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## Beyond the tripartite cognition-emotion-interoception model of the human insular cortex

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### Abstract

Functional MRI studies report insular activations across a wide range of tasks involving affective, sensory, and motor processing, but also during tasks of high-level perception, attention, and control. While insular cortical activations are often reported in the literature, the diverse functional roles of this region are still not well understood. We used a meta-analytic approach to analyze the coactivation profiles of insular subdivisions -- dorsal anterior, ventral anterior, and posterior insula -- across fMRI studies in terms of multiple task domains including emotion, memory, attention, and reasoning. We found extensive coactivation of each insular subdivision, with substantial overlap between coactivation partners for each subdivision. Functional fingerprint analyses revealed that all subdivisions cooperated with a functionally diverse set of regions. Graph-theoretic analyses revealed that the dorsal anterior insula was a highly “central” structure in the coactivation network. Furthermore, analysis of the studies that activate the insular cortex itself showed that the right dorsal anterior insula was a particularly “diverse” structure in that it was likely to be active across multiple task domains. These results highlight the nuanced functional profiles of insular subdivisions and are consistent with recent work suggesting that the dorsal anterior insula can be considered a critical functional hub in the human brain.

### Keywords

anterior insula; brain network; functional connectivity; coactivation meta-analysis; graph theory

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## Introduction

The insular cortex is a functionally heterogeneous brain region that has been characterized by its involvement in somatic and visceral sensory processes, autonomic regulation, as well as motor processing (Augustine, 1985, 1996). Earlier views of the insula as primarily a low-level, “limbic” structure have given way to more complex and multifaceted views of insular function in recent years. In concert, it has been suggested that the anterior portion of the human insula may not have an equivalent in the rat or monkey brain ((Bud Craig, 2009), but see (Nieuwenhuys, 2012) for alternate views). Furthermore, citing evidence for substantial variability with respect to extent, shape, gyral and sulcal patterns, and laminar organization of insular cortex, a recent study across several species suggests “it is not possible to identify a general model of organization for the mammalian insular cortex” (Butti & Hof, 2010), although earlier comparative anatomical work suggests substantial overlap between the human insula and that of other hominoids (see (Nieuwenhuys, 2012) for review). These controversies regarding anatomical organization have made *functional* characterization of the insula in the human brain all the more challenging.

Recent critical thinking regarding insula function in humans has focused on its role in the experience of emotion derived from information about bodily states (Critchley, Mathias, & Dolan, 2001), in line with earlier theories suggesting that signals from the autonomic nervous system shape emotional experience (Damasio, 1996). Functional neuroimaging studies have shown that the right anterior insula (AI) in particular is active during a wide variety of tasks involving interoception and the subjective awareness of both positive and negative feelings, including anger, disgust, judgments of trustworthiness, and sexual arousal (see (Craig, 2002) for review). The AI is also involved in empathy, or the “capacity to understand emotions of others by sharing their affective states” (Singer, 2006). While the posterior insula has been shown to be activated when subjects receive painful stimulation, AI activates both during pain perception and during witnessing a loved one experiencing pain, suggesting that AI activation contributes to the experience that is linked to the understanding of the feelings of others (empathy) and ourselves (Singer et al., 2004). A study using alexithymia and empathy scales to assess emotional awareness of the self and others, respectively, reported that difficulties in emotional awareness were related to hypoactivity in the AI of both autistic individuals and controls (Silani et al., 2008). Taken together, these studies reveal a role for the AI in social and affective processes involving perception and integration of information from multiple sources.

In addition to the well-documented involvement of the AI in affective processing, reports of AI involvement in cognition are emerging. In a recent special issue of the journal *Brain Structure and Function*, the functional roles ascribed to the human AI ranged from salience detection (Menon & Uddin, 2010) to attentional control (Nelson et al., 2010), risk prediction (Bossaerts, 2010), and subjective awareness or consciousness (Craig, 2010). Partly because of the region’s participation in multiple cognitive tasks, it has recently been argued that the AI is a key node in a large-scale brain network including the anterior cingulate cortex (Seeley et al., 2007). This “salience network” is thought to detect salient events and initiate switches between networks involved in self-related, internally-oriented processing and those involved in goal-directed, externally-oriented processing (Menon & Uddin, 2010; Sridharan,

Levitin, & Menon, 2008; Uddin & Menon, 2009). It has been proposed that the AI can be considered a “causal outflow hub” due to its role in coordinating other large-scale brain networks (Uddin, Supekar, Ryali, & Menon, 2011).

