Spatial modeling of phMRI data with a functional basis set

A. J. Schwarz[1], V. Kiviniemi[2], S. de Simoni[3], S. C. Williams[3], and M. A. Mehta[3]
[1]Translational Medicine, Eli Lilly and Company, Indianapolis, IN, United States, [2]Diagnostic Radiology, Oulu University Hospital, Oulu, Finland, [3]Centre for Neuroimaging Sciences, Institute of Psychiatry, London, United Kingdom

Background and Objectives: Direct pharmacological effects on resting brain activity are increasingly being investigated using pharmacological MRI (phMRI) approaches. NMDAR antagonists such as ketamine induce a widespread phMRI response; voxel-wise analyses can map these effects at a relatively high spatial resolution, but the stability of the responses across subjects and cohorts at this scale may be affected by neuroanatomical variation and residual differences in spatial normalization. Volume of interest (VOI) analyses may be more robust to these effects, but are typically derived from anatomical, rather than functional, parcellation. Based on the premise that functional units and connected brain regions are engaged by the stimulus, we examined the use of an independently-generated set of task-free independent components as a "functional basis set" to model the spatial phMRI response to ketamine.

Methods: BOLD phMRI data (15min) were obtained from 10 young healthy male volunteers on two occasions at 3T. Ketamine infusion began after 5 min using a target controlled infusion model (50ng/ml [n=5], 75ng/ml [n=5]). For each subject/session, a response amplitude map was calculated by temporal GLM analysis using a gamma-variate signal model with head motion and drift covariates. A functional segmentation derived by high model order ICA,[1] covering 94% of grey matter, was then used as a basis set of 42 components to model each amplitude map within a spatial GLM framework. Individual component coefficients and the basis-reconstructed map were then examined at the group level.

Results: Ketamine administration evoked a strong phMRI response involving (peri-)cingulate, prefrontal and opercular structures (**Fig-a**). The cingulate and opercular regions comprise one of the anatomically distributed functional components in the basis set ("salience network[2]," **Fig-b**) that also shows a coordinated univariate response to ketamine (**Fig-a,d**). Group maps constructed from the model fits to individual subject response maps (**Fig-c**) captured most cortical features of the voxel-wise map. At the group-level, basis component coefficients revealed good reproducibility (**Fig-e**), dose-dependence and strong effect sizes (2.2 < Cohen's d < 3.8, high dose) (**Fig-f**) in components involving the above regions.

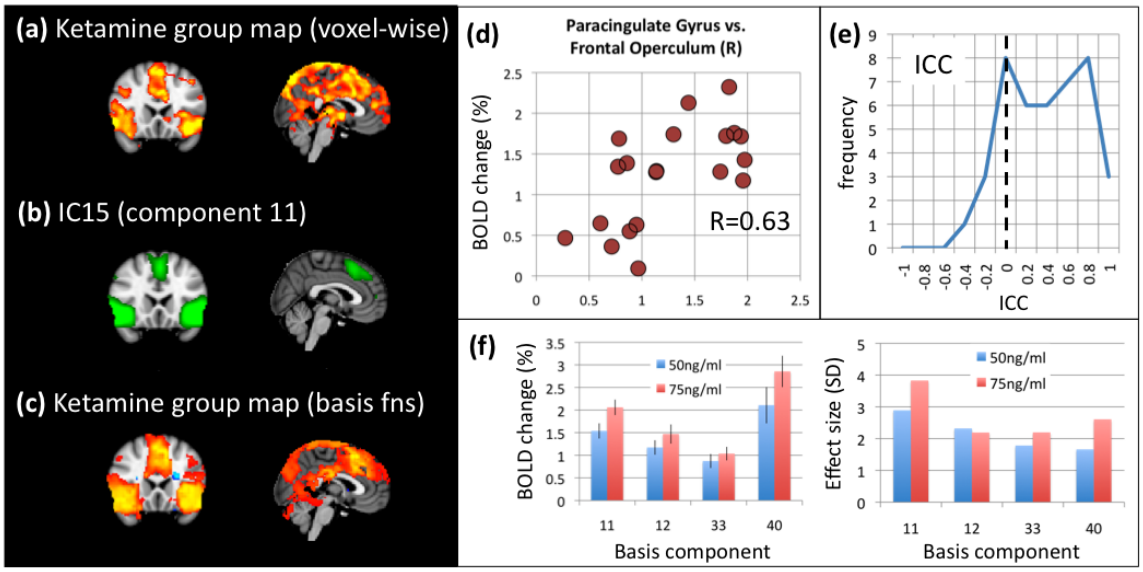

Figure: *(a) Voxel-wise group map of ketamine (T>6). (b) One of the basis set components, comprising anatomically distributed but 'connected' brain regions. (c) Group map from basis set fit to individual responses (T>8 to highlight concordance with (a)). (d) Responses within (b) are correlated across subjects. (e) Histogram of compenent reproducibility. (f) BOLD signal change and effect size for selected, strongly responding basis components.*

Discussion: The phMRI response to ketamine can be accurately and sensitively modeled as a linear superposition of stable, independently derived, functional units. These can be spatially distributed and overlapping, unlike anatomical VOIs, and robust to high spatial frequency differences across subjects.

References: [1]Kiviniemi *et al*. (2009) *Hum Brain Mapp* 30(12) 3865. [2]Sridharan *et al*. (2008) *PNAS* **105**(34) 12569.