

Decoding the Role of the Insula in Human Cognition: Functional Parcellation and Large-Scale Reverse Inference

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Recent work has indicated that the insula may be involved in goal-directed cognition, switching between networks, and the conscious awareness of affect and somatosensation. However, these findings have been limited by the insula's remarkably high base rate of activation and considerable functional heterogeneity. The present study used a relatively unbiased data-driven approach combining resting-state connectivity-based parcellation of the insula with large-scale meta-analysis to understand how the insula is anatomically organized based on functional connectivity patterns as well as the consistency and specificity of the associated cognitive functions. Our findings support a tripartite subdivision of the insula and reveal that the patterns of functional connectivity in the resting-state analysis appear to be relatively conserved across tasks in the meta-analytic coactivation analysis. The function of the networks was meta-analytically "decoded" using the Neurosynth framework and revealed that while the dorsoanterior insula is more consistently involved in human cognition than ventroanterior and posterior networks, each parcellated network is specifically associated with a distinct function. Collectively, this work suggests that the insula is instrumental in integrating disparate functional systems involved in processing affect, sensory-motor processing, and general cognition and is well suited to provide an interface between feelings, cognition, and action.

Keywords: connectivity, insula, meta-analysis, parcellation, reverse inference

Introduction

The insula is one of the most frequently activated regions in functional neuroimaging research (Duncan and Owen 2000; Nelson et al. 2010; Yarkoni et al. 2011). Insular activation is reliably reported in a broad range of cognitive domains (Augustine 1996; Shelley and Trimble 2004), yet a detailed understanding of the functional anatomy of the insula is only now beginning to emerge (Craig 2009; Singer et al. 2009). Recent studies employing a diverse range of methodological approaches—including cytoarchitectonic mapping (Mesulam and Mufson 1982; Kurth, Eickhoff, et al. 2010), tractography (Nanetti et al. 2009), meta-analysis of task-related functional magnetic resonance imaging (fMRI) data (Wager and Feldman-Barrett 2004; Mutschler et al. 2009; Kurth, Zilles, et al. 2010), and functional connectivity (Nelson et al. 2010; Cauda et al. 2011; Deen et al. 2011)—appear to converge on the functional parcellation of the insula into at least 3 functionally distinct subregions. These include a ventroanterior region associated

with chemosensory (Pritchard et al. 1999) and socio-emotional processing (Sanfey et al. 2003; Chang et al. 2011), a dorsoanterior region associated with higher cognitive processing (Dosenbach et al. 2006; Eckert et al. 2009), and a posterior insula region associated with pain and sensorimotor processing (Craig 2002; Wager et al. 2004).

Despite the emerging consensus, several important questions about the role of insula activation in cognition remain unanswered. First, parcellation-based methods of resting-state data are inherently limited in their ability to directly link networks to specific functions due to the absence of any cognitive manipulation. At least one study has proposed that connectivity patterns in the insula may change according to the function being probed (Jabbi et al. 2008). Moreover, most studies have focused on one type of analysis (e.g., functional connectivity, meta-analysis, etc.); it remains unclear to what extent functional distinctions are consistent across different kinds of data.

Second, efforts to map distinct insula regions onto specific cognitive functions have focused disproportionately on a few psychological domains (Wager and Feldman-Barrett 2004; Mutschler et al. 2009). But systematic functional-anatomical mapping requires a comprehensive representation of psychological tasks and states in order to quantify both how consistent and how specific activations of different insula regions are (Wager et al. 2009). "Consistency" is necessary for determining whether a particular region is reliably associated with a particular cognitive process (i.e., the degree to which a cognitive function implies a particular brain activation), while "specificity" is essential for performing reverse inference (i.e., the degree to which a particular brain activation implies a cognitive function) (Poldrack 2006). Establishing specificity is particularly crucial because insula regions differ considerably in activation likelihood. Whereas the dorsal anterior insula is activated in virtually all tasks involving goal-directed cognition (Duncan and Owen 2000; Dosenbach et al. 2006; Yarkoni et al. 2009), posterior and ventroanterior insula activations are reported much less frequently. Failing to account for such differences could lead to misattribution of the functional role of different subregions.

The present study used a data-driven approach to insula parcellation that combined functional connectivity analysis with a new framework for meta-analysis that enables quantification of both the consistency and specificity of network brain activity (Neurosynth; Yarkoni et al. 2011). We first parcellated the insula using a clustering analysis of functional connectivity patterns in resting-state fMRI data and replicated

the tripartite division observed in previous studies. We then identified broader networks that were functionally coactivated with the insula regions both at rest and in over 4400 studies and used the NeuroSynth framework to meta-analytically “decode” the functional role of these networks. Our results corroborate previous functional divisions and importantly extend these results by demonstrating a striking difference in the specificity of activation across different insula regions.

Materials and Methods

Participants

Eighteen participants (mean age = 20.4, standard deviation = 2.6, female = 56%) were recruited to participate in this study via advertisements posted on the University of Arizona campus. All participants were screened for significant health-related or neuropsychiatric disorders and none were currently taking psychoactive medication. One participant was excluded from the analysis for technical reasons (corrupted data). All participants gave informed consent according to procedures approved by the University of Arizona's Institutional Review Board.

Data Acquisition

Data were collected at the conclusion of a social decision-making experiment (Chang and Sanfey 2009, 2011). Participants were instructed to close their eyes and keep their head as still as possible and encouraged to let their minds wander. Each scanning session included a T_1 -weighted magnetization prepared rapid gradient echo structural scan (time repetition [TR] = 11 ms, time echo [TE] = 4 ms, matrix = 256×256 , slice thickness = 1 mm, gap = 0 mm). The functional resting scan lasted 2 min and 24 s and acquired 72 volumes using a 3-shot multiple echo planar imaging GRAPPA sequence that was optimized to maximize signal in regions associated with high susceptibility artifact, such as orbitofrontal cortex and medial temporal lobe (Stocker et al. 2006; Weiskopf et al. 2006) (TR = 2000 ms, TE = 25 ms, matrix = 96×96 , field of view = 192 mm, slice thickness = 3.0 mm, 42 axial slices, voxel size $2 \times 2 \times 3$).