One strategy to understanding the functional role of a brain region is to focus on its *functional connectivity*. Recent reports have taken advantage of the existence of large databases of functional neuroimaging studies (<http://www.brainmap.org/> and <http://neurosynth.org/>) to perform coactivation meta-analyses of the human insula. These studies operationalize functional connectivity in terms of the tendency for different brain regions to be *simultaneously* active across experiments (Anderson, Brumbaugh, & Suben, 2010; Toro, Fox, & Paus, 2008). A recent coactivation meta-analysis of insular subdivisions suggests that the dorsal anterior subdivision is more involved in high-level cognitive processes (e.g., switching, inhibition, and error processing), the ventral anterior with affective processes (e.g., emotion and anxiety), and the posterior with sensorimotor processes (e.g., pain) (Chang, Yarkoni, Khaw, & Sanfey, 2012). Indeed, both resting-state functional connectivity (Deen, Pitskel, & Pelphrey, 2010) and task-based meta-analytic approaches are beginning to converge on the finding that the AI can be subdivided into dorsal and ventral (Chang et al., 2012; Kelly et al., 2012; Kurth, Zilles, Fox, Laird, & Eickhoff, 2010) as well as anterior and posterior (Cauda et al., 2012) subregions.

The parcellation suggested by these investigations has shed light on the multifaceted nature of insular function. However, several open questions remain regarding the resulting tripartite framework of the anterior insula: a cognitive dorsal AI, an affective ventral AI, and a sensory posterior insula. In particular, the putative distinction between a dorsal “cognitive” subdivision and a ventral “affective” subdivision is potentially problematic given that a general cognitive/affective dichotomy has become increasingly challenged (Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012; Pessoa, 2008). Furthermore, the cognitive/affective distinction proposed for dorsal and ventral AI is not always clearly observed. One of the first meta-analyses investigating insular function provided evidence that the dorsal AI is involved in all task domains examined, with the exception of somatosensation and motion, raising the possibility that this region may play a basic functional integrative role common to multiple tasks (Kurth et al., 2010). A recent study examining intrinsic functional connectivity of the dorsal and ventral AI found that although the regions exhibit distinct patterns of connectivity consistent with purported cognitive and affective functions, the two regions share connectivity with portions of orbitofrontal cortex, frontal operculum, anterior cingulate cortex, and ventral putamen (Touroutoglou, Hollenbeck, Dickerson, & Feldman Barrett, 2012). Thus, several open questions with regards to the functions of putative insular subdivisions remain unresolved.

To quantitatively capture and assess the functional complexity of the insula, we adopted and extended the notion of a *functional fingerprint*: the observed activity or response properties of a region under various task conditions (Passingham, Stephan, & Kotter, 2002). We leverage large amounts of publicly available neuroimaging data to perform a coactivation meta-analysis of the three functional subregions of the human insula. This allowed us to characterize the functional fingerprint of insular subdivisions, as well as the fingerprint of their coactivation *partners* i.e., “target” regions). The determination of functional

fingerprints allowed us to also assess functional *diversity*. A brain region with high diversity is engaged by tasks in multiple task domains, whereas a low diversity region is more specialized, being engaged by tasks in fewer domains (Anderson & Penner-Wilger, 2012; Anderson & Pessoa, 2011). Finally, we computed graph-theoretical metrics of *centrality* that index the relative influence of each insular subdivision in the brain coactivation network. Combined, our approach allowed us to unravel both commonalities and differences of putative insular subregions. In particular, previous studies have not characterized the degree of functional differentiation and functional overlap of insular coactivation patterns. Understanding the broad, diverse set of brain regions with which the insula interacts during task performance is critical to building models of insular function in the healthy brain, and can potentially provide insights into disorders resulting from insular dysfunction.

## Materials and Methods

### Insular subdivisions

The general methodology for performing coactivation analyses is discussed in detail in previous publications (see (Anderson et al., 2010; Toro et al., 2008). The three main steps are as follows. 1) Choose a scheme for spatial subdivision of the brain; 2) Assign experimental activations to the subdivisions; 3) Determine which regions are statistically likely to be active at the same time (active during the same brain imaging experiments).

