Meta-analytic Functional Connectivity: Finding Brain Regions' Multi-way Interactions

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Introduction

In recent work [1] the BrainMap (BM) task activation database has been used to map networks of coactivation, which are shown to be in correspondence with those extracted from the resting brain [2]. Such correspondences in brain regions' multi-way interactions, however, are yet to be assessed (e.g., using graphical models). In this work we consider network models where each 'node' corresponds to one of these component maps of coactivation.

However, like others [1] we have found that network modelling using a high number of nodes is not robust. Thus, we consider only 3 nodes at a time with a log-linear graphical model (LLGM) and test for interactions; triplets of functional 'nodes' that demonstrate a 3-way interaction indicates that one node modulates the functional connection between the other two.

A joint multivariate exploratory analysis of 36 subjects' resting-state FMRI (rFMRI) data and 7342 pseudo-activation-maps derived from the BM database is carried out, resulting in the spatial components and their associated 'experiment-series' and resting time-series. Next these experiment-/time-series are thresholded and binarised and triplets of components are composed into 3-way contingency tables. Each table is then fit with a LLGM and tested for 3-way interactions, for rFMRI and BM separately, which identified interpretable triplets of regions. Striking correspondence was found between the set of significant rFMRI and BM triplets, extending the single component-matching in [2].

Methods

7342 distinct task experiments are extracted from the BM database and converted to pseudo-images (akin to ALE [4], 12mm kernel); one per study. Concatenating all pseudo-images and converting the resulting volume to a 2D matrix, we obtain a #studies-by-#voxels data matrix X_{BM}. Concatenating the rFMRI data X_{rFMRI} of all subjects (#subjects*time-by-#voxels) to X_{BM} in the second dimension forms the new matrix X, which is then subject to an independent components analysis (ICA) decomposition. ICA estimates W and H in X=WH +U model by maximizing the statistical independence between the rows (spatial components) of H. The resulting spatial maps each have one experiment-series and one resting time-series associated with them whose interdependencies can reveal their causal influence on each other. We considered a 150-component decomposition (with 25 identified as artifact, i.e., 125 nodes in total).

We model each set of 3 nodes with a LLGM by binarising each node's time-/experiment-series; we considered a range of thresholds to understand the dependence on this parameter. For each triplet of components, say {X,Y,Z}, a 3-way, 2x2x2 contingency table with 8 cells is formed with frequency of {X=0&Y=0&Z=0}…{X=1&Y=1&Z=1} in cells 1…8. The LLGM uses a traditional design matrix to model main and interaction effects in the observed 3-way table of counts. A likelihood ratio test (LRT) for the saturated model against the same model without the XYZ interaction gives a $\chi 2$ statistic and P-value for the evidence of non-additive behaviour that cannot be explained by any main effect or 2-way interaction. A significant P-value indicates inseparability, i.e. the relationship between any two components depends on the third component. We visualize the log of Odds Ratios (OR); the OR for (say) X is P(X)/(1-P(X)) and is how many times more likely X is to occur than not occur.

For each triplet, Z-values are defined differently for BM and rFRMI: For BM (as previously described) the Z-value is obtained directly from the LLGM fit to all studies' binarised counts; for rFMRI a LLGM is fit to each subject, producing one Z-value for each subject, and these Z-values are submitted to a one-sample T-test, producing a random-effects-like Z-value. These two different approaches are appropriate because the BM database is mostly comprised of random-effects inferences, and thus the random effects rFMRI Z-values should be more comparable. The extent of correspondence between rFMRI and BM in their multi-way interaction, is then quantified as the number of identical triplets with positive interaction that survive the FDR correction in both rFMRI and BM.

