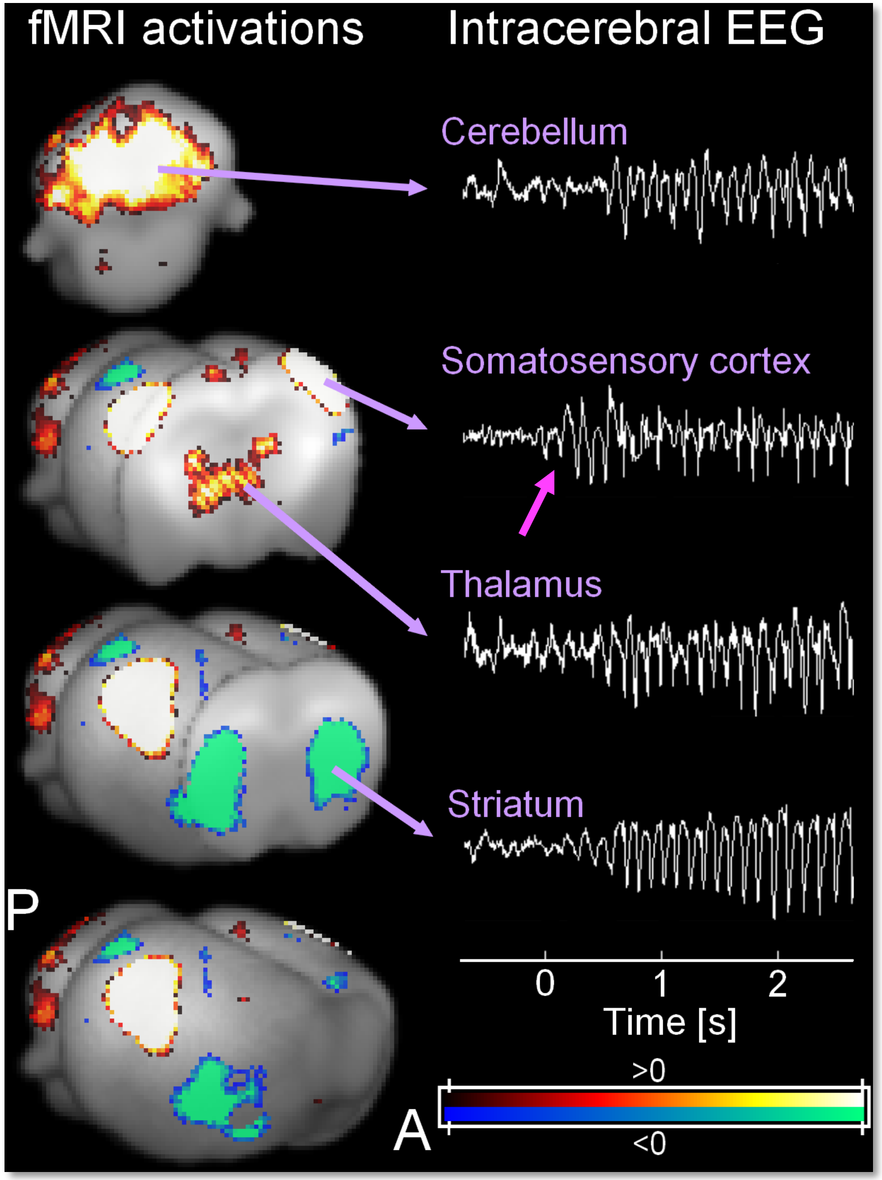
$$m(t) = s(t) \otimes h(t) + \varepsilon(t)$$