Data Preprocessing

Functional imaging data were preprocessed and analyzed using the FSL Software package 4.1.4 (FMRIB, Oxford, UK). The first 3 volumes of each functional run were discarded to account for T_1 equilibrium effects. Images were corrected for slice scan time using an ascending interleaved procedure. Head motion was corrected using MCFLIRT using a 6-parameter rigid-body transformation. Images were spatially smoothed using a 5-mm full-width at half-maximum Gaussian kernel. A high-pass filter was used to cut off temporal periods longer than 100 s. All images were initially coregistered to the participant's high-resolution structural scan and were then coregistered to the Montreal Neurological Institute 152 person 2-mm template using a 12-parameter affine transformation. Nine covariates and their temporal derivatives (18 covariates total) were regressed out and the resulting residual (with a mean of 10 000) was used in all subsequent analyses. The covariates included 1) average global signal (Fox et al. 2009), 2) average CSF activity in two 2-mm diameter spheres placed in the lateral ventricles ($-24, -44, 8$ and $26, -44, 8$) (Fox et al. 2005, 2009), 3) average activity in two 7-mm diameter spheres placed in white matter in the prefrontal cortex ($24, 40, 4$ and $-24, 40, 4$) (Fox et al. 2005, 2009), and 4–9) 6 estimated head movement parameters from MCFLIRT procedure (Lund et al. 2005). The spheres were coregistered from stereotactic space to subject space before extracting mean activity. These covariates remove fluctuations unlikely to occur as a result of regional correlations.

Functional Parcellation Analysis

We used a data-driven approach to parcellate the right insula into distinct anatomical subregions based on shared connectivity profiles

with the rest of the brain. The right insula was selected because of its more frequent association with emotions and interoception (Craig 2002; Singer et al. 2009). This approach shares conceptual similarity with other studies that have used diffusion tensor imaging to examine white matter connectivity (Johansen-Berg et al. 2004; Beckmann et al. 2009) and more recently with resting-state fMRI (Cauda et al. 2011; Deen et al. 2011). First, we created a 2D matrix of time series cross-correlations for every voxel in the insula ($n = 1252$ defined by the Harvard-Oxford cortical atlas) with every voxel in the rest of the brain (see Fig. 2, panel A). To reduce the search space, we downsampled voxels outside of the insula to $5 \times 5 \times 6 \text{ mm}^3$ (approximately 13 000). We then created a correlation matrix of voxels in the insula based on the similarity of their connectivity profile with voxels in the rest of the brain for every participant (see Fig. 2, panel B upper matrix). We sorted this matrix using an unsupervised clustering technique (see Fig. 2, panel B lower matrix). This process involved applying a k -means clustering algorithm to find voxels in the insula that shared similar connectivity profiles to voxels in the rest of the brain. We did not place any spatial constraints on the algorithm, thus voxels were more likely to be clustered together the greater their similarity in connectivity profiles with the rest of the brain. We used the k -means algorithm implemented in Matlab using the best solution from 100 replicates. Because we did not have a strong *a priori* hypothesis about the possible number of subregions other than the 3 distinct cytoarchitectonic regions, we used an objective validity indicator (VI) to determine the optimal number of clusters. The VI maximizes the ratio between the average intercluster distance to the average intracluster distance. Finally, to create group maps for the clusters, we coregistered the individual subject maps to stereotactic space and summed the number of subjects that loaded on each cluster for every voxel in the insula. Thus, the group maps were determined by the number of subjects that had a similar spatial clustering solution. We used an arbitrary cutoff of $n = 10$ participants to threshold the map (other thresholds yielded similar cluster centers).

Determining Optimal Number of Clusters Using the VI

The k -means algorithm attempts to find cluster solutions that minimize the Euclidean distance between each data point and the cluster center. To select the number of extracted clusters, we ran the clustering algorithm on the restricted set of $k_{[2,10]}$ and used a VI to empirically select the optimal clustering solution. Our VI is similar to those proposed by others (Ray and Turi 1999) and represents the average intercluster to intracluster distance ratio across subjects. First, we calculate the average within-cluster sum of squares (intra)

$$\text{Intra} = \frac{1}{N} \sum_{i=1}^k \sum_{x \in C_i} \|x - z_i\|^2 \quad (1)$$

where N represents the number of voxels in the matrix and K reflects the number of clusters. We take x to be each voxel and z_i to be the center of cluster C_i . Second, we calculate the average between-cluster sum of squares

$$\text{Inter} = \text{mean}(\|z_i - z_j\|^2, i=1, \dots, k-1, j=i+1, \dots, k) \quad (2)$$

Finally, VI can be calculated as the max of the intercluster to intracluster distance ratio, averaged across subjects.

$$\text{VI} = \frac{\sum_{i=1}^n \arg\max(\frac{\text{Inter}}{\text{Intra}})}{n} \quad (3)$$

where n represents the number of subjects.

Identifying Parcellated Network Analysis

To identify the brain networks that connect with each of the insular subregions identified by the cluster analysis, we utilized a multilevel multiple regression approach. Importantly, this method ensures that the networks were statistically independent from activity in the other subregions and were spatially consistent across subjects. We first extracted the average time series for each of the 3 subregions classified by the clustering algorithm in subject space and entered them into

a first-level general linear model. We then summarized these results at the group level using a mixed effect model with full Bayesian inference (Woolrich et al. 2004). We employed whole brain cluster correction using an initial cluster threshold of $Z > 2.3$ and a Family Wise Error corrected threshold of $P < 0.05$ (Worsley et al. 1992).

Meta-Analytic Coactivation Analysis

If the subregions identified by the clustering analysis reflect meaningful functional divisions, they should emerge not only in time course-based analyses but also in large-scale analyses of entire studies (Toro et al. 2008; Smith et al. 2009). Previous meta-analysis studies that sought to identify functional divisions within the insula have focused on a relatively small number of psychological domains (e.g., different sensory modalities, cognitive control, etc.; Wager and Feldman-Barrett 2004; Mutschler et al. 2009; Kurth, Zilles, et al. 2010); however, such analyses are susceptible to bias since researchers understandably tend to choose those domains for analysis that were already thought to be related to insula functionality. To provide a more comprehensive and unbiased window into coactivation of the insula with other regions, we instead relied on the “Neurosynth” database (<http://neurosynth.org>), which at present contains activation coordinates for nearly 4400 fMRI studies that were selected without regard for the psychological process under investigation. Collectively, these studies comprise over 145 000 reported activations, representing the largest extant database of fMRI activations (The references for all the individual studies can be found on the Neurosynth website (www.neurosynth.org). The website provides multiple interfaces for identifying specific studies, including 1) listing all studies included in each term-based meta-analysis; 2) listing all studies that report activation within 10 mm of a given coordinate; and 3) a search interface displaying all studies that contain a specified keyword or author name.).

