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Technical Note

Meta-analytic connectivity modeling revisited: Controlling for activation base rates

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ABSTRACT

Co-activation of distinct brain regions is a measure of functional interaction, or connectivity, between those regions. The co-activation pattern of a given region can be investigated using seed-based activation likelihood estimation meta-analysis of functional neuroimaging data stored in databases such as BrainMap. This method reveals inter-regional functional connectivity by determining brain regions that are consistently co-activated with a given region of interest (the "seed") across a broad range of experiments. In current implementations of this meta-analytic connectivity modeling (MACM), significant spatial convergence (i.e. consistent co-activation) is distinguished from noise by comparing it against an unbiased null-distribution of random spatial associations between experiments according to which all gray-matter voxels have the same chance of convergence. As the a priori probability of finding activation in different voxels markedly differs across the brain, computing such a quasi-rectangular null-distribution renders the detection of significant convergence more likely in those voxels that are frequently activated. Here, we propose and test a modified MACM approach that takes this activation frequency bias into account. In this new specific co-activation likelihood estimation (SCALE) algorithm, a null-distribution is generated that reflects the base rate of reporting activation in any given voxel and thus equalizes the a priori chance of finding across-study convergence in each voxel of the brain. Using four exemplary seed regions (right visual area V4, left anterior insula, right intraparietal sulcus, and subgenual cingulum), our tests corroborated the enhanced specificity of the modified algorithm, indicating that SCALE may be especially useful for delineating distinct core networks of co-activation.

Introduction

Understanding the functional organization of the human brain requires the consideration of both regional specificity and interregional interaction (Eickhoff and Grefkes, 2011). The advent of modern neuroimaging methods, especially functional magnetic resonance imaging (fMRI), has spurred investigations into both aspects. With respect to interregional coupling, several dimensions of brain connectivity have been explored non-invasively, including structural connectivity using diffusion-weighted imaging (Dell'Acqua and Catani, 2012), effective connectivity during task performance using Dynamic Causal Modeling (Friston et al., 2003), and functional connectivity during task-dependent or task-unconstrained ("resting state") cognition (van den Heuvel and Hulshoff Pol, 2010).

An alternative approach to exploring the brain-wide functional connectivity (FC) pattern of a given brain region is provided by meta-analytic connectivity modeling (MACM; Laird et al., 2013). This approach examines which brain regions are co-activated above chance with a given seed region across a large and diverse set of neuroimaging experiments (Eickhoff et al., 2010; Robinson et al., 2010). To this end, MACM capitalizes on databases such as BrainMap, in which a great many of published results from neuroimaging studies are stored (Laird et al., 2009a, 2011). Such databases are first filtered to identify all experiments reporting activations in or near a given seed region. Subsequently, the identified subset of experiments is meta-analyzed by a coordinate-based algorithm such as activation likelihood estimation (ALE) to determine the convergence of the reported activation foci in these experiments (Eickhoff et al., 2009; Turkeltaub et al., 2002). As all experiments were defined by activation in the seed region, the highest convergence will consequently be found there. Significant convergence outside the seed, in turn, indicates significant across-study co-activation (i.e., FC; cf. Amft et al., 2014; Hoffstaedter et al., 2014; Reetz et al., 2012; Jakobs et al., 2012). Thus, MACM exploits the

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accumulated wealth of data on brain activity associated with many kinds of psychological processes and conditions. In contrast to resting-state FC analyses, MACM provides a measure of FC during task-constrained states and, by way of analyzing the descriptive meta-data associated with each databased activation, enables the functional characterization of the resulting set of consistently co-activated regions (Kellermann et al., 2013; Müller et al., 2013; Rottschy et al., 2013).

It should be noted, however, that findings from functional neuroimaging experiments are not equally distributed across the entire brain. Rather, from large compilations of findings in databases such as BrainMap (Laird et al., 2009a) or Neurosynth (Yarkoni et al., 2011) it becomes evident that certain locations are found much more frequently activated than others (cf. Fig. 1). The results of a MACM analysis, in turn, may be influenced by such non-stationary a priori probabilities for each voxel to be activated across the entire database. That is, if a given voxel is frequently activated in the databased experiments, the likelihood of this voxel to co-activate with any given seed region is increased a priori. The frequency of activation across all databased experiments is naturally high for heteromodal regions that are involved in a wide range of tasks (e.g., anterior insula; cf. Kurth et al., 2010), but it also depends on experimental epiphenomena such as the high prevalence of neuroimaging experiments using visual stimulus input, manual responses, and/or tasks with verbal material. When using the standard MACM approach, this frequency bias of activated regions may lead to partially unspecific or generic co-activation patterns. To address this potential bias, we propose a modification to MACM that takes this frequency bias into account in order to map more specific co-activation patterns of seed regions.

The key idea behind the proposed modification is to abandon the quasi-rectangular null-distribution reflecting an unbiased random spatial association between experiments, in favor of a random association structure that reflects the a priori probability of each voxel being activated across the entire database. That is, rather than testing for voxels that show higher convergence than expected from a flat distribution of random associations, the new specific co-activation likelihood estimation (SCALE) algorithm tests for voxels that show higher convergence than expected given their a priori likelihood of activation.