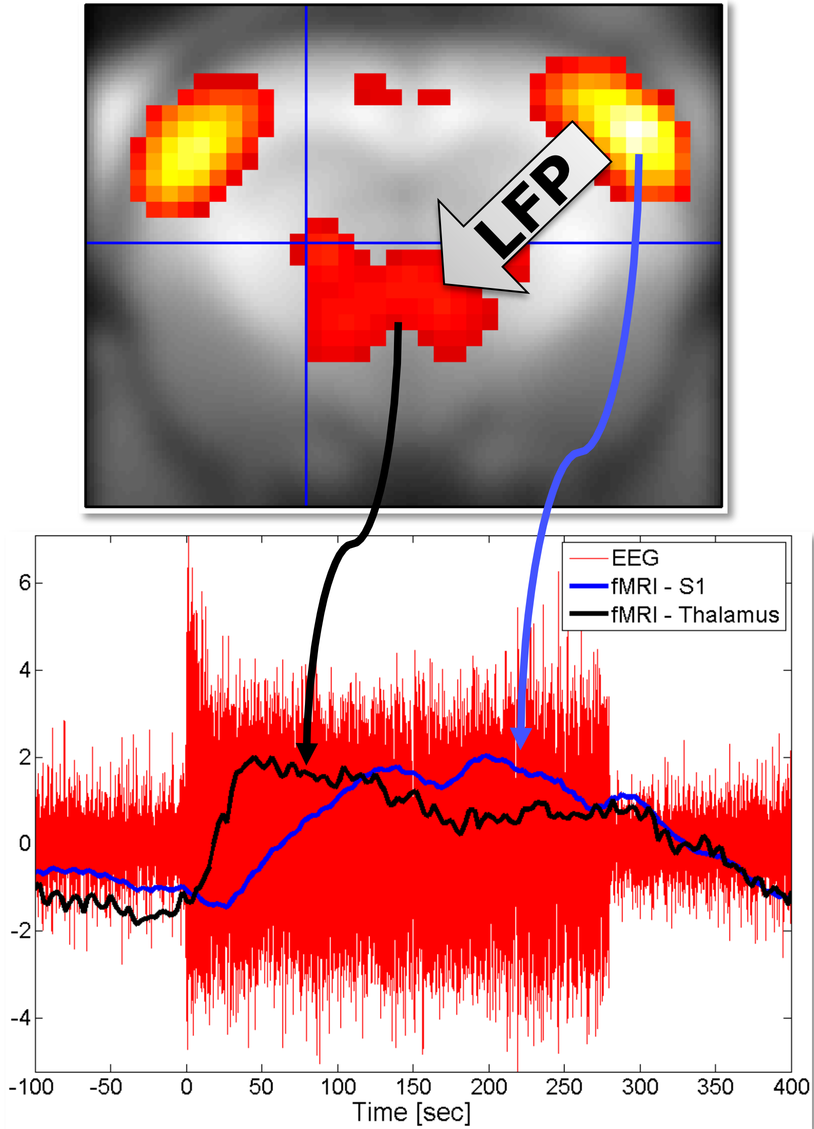
General Linear Model

Directionality and hemodynamic variability



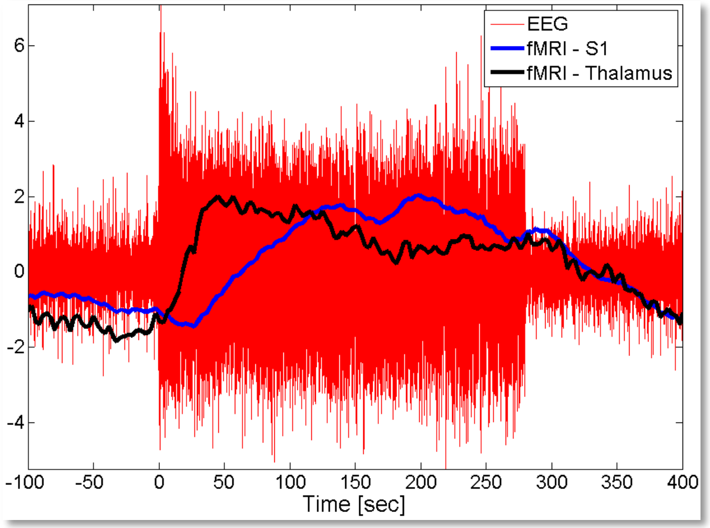
Rat model of absence epilepsy





David et al., PLoS Biol, 2008

Granger Causality



- **Granger Causality:**
  - Based on temporal precedence of fMRI time series.
  - Uses vector regression models.

Prediction	Quality of prediction
x & y separately	
$x(n)=\sum_{i=1}^{p}A_x(i)x(n-i)+u(n)$	$\mathrm{var}(u(n))=\Sigma_1$
$y(n)=\sum_{i=1}^{p}A_y(i)y(n-i)+v(n)$	$\mathrm{var}(v(n))=\mathrm{T}_1$
x & y together	
$q(n)=\begin{bmatrix}x(n)\\y(n)\end{bmatrix}$	$\mathrm{var}(w(n))=Y$
$=\sum_{i=1}^{p}A_q(i)q(n-i)+w(n)$	$=\begin{bmatrix}\Sigma_2 & C\\C^T & \mathrm{T}_2\end{bmatrix}$

- **From x to y :** $F_{x\to y}=\ln(\lvert\mathrm{T}_1\rvert/\lvert\mathrm{T}_2\rvert)$
- **From y to x :** $F_{y\to x}=\ln(\lvert\Sigma_1\rvert/\lvert\Sigma_2\rvert)$

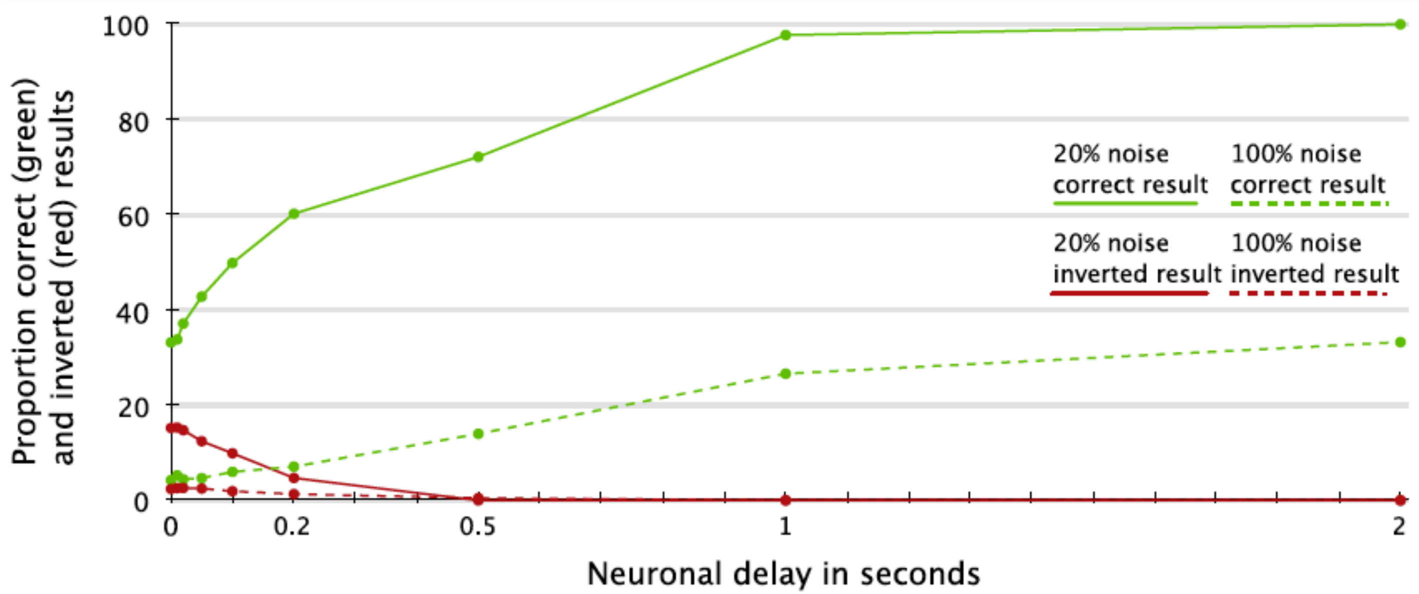
Goebel et al., Magn. Reson. Imaging, 2003

Effect of HRF variability: Granger Causality simulations

- **Single subject level:**
  - In the **absence of HRF variability**, even **tens of milliseconds** of neuronal delay can be inferred from GC analysis of fMRI.
  - In the **presence of HRF delays** which oppose neuronal delays, the minimum detectable neuronal delay may be **hundreds of milliseconds**.