To identify networks associated with the cluster centers from each insular subregion across studies in the Neurosynth database ($n = 4393$), we identified regions in which activations were coreported with activations in each of the insula subregions. Each voxel in the binary database was coded as a 1 if it fell within 10 mm of a focus reported in the study (cf. Wager et al. 2009). Specifically, for each voxel in the brain ($n = 231\,202$), we conducted a multiple logistic regression, predicting coactivation status (present or absent in each of the studies) from binary indicators of activation in each of the insula cluster centers (again, coding presence vs. absence in each study). Each map was thresholded using cluster correction with an initial cutoff of $z > 4.5$ and a corrected $P < 0.05$. We also quantified the spatial coherence of the resting state and the meta-analytic coactivation networks by computing the Pearson correlation between pairs of maps across all voxels (Smith et al. 2009). It is important to note that all 4393 studies were used to estimate the connectivity beta parameters—co-occurrences and non-occurrences both provide important sources of information in understanding coactivation.

Meta-Analytic Decoding of Network Function

An important benefit of the Neurosynth framework is that it enables quantitative inferences about the potential cognitive functions associated with distributed patterns of activation. The database contains automatically generated meta-analysis maps for several thousand psychological terms and topics (Poldrack et al. 2011; Yarkoni et al. 2011); importantly, these meta-analysis maps can distinguish “forward inference” from “reverse inference” (Poldrack 2006). Forward inference reflects the probability of observing activity in a region given knowledge of the psychological process; this is the type of inference produced by most fMRI studies, which start from a known experimental manipulation and observe the pattern of brain activity associated with that manipulation. In contrast, reverse inference reflects the probability of a psychological process being present given knowledge of activation in a particular brain region. Reverse inference is analogous to “decoding” mental states from brain activity and is arguably what researchers are interested in most of the time; however, it is rarely possible to produce such inferences in individual fMRI studies, since knowing the probability with which a given brain state implies a given mental state implicitly requires knowledge of the probability with

which the same brain state implies many other mental states. Because the Neurosynth framework contains a relatively comprehensive set of term-to-activation mappings, it is possible to compute whole-brain maps for individual psychological concepts in both the forward direction (i.e., $P(\text{Activation}|\text{State})$) and the reverse direction (i.e., $P(\text{State}|\text{Activation})$). Statistical inference is then performed using a chi-square test to generate P value maps, and the resulting maps are FDR-corrected for multiple comparisons (for full details, see Yarkoni et al. 2011). Thus, one can establish both how consistently a particular task or state activates a given region and how specific activation in that region is to the task—effectively decoding mental states from brain activity.

In the present study, we used the Neurosynth database to meta-analytically decode the functional role of distinct insula-based networks. For each meta-analytic insula coactivation map (see above), we computed the voxel-wise Pearson correlation with each of 200 topic-based meta-analysis maps in the Neurosynth database (see <http://neurosynth.org>). The topics were generated by applying Latent Dirichlet Allocation (LDA) to the full text of all articles in the Neurosynth database. LDA is a generative model for text (Blei et al. 2003) and assumes that each article is generated by sampling words from a set of topic distributions. The distribution of words over topics and topics over articles was inferred using Bayesian inference as implemented by MALLET (McCallum 2002). Topic loadings were computed for all articles and were used to identify articles with high loadings on each topic (for full details, see Poldrack et al. 2011). Contrast maps for each individual topic were created by comparing studies that loaded highly on that topic with all other studies. Whole-brain forward and reverse inference maps for each topic were computed in an identical manner to that described previously for term-based analyses in Yarkoni et al. (2009, 2011) (see also <http://neurosynth.org>). We conducted separate correlation analyses for forward inference and reverse inference topic maps. The resulting coefficients were then used to generate a ranking of the psychological topics most consistently or specifically associated with each insula network, where the consistency analysis indicated the extent to which the insula network resembled the one activated by a particular task, and the specificity analysis indicated the degree to which activation of the insula network implied that a task or state was likely to be present.

Results

Functional Parcellation

While the optimal cluster solution ranged from a k of 2 to 5 for individual subjects, the VI metric converged on a 3-cluster solution for the group (see Fig. 1, panel C). The 3D cluster solution for a representative subject can be seen in Figure 1, panel D. As is evident in this subject’s ordered insular correlation matrix (Fig. 1, panel B), the clustering algorithm was able to successfully group voxels together that shared similar patterns of connectivity with the rest of the brain. Importantly, the individual cluster solutions were associated with a consistent spatial profile across participants (Fig. 2). Figure 2 depicts voxels that were classified similarly for at least 10 participants (approximately 70% of the sample). Our data-driven approach finds 2 main subdivisions of the insula. The first subdivision is between voxels in the anterior and posterior insula (−38, −10, 6). The anterior insula further parcellates into dorsal (−38, 12, −2) and ventral (−34, 8, −8) subregions. These results successfully replicate other parcellation studies, which have found a 3-cluster solution (Deen et al. 2011).

Resting-State Network Connectivity

As described above, the parcellation analysis identified 3 distinct insular subregions. Our connectivity analysis demonstrates that these subregions were associated with distinct

