NeuroImage 61 (2012) 1129–1142

Contents lists available at SciVerse ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

A convergent functional architecture of the insula emerges across imaging modalities

Clare Kelly [a,*], Roberto Toro [b,c,d], Adriana Di Martino [a], Christine L. Cox [a], Pierre Bellec [e], F. Xavier Castellanos [a,f], Michael P. Milham [f,g,**]

[a] Phyllis Green and Randolph Cowen Institute for Pediatric Neuroscience, New York University Child Study Center, New York, NY, USA
[b] Human Genetics and Cognitive Functions, Institut Pasteur, Paris, France
[c] CNRS URA 2182 'Genes, synapses and cognition', Institut Pasteur, Paris, France
[d] Univ. Paris Diderot, Sorbonne Paris Cité, Human Genetics and Cognitive Functions, Paris, France
[e] Centre de recherche de l'institut de Gériatrie de Montréal CRIUGM, 4565 Chemin Queen Mary, H3W 1W5 Montreal, Quebec, Canada
[f] Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY, USA
[g] Center for the Developing Brain, Child Mind Institute, 445 Park Ave, New York, NY, USA

ARTICLE INFO

Article history:
Accepted 1 March 2012
Available online 13 March 2012

Keywords:
Insula
Clustering
Functional connectivity
Structural covariance
Coactivation
Behavioral domains

ABSTRACT

Empirical evidence increasingly supports the hypothesis that patterns of intrinsic functional connectivity (iFC) are sculpted by a history of evoked coactivation within distinct neuronal networks. This, together with evidence of strong correspondence among the networks defined by iFC and those delineated using a variety of other neuroimaging techniques, suggests a fundamental brain architecture detectable across multiple functional and structural imaging modalities. Here, we leverage this insight to examine the functional organization of the human insula. We parcellated the insula on the basis of three distinct neuroimaging modalities — task-evoked coactivation, intrinsic (i.e., task-independent) functional connectivity, and gray matter structural covariance. Clustering of these three different covariance-based measures revealed a convergent elemental organization of the insula that likely reflects a fundamental brain architecture governing both brain structure and function at multiple spatial scales. While not constrained to be hierarchical, our parcellation revealed a pseudo-hierarchical, multiscale organization that was consistent with previous clustering and meta-analytic studies of the insula. Finally, meta-analytic examination of the cognitive and behavioral domains associated with each of the insular clusters obtained elucidated the broad functional dissociations likely underlying the topography observed. To facilitate future investigations of insula function across healthy and pathological states, the insular parcels have been made freely available for download via http://fcon_1000.projects.nitrc.org, along with the analytic scripts used to perform the parcellations.

Introduction

Mounting evidence suggests that patterns of intrinsic functional connectivity (iFC), subtended by temporally correlated spontaneous fluctuations in the resting state fMRI (R-fMRI) signal, are sculpted by a history of task-evoked coactivation (Deco and Corbetta, 2011; Smith et al., 2009). A credible hypothesis for the neurophysiologic significance of iFC is thus that correlated intrinsic activity serves to maintain the integrity of neuronal networks supporting cognition and action, even in the absence of processing demands. Convergence among large-scale networks defined by iFC (intrinsic connectivity networks; ICNs) and those delineated using a variety of other modalities, including task-based coactivation (Smith et al., 2009; Toro et al., 2008), electrophysiological measures of neuronal activity (He et al., 2008; Keller et al., 2011), and static measures of brain structure (Mars et al., 2011a; Seeley et al., 2009) supports this hypothesis and suggests a fundamental brain architecture governing both structure and function.