Deshpande et al., NeuroImage, 2010

- **Group level:**
  - Resting state activity (stationary)

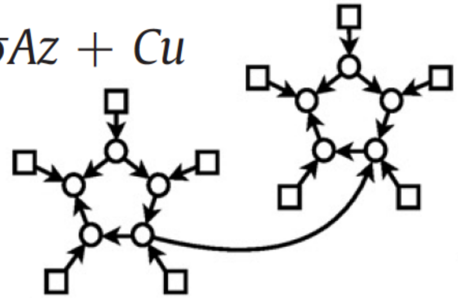


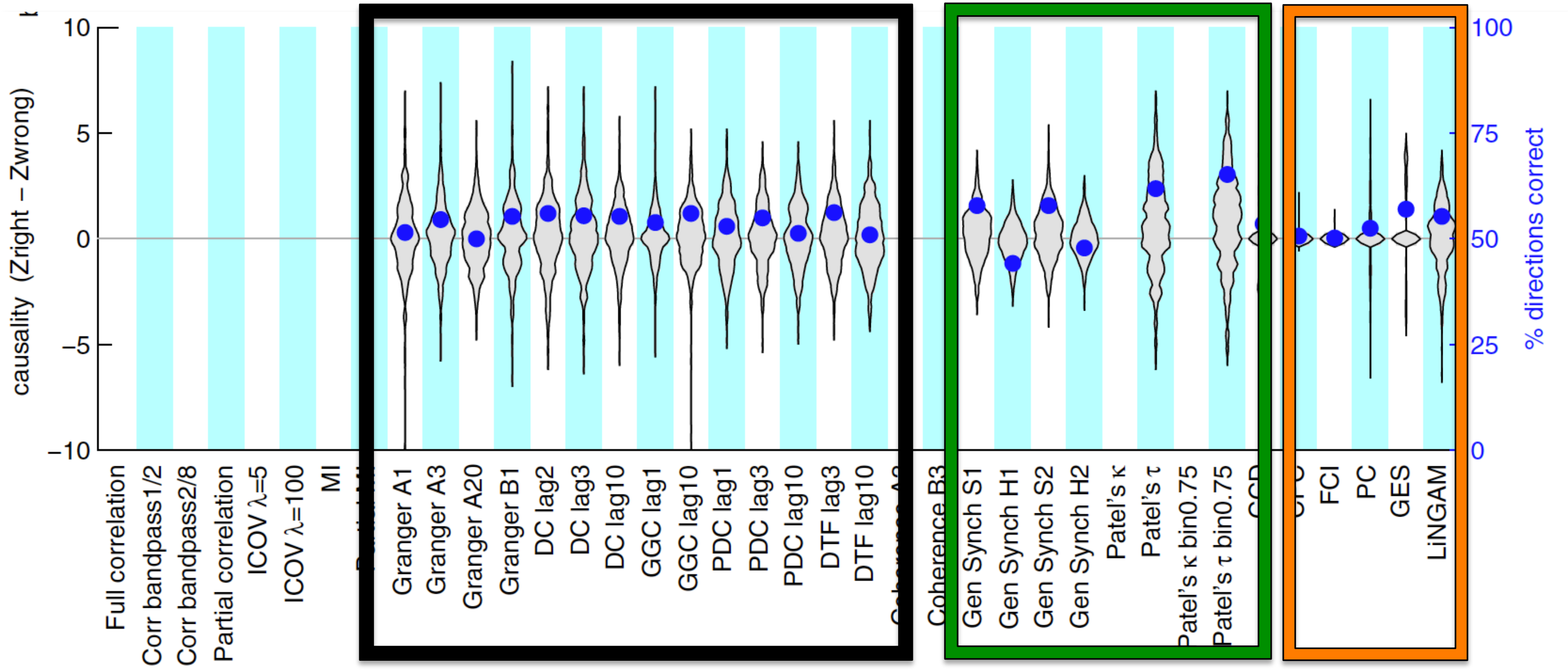
Schippers et al., NeuroImage, 2011

Directionality measures have different sensitivity

- **Measures of directionality:**
  - Lag-based (e.g. Granger)
  - Conditional independence (e.g. Bayes nets)
  - Higher order statistics (e.g. Patel's conditional probability)