Results

The 125 functional nodes result in 317,750 triplets each with two P-values (and their two corresponding Z-stats); one from BM, one from rFMRI time-series LLGM analysis. Various numbers of these triplets survive FDR with q=0.05 at each binarisation threshold, among which some are seen in both BM and rFMRI. Fig. 1 displays the number of survivors in BM and rFMRI, and their overlap. For detailed analysis, we focus on the triplets surviving the FDR correction (q=0.05) in both rFMRI and BM (when time-series are binarised at their 90th percentile) and have positive Z-stat (i.e., positive interaction). Fig. 2 shows a group of 12 triplets that are commonly seen in triplets fulfilling these constraints. In a more detailed analysis, Fig. 3 describes the triplet {X,Y,Z}={**06,07,11**} (see Fig. 2 for numbers and their corresponding spatial maps) by their Z-stat for XYZ interaction and log(OR) using BM and rFMRI. This triplet's BM analysis uses all studies (grouped into 66 behavioural domains) or a subset of them belonging to a particular behavioural domain, while its rFMRI analysis uses either one subject's data or pools the results from all 36 subjects. This triplet of lateral-frontal (X), lateral-default-mode (Y) and cerebellum (Z) regions shows a strong 3-way interaction, e.g., activation of one node causes an increase in interaction between the other two when all studies are used, however, result is specifically observed in the cognition_language domain. In a similar analysis using rFMRI, this 3-way interaction is observed in most subjects; positive values in the final column indicate that the OR for any pair of regions is greater when the 3rd region is on relative to when it is off. The close-to-zero interaction between regions X and Y (bottom row of Fig. 3b) indicates that the frequency that these two regions co-occur is close to what is expected by their individual occurrence rates in the BM database; further, the 3-way interaction of these regions indicates that the rate of co-occurrence of all three regions is greater than can be accounted for by the individual occurrence rates and any pair-wise non-additive effects.

Conclusions

We have applied multivariate methods 'jointly' to meta-analytic pseudo-images and rFMRI data to find distinct brain regions and their interconnections. With over 7000 functional contrasts and rFMRI from 36 subjects involved we expected powerful and generalisable results. Our results confirm the existence of a strong inseperability among different functionally-distinct brain regions in both activation and rest (Fig. 1), with a striking correspondence (Fig. 1). We find that some areas are involved in such multi-way interactions more than others (Fig. 2), the extent of which varies across different behavioural domains and in different individuals (Fig. 3).

From a methodological viewpoint, the introduced method can be extended from a 3-way to an N-way interaction simply by using N variables to form the contingency table and LLGM.

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References

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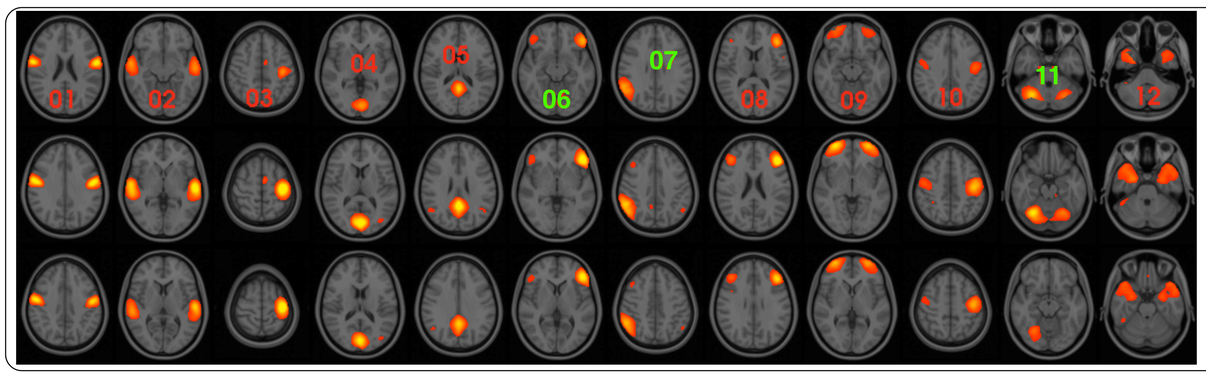

Figure 2: Three slices from the 12 components (i.e., nodes) that are the most common among strongly-interacting triplets. It consists of frontal (presumably modulators) and sensory-motor regions (presumably modulated). Green numbers mark the triplet with results shown in Figure 3.

