Heterogeneous fractionation profiles of meta-analytic coactivation networks

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ABSTRACT

Computational cognitive neuroimaging approaches can be leveraged to characterize the hierarchical organization of distributed, functionally specialized networks in the human brain. To this end, we performed large-scale mining across the BrainMap database of coordinate-based activation locations from over 10,000 task-based experiments. Meta-analytic coactivation networks were identified by jointly applying independent component analysis (ICA) and meta-analytic connectivity modeling (MACM) across a wide range of model orders (i.e., d=20–300). We then iteratively computed pairwise correlation coefficients for consecutive model orders to compare spatial network topologies, ultimately yielding fractionation profiles delineating how "*parent*" functional brain systems decompose into constituent "*child*" sub-networks. Fractionation profiles differed dramatically across canonical networks: some exhibited complex and extensive fractionation into a large number of sub-networks across the full range of model orders, whereas others exhibited little to no decomposition as model order increased. Hierarchical clustering was applied to evaluate this heterogeneity, yielding three distinct groups of network fractionation profiles: high, moderate, and low fractionation. BrainMap-based functional decoding of resultant coactivation networks revealed a multi-domain association regardless of fractionation complexity. Rather than emphasize a cognitive-motor-perceptual gradient, these outcomes suggest the importance of inter-lobar connectivity in functional brain organization. We conclude that high fractionation networks are complex and comprised of many constituent sub-networks reflecting long-range, inter-lobar connectivity, particularly in fronto-parietal regions. In contrast, low fractionation networks may reflect persistent and stable networks that are more internally coherent and exhibit reduced inter-lobar communication.

Introduction

Enhanced insight into the network-level functional organization of the human brain may provide a more complete and coherent framework to appreciate the spectrum of human mental abilities. For example, functional connectivity analyses utilizing multivariate independent component analysis (ICA) have characterized the spatial topography of consistently identified brain networks in resting state functional magnetic resonance imaging (rs-fMRI) data (Beckmann, 2012; Calhoun and Adali, 2012). ICA-derived resting state networks (Beckmann et al., 2005; De Luca et al., 2006) extend across anatomically distributed regions, are consistent across studies (Damoiseaux et al., 2006; Zuo et al., 2010) and species (Wey et al., 2014; Vincent et al., 2007; Moeller et al., 2009), and reliably define functional neural systems, such as the default mode (Raichle et al., 2001), perceptual (e.g., visual or auditory), sensorimotor (e.g., motor-hand, motor-speech, premotor), and high-level cognitive networks (e.g., unilateral and bilateral fronto-parietal regions associated with memory, language, and central executive function) (Damoiseaux et al., 2006; Kiviniemi et al., 2009; Biswal et al., 2010; Allen et al., 2011). We previously

demonstrated that this network-based architecture persists across both resting and task states, as shown in a database-driven meta-analysis from thousands of task conditions (Smith et al., 2009). Using ICA, a primary set of activation networks was identified, which represented the major modes of co-occurrence across the diverse range of activations reported in the literature. Subsequently, we reported a novel approach in connectome discovery science in which ICA and pattern classification techniques were jointly applied to characterize the functional similarity across meta-analytic networks (Laird et al., 2011a). Using this approach, we identified four groupings of the major coactivation networks with similar behavioral properties across studies: (a) motor and visuospatial integration, coordination, and execution, (b) visual processing, (c) emotion and interoceptive processing, and (d) higher cognition. Networks in the first three functional groups exhibited strongly thematic functional properties, whereas the fourth group was associated with a divergent set of properties that differed across networks, yet all involved high-level cognitive processing.

While the spatial topographies of these canonical neural systems have been consistently observed across studies, it is unclear how this functional architecture translates across different scales. Indeed, although *multivariate* analyses of fMRI data have become commonplace, such analyses are typically not yet *multi-scale*. Evidence from graph theory approaches (Bullmore and Sporns, 2009) suggests that the brain follows a modular organization, with communication hubs (Achard et al., 2006; Hagmann et al., 2008; Buckner et al., 2009) and properties similar to those of small-world networks (Salvador et al., 2005; Meunier et al., 2009; He et al., 2009). However, there remains much to be understood regarding the fractionation scheme that defines how large-scale core systems are decomposed into sub-systems. ICA is typically performed at a pre-selected model order d (e.g., generally, a low order/scale of 20–40 components), rather than across multiple scales. Although prior work has sought to develop analytic strategies for automatically identifying an optimal model order of interest (Beckmann and Smith, 2004; Himberg et al., 2004; Li et al., 2007; Ray et al., 2013), these methods are somewhat arbitrary and usually depend upon a number of factors (e.g., field strength, number of time points, number of subjects, and data quality). A recent study established the importance of this dimensionality parameter (Wang and Li, 2015), demonstrating that the number of components can critically affect ICA results. Only a few studies have directly compared ICA-based resting state networks across different model orders (Smith et al., 2009; Kiviniemi et al., 2009; Abou-Elseoud et al., 2010; Pamilo et al., 2012), suggesting a hierarchical network structure (i.e., the 20 networks observed at a low-dimensionality ICA can be decomposed into distinct sub-networks at a model order of 70). However, no study has yet synthesized the dynamic nature of these networks by scaling across a wide range of model orders.