$$\dot{z} = \sigma A z + C u$$

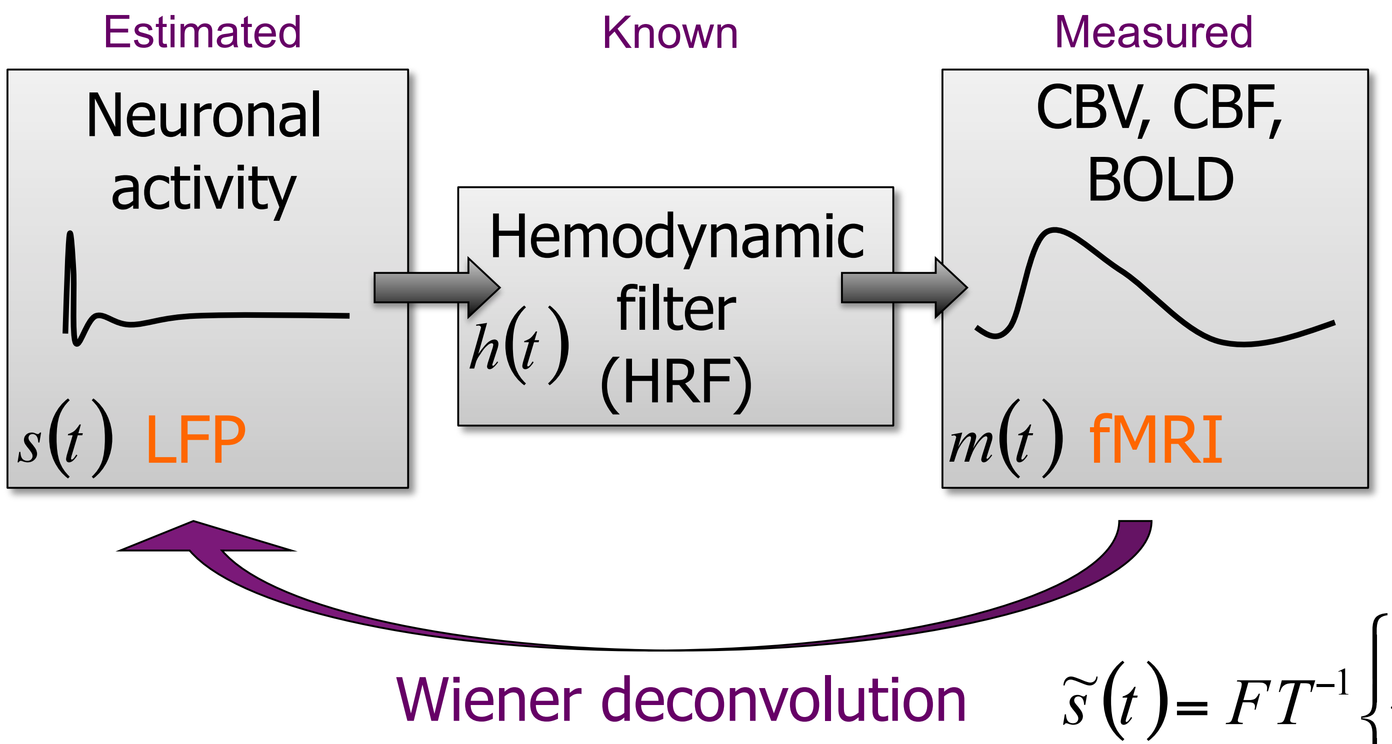




Smith et al., NeuroImage, 2011

Directionality from hidden neural states might help

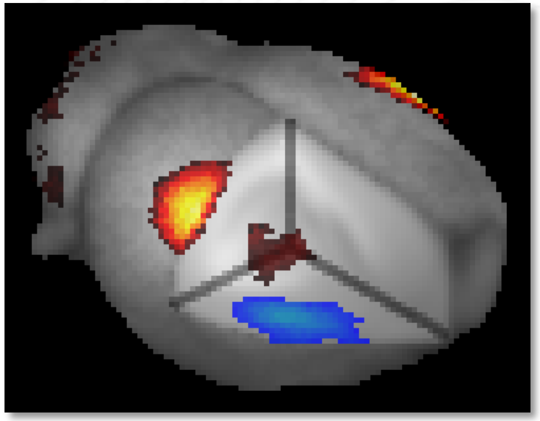
- **Deconvolution of hemodynamic effects**
  - Prior knowledge on hemodynamic kernels
- **Extended biophysical modelling including neural connectivity and hemodynamics**
  - Dynamic Causal Modelling

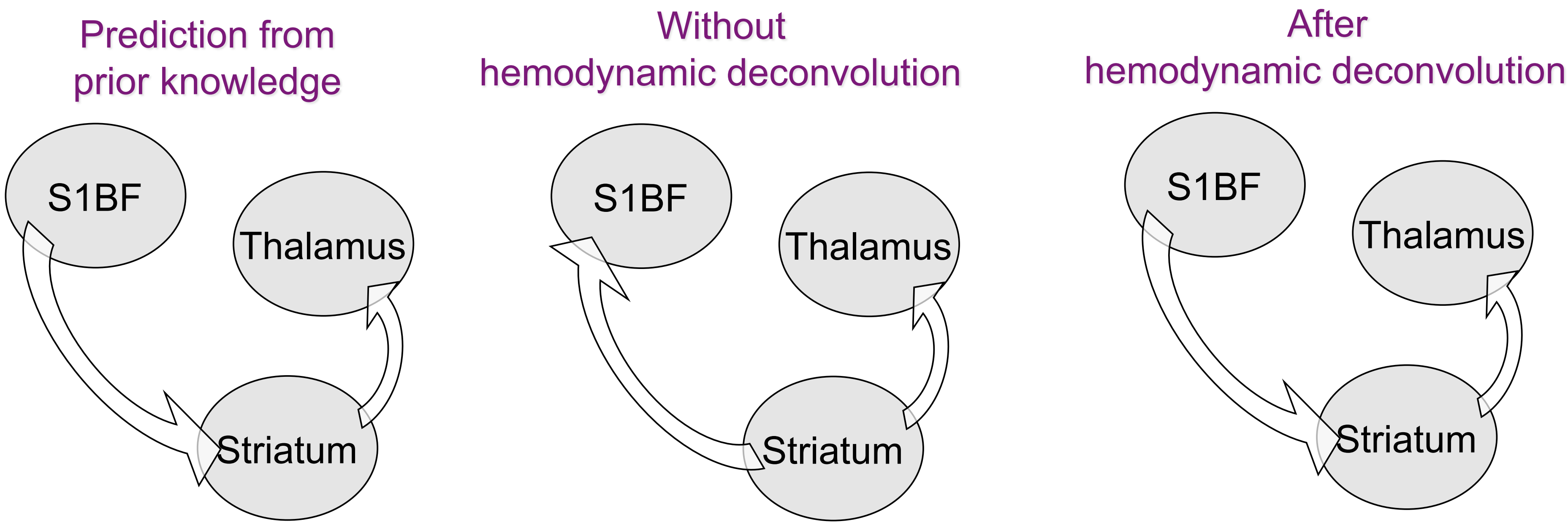


$$\tilde{s}(t) = FT^{-1}\left\{\frac{H^*(\omega)M(\omega)}{|H(\omega)|^2 + \varepsilon_0^{\,2}}\right\}$$

Glover, NeuroImage, 1999

Hemodynamic deconvolution and Granger Causality





- At group level, Granger Causality performs well only when hidden neural states are first estimated