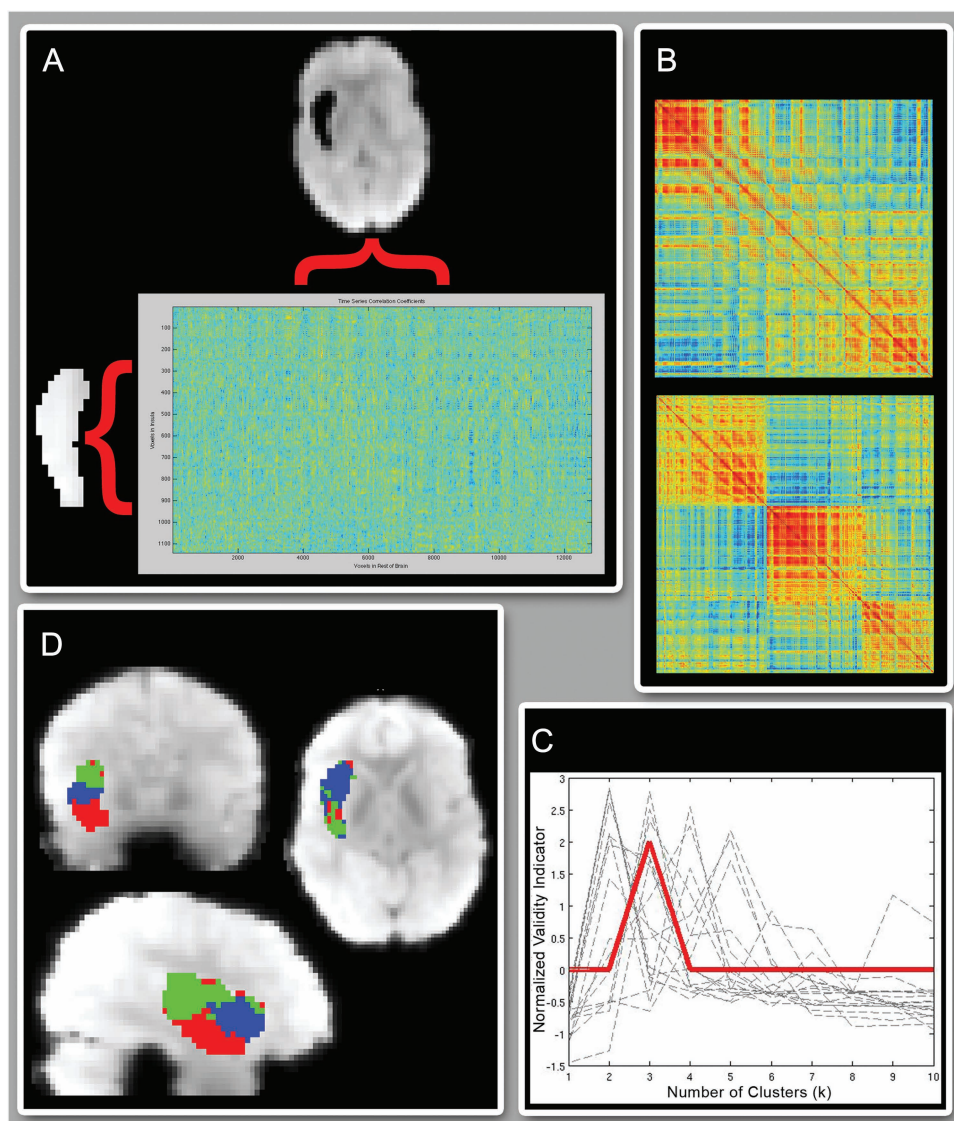


Figure 1. Functional parcellation method. Panel A depicts a high-resolution right insula ($2.5 \times 2.5 \times 3 \text{ mm}^3$) by low-resolution rest of brain matrix ($5 \times 5 \times 6 \text{ mm}^3$) of voxel-wise time series correlations. Panel B depicts 2 correlation matrices of voxels in the insula based on their pattern of connectivity with the rest of the brain. The upper matrix is the unordered matrix for one subject. The lower matrix is the same matrix ordered by the clustering algorithm. Panel C depicts the VI metric, which selects 3 as the optimal number of clusters (k). Panel D depicts the 3D spatial maps sorted by the results of the cluster analysis.

functional networks. The first network was associated with the ventroanterior portion and was functionally connected to primarily limbic areas including the amygdala, ventral tegmental area (VTA), superior temporal sulcus, and posterolateral orbitofrontal cortex. The second network was functionally connected to the dorsoanterior portion of the insula and included the anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC). The third network was functionally connected to the posterior insula and included the supplementary motor area (SMA) and somatosensory cortex. The 3 divisions of the insula and their associated functionally connected networks can be seen in Figure 3. These results are similar to those reported by Deen et al. (2011) but are more discriminated as a result of our multiple regression procedure.

Meta-Analytic Coactivation Networks

We were further interested in whether the networks we observed in our resting-state data were task specific or could

also be found in studies that manipulated cognitive states. We used the cluster centers identified in the parcellation analysis in a multiple logistic regression in order to identify networks that were independently coactivated across the 4400 studies in the Neurosynth database. This meta-analytic coactivation analysis (Robinson et al. 2010) identified similar networks found in the resting-state functional connectivity analysis. The ventroanterior cluster was coupled primarily to limbic regions including the bilateral amygdalae, ventral striatum, VTA, temporal poles, LOFC, and MPFC. The dorsoanterior cluster was coupled to bilateral DACC, DLPFC, dorsal striatum, and TPJ. Finally, the posterior region was connected to the SMA, posterior temporal lobes, somatosensory cortex, right hippocampus, and rostral ACC. We observed a strong spatial coherence between the resting-state parcellated networks and the meta-analytic coactivation networks with moderate to strong overlap in all 3 cases ($r = 0.36$, 0.51 , and $r = 0.48$ for ventroanterior, dorsoanterior, and posterior insula, respectively). The