The insular cortex was defined using maps provided by Deen and colleagues (Deen et al., 2010), who subdivide the insula into three functional regions based on a clustering analysis of resting-state functional connectivity of the whole insula (Figure 1). Mean coordinates of these insular subdivisions are shown in Table 1. Note that while Deen et al. label the posterior-most subdivision as “posterior insula”, this subdivision also includes portions of mid-insula regions that have been described as functionally distinct in previous meta-analyses (Kurth et al., 2010)

### fMRI Databases

Task-based coactivation was determined using a collection of neuroimaging studies obtained from the Neurosynth database (Yarkoni, Poldrack, Nichols, Van Essen, & Wager, 2011). At the time of access (Jan 1, 2012), Neurosynth contained 144,680 activation peaks from 4,393 studies. Neurosynth does not categorize studies by domain or task, and articles are included in the database regardless of the type of task used or function investigated. We investigated coactivation using both a voxel-wise “searchlight” approach, as well as a region-of-interest (ROI)-based approach. For voxel-wise analysis, a given voxel was considered active during an experiment if an activation peak was reported within 10mm of its location. When ROIs were considered, a given ROI was considered active during an experiment only if an activation peak fell directly in that ROI.

To gauge the reproducibility of our results, we employed an index commonly utilized in the literature (Raemaekers et al.):

$$R_{\text{overlap}} = \frac{2V_{\text{overlap}}}{V_1 + V_2}$$

where  $V_1$  and  $V_2$  are the number of voxels significantly active in each half and  $V_{\text{overlap}}$  is the number of voxels significantly active in both halves. The ratio can thus vary between 1 (perfect reproducibility) and 0 (no reproducibility). Here, we split our dataset into two random halves. For the analysis shown in Figure 4,  $R_{\text{overlap}}$  values for all 6 insula subdivisions (3 per hemisphere) ranged from .52 to .61. These values are comparable, for instance, to those observed for test-retest  $R_{\text{overlap}}$  values of the posterior cingulate cortex – a key node of the default mode network – identified using independent component analysis of resting state fMRI data, which one study reported between .49 and .59 (Meindl et al.). Comparable results were also observed for motor-related activation (Kristo et al.).

For the investigation of functional fingerprints and diversity, we analyzed studies from the BrainMap database (Laird, Lancaster, & Fox, 2005). As there are no widely accepted ontologies of mental processes (Price & Friston, 2005; Yarkoni, Poldrack, Van Essen, & Wager, 2010), we employed the BrainMap taxonomy, which has undergone considerable refinement in the past decade (Fox et al., 2005; Fox & Lancaster, 2002; Laird, Lancaster, & Fox, 2009). Thirty-two task domains were considered, spanning perception, action, cognition, and emotion, an approach similar to that employed in recent studies (Laird, Eickhoff, et al.; Smith et al., 2009). All studies considered involved healthy adults and used a within-subjects, whole-brain, univariate design. That is, for all the studies in the dataset, brain activity during an experimental task was observed over the whole brain and compared voxel-wise to activity observed in the same participant during a control task. Here, we use the term “observation” to refer to the pairing of a reported activation and a task domain. For example, for an experiment filed in the database under both the “working memory” and “vision” domains (due to the task manipulation), each reported activation would count as two observations (one per domain) at its activation site.

### Functional fingerprint and diversity analyses

A *functional fingerprint* was defined as a 32-dimensional vector, each dimension corresponding to a task domain from the Brainmap database. Each of the 32 values represented the proportion of observations in the corresponding task domain (local number of observations divided by global number of observations), normalized (i.e., all 32 values summed to 1) (Figure 2). We computed functional fingerprints of the coactivation partners of each insular subdivision, as well as a “common” fingerprint consisting of the average of all insular subdivisions. Specifically, we constructed fingerprints by considering task domains observed in the “*target*” voxels coactivating with each insula subdivision. Task coactivation was determined between each insula subdivision and all other voxels in the brain. To determine a measure of coactivation that described the relationships of each insula region separate from the rest, partial Pearson correlations were computed that included the influence of the other five insula regions. Correction for multiple comparisons used false discovery rate (FDR) correction (Benjamini, Drai, Elmer, Kafkafi, & Golani, 2001), such

that correlations that did not survive ( $q = 0.05$ ) were set to zero. In addition, negative correlations were set to zero.