David et al., PLoS Biol, 2008

Neuronal activity and fMRI are not consistently correlated

Effect	Metabolic signals and spike rate correlated	Metabolic signal and spike rate dissociated	Metabolic signal and LFP correlated	Metabolic signal and LFPs dissociated	LFP vs. spike rate correlated	LFP vs. spike rate dissociated
Region						
Visual cortex	Rees et al., 2000; Logothetis et al., 2001; Kim et al., 2004; Shmuel et al., 2006; Goense and Logothetis, 2008;	Kayser et al. , 2004; Niessing et al., 2005; Maier et al., 2008; Rauch et al., 2008; Viswanathan, 2008; Sirotin and Das, 2009.	Logothetis et al., 2001; Moosmann et al., 2003; Niessing et al., 2005; Koch et al., 2006; Shmuel et al., 2006; Goense and Logothetis, 2008	Logothetis et al., 2001; Koch et al., 2006; **Maier et al., 2008; Sirotin and Das, 2009**	Nase et al., 2003; Henrie and Shapley, 2005;	Logothetis et al., 2001; Viswanathan and Freeman, 2007; Rauch et al., 2008.
Primary auditory cortex	Mukamel et al., 2005; Nir et al., 2007.	Nir et al., 2007.	Mukamel et al., 2005; Nir et al., 2007.		Mukamel et al., 2005.	
Neocortex (includes parietal and frontal cortex)	Smith et al., 2002; Hyder, 2004; Kida et al., 2006.	Devor et al., 2007.	Brinker et al., 1999; Goldman et al., 2002; Laufs et al., 2003a; Laufs et al., 2003b; Ureshi et al., 2004; Debener et al., 2005; Hewson-Stoate et al., 2005; Kida et al., 2006; Gsell et al., 2006; Martin et al., 2006; Devor et al., 2007 Masamoto et al., 2008; Huttunen et al., 2008; Scheeringa et al., 2009.	Hewson-Stoate et al., 2005; Masamoto et al., 2008; Meltzer et al., 2008	Spinks et al., 2008.	Kreiman et al., 2006; Spinks et al., 2008
Hippocampal area	Englot et al., 2008; 2009.	Schridde et al., 2008; Ekstrom et al., 2009. Ojemann et al., 2009.	Canals et al., 2008; Englot et al., 2008; 2009; Ekstrom et al., 2009; Ojemann et al., 2009.	Sanchez-Arroyos et al., 1993; Uecker et al., 1997; **Schridde et al., 2008; Angenstein et al., 2009; Ekstrom et al., 2009**.	Manning, 2009.	Kraskov, 2007; Ekstrom et al., 2007. Ekstrom et al., 2009.
Cerebellum		Mathiessen et al., 1998; 2000. Caesar et al., 2003; Thomsen et al., 2004.	Mathiesen et al., 1998; 2000. Thomsen et al., 2004.	**Caesar et al., 2003**.		

Ekstrom, Brain Res Rev, 2009

Forward models must be improved for accurate fMRI simulations of causality

- **Standard model of BOLD:**
  - BOLD-LFP coupling model
  - fMRI prediction from EEG recordings (EEG/fMRI)

Ekstrom, Brain Res Rev, 2009

Forward models must be improved for accurate fMRI simulations of causality

- **Standard model of BOLD:**
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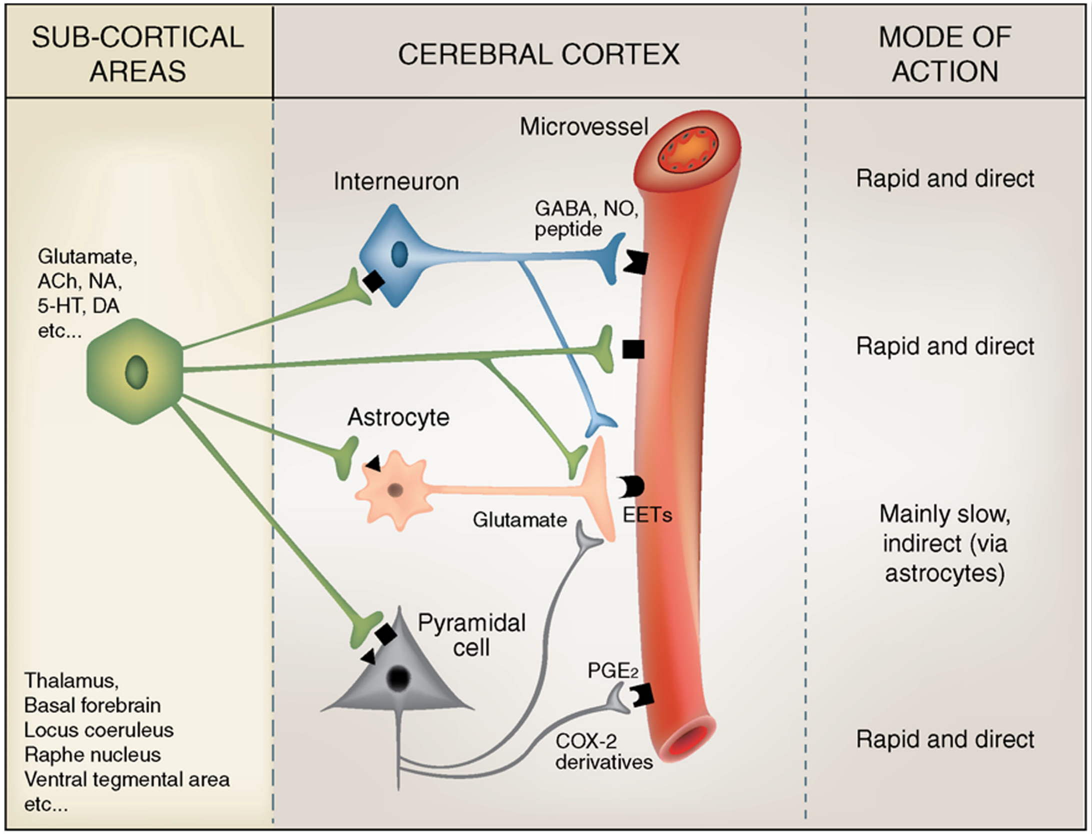
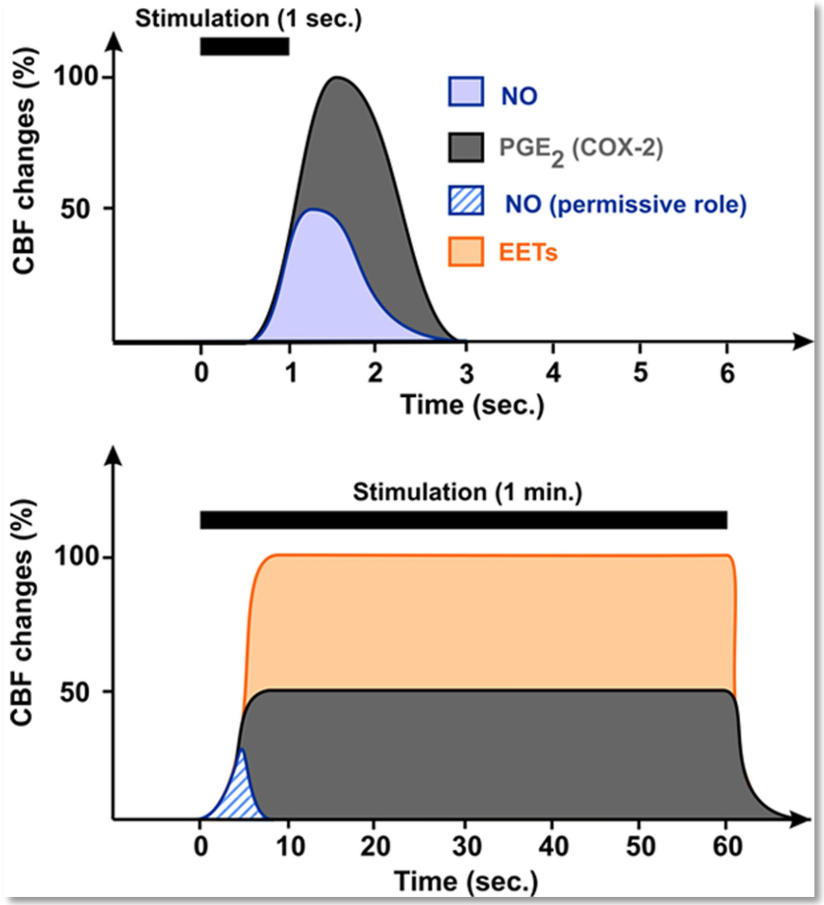
  - fMRI prediction from EEG recordings (EEG/fMRI)