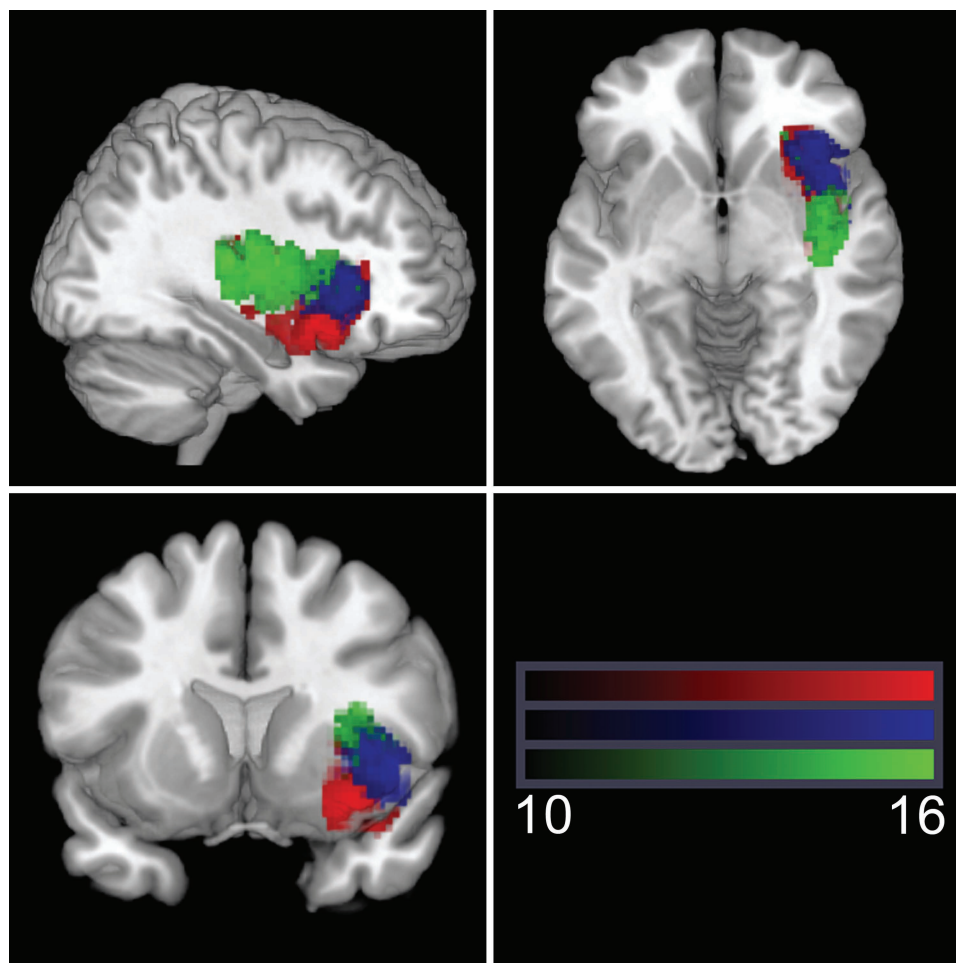


Figure 2. Results of the functional parcellation analysis. Figure 2 depicts the number of subjects loading on each cluster for each voxel in the insula.

convergence of these networks is particularly remarkable given that they were identified from very different levels of analysis. These results suggest that network connectivity is highly robust and relatively invariant to task.

Meta-Analytic Decoding of Network Function

Finally, we used the Neurosynth database to meta-analytically decode the psychological processes associated with each distinct insula network. To do this, we correlated each meta-analytic insula coactivation network with the forward and reverse inference meta-analysis maps for 200 distinct topics (We ran all the analyses initially on a subset of the database (~3000 studies) prior to the expansion of the database and found virtually identical results, which suggests that these findings are stable and will likely not dramatically change as new studies are added to the database.). Table 1 illustrates the 5 unique topics (and accompanying terms) most associated with each network that were present in both forward and reverse inference analyses and did not describe either a methodological technique or statistical analysis (e.g., BOLD, cluster, TMS, etc.). The full table of correlation values for the forward and reverse inference analyses for all 200 topics can be found on our website (http://www.u.arizona.edu/~ljchang/NewSite/papers/Changetal_InsulaTopicCorrelations.xls). The top 15 unique topics implied by each network maps that were not about methods can be seen in Figure 4.

A forward inference analysis, which tested for consistency of activation, revealed that the dorsoanterior insula network was more consistently activated than the ventroanterior and posterior networks for nearly all topics (Fig. 5). This finding replicates several recent studies demonstrating that the dorsoanterior insula and functionally connected regions such as the ACC tend to show substantially higher rates of activation than other regions in neuroimaging studies (Duncan and Owen 2000; Nelson et al. 2010; Yarkoni et al. 2011), which has lead some to conclude that the network is processing goal-directed cognition (Dosenbach et al. 2006; Yarkoni et al. 2009).

However, correlating each meta-analytic insula coactivation network with reverse inference meta-analysis maps—effectively decoding mental states from brain activation—revealed clear functional dissociations between insula networks (Fig. 5). The ventroanterior insular network was associated with topics related to emotion, chemosensation, and autonomic function; the dorsoanterior insular network was associated with topics related to higher cognitive tasks and executive control; and the posterior insular network was associated primarily with pain, sensorimotor, and language-related topics. Figure 5 displays the relative specificity of activation of each insular network across a number of relevant topics. These results extend previous conceptualizations of the insula that have used region of interest (ROI)-based meta-analyses (Wager and Feldman-Barrett 2004; Mutschler et al. 2009; Kurth, Zilles, et al. 2010).

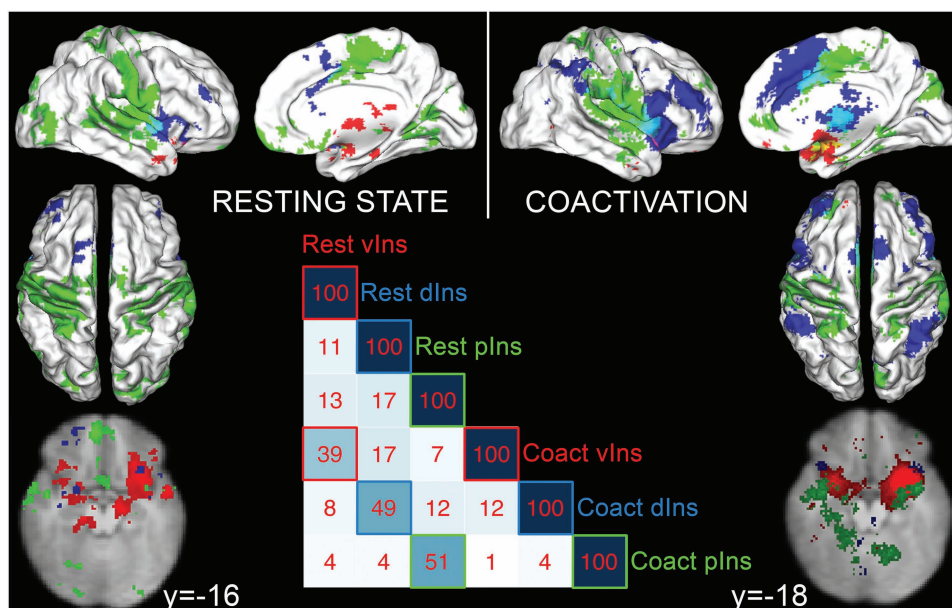


Figure 3. Positively connected functionally parcellated networks. Figure 3 depicts the brain networks that are functionally coupled to each insular subregion controlling for activity in other subregions. The resting-state analysis assesses functional connectivity using multilevel multiple regression. The coactivation analysis highlights networks that are coactive across studies in the Neurosynth database using multiple logistic regression. vlns (red) = networks connected to the ventroanterior region of the insula. dlns (blue) = networks connected to the dorsoanterior region of the insula. plns (green) = networks connected to the posterior insular region. Images are presented using neurological conventions (i.e., right = right). Both analyses are thresholded using whole brain cluster correction with an initial cluster threshold of $Z > 2.3$ for the resting state and $Z > 4.5$ for the coactivation and a Family Wise Error corrected threshold of $P < 0.05$. The correlation matrix reflects the spatial coherence of the networks using Pearson correlations multiplied by 100.