For each insular subdivision, a fingerprint was formed by pooling all observations falling within the set of significantly correlated voxels (as if they comprised a single "target area"). The pooling procedure was weighted such that the contribution of a voxel's observations was based on the partial correlation value. The weighting procedure involved a simple multiplication before pooling the observations. Thus, for instance, a voxel with a partial correlation of 1.0 would contribute as normal, while a voxel with a partial correlation of 0.5 would have its observations halved prior to summing (Figure 3A).

There are many measures of diversity in the literature, particularly in biology and economics (e.g., Magurran, 2004). Here, the Shannon diversity,  $H$  (Shannon, 1948), of a region of insula was defined as:

$$H = - \sum_{i=1}^S p_i \ln p_i$$

where  $S = 32$  was the number of task domains investigated and  $p_i$  corresponded to the  $i^{\text{th}}$  domain proportion. As Shannon diversity is negatively biased (i.e., it tends to underestimate diversity), as proposed by Chao and Shen (2003), we used the correction term  $S-1/(2n)$  added to  $H$ , where  $n$  is the number of observations used in the determination of the fingerprint. This correction is suggested if  $n > S$ ; however, the number of observations for each insula subdivision varied considerably, and some were under 32. Thus, we report relative diversity values (percentiles) for insula as a whole and for the subdivisions with sufficient observations to allow a reliable estimate to be made. Note that the lower bound on the number of observations is based on statistical considerations, and does not imply that each subdivision must be active in each of the 32 domains. The 32+ observed activations could be in a single or in several different domains.

### Region-of-interest generation

ROIs were automatically generated using a spatially constrained clustering algorithm (Craddock, James, Holtzheimer, Hu, & Mayberg, 2012). This method calculated voxel-wise correlations among neighboring voxels, while ignoring long-distance correlations, to produce a set of spatially contiguous ROIs. In the present case, we applied the algorithm to voxel-wise task-based coactivation values. The process requires that one specify a target number  $k$  of ROIs to produce. The main results presented come from an analysis using  $k=160$ . To reduce "cross-contamination" between ROIs, or activations on the boundaries that could be assigned to either ROI, we eroded the boundaries of each ROI by  $e$  mm; thus the ROIs we investigated were physically isolated from one another.

To ensure that our results were not specific to the parameter choices, we explored other settings in addition to those reported here. For  $k$ , results were stable between  $k=120$  and 200. For  $e$ , results were stable for erosions between 2 and 5 mm. Overall, the results were relatively insensitive to the settings as long as the resulting ROIs were "reasonably sized".



Briefly, on the one hand, large enough to receive enough “hits” from studies; on the other hand, small enough to ensure proper “granularity” (e.g., very large ROIs would be functionally diverse simply due to their large size).

Subsequently, the six insular ROIs were added to the set generated via clustering, replacing any of these with which it overlapped. The hemisphere of each ROI was determined according to its center of mass. Finally, we only retained ROIs that contained a sufficient number of observations (32; see above) to allow proper estimation of coactivation and functional diversity. Hence, ROIs in the posterior part of the brain were not included, resulting in a total of 97 ROIs in the network analysis (Figure S1).

## Network analyses

Although network analysis of neuroimaging data can be performed on a voxel-wise manner, it is more commonly performed (and more stable) at the ROI level. Here, a graph was formed that comprised the ROIs described in the previous section. For each ROI, “activity” was observed in the region if a reported location of task peak activation fell within the region. Studies from the NeuroSynth database were considered. We then performed a pair-wise ROI-to-ROI quantification of “activity” correlation, which captured the tendency of region pairs to be active during the same experimental task. Specifically, coactivation was defined as the Pearson’s correlation of the “activation” histories. As before, we applied FDR correction and removed negative correlations. Note that partial correlations were not employed in the network analysis because the goal here was to understand the properties of insular subregions in the context of all other ROIs (Figure 3B).