- **Other possible models of BOLD:**
  - Local circuitry based model
    - Local differences between efferent (spikes) and afferent (LFP) connections
  - Vascular based model
    - Local differences in vasculature properties
  - Tripartite model
    - Neuron / Astrocyte / Vascular tone

Ekstrom, Brain Res Rev, 2009

Different dynamics of neurovascular coupling

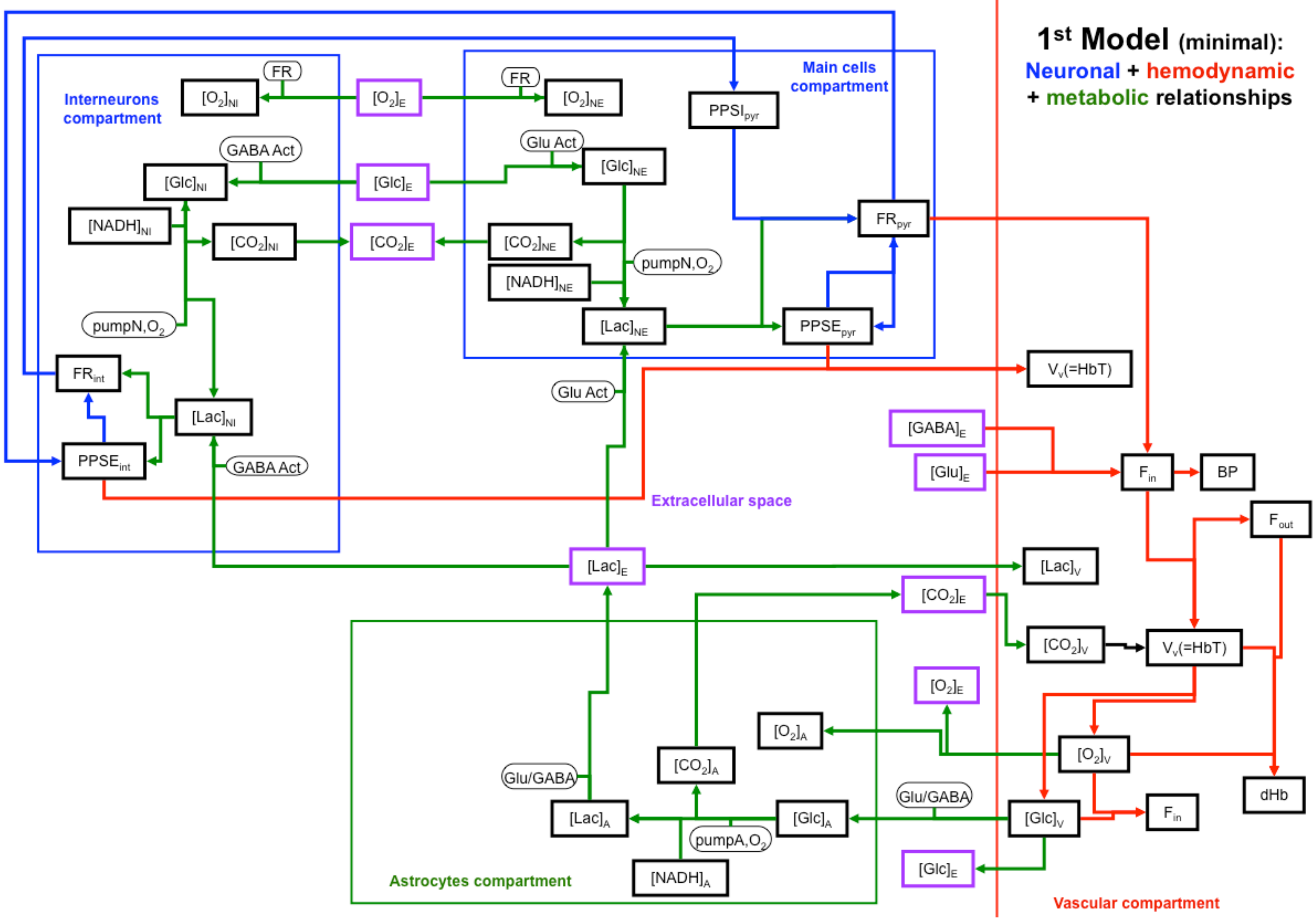




Forward model may be different between resting state, event-related and block designs.

Cauli & Hammel, Frontiers in Neuroenergetics, 2009

What physiological processes to be modelled for fMRI causality?



1st Model (minimal):
Neuronal + hemodynamic
+ metabolic relationships

Courtesy S. Blanchard

The Role of Blood Flow in Information Processing?

