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A novel meta-analytic approach: Mining frequent co-activation patterns in neuroimaging databases

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ABSTRACT

In recent years, coordinate-based meta-analyses have become a powerful and widely used tool to study co-activity across neuroimaging experiments, a development that was supported by the emergence of large-scale neuroimaging databases like BrainMap. However, the evaluation of co-activation patterns is constrained by the fact that previous coordinate-based meta-analysis techniques like Activation Likelihood Estimation (ALE) and Multilevel Kernel Density Analysis (MKDA) reveal all brain regions that show convergent activity within a dataset without taking into account actual *within*-experiment co-occurrence patterns. To overcome this issue we here propose a novel meta-analytic approach named PaMiNI that utilizes a combination of two well-established data-mining techniques, Gaussian mixture modeling and the Apriori algorithm. By this, PaMiNI enables a data-driven detection of frequent co-activation patterns within neuroimaging datasets. The feasibility of the method is demonstrated by means of several analyses on simulated data as well as a real application. The analyses of the simulated data show that PaMiNI identifies the brain regions underlying the simulated activation foci and perfectly separates the co-activation patterns of the experiments in the simulations. Furthermore, PaMiNI still yields good results when activation foci of distinct brain regions become closer together or if they are non-Gaussian distributed. For the further evaluation, a real dataset on working memory experiments is used, which was previously examined in an ALE meta-analysis and hence allows a cross-validation of both methods. In this latter analysis, PaMiNI revealed a fronto-parietal "core" network of working memory and furthermore indicates a left-lateralization in this network. Finally, to encourage a widespread usage of this new method, the PaMiNI approach was implemented into a publicly available software system.

Introduction

Over the last decades, functional neuroimaging has been evolved to the most prevalent tool in cognitive neuroscience and the key method for investigations into the functional organization of the human brain. As a consequence, the neuroimaging community has generated a tremendous amount of studies concerning the localization of almost all cognitive domains. This growing number of published neuroimaging literature has prompted the development of meta-analysis techniques, which exploit the substantial amount of neuroimaging data in order to draw robust and more general inferences. Particularly coordinate-based meta-analyses (CBMA) provide powerful and easily accessible techniques, which operate on the three-dimensional coordinates of peak activation foci reported by these studies in standard reference space, i.e. the MNI (Evans et al., 1992) or Talairach (Talairach and Tournoux, 1988) spaces. CBMA allow a straightforward analysis of (the entire) previous literature, as it only relies on the published peak coordinates and hence may be employed without the need for obtaining additional data from the respective authors, e.g. image files. The latter aspect usually limits the capability of image-based methods to cover a broad range of (in particular older) studies. Furthermore, the work on those sparse representations of the image data is also profitable from a computational perspective. CBMA are particularly facilitated by large scale databases like BrainMap (www.brainmap.org) (Fox and Lancaster, 2002; Laird et al., 2005) or NeuroSynth (www.neurosynth.org) (Yarkoni et al., 2011) that collect the information and peak coordinates of neuroimaging studies and make them accessible.

The most common previous CBMA techniques are Activation Likelihood Estimation (ALE: Eickhoff et al., 2009, 2012; Turkeltaub et al., 2002) and (Multilevel) Kernel Density Analysis (KDA and MKDA: Wager et al., 2004; Wager et al., 2007). In principle, both methods rely on similar concepts: first, they model each focus of a dataset; in ALE

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the activation foci are modeled as Gaussian distributions, in MKDA as spheres. Then, these representations are combined across experiments; in ALE via the union of the modeled activation (Turkeltaub et al., 2012), in MKDA via weighted averages of the modeled maps representing the studies (Wager et al., 2007). Finally, the resulting activation maps are tested for significance, i.e. above-chance convergence, using permutation tests. The results of both techniques, ALE and MKDA, are maps that indicate those locations in the brain, where the reported activations of all experiments in the underlying dataset significantly converge. The brain regions featuring this convergence of activity can then be interpreted as being robustly involved in the cognitive processes addressed by the experiments of the set. The co-activation patterns shown by the resulting maps can generally be regarded as functionally connected (Caspers et al., 2013; Eickhoff et al., 2010; Jakobs et al., 2012). That is, they fulfill the criteria of functional connectivity by representing temporal coincident and spatially distant neural activity (Friston, 1994). However, both described CBMA approaches have some disadvantages, when trying to evaluate connectivity, i.e. within experiment co-activity. That is, the resulting maps of ALE and MKDA indicate all brain regions consistently active within a specific dataset, without taking into account, if those brain regions are really co-active within single experiments. Hence, there is no information on the distributions of specific co-activation patterns across experiments. In order to demonstrate this aspect, we simulated a dataset containing two divergent subsets of experiments and subjected it to a standard ALE analysis (Fig. 1): While set A featured experiments with activation in the inferior frontal cortex and on the middle temporal gyrus, the experiments of set B provided activation foci in the intraparietal sulcus and on the middle occipital gyrus (Fig. 1, left). To simulate noise, all experiments had additional activation foci randomly distributed over the whole brain. The simulated dataset was analyzed with the latest version of the ALE algorithm (Eickhoff et al., 2012). The resulting ALE map revealed convergent activity in all four input regions (Fig. 1, right). However, the segregation into two underlying subsets cannot be recognized anymore in the ALE map as all four regions likewise show significant convergence. This leads to possible misinterpretations regarding co-activity within the ALE map. All four regions are represented in the same map, although there was for example no experiment within the simulation dataset in which the inferior frontal cortex was co-active with the intraparietal sulcus.