We analyzed the resulting coactivation graph both as a binary and, separately, as a weighted structure. A binary undirected graph was constructed such that edges only existed between ROIs with statistically significant correlations. A weighted undirected graph was constructed from the binary graph by assigning correlation coefficients between ROIs as edge weights (Sporns, 2011). Nodes of a binary graph are primarily characterized by their *degree* (the number of other nodes they are connected to). The degree of a node is one way to measure its *centrality* in a graph, but there are other interesting measures, too. For instance, *betweenness centrality* evaluates the paths through the graph that a given node lies along, and provides an indication of node importance to the overall information flow through a network. Similarly, node *strength* is an estimate of the importance of a node in a weighted graph based on the sum of weights of all its connections (Barrat, Barthelemy, Pastor-Satorras, & Vespignani, 2004). To compute degree, betweenness centrality, and strength, we used the Connectivity Toolbox (Rubinov & Sporns, 2010; Sporns, 2002).

## Results

### Coactivation maps and functional fingerprints

Task-based coactivation analysis was conducted to capture the tendency of insular subdivisions to be active together with other brain areas during the same experimental task. Each of the six insular subdivisions served as a seed region (Table 1) and coactivation was determined by moving a searchlight across the brain in a voxel-wise manner (in order to

account for the influence of the other five insular subdivisions, partial correlations were computed). For each insular subregion, extensive coactivation was observed (Figure 4). Furthermore, coactivation overlap was extensive (Figures 5 and 6).

Next, we determined the functional fingerprint of the coactivating partners of each insular subdivision. For example, for the left dorsal AI, we considered “activations” in all voxels shown in Figure 4 (top, left), as if they were a single “region”. Figure 7 displays the “common” fingerprint for the insular subdivisions. To obtain it, we first computed six fingerprints (one for each subregion; not shown) and took the minimum value for each task domain (to show that each subregion was engaged “at least that much”). The common fingerprint was functionally diverse and encompassed all 32 task domains probed. Furthermore, to understand what each insular subdivision expressed to a greater extent relative to their mean, we also determined profiles for each insular subregion by first subtracting a “mean fingerprint” (not shown). Figure 8 shows that functional differentiation is also evident in insular territories.

### Network analysis

To further characterize the coactivation structure of insular subregions, we performed a graph-theoretic analysis. In particular, given recent suggestions that the anterior insula is an important hub governing information flow, we reasoned that patterns of coactivation involving the insula would also reflect those properties. To perform network analysis, the brain was subdivided into ROIs based on local clusters of coactivating voxels. In addition, the insular subregions were added to the set of ROIs considered. The final set of ROIs comprised those regions with sufficient observations and was used as the set of nodes for graph-theoretic analysis (Figure S1). Table 2 lists the six insular subregions examined in terms of percentiles. *Degree* is the number of connections of a node in a graph (in this case significant coactivation links between ROIs). Notably, the values for the dorsal anterior insula were very high, especially on the left hemisphere. Degree does not consider edge weight, so it is notable that differences between left and right hemispheres were observed for node *strength*, too. Strength percentile was determined relative to an ROI’s hemisphere because the actual values for the right hemisphere were relatively low when all ROIs were considered; yet, percentiles within the right hemisphere were high for dorsal AI, especially. *Betweenness centrality* attempts to capture a node’s influence to the “flow” of signals in a graph. Betweenness centrality was highest for the left dorsal anterior insula.

Finally, we determined the functional diversity across ROIs so as to compare them to that of insular subregions. Diversity reflects the range of tasks that a region is engaged by and was computed for the entire insular cortex as well as for its subdivisions with enough observations to compute the measure. In previous work, we have described functional diversity values across ROIs spanning the entire brain (M. L. Anderson, Kinnison, & Pessoa, 2013). Here, considering the entire left and right insulas separately (in each case, combining the subregions), we found that they were more diverse than 86% and 100% of non-insula ROIs, respectively. The left and right dorsal anterior insula subregions were more diverse than 77% and 89% of non-insula ROIs, respectively.



## Discussion

Investigating the insula is a challenge for various reasons, including its functional complexity and uncertainty regarding its internal structural organization. We addressed these challenges by adopting the concept of a functional fingerprint, which allows one to qualitatively describe a region's functional repertoire, as well as quantify the associated functional complexity. We took advantage of recent work reporting a tripartite parcellation of the insula (Deen et al., 2010), which allowed us to characterize the potential functional differentiation of insular subdivisions and more thoroughly investigate their roles relative to other ROIs in the brain.