Discussion

While previous studies have begun to delineate the dissociable functional roles of different insula regions, the present study is the first to combine time series-based analyses of the insula with large-scale, data-driven meta-analysis of the extant neuroimaging literature. We demonstrated a marked convergence across time series and meta-analytic approaches and provided strong evidence for functional specificity in distinct insula networks. Importantly, our analyses were performed on a large, representative set of studies and terms, and thus provide relatively unbiased estimates of the functional specificity and consistency of activation in different insula regions. Our approach enabled us to not only functionally distinguish different regions within the insula but to quantitatively estimate the relative degree of functional specificity displayed by each region.

Functional Dissociations within the Insula

Our findings converge with prior cytoarchitectonic studies (Mesulam and Mufson 1982; Kurth, Zilles, et al. 2010), meta-analyses (Wager and Feldman-Barrett 2004; Mutschler et al. 2009; Kurth, Zilles, et al. 2010) and functional connectivity studies (Deen et al. 2011) in identifying 3 functionally distinct regions within the human insula. The dorsal/ventral distinction we observed in the anterior insula is consistent with that found by Nelson et al. (2010), which used an edge detection algorithm to find functional borders in the anterior insula based on patterns of resting-state connectivity. Our results diverge slightly from another parcellation study, which employed a very coarse resolution (only 10 insular ROIs compared with our 1252) and a priori fixed the number of clusters to 2 (Cauda et al. 2011). However, in their hierarchical clustering analysis, they also observed modest support for

a 3-cluster solution. Despite these technical differences, our results appear to be highly consistent with extant literature and suggest that the insula may be parcellated into at least 3 different regions.

The ventroanterior agranular insula appears to be involved in the processing of chemosensory information such as olfaction and gustation (Yaxley et al. 1990; Pritchard et al. 1999). In contrast, the posterior granular insula seems to be a multimodal convergence zone for sensory information and processes exteroceptive information (e.g., touch, temperature, and pain), interoceptive information (e.g., somatovisceral sensations) (Craig 2002, 2003), auditory information (Bamiou et al. 2003), and vestibular information (Guldin and Grusser 1998; Brandt and Dieterich 1999).

The convergence of multimodal sensory information and ability to readout subjective states (Craig 2009; Ullsperger et al. 2010) likely explains why the insula is intimately involved in affective processing (Damasio et al. 2000; Wager and Feldman-Barrett 2004). In particular, it has been associated with both the experience and observation (Wicker et al. 2003) of disgust to both taste and smell (Phillips et al. 1997), anticipatory anxiety (Phelps et al. 2001; Berns et al. 2006), feelings of anger (Damasio et al. 2000; Denson et al. 2009), guilt (Chang et al. 2011), and also moral violations (Sanfey et al. 2003). Affective processing is functionally important for detecting salient information and signaling the recruitment of additional attentional resources and cognitive control. Thus, the insula is also well suited to interface between physiological sensations and higher order cognitive systems and in accordance with this conceptualization has routinely been implicated in a variety of cognitive processes (Duncan and Owen 2000; Dosenbach et al. 2006; Eckert et al. 2009; Van Snellenberg and Wager 2009; Yarkoni et al. 2009). In fact, the insula has been demonstrated to be functionally connected with the anterior cingulate,

Table 1
Results of consistency and specificity analyses

Topic	ID #	N studies	FI ventral	FI dorsal	FI posterior	RI ventral	RI dorsal	RI posterior
Emotion Emotional neutral emotion valence arousal affective regulation cognitive negative processing emotions mood affect unpleasant emotionally responses pleasant reappraisal induction ratings aversive content arousing compared film behavioral sadness positive images lateral.	116	221	0.35	0.47	0.24	0.49	−0.17	0.03
Gustation Food foods hunger eating BMI calorie weight hungry satiety obese motivational reward satiated images caloric appetizing value factors intake energy taste individuals obesity eat cues meal consumption body lateral response.	23	36	0.41	0.23	0.09	0.44	−0.09	0.05
Face Facial neutral expressions emotional emotion fearful happy expression fear processing angry sad emotions anger recognition compared social perception disgust dynamic happiness information gender intensity role versus identity affect affective sadness.	103	167	0.36	0.34	0.17	0.44	−0.29	−0.07
Anxiety Anxiety threat avoidance trait fear activation aversive anxious response attachment threatening individuals scores STAI behavioral reactivity panic disorders responses approach individual behavior bias increased analyses levels temperament harm contrast sd.	39	69	0.38	0.48	0.25	0.43	−0.14	0.02
Olfaction Olfactory odor taste swallowing air odors pleasantness water intensity sensory stimulus odorants stimulation pleasant gustatory flavor primary oral odorant saliva activated sucrose concentration smell sweat smelling chemosensory perceived produced cm.	156	52	0.42	0.51	0.44	0.39	0.01	0.23
Switching Switch switching ocd repeat task rule stimulus set switches cost response informatively costs associated control pre preparation bivalent rules cfs behavioral cognitive relevant contrast rt cued type locked univalent positivity.	189	51	−0.08	0.63	0.06	−0.18	0.36	−0.16
Inhibition Inhibition response nogo inhibitory trials inhibit motor inhibited prepotent cognitive responses voluntary behavior inhibiting normal selection event pre suppression executive commission ms successful inhibitions preparation respond hypnosis stops errors decide.	152	67	0.00	0.68	0.18	−0.06	0.34	−0.01
Error processing Error errors correct monitoring incorrect response processing trials responses correction detection rates ern signal following rate likelihood corrected adjustments erroneous correctly conflict failure commission event performed pre behavior role button.	125	63	−0.02	0.69	0.14	−0.11	0.33	−0.12
Conflict Conflict response flanker incompatible ci simon cognitive meditation processing compatible conflicts based arrow monitoring stimulus compatibility analysis control resolution pre meditators direction selection ms types responses level error arrows associated.	51	48	−0.06	0.65	0.13	−0.18	0.28	−0.10
Feedback Feedback rule rules correct contrast performance activation based response following pre frn feedforward received estimation error probabilistic behavior subject incorrect tail trial violation sensitive informative loop guess lat directed reinforcement.	44	48	0.03	0.64	0.24	−0.02	0.25	0.09
Pain Pain intensity painful stimulation ratings stimulus noxious sensory nociceptive thermal rating unpleasantness heat processing perception temperature somatosensory affective chronic analgesia evoked threshold scale vas modulation perceived imaging experimental sensation mid.	64	180	0.14	0.68	0.55	0.14	0.32	0.51
Somatosensory Stimulation tactile somatosensory sensory touch activation ipsilateral activated finger stimulated electrical stimulus evoked study vibrotactile representation rest body primary somatotopic subject input secondary stimulations applied system information fingers activations leg.	86	126	0.05	0.57	0.55	−0.01	0.05	0.48
Sensorimotor Motor primary pre sensorimotor sensory execution simple movement somatosensory planning movements action output performed role performance proper bilaterally coordinates rest associated secondary behavior functional central network tasks changes performing multiple.	89	143	−0.04	0.58	0.37	−0.14	0.21	0.33
Music Music musical musicians vocal singing pitch ap melody melodies listening piano tonal pianists note non-musicians auditory melodic notes pieces excerpts playing compared professional instrument study perception tasks played improvisation integration.	151	54	0.03	0.43	0.42	−0.01	0.02	0.32
Auditory Auditory sounds sound processing noise ear db acoustic hearing primary temporal stimulation listening vocalizations scanner intensity activated silent heard headphones hz animal produced silence acquisition information perception amplitude binaural tones.	197	143	−0.06	0.47	0.32	−0.14	0.07	0.25

