Mapping threshold-independent drug effects in graph theoretic analyses of functional connectivity networks: the opioid analgesic buprenorphine preferentially modulates network topology in pain-processing regions

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Introduction

Graph theoretic analyses of functional connectivity networks report on topological properties of the brain [1] and may provide a useful probe of disease [2] or drug [3] effects. However, binarization of the raw weighted networks involves the choice of a particular threshold. When dealing with local properties of large networks defined by functional imaging data at the voxel scale, *post hoc* verification of findings generated at different binarization thresholds is impractical and often subjective. Here we present a straightforward method for calculating node-wise network parameters that are robust to binarization threshold. The method is applied to mapping drug modulation of localized functional network topology by the opioid analgesic buprenorphine in healthy human subjects.

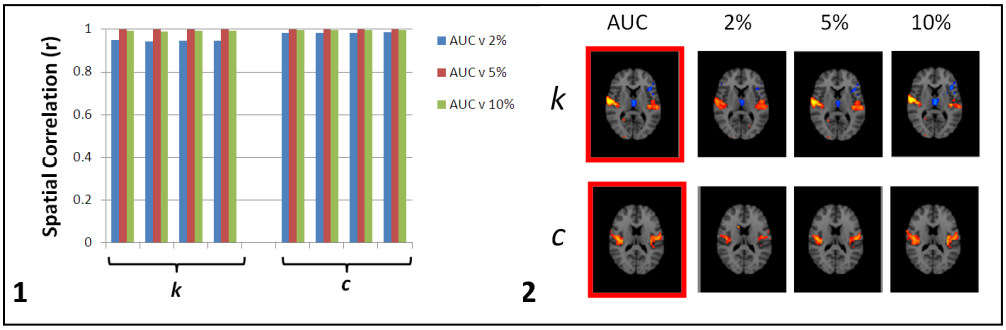
Methods

Data acquisition and preparation: Task-free EPI time series of 25min were obtained from N=12 healthy male subjects at 3T in two scanning visits, during which they received an infusion of either 0.2mg/70kg of buprenorphine or saline in a randomized, crossover phMRI design. The infusions were administered between 7-12min. The first and last 5min periods of each time series were extracted as pre- and post-infusion resting state scans. Following image pre-processing and spatial normalization, mean CSF and white matter signals were deconvolved from each scan, followed by 0.01-0.1Hz band-pass filtering. Voxel-scale correlation matrices were calculated for each scan and cell values (edge weights) were converted to z-scores using Fisher's r-to-z transformation. These were then binarized as described in the following prior to computation of graph parameters.

Threshold-independent parameter calculation: Based on the observation that many node-wise network parameters vary slowly and (on average) monotonically with binarization threshold, for each node the area under the curve (AUC) of a given parameter '*p*' against a range of binarization thresholds, expressed as network 'costs' (% of positive edges retained, *t*), can be calculated as:

$$p_{AUC} = \frac{1}{2}\sum_{m=1}^{n_t-1}(t_{m+1}-t_m)(p_{t=t_{m+1}}+p_{t=t_m})$$

We evaluate and apply this method to mapping the effect of buprenorphine on the particular node-wise parameters *degree* (*k*) and *clustering coefficient* (*c*) for costs *t* = 2%, 5%, 10%, within the small-world regime. The degree of a node is the number of connections that link it to the rest of the network and the clustering coefficient quantifies the 'cliquishness' of a node's connections, expressed as the fraction of all possible connections between the nodes to which a node is directly linked that are actually present.



Results

• Individual subject maps of k_{AUC} and c_{AUC} were highly spatially correlated ($0.94 < r < 1.0$) with maps calculated at individual binarization thresholds for all conditions (fslcc, pre/post-drug/placebo; **Fig. 1** (inter-subject s.d.<0.02)).

• At the group-level, paired comparisons also yielded drug effects on k_{AUC} and c_{AUC} whose main features were consistent with those obtained by comparisons of individually-thresholded networks (**Fig. 2**).

• The threshold-independent effect of buprenorphine on network topology was to alter both *k* and *c*, particularly localized to sensory pathways despite the absence of any applied stimulus (**Figs. 2, 3**; T>2.2). In particular, k_{AUC} and c_{AUC} both increased in SI and SII, c_{AUC} increased in the sensorimotor nuclei of the thalamus; k_{AUC} also decreased in the anterior midline thalamus.

Discussion

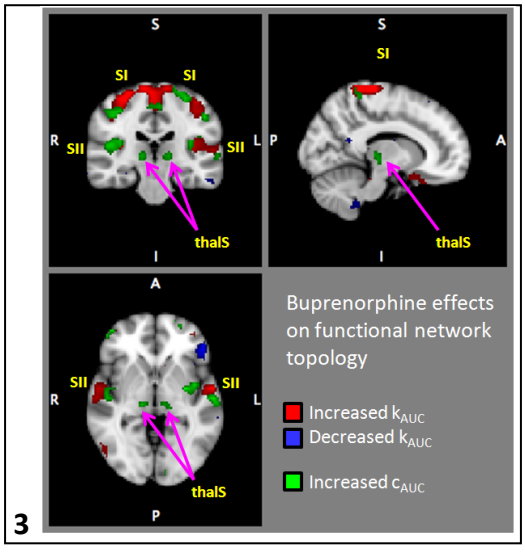
• This method provides a straightforward and practical approach to calculating local (node-wise) graph theoretic parameter values that are robust to binarization threshold, greatly facilitating the mapping of anatomically-specific effects of drug or disease in voxel-scale networks derived from functional imaging data.

• For parameters that are largely invariant over a range of thresholds, the average can be computed by a simple scaling, retaining a value within a meaningful range (e.g., $0 < c < 1$).

• The AUC or average parameter value can be estimated from a relatively sparse sampling of the parameter v cost curve.

• Binarization at different thresholds occurs at the node parameter computation stage and inference is performed on the single derived parameter values, not as a *post hoc* (and possibly subjective) verification of threshold (in)dependence at the group level.

• The increased node degree and clustering in the sensory pathways following buprenorphine infusion reflect stronger intra-pathway connections within this sub-network and its decoupling from other brain regions, consistent with results from seed region analyses.



References: [1] Bullmore & Sporns 2009 *Nat Rev Neurosci* **10**(3) 186 [2] Supekhar et al 2008 *PLoS-CB* **4**(6) e1000100 [3] Achard et al 2007 *PLoS-CB* **3**(2) e17.