The seemingly ubiquitous nature of insular cortical activation can in part be explained by taking into account functional heterogeneity within this region, as has been demonstrated by recent resting-state functional connectivity (Deen et al., 2010; Taylor, Seminowicz, & Davis, 2009) and meta-analytic analyses (Cauda et al., 2012; Chang et al., 2012; Kelly et al., 2012; Kurth et al., 2010). However, several questions with regards to the functional repertoire of insular subdivisions, as well as their network properties, remain unanswered. In particular, it has not been investigated whether purported subdivisions of the insular cortex demonstrate truly unique coactivation patterns. In the present study, we conducted meta-analytic coactivation, functional fingerprint, diversity, and graph theoretical analyses to address open questions about insular organization and provide further insight into this increasingly popular brain region (Behrens, Fox, Laird, & Smith, 2012).

Analysis of functional task coactivation revealed that insular subregions are engaged by a broad set of neural partners. On the lateral surface, the posterior insula coactivated with regions surrounding the lateral fissure, extending superiorly to somatomotor regions in the vicinity of the central sulcus. Notably, little or no coactivity was observed with dorsolateral prefrontal cortex (PFC) or related areas in superior parietal cortex. On the medial surface, coactivation was quite extensive, especially for the left hemisphere. For the ventral AI, coactivation with inferior frontal regions extending into the orbitofrontal cortex, as well as the anterior temporal lobe, was evident. Finally, turning to the dorsal AI, coactivation with lateral PFC regions, superior parietal cortex, and midcingulate gyrus were conspicuous. In broad strokes, the coactivation results are in agreement with the findings from resting-state connectivity (Deen et al., 2010), and indicate a more “cognitive” dorsal AI, a more “emotional” ventral AI, and a “somatomotor” posterior insula – see also (Chang et al., 2012; Deen et al., 2010; Kelly et al., 2012; Kurth et al., 2010; Taylor et al., 2009). Yet, this is an oversimplification, as the intersection results of Figure 5 illustrate. Many of the regions highlighted above were robustly coactive with *at least* two of the three insular subdivisions. Notably, overlap between all three insular subregions was also identified across multiple brain sites, including both cortical (e.g., anterior cingulate cortex, left temporo-parietal junction) and subcortical (e.g., thalamus) areas. Notably, these regions of overlap resemble the “salience network” which is involved generally in identifying relevant internal and external stimuli (Seeley et al., 2007). From this vantage point, the tripartite scheme previously proposed for the functional organization of the insula breaks down. In all, a more complete characterization of the insula requires acknowledging the observed overlap, at least when task coactivation is considered.

The functional fingerprint analysis painted a similar picture. When differences from the mean profile are highlighted, it is possible to describe the dorsal AI as more “cognitive” and the ventral AI as more “emotional”, for instance. But that characterization misses the strong functional overlap that is unveiled by the “common” fingerprint. Thus, the neural partners of insular subregions were active at least some of the time in all of the task domains investigated. Intriguingly, even the profiles with the average removed revealed important similarities between the ventral AI and the posterior insula – both of which were quite *dissimilar* from the dorsal AI. Thus, while previous reverse inference mappings have focused on functional dissociations within the insula (Chang et al., 2012), our fine-grained analyses, which included a more detailed task domain structure, suggest a more complex and nuanced picture of the functionality of insular territories.

The left and right dorsal AI displayed high functional diversity relative to noninsula brain regions. This finding is consistent with a recent meta-analysis reporting more widespread participation of the anterior than posterior insula across task domains (Cauda et al., 2012). Furthermore, here, betweenness centrality and node strength measures were highest for AI subregions (within their hemisphere) compared to the other insular subdivisions. High betweenness centrality is suggestive of node importance to overall information flow through a graph. The current findings suggest that the dorsal AI may function as an important node for integrating information across multiple brain networks. This is consistent with recent work pointing to a central role for the dorsal AI in influencing switches between the central-executive network and the default-mode network (Sridharan et al., 2008; Uddin et al., 2011), as well as previous work identifying the AI as a key cognitive control region (Cole & Schneider, 2007; Dosenbach et al., 2007; Levy & Wagner, 2011). The AI is thought to be part of a larger “salience network” comprised of this region along with dorsal anterior cingulate cortex (Seeley et al., 2007). A proposed function of this network is to detect salient events in the environment and initiate appropriate control signals (Menon & Uddin, 2010). The current findings add further support to recently proposed theories positing a unique role for the AI and the salience network in orchestrating access to attention and control systems (Menon & Uddin, 2010). They also align with emerging conceptualizations of large-scale brain networks that support domain-general functions across a range of emotional, social, and cognitive tasks (Barrett & Satpute, 2013).