Notes: Terms associated with each topic from consistency and specificity analyses. All values reflect Pearson correlation coefficients. N studies = number of studies associated with each topic. FI = forward Inference, RI = reverse Inference.

amygdala, and VTA to form a “salience detection” network (Seeley et al. 2007) and appears to be integrally involved in switching between the executive control and default networks (Sridharan et al. 2008; Menon and Uddin 2010).

Our work addresses a number of limitations associated with previous functional connectivity (Cauda et al. 2011; Deen et al. 2011) and meta-analyses (Wager and Feldman-Barrett 2004; Mutschler et al. 2009; Kurth, Zilles, et al. 2010) studies. First, due to the very nature of the type of data (i.e., no manipulation of function), parcellation of resting-state connectivity patterns cannot directly link networks to a specific function. It is important to note this limitation because at least one previous study has suggested that the insula’s connectivity patterns may change as a function of the active cognitive state. For example, while the anterior insula is involved in both experiencing and imagining disgust, it appears to be differentially functionally coupled to networks associated with somatosensory or cognitive functions, respectively (Jabbi et al. 2008). Our results provide evidence countering this argument as we replicated the resting-state functional connectivity networks in our meta-analytic coactivation analysis of nearly 4400 neuroimaging studies. This suggests that rather than the insula changing

connectivity patterns based on cognitive state, it may be the degree of involvement of different insular subregions and (relatively conserved) associated networks that change depending on the function being probed.

Distinguishing Consistency from Specificity

Although previous studies have identified functional dissociations between different insula regions, our approach allowed us to expand on this work by separately quantifying both the specificity and the consistency of insula activation for different psychological processes. Forward inference analysis revealed that the dorsoanterior insula network was more consistently activated than the ventroanterior and posterior networks for nearly all topics. This finding is in accord with recent work demonstrating that the dorsoanterior insula and ACC tend to show substantially higher rates of activation than other regions in neuroimaging studies (Duncan and Owen 2000; Nelson et al. 2010; Yarkoni et al. 2011), which has lead some to conclude that the network is nonspecifically involved in general goal-directed cognition (Dosenbach et al. 2006; Yarkoni et al. 2009). However, our reverse inference/decoding analysis revealed

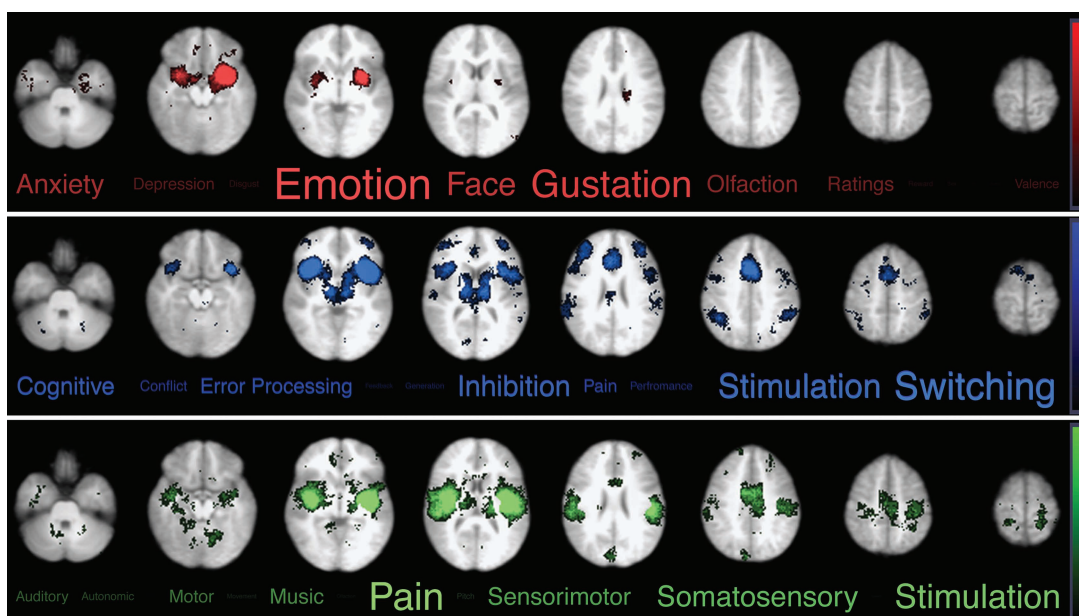


Figure 4. Functional rankings of coactivation maps. Figure 4 depicts the results of the decoding analysis. The top 15 topics from the reverse inference analysis that were associated with each Meta-Analytic Functional Coactivation Analysis network map. Red = network associated with ventroanterior insula. Blue = network coupled with dorsoanterior insula. Green = network connected to posterior insula. Images are presented in neurological orientation and thresholded using whole brain cluster correction with an initial cluster threshold of $Z > 4.5$ and a Family Wise Error corrected threshold of $P < 0.05$ size and transparency of word clouds reflect rank-ordered correlation coefficients exponentiated to the 2nd power, which emphasizes terms that are most associated with each network (Poldrack et al. 2009).