- **The Hemo-Neural hypothesis:**

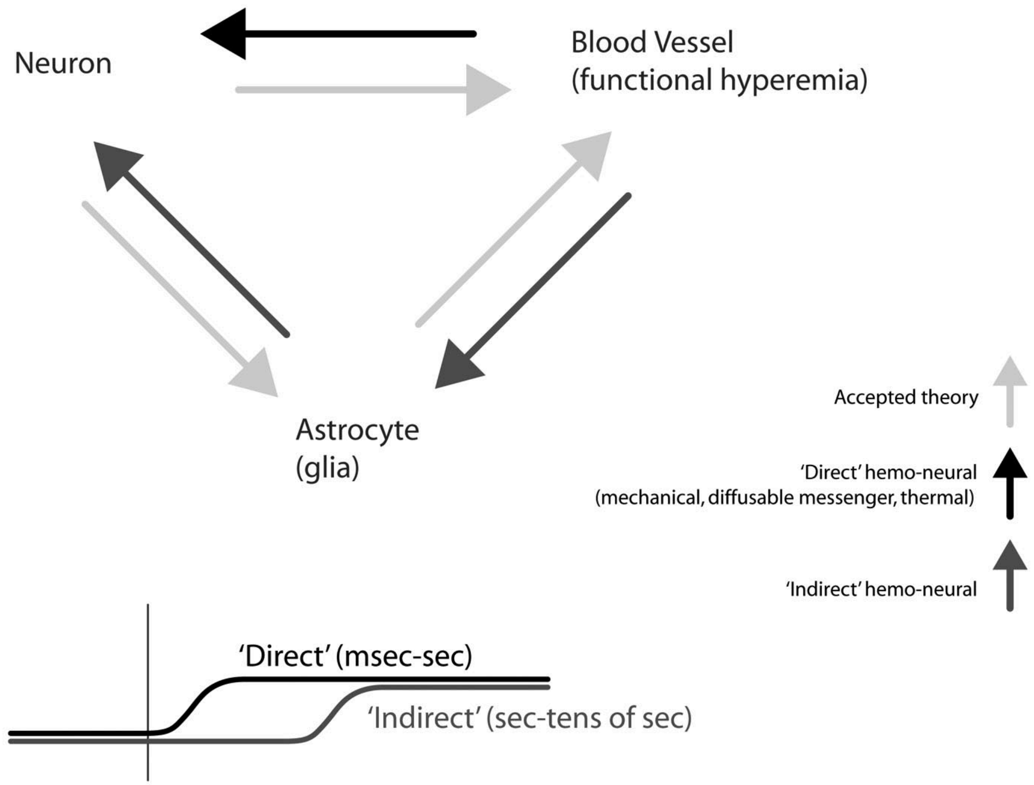
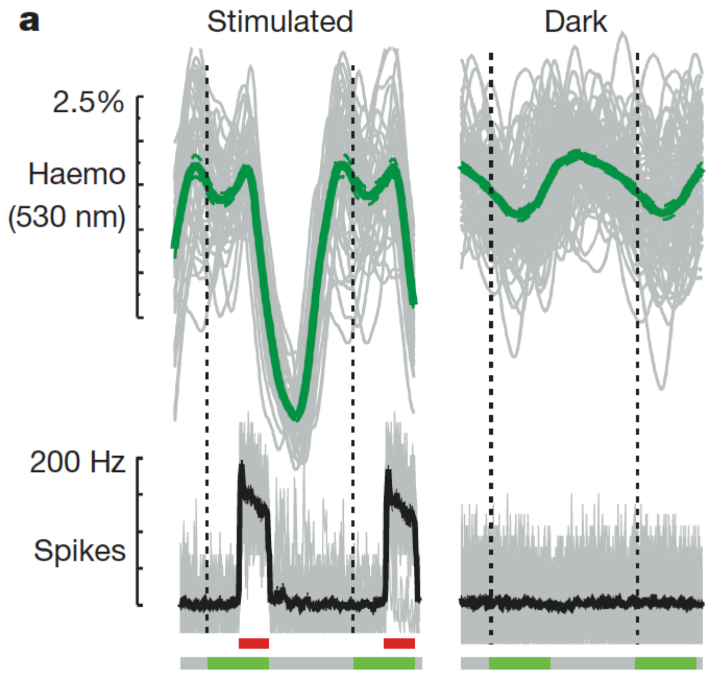


Diagram courtesy Julian Wong (artist) and Christopher Moore (McGovern Institute)