More broadly, the findings highlight the need to carefully re-think our approach to function-structure mapping in the brain. There has been increasing awareness of the inadequacy of single task-based functional attributions to individual brain regions (Anderson, 2010; Anderson et al., 2013; Barrett & Satpute, 2013; Poldrack, 2006, 2010). The current work further cements the need to take account of three fundamental features of the functional organization of the brain: (1) the functional *diversity* of individual regions of the brain; (2) the functional *differentiation* of individual regions of the brain; and (3) the frequent functional *overlap* between different brain networks. Nodes in brain networks are active across a range of tasks in different domains, participate in multiple networks, and yet remain functionally distinguishable. How should function-structure mapping be understood in a way that is sensitive to all of these facts?

One common theme in work addressing this question has been a call for a reform of the cognitive ontology, the concepts we use to organize and differentiate between psychological tasks (Anderson, 2010; Barrett & Satpute, 2013; Lindquist et al., 2012; Pessoa, 2008; Poldrack, 2010; Poldrack, Halchenko, & Hanson, 2009). Some have suggested that a cognitive ontology better suited to the neurosciences will reveal a set of primitive operations (or processes) that selectively engage individual nodes and networks (Poldrack, 2010). Others (Anderson et al., 2013; Anderson, Richardson, & Chemero, 2012; Barrett & Satpute, 2013; Lindquist et al., 2012; Pessoa, 2013) have expressed doubts that this will prove possible. One intriguing possibility that would appear to respect the three organizational features of the brain emphasized above is that analysis of the multi-dimensional functional fingerprints of brain regions and networks will reveal a set of primitive psychological factors, or “ingredients”, that capture the underlying functional contributions of regions and networks to overall behavior (Barrett & Satpute, 2013; Gold, Havasi, Anderson, & Arnold, 2011; Lindquist et al., 2012; Poldrack, 2010; Poldrack et al., 2009). According to this perspective, psychological states like anger and fear, as well as processes like attention and cognitive control, would involve different mixtures of many of the same domain-general ingredients. It is expected that more than one brain region will likely be involved in implementing or contributing each of those psychological ingredients to a given state or process, and each brain region will have a role in generating or contributing more than one ingredient. That is, brain regions and networks will differ in their loadings on this set of primitive psychological factors (but see (Pessoa, 2012)).

In the current case, such an approach could lead to the identification of the set of functional factors that characterize insula function - both the common contributions offered by the insula subdivisions, as well as the contributions that differentiate them. Whether or not each subdivision of the insula makes a single, domain-general functional contribution—that is, loads on a single psychological factor or several—remains to be investigated, although the diversity of their functional partnerships and fingerprints might seem to favor the latter possibility. For instance, the overlap between some nodes of the anterior insula network and nodes in the so-called salience network might be taken to indicate their common contribution to one of the fundamental ingredients of attentional control. At the same time, the contribution of the insula to a variety of emotional states, on the one hand, as well as to abstract domains like mathematics, on the other, might hint at a repertoire of capacities broader than a single function or ingredient.

## Conclusions

We conducted an fMRI task coactivation meta-analysis to examine functional and connectional properties of the human insular cortex. In broad strokes, our findings agree with recent studies suggesting a functional differentiation within this cortical region. Yet, at a finer level of analysis, our findings question the legitimacy of a simple tripartite scheme. For example, *both* dorsal and ventral AI share coactivation partners with dorsolateral PFC, a region that is often described as “cognitive”. This was the case even though our procedure determined coactivation via partial correlation in order to account for the presence of all insular subdivisions. Our network analysis indicates the potential of the dorsal AI to be an influential structure due to its “centrality” properties, as well as its very high functional

diversity. We hope that the present characterization of insula function will provide a framework for future interpretations of the role of this multifaceted brain structure in typical and atypical behaviors.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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