Leveraging this insight, studies have demonstrated that data-driven clustering methods based on iFC measures can partition the brain into distinct functional systems, thus revealing its functional "building blocks" (e.g., Bellec et al., 2010; Craddock et al., 2011; Nelson et al., 2010a,b; Yeo et al., 2011). These studies have revealed much about the functional architecture of the brain at multiple spatial scales, from subregions and boundaries within specific functional areas to the organization of these areas into large-scale networks. This multiscale organization is consistent with the observation that many large-scale brain regions (e.g., prefrontal cortex) exhibit activation and connectivity profiles that evince both local functional heterogeneity as well as

* Correspondence to: C. Kelly, Institute for Pediatric Neuroscience, 215 Lexington Ave, 14th Floor, New York, NY 10016, USA.
** Correspondence to: M.P. Milham, Child Mind Institute, 445 Park Ave, New York, NY 10022, USA.
E-mail addresses: clare.kelly@nyumc.org (C. Kelly), michael.milham@childmind.org (M.P. Milham).

1053-8119/$ – see front matter
doi:10.1016/j.neuroimage.2012.03.021

agglomerative or locally integrative functions (Duncan and Owen, 2000; Wilson et al., 2010). Data-driven iFC-based parcellation of functionally complex regions may therefore provide insights into this multiscale organization.

The insula constitutes one such region. Although its importance was long belied by its seclusion within the depths of the Sylvian fissure, the insula is now recognized as a nexus of sensory, somatic, interoceptive, cognitive and emotional processing, the integration of which may provide the neural substrate for human phenomenological experience (Craig, 2009a,b, 2011). Anatomically, the insula is positioned at the confluence of several neural pathways: besides being densely interconnected with itself and with virtually all cortical association regions, it receives sensory, somesthetic and interoceptive inputs from cortical areas and via the thalamus. It is also interconnected with the medial temporal lobe, amygdala, and basal ganglia (Augustine, 1996; Dum et al., 2009; Mesulam and Mufson, 1982b; Mufson and Mesulam, 1982).

Given this diverse connectivity, it is unsurprising that insular activation has been observed across a wide array of functional contexts, including sensory perception (from gustation and olfaction, to music perception; e.g., Molnar-Szakacs and Overy, 2006; Small, 2010; Small et al., 2003), vestibulo-proprioceptive processing, interoception (including satiety and craving; e.g., Critchley et al., 2004; Naqvi and Bechara, 2009), somesthesis (including nociception; e.g., Brooks et al., 2005; Starr et al., 2009), somatic control (including the regulation of cardioregulatory, vasomotor and visceromotor function; e.g., Cheung and Hachinski, 2000; Lerner et al., 2009; Shelley and Trimble, 2004), motor function (particularly speech; e.g., Ackermann and Riecker, 2010; Nestor et al., 2003), emotion (particularly empathy and disgust; e.g., Adolphs et al., 2003; Jabbi et al., 2007; Singer et al., 2009; Wicker et al., 2003), and cognition (including attention and language processing; e.g., Chee et al., 2004; Eckert et al., 2009; Nelson et al., 2010b; Steinbrink et al., 2009). Its implication across these myriad behavioral contexts has led to the suggestion that activation of the insula, in concert with activation of anterior cingulate cortex, likely subserves emergent integrative functions such as conscious awareness (Craig, 2009b; Medford and Critchley, 2010), salience detection (Seeley et al., 2007), task-set maintenance (Dosenbach et al., 2007, 2008) or focal attention (Nelson et al., 2010a). Insula dysfunction across several clinical and psychiatric disorders involving impairments in somatic and social awareness, attention and emotion, such as autism (Di Martino et al., 2009a; Uddin and Menon, 2009), addiction (Goldstein et al., 2009), anxiety disorders (Paulus and Stein, 2006) and behavioral-variant fronto-temporal dementia (Seeley, 2010) further underscores the importance of this heterogeneous area to our understanding of brain function.