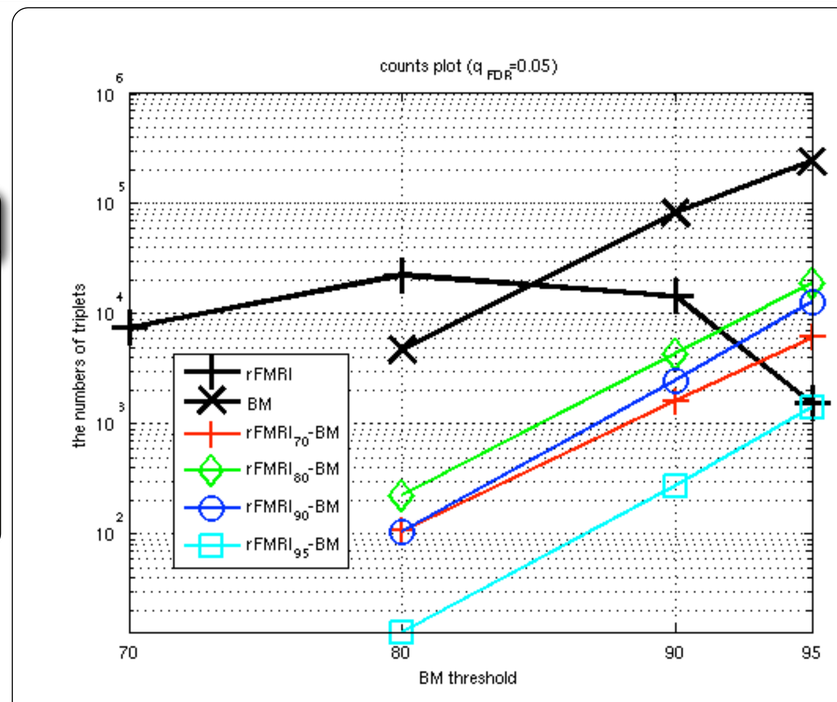

Figure 1: The number of triplets surviving the FDR threshold of 0.05 are shown in black lines. The colour lines display the number of triplets that survive this FDR thresholding in both BM and rFMRI. The x-axis represents the threshold at which BM is binarised, while each colour codes this threshold for rFMRI (please see the legend). The numbers on the x-axis and in the legend represent the percentile at which each node's time series is binarised.

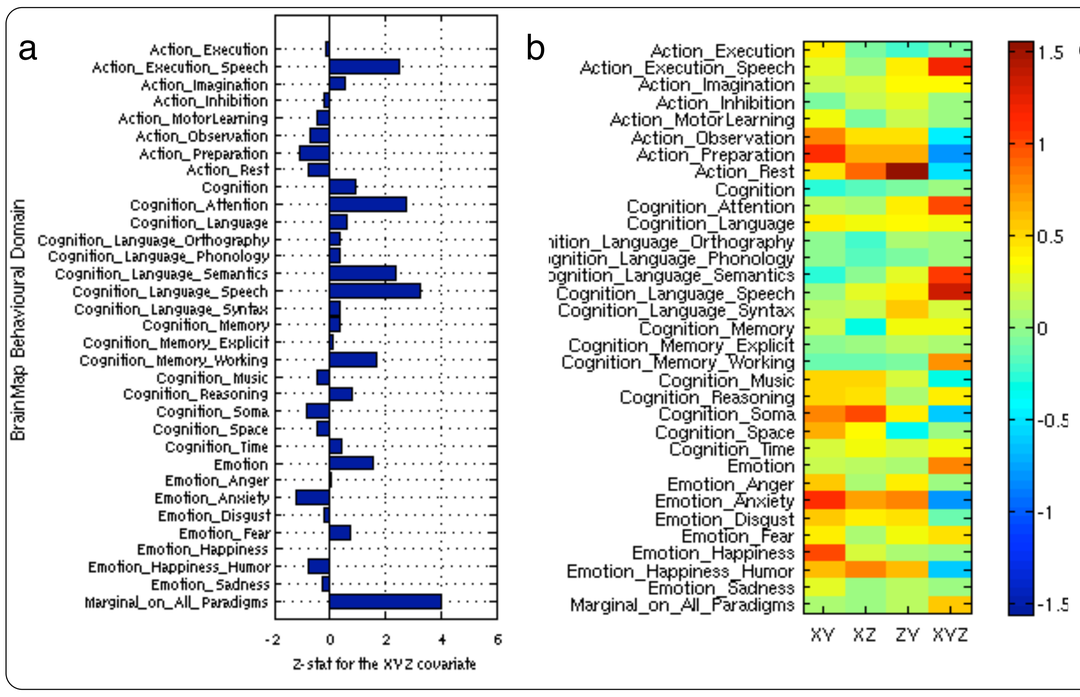

Figure 3: The log(OR) for assessing the effect of one region on the other two regions' interaction for triplet {X,Y,Z}={**06,07,11**}. Panel (a) displays the 3-way interaction's Z-stat when using the BM time-series of all or a subset of studies (on the y-axis). The log(OR) for the same data that generated the Z-stats can be found in panel (b). The XYZ on the x-axis represents the log(OR{XY|Z=1}/OR{XY|Z=0}), which captures the log(OR) of the three-way interaction. Panels (c) and (d) display the corresponding results for rFMRI time-series with each row of the image representing one subject (see the y-axis). The pooled Z-stat for all subjects results from a one-sample T-test of all individuals' Z-stats. Using these plots, it can be concluded that the 3-way interaction exists in general in rest and activation, the extent of which can vary under different interventions (i.e., different behavioural domains) and for different individuals.