In a previous study, we examined meta-analytic task co-occurrence networks across multiple model orders using the BrainMap database, and demonstrated a model order of 20 components provides an optimal decomposition for low model order ICA, while 70 components is optimal for higher model orders (Ray et al., 2013). Although multiple model orders were analyzed, our results did not include an integrative assessment of the decomposition trajectories across all model orders, for all networks. Here, we more fully explored how large-scale distributed meta-analytic coactivation networks fractionate into smaller sub-networks and/or individual nodes using a multivariate, multi-scale analysis. The emphasis of the present study is not on a single model order, nor is it our objective to propose that higher model orders are more or less meaningful than lower model orders. Rather, we sought to characterize meta-analytic coactivation networks from a wider lens and evaluate the dynamic range of fractionation profiles across many model orders. To this end, we leveraged two complementary neuroimaging meta-analytic techniques to examine how "*parent*" functional brain systems can be decomposed into constituent "*child*" sub-networks, thereby providing insight into the fractionation properties of functional brain architecture. First, we applied ICA using a range of model orders to a database of task-based activations reported in the literature. Second, we applied meta-analytic connectivity modeling (MACM; Laird et al., 2009a; Robinson et al., 2010; Eickhoff et al., 2010) to the resultant ICA components to identify a set of large-scale coactivation networks at each model order. Meta-analytic coactivation networks are derived from activation patterns reported across a range of experimental neuroimaging tasks and paradigms, are complementary to seed-based resting state correlations, and have been validated in a series of papers comparing findings to other network mapping techniques (Robinson et al., 2010, 2012; Eickhoff et al., 2010, 2011; Narayana et al., 2012; Jakobs et al., 2012; Reetz et al., 2012). Pairwise correlation matrices quantifying the similarity between networks at sequential dimensionalities were calculated to construct fractionation profiles describing how the parent networks were decomposed into child sub-networks. Consistent with and extending our previous work, we hypothesized that *perceptual and motor* parent networks would yield simple fractionation profiles with relatively few numbers of child sub-networks. Conversely, we additionally hypothesized that *cognitive* parent networks would yield complex fractionation profiles with relatively large numbers of child sub-networks. We observed that the fractionation profiles differed dramatically across canonical networks, with some exhibiting complex fractionation into a large number of sub-networks and others exhibiting little to no decomposition. Hierarchical clustering of the heterogeneous fractionation profiles allowed us to then classify networks into three distinct groups: high fractionation, moderate fractionation, and low fractionation. Our results demonstrate that varying model order provides enhanced insight into the heterogeneous fractionation profiles of meta-analytic coactivation networks.

Methods

Independent component analysis of the BrainMap database

Following procedures established in our prior work, meta-analysis was carried out using data archived in the BrainMap database (http://brainmap.org; Fox and Lancaster, 2002; Laird et al., 2005a, 2009b, 2011b). Peak coordinates were extracted from 10,899 neuroimaging experiments representing activation locations observed among 100,861 healthy participants across a wide range of behavioral task conditions. Experiments were filtered to exclude patient populations, thereby mitigating potential bias due to effects of disease or treatment effects. Coordinates reported in MNI space (Evans et al., 1993; Collins et al., 1994) were converted into Talairach space (Talairach and Tournoux, 1988) using the Lancaster transformation (Lancaster et al., 2007), reducing spatial disparity across normalization templates (Laird et al., 2010). The coordinates were then modeled with a three-dimensional Gaussian probability distribution reflecting the spatial uncertainty of each focus based on an estimation of the inter-subject and inter-laboratory variability typically observed in neuroimaging experiments, weighted by the number of subjects included in each experiment (Eickhoff et al., 2009). This algorithm limits the meta-analysis to an anatomically constrained space specified by a grey matter mask, and includes a method that calculates the above-chance clustering between experiments (i.e., random-effects analysis), rather than between foci (i.e., fixed-effects analysis), and also accounts for differences in sample sizes across included studies (Eickhoff et al., 2009). The probabilities of all foci reported in a given experiment were computed, resulting in a modeled activation (MA) map for each experiment (Fig. 1, Step 1). The per-experiment MA probability maps were converted into feature vectors of voxel values and concatenated horizontally to form an array of size *n=10,899* experiments by *v* voxels. The spatial resolution of the images was 2 mm×2 mm×2 mm, and v was equal to 226,654 voxels.

Spatial ICA at a model order of *d* was applied to these data using FSL's MELODIC (multivariate exploratory linear optimized decompo-