Efforts to delineate the organization of the insula have utilized a wide variety of techniques from electrical stimulation and neuropsychological studies of human patients (Cereda et al., 2002; Penfield and Faulk, 1955), to stereological and anatomical tracing studies of nonhuman primates (Mesulam and Mufson, 1982a, b; Mufson and Mesulam, 1982). Most recently, the dramatic upsurge in neuroimaging probes of the insula has prompted several studies specifically aimed at parcellating this region based on its structural and functional properties. Functional differentiation revealed by patterns of task-based activation, cytoarchitecture, structural connectivity (diffusion imaging-based) and intrinsic (i.e., task-independent or "resting state") functional connectivity (iFC) has been described (Cauda et al., 2011; Deen et al., 2011; Kurth et al., 2010a,b; Nanetti et al., 2009; Nelson et al., 2010b). Here, we build on previous work by performing a network-based data-driven parcellation of the insula. We aimed to examine the extent to which parcellations are consistent across three distinct imaging modalities, namely, R-fMRI-based iFC, gray matter structural covariance and meta-analytic patterns of task-based coactivation. Gray matter structural covariance and task-based coactivation are two covariance-based methodological techniques that use structural (gray matter volume) and task-evoked functional data, respectively. Previous studies have demonstrated that the large-scale networks delineated using these approaches exhibit strong correspondence with those derived using iFC methods (Mennes et al., 2012; Seeley et al., 2009; Smith et al., 2009; Toro et al., 2008), suggesting that all three modalities capture similar properties of the brain's functional organization.

We adopt a *network*-based voxel-wise clustering approach whereby individual insular voxels are grouped together if they exhibit similar whole-brain patterns of iFC, structural covariance or task-based coactivation. Further, we use a multi-site large-*n* dataset (www.nitrc.org/projects/fcon_1000) and the publicly available coactivation map analysis (Toro et al., 2008; http://coactivationmap.sourceforge.net) of the BrainMap database (Laird et al., 2005; http://brainmap.org). Despite the different methodological techniques and assumptions underlying these three modalities, we demonstrate strong cross-modal convergence in the parcellations obtained, at multiple spatial scales (i.e., from the relatively coarse scale of 2 clusters, to finer scales of ~9 clusters). That is, we show that the insula exhibits a multiscale organization that is embedded in shared (co-varying) patterns of activity and structure that likely reflect a history of functional interaction. This multiscale organization is consistent with work suggesting that the insula exhibits both subregional functional distinctions (functional heterogeneity) as well as emergent or integrative functions that span multiple subregions (e.g., Craig, 2011; Kurth et al., 2010b). Given the implication of the insula across several clinical and psychiatric disorders, including autism and addiction (Di Martino et al., 2009a; Naqvi and Bechara, 2009), delineating these connectivity-based functional building blocks of the insula will inform investigations of the role of this enigmatic area in both normal and pathological brain states.

Material and methods

Analysis overview

Fig. 1 provides a schematic of the data analysis stream. Briefly, processing comprised the following steps:

Step 1. For each voxel within ROIs encompassing the right (134 voxels) and left (117 voxels) insula (MNI152 4 mm space), we computed voxel-wise maps of (1) Pearson correlation-based iFc for an equal sampling of participants from each of 20 data collection sites included in the 1000 Functional Connectomes Project (http://fcon_1000.projects.nitrc.org), (2) whole-brain gray-matter inter-subject structural covariance computed using the same participants from the same 20 data collection sites, and (3) phi-correlation task-based coactivation (Toro et al., 2008; http://coactivationmap.sourceforge.net) across >75,000 peak coordinates from ~2000 articles currently available in the BrainMap database (Laird et al., 2005; http://brainmap.org).

Step 2. Separately for each of the 3 data types, we used eta^2 to quantify the similarity between all possible pairings of the covariance maps associated with each of the 117 voxels in the left insula (i.e., $((117*117)-117)/2=6786$ pairs) and separately, the 134 voxels in the right insula (8911 pairs). We then used spectral clustering to partition the insula into groups (clusters) of voxels such that intra-cluster similarity was maximized and inter-cluster similarity was minimized. We derived clustering solutions for $K=2, \ldots, 15$.

Step 3. For the iFC data, we were able to apply a *consensus clustering* approach (Bellec et al., 2010; Kelly et al., 2010; van den Heuvel et al., 2008) to identify the most stable clustering solutions across subjects within each data collection site (site-level solutions) and then across the 20 data collection sites (multi-site solutions). For structural covariance, which is a group-level, rather than participant-level measure, we were able to perform consensus clustering across the 20 data