V1 - fixation task
optical imaging

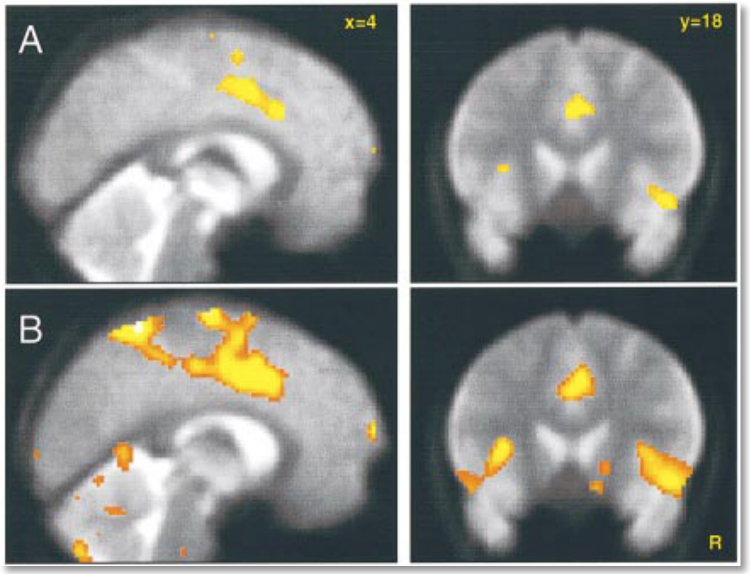


Moore & Cao, J Neurophysiol, 2008

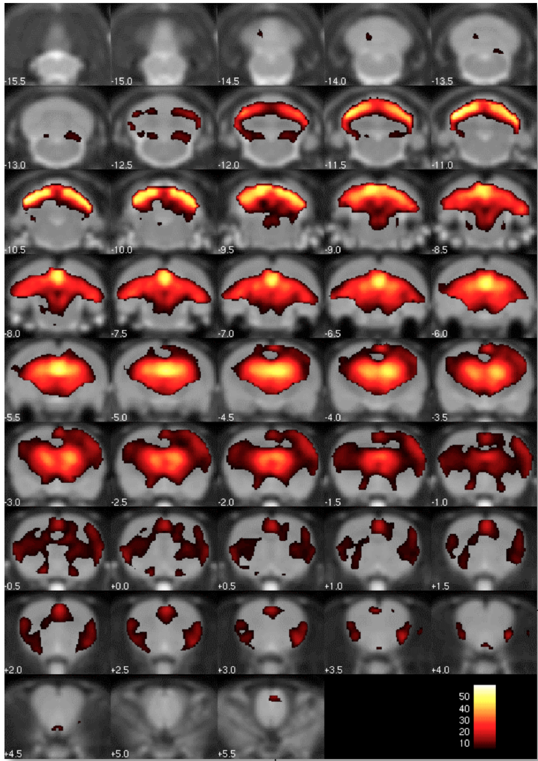
Sirotin & Das, Nature, 2009

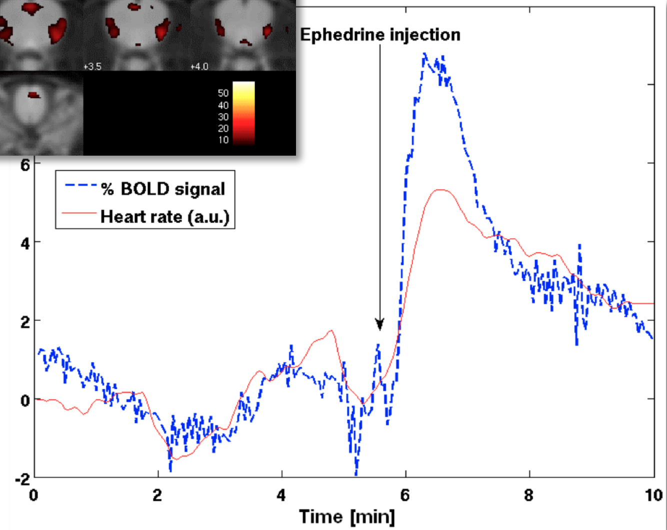
Physiological confounds

- **Origins:** *Gray et al., NeuroImage, 2009*
  - Heart
  - Circulation
  - Respiration
  - Skin and sweat
  - Gastrointestinal responses
  - Other autonomic changes



Critchley et al., Brain, 2003

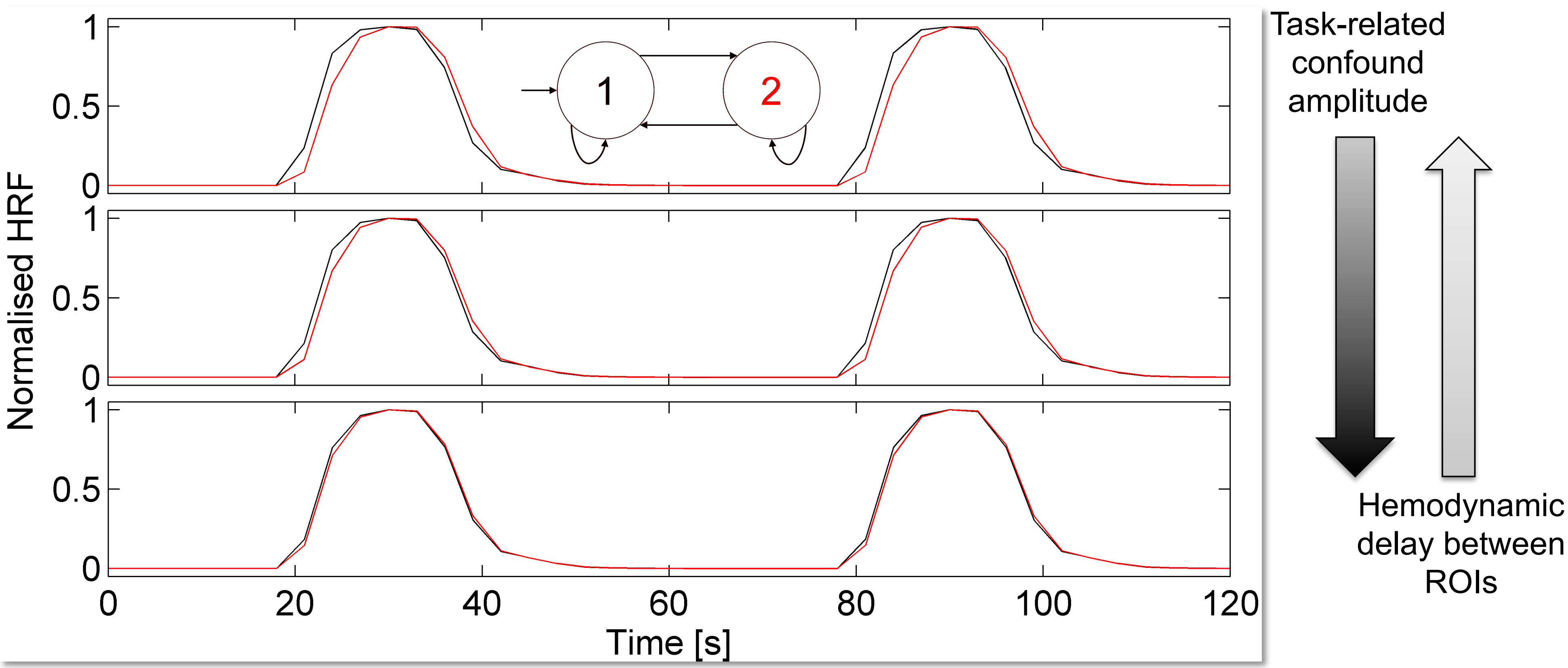




Reyt et al., NeuroImage, 2010

Physiological confounds
Simulation

- **Effect of a global counfound (e.g. heart rate) on directionality estimates:**
  - DCM simulation



Reyt et al., NeuroImage, 2010

Conclusion

- **It is possible to estimate directionality of "information flow" up to some resolution.**
  - Tens of ms in "ideal" situation
  - Hundreds of ms in more "realistic" cases

- **Current limitations:**
  - Several directional measures perform well but start to fail when:
    - TR is too large
    - HRF variability is introduced
  - Forward models need improvements:
    - Better integration of astrocytes and vascular tone and of their feedback on neuronal activity
    - May be adapted to the stimulation protocol (resting state, event-related, block)
  - Effects of physiological confounds have been neglected, though they may be very important:
    - Autonomic responses to stimuli
    - Baseline

Institut des Neurosciences
GRENOBLE

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