Methods

Sample

All MACM analyses were performed using the BrainMap database (Laird et al., 2009a) (www.brainmap.org). From that database, we included only those experiments that reported coordinates in standard stereotaxic space from normal functional mapping studies (i.e., no interventions such as pharmacological challenges or practice and no interindividual-differences analyses) in healthy participants using either fMRI or positron emission tomography. Apart from that, we refrained from any pre-selection based on descriptive BrainMap meta-data (i.e., taxonomic categories). In total, this yielded 7209 eligible experiments at the time of analysis.

To evaluate the performance of our bias-adjusted MACM algorithm, both standard and modified algorithms were applied to four exemplary seed regions (Fig. 2). These four regions comprised (1) the cytoarchitectonically defined right visual area V4 (hOC4v; Rottschy et al., 2007) as well as three functionally defined clusters in: (2) left anterior insula (aIns), (3) right intraparietal sulcus (IPS; extending to adjacent superior and inferior parietal lobules), and (4) the subgenual cingulum (SGC). Both left aIns and right IPS clusters were derived from a conjunction map across two previous neuroimaging meta-analyses on working memory (Rottschy et al., 2012) and sustained attention (Langner and Eickhoff, 2013). The SGC cluster, in turn, was derived from a conjunction across two previous meta-analyses on brain activity at rest (i.e., the so-called default mode) and affective processing, respectively (Schilbach et al., 2012; see also Amft et al., 2014). These four seed regions were chosen on the basis of their spatial and functional heterogeneity, given that they are representative of varying locations in the brain, extend across multiple functional systems, and are marked by different degrees of functional specialization.

Filtering the BrainMap database for experiments that reported at least one focus of activation in the given seed regions, we found: (1) 367 experiments reporting activation in right area hOC4v (in total: 5467 foci, 4771 participants); (2) 354 experiments reporting activation in the left aIns cluster (5725 foci, 4952 participants); (3) 220 experiments reporting activation in the right IPS cluster (3385 foci, 2768 participants); and (4) 100 experiments reporting activation in the SGC cluster (1192 foci, 1520 participants).

Standard and modified MACM algorithms

Standard algorithm

Following established procedures (Balsters et al., 2013; Bzdok et al., 2013b; Clos et al., 2013; Roski et al., 2013), we first computed the task-based functional connectivity (i.e., co-activation patterns) for each of the four seed regions using the standard MACM implementation: First, we identified the experiments in our sample that reported activation in the currently considered seed region. The brain-wide co-activation pattern for each individual seed voxel was then computed by a meta-analysis over the retrieved experiments. That is, experiments were defined by activation in the particular seed region, and a quantitative meta-analysis of all foci reported in these experiments was performed to assess how likely any other voxel throughout the brain co-activated with the given seed voxel. Meta-analysis was performed using the revised version of the ALE approach (Eickhoff et al., 2009, 2012; Turkeltaub et al., 2012). This algorithm treats activation foci reported from a given experiment as centers of 3-D Gaussian probability distributions that reflect the spatial uncertainty associated with neuroimaging results. The probability distributions of all reported foci were combined into a modeled activation (MA) map for each experiment. The voxel-wise union of these MA maps across all experiments associated with a particular seed voxel then yielded an ALE score for each voxel of the

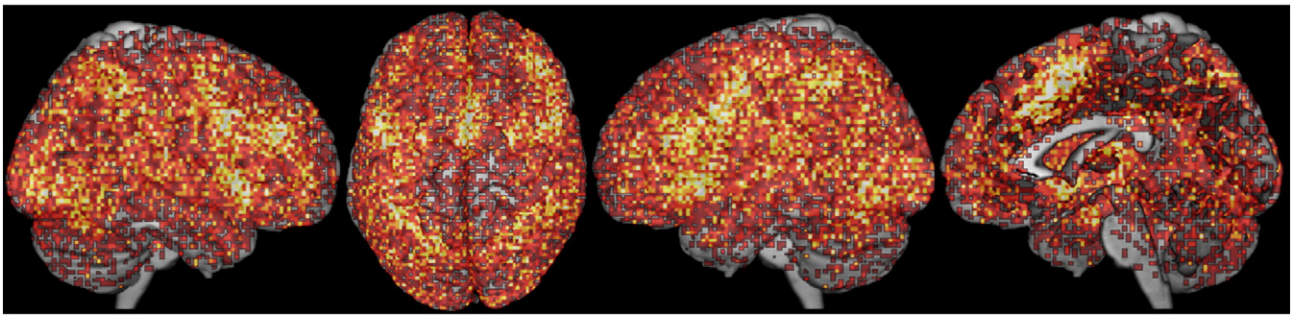

Fig. 1. The population of activation foci contained in the BrainMap database (at that time) rendered on a standard template brain. Color lightness codes frequency of activation of a given voxel, with lighter colors indicating higher frequencies.