Transient signal changes in pharmacological fMRI: Effects of no interest?

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Introduction

Cerebral responses to drugs often provide rich spatio-temporal data sets. However, no studies to our knowledge have employed standard GLM analyses to model the response to drug-induced activation. We employ GLM analyses of rodent data to account for multiple drugs and effects, which may be overlapping, and ask the simple question: should transient signals that correlate with changes in blood pressure (BP) always be treated as non-neural effects of no interest?

Methods and Results I: Simple GLM regressors

In a simple GLM implementation, gamma-variate vectors (representing the cerebral response to a drug) replace the square paradigm vectors of the standard sensory GLM model. The experimental design consisted of IV cocaine (1 mg/kg) at time 0, a 5-Ht antagonist at 1 hour, and a secondary cocaine injection 15 minutes later. Fig. 1 shows whole-brain (18 slices of 1mm) signal evolution. Each drug is modeled as both a main effect and a transient signal for which the peak matches the peak change in BP. Cocaine produced mild (~ 5 torr) increases in BP, whereas the antagonist metergoline produced large (~ 20 torr = 20%) drops in BP. Statistical maps separate these effects, and show the effects of cocaine, the slow component of the antagonist, and the rapid effect correlated with BP. Throughout the brain, this and other 5-Ht antagonists produced signals correlated with BP and mapped onto high blood volume regions, suggesting a non-specific effect of CBF autoregulation. However, the small, rapid component of the cocaine response mapped onto dorsal medial striatum.

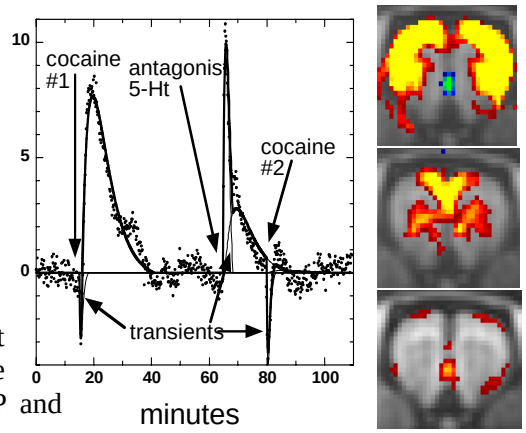

Fig. 1 LEFT: Time course of whole-brain response of CBV (n=7). A GLM produces spatial separation of cocaine #1 (top), metergoline (middle), and the rapid transient signal that correlated with the blood pressure drop due to the antagonist (bottom).

Methods and Results II: FIR design using variable injection rate

Remifentanil is a rapidly acting mu opioid receptor agonist with addictive properties. Injection of 10 ug/kg over 30 seconds produced a 30 torr drop in BP that reached maximum at 2 minutes. The functional brain response included both positive and negative components that could be dissociated temporally, with the slower component correlating better with BP. CBV response was reproducible with repeated injection and mapped almost entirely onto parenchymal brain regions.

To dissociate signal from BP, we employed variable injection rates of 10 ug/kg dose using infusion times of 30 sec, 2 min, 5 min, and 10 min. A finite impulse response (FIR) analysis employed a 2-step convolution procedure: the first step converted an infusion paradigm to a blood concentration of drug, and the second step represented induction of the cerebral response. Fig. 2 demonstrates the fit to data and a functional map corresponding to the summated temporal effects. BP dropped transiently at slower infusion rates and no longer correlated with signal. Because data was so well described by a linear model, we conclude that the correlation of BP and signal at rapid infusion rates was coincidental.

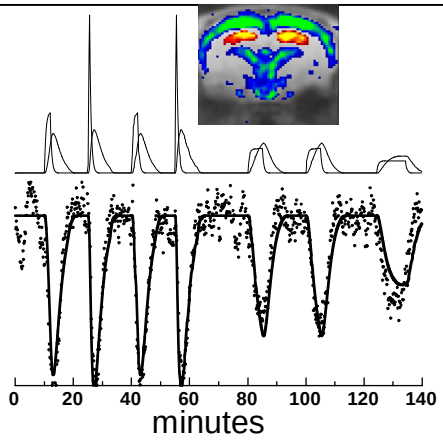

Fig. 2 TOP: Estimated blood plasma concentration, and the slow component of the neural estimator. BOTTOM: Data (n=2) and GLM fit. IMAGE: Positive (yellow) and negative (green) response at the level of the hippocampus.

Summary and Conclussions

fMRI signal can correlate with BP due to 1) neural hemodynamic regulation independent of local neural activity, 2) other vascular effects (anesthetic or receptor-mediated) that may not represent neural activity, or 3) neural activity unrelated to BP. While we find that effects of BP on fMRI signal are small within autoregulatory limits, transient effects can be mapped by sufficient averaging and appropriate modeling. Minimizing changes in blood pressure is important, but eliminating BP changes may not be possible in all cases, or may not accurately reflect doses and rates of injection in practice (e.g., abuse). Spatial and temporal segmentation, together with variable experimental designs, can help dissect the origin of signal.