Spatial GLM analyses of phMRI data: anatomical segmentation and transient effects of no interest

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Goals

Analyses of phMRI data should …

- describe bi-phasic responses,
- handle temporal overlap of responses (e.g., antagonist experiments),
- reduce responses to a few biologically informative component elements,
- identify/remove potential "effects of no interest" associated with changes in systemic physiology,

… which sounds like the general linear model (GLM) using modeling of the cerebral response, a method not previously employed for such analyses (surprisingly).

Hypothesis

- Many complex drugs that impact multiple neurotransmitter systems should produce regional responses that represent a summation of several temporal components associated with the underlying kinetics of neural signal.

Background

Previously described analysis procedure for phMRI include …

- block comparisons of temporal data (Student's T, KS) [1], or the GLM equivalent
- individual single-regressor correlation analysis,
- voxel-wise non-linear fits of both shape and magnitude, together with binary selection criteria [2],
- wavelet-based cluster analysis [3].

GLM subsumes the 1st two approaches above. Signal modeling (this report) only makes sense in the high CNR regime, as enabled by contrast agent or ultra-high magnetic fields, where regional temporal kinetics can be identified for each voxel.

1] Breiter H et al. (1997). Neuron **19**: 591-611; Chen Y. I. et al. (2001). J. Magn. Reson. Imaging **14**(5): 517-524; Lowe A. S. et al. (2002). Neuroimage **17**(2): 902-10; Mandeville J. B. et al. (2004). Magn Reson Med **52**(6): 272-81; Marota J. J. A. et al. (2000). NeuroImage **11**(1): 13-23; Schwarz A. J. et al. (2004). Neuroimage **23**(1): 296-304.
2] Bloom A. S. et al. (1999). " Hum Brain Mapp **8**(4): 235-44.
3] Whitcher B., A. et al. (2005). Neuroimage **24**(2): 281-95.

MRI

- Multi-shot EPI, 10-16 segments
- 1 mm slice thickness, 20 slices
- 310-380 micron in-plane resolution
- 10 seconds per brain volume
- TE = 5-10 ms
- MION contrast agent
- 2, 4.7, and 9.4 Tesla
- T/R surface coil

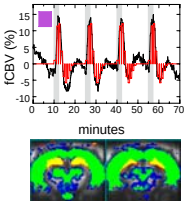
Animal model

- Halothane-anesthetized rats
- Mechanical ventilation to control blood gases
- Continuous monitoring of blood pressure, periodic monitoring of blood gases
- Injection of drugs in 1 ml/kg volume

Spatio-temporal linearity

Some drugs (a small subset) may exhibit **temporal**, as well as spatial, linearity.
Example: **remifentanil**, a designer mu-opioid receptor agonist with a short blood half life.

Reproducible bi-phasic hippocampus signal;
GLM unbiased IRF analysis



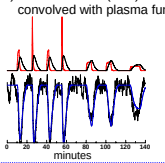
10 ug/kg over 2 min
x 4 injections (n=7)

Map generated by F test

Useful for detecting
bi-phasic signal,
but not very informative

Is the signal temporally linear?

1) Vary injection rate:
2 min, 30 sec, 2 min, 30 sec, 5 min, 5 min, 10 min
2) Convolve injection paradigm with exponential to obtain estimate of plasma concentration (red)
3) Determine IRF (blue) that reproduces data when convolved with plasma function.

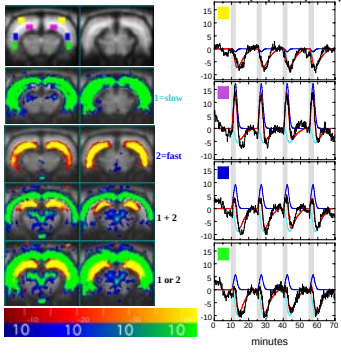


Temporal linearity !

n = 2

Test hypothesis of spatial linearity

Rather than unbiased estimators (top left), expand IRF method (top right) to 2 components



mono-phasic, only slow component

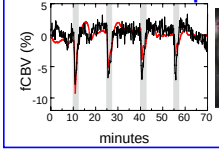
bi-phasic, dominated by fast component

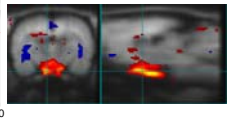
bi-phasic, dominated by slow component

mono-phasic with temporal shift;
consistent with 2 component contribution

Hypothesis: excitation from inhibition of GABAergic interneurons

Blood pressure regressor: effect of no interest?



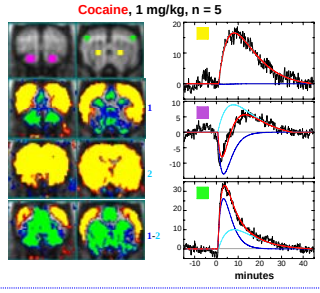


In addition to the 2 components above, measured blood pressure was employed as a 3rd regressor. The graph shows a positive correlation between BP and signal in the hypothalamus (crosshairs), but most brain regions showed a very small negative correlation, consistent with autoregulation.

Spatial, but not temporal linearity

Most drugs do not exhibit temporal linearity. For instance, cocaine exhibits "acute tolerance", or progressively smaller responses with each dose, except after a long recovery time. However, such drugs may still exhibit spatial linearity.

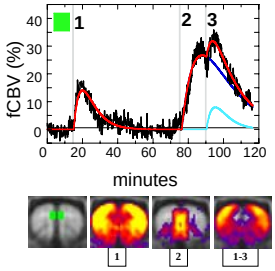
Cocaine, 1 mg/kg, n = 5



mono-phasic, slow response only

bi-phasic, + slow - fast

mono-phasic, + slow + fast



Analysis with temporal overlap

1 = D1 agonist (10 ug/kg SKF-82958, n=6)

2 = methiothepin (5-Ht & D1 antagonist)

3 = D1 agonist; same shape, separate magnitude

Conclusions

- Two drugs with complex actions (cocaine, remifentanil) exhibit spatial linearity, presumably representing a summation of neural circuits associated with separate transmitter systems or circuits. Other drugs (e.g., D1 agonist) were well described by a single regressor.

- GLM provides a natural framework for segmenting phMRI responses based upon temporal kinetics. This additional spatio-temporal information should be valuable for interpreting functional responses to drugs, and for assessing neuro-adaptations in the response due to prior drug exposure.