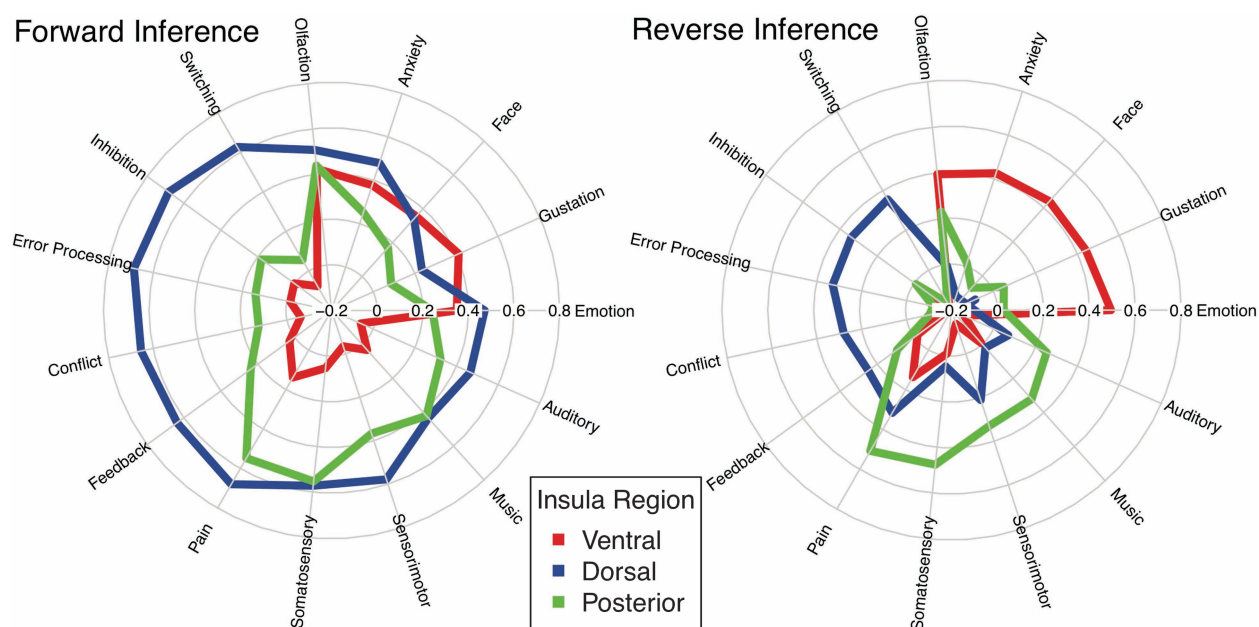


Figure 5. Consistency and specificity of functions associated with meta-analytic coactivation of parcellated insular networks. The correlation values for the top 5 topics for each cluster using forward and reverse inference. Topics were selected if they were present in both forward and reverse inference analyses and represented nonmethod terms.

a marked degree of functional specificity for all 3 insula networks. The ventroanterior insular network was associated with topics related to emotion, chemosensation, and autonomic function; the dorsoanterior insular network was associated with topics related to higher cognitive tasks and executive control; and the posterior insular network was associated primarily with pain, sensorimotor, and language-related topics.

The fact that the dorsoanterior network is reliably activated by a broad range of goal-directed tasks despite showing considerable specificity in our decoding analysis suggests that while the higher cognitive functions supported by this network may be relatively circumscribed, those functions are probably a prerequisite for many different forms of goal-directed cognition. Put differently, many different kinds of tasks—for example, attending to sensory stimuli, viewing emotional

pictures, etc.—are likely to require the capacity to sustain attention, monitor goals, and modulate arousal level (Dosenbach et al. 2006; Nelson et al. 2010). But this does not imply that the role of dorsoanterior insula is to attend to sensory stimuli or process emotion. Thus, our findings underscore the importance of distinguishing between consistency and specificity of activation and provide additional support to extant hypothesis-driven and ROI-based meta-analytic work (Wager and Feldman-Barrett 2004; Mutschler et al. 2009; Kurth, Zilles, et al. 2010).

Limitations

While we believe our findings provide an important step in using data-driven approaches to infer the functional neuroanatomy of the insula and identify likely associated cognitive functions based on network connectivity, there are a number of important caveats in interpreting these results (for extended discussion, see Yarkoni et al. 2011). First, our automated methods assume that frequently occurring terms in an article will accurately reflect the cognitive processes reflected in brain findings presented in the accompanying tables. At present, the software does not take into account methodological details that might impact the findings (e.g., stereotactic space, direction of contrast, type of paradigm, etc.). However, it is important to note that these potential problems should primarily result in random variation and thereby not reflect any systematic bias. In other words, these potential shortcomings will only make it more difficult to find significant results and should not systemically influence the results it does detect. In addition, random fluctuations will theoretically be minimized as the number of studies in the database increases in size.

Second, this approach is effective primarily for relatively coarse cognitive processes that can be adequately captured by broad terms (e.g., emotion); it currently has little ability to capture more nuanced distinctions (e.g., disgust vs. fear). Despite this limitation, the automated Neurosynth software has been highly successful at replicating findings using manually coded methods and decoding broad cognitive states in individual human subjects (Yarkoni et al. 2011), and we are currently working to improve specificity via alternative coding and modeling approaches (e.g., Poldrack et al. 2011).

Finally, the Neurosynth software cannot account for confirmation bias present in the literature. For example, the fact that people routinely associate amygdala activation with emotion (and hence are more likely to publish this association) will increase the likelihood that the software will determine that amygdala activity implies an emotional state. This is an important limitation, as it presently constrains the promise of a fully automated and completely unbiased analytical approach. However, this problem is also present in every other method not excluding our own inherent assessments. The benefit of our approach is that it minimizes the potential of introducing further biases at various stages of analysis.

Conclusions

Combining resting-state connectivity—based parcellation of the insula with large-scale meta-analysis, this study applied a relatively unbiased data-driven approach to understand how the insula is anatomically organized based on functional connectivity patterns and the consistency and specificity of

associated cognitive functions. Our findings support a tripartite subdivision of the insula, with dorsoanterior, ventroanterior, and posterior regions broadly mapping onto cognitive, affective-chemosensory, and sensorimotor processing, respectively. We also find evidence that different tasks elicit differential engagement of relatively conserved insula networks rather than altering large-scale connectivity patterns with insula subregions. Finally, we find that while the dorsoanterior insula is more consistently involved in human cognition than ventroanterior and posterior networks, each parcellated network is specifically associated with a distinct function. Collectively, this work suggests that the insula is instrumental in integrating disparate functional systems involved in processing affect, sensory-motor processing, and general cognition and is well suited to provide an interface between feelings, cognition, and action.

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