To address this issue and provide a method for a more specific identification of co-activation patterns across experiments, we developed a novel meta-analytic approach based on well-established data-mining techniques. The proposed method identifies frequent co-activation patterns in coordinate-based neuroimaging datasets and reveals how often a specific brain region is co-active with other brain regions within the dataset. Here we present the novel method, named PaMiNI (Pattern Mining in NeuroImaging), and its implementation into a software tool. Some aspects of the PaMiNI method have already been described in (Caspers et al., 2012a, 2012b). The method is evaluated by means of five simulations and cross-validated with ALE using a real dataset on working memory.

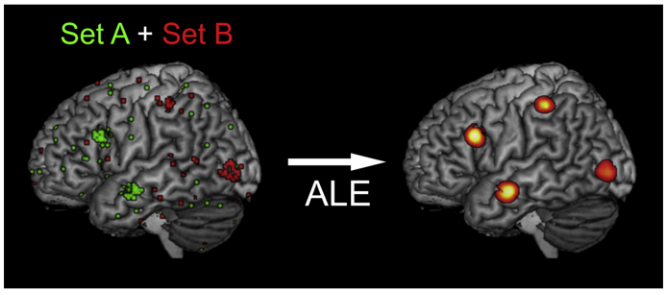

Fig. 1. Left: Simulated dataset of two sets of experiments (*simulation 2*). Activation foci of all experiments are projected onto the MNI single subject brain. Set A (green) contained foci centered around the inferior frontal gyrus and the middle temporal gyrus, set B (red) contained foci centered around the intraparietal sulcus and the middle occipital gyrus. For both sets noise foci were generated. Right: ALE meta-analysis of the simulated dataset. The resulting ALE map is projected onto the MNI single subject brain.

Material and methods

The aim of the proposed method is to find frequent co-activation patterns, i.e. combinations of brain regions that frequently show co-occurrent activation in a dataset of neuroimaging experiments. It is based on the concepts of CBMA, that is, all information is provided as three-dimensional coordinates of activation maxima in the individual experiments. The method itself is then composed of two steps: first, the brain regions consistently activated in a specific dataset (set of experiments, each providing at least one focus of activation) are modeled using Gaussian mixture modeling on the three-dimensional coordinates making up this dataset, and the activation foci are assigned to the identified brain regions. In the second step, frequent co-activations patterns across experiments are identified using association analysis.

The method as well as the implemented software system will be referred to as *PaMiNI*, which stands for *Pa*ttern *Mi*ning in *N*euro*I*maging.

Modeling of brain regions underlying a dataset

Let $D = \{E_1,\ldots,E_n\}$ be a dataset of experiments where every experiment E_i is a set of three-dimensional peak coordinates $E_i = \left\{C_1^i,\ldots,C_{m_i}^i\right\}$ with $m_i \geq 1$ representing the number of peak coordinates of experiment E_i. The coordinates are triplets $C_j^i = (x_j^i,y_j^i,z_j^i)$ where x_j^i, y_j^i and z_j^i are the coordinate components for the three spatial dimensions in MNI reference space (Evans et al., 1992). If coordinates are given in Talairach space (Talairach and Tournoux, 1988), they are converted to the MNI reference space using the Lancaster transform (Laird et al., 2010; Lancaster et al., 2007). Hence, the set of coordinates in a dataset is given in a discrete metric space.

To reveal convergent activity within the coordinate data of the entire dataset D, common subsets of coordinates based on their spatial location are identified by applying Gaussian mixture modeling on the pooled coordinates $C = \left\{C_1^1,\ldots,C_{m_1}^1,\ldots,C_1^n,\ldots,C_{m_n}^n\right\}$ of all experiments in the dataset. That is, considering the coordinates as instances randomly drawn from a mixture of K_{opt} three-dimensional Gaussian distributions and thus fitting the Gaussians to optimally represent the coordinate data. K_{opt} indicates the optimal number of Gaussian distributions, which still has to be specified. The probability density function with which a coordinate C_j^i is drawn from the mixture can be formalized as

$$f\left(C_j^i\right) = \sum_{k=1}^{K_{opt}} p_k \cdot \mathcal{N}\left(C_j^i \middle| \mu_k, \Sigma_k\right)$$

where p_k specifies the proportion of distribution k in the mixture of distributions with $0 < p_k < 1$ and $\sum_{k=1}^{K_{opt}} p_k = 1$. $\mathcal{N}\left(C_j^i \middle| \mu_k, \Sigma_k\right)$ denotes the value of the Gaussian density function with the three-dimensional mean vector μ_k and the 3×3 full covariance-matrix Σ_k at C_j^i. Thus, in order to model the K_{opt} Gaussian distributions to the given coordinates the parameters for the proportion of each of the K_{opt} Gaussians in the mixture, their mean (location) and co-variance $\Theta = \theta_1,\ldots,\theta_{K_{opt}} = p_1,\ldots,p_{K_{opt}},\mu_1,\ldots,\mu_{K_{opt}},\Sigma_1,\ldots\Sigma_{K_{opt}}$ have to be estimated, which is done by maximum-likelihood estimation. At this, the log-likelihood function

$$\begin{aligned} LL(\Theta|\, C) &= \ln f\left(C_1^1,\ldots,C_{m_1}^1,\ldots,C_1^n,\ldots,C_{m_n}^n\right) \\ &= \sum_{i=1}^{n}\sum_{j=1}^{m} \ln\left[\sum_{k=1}^{K_{opt}} p_k \cdot \mathcal{N}\left(C_j^i \middle| \mu_k, \Sigma_k\right)\right] \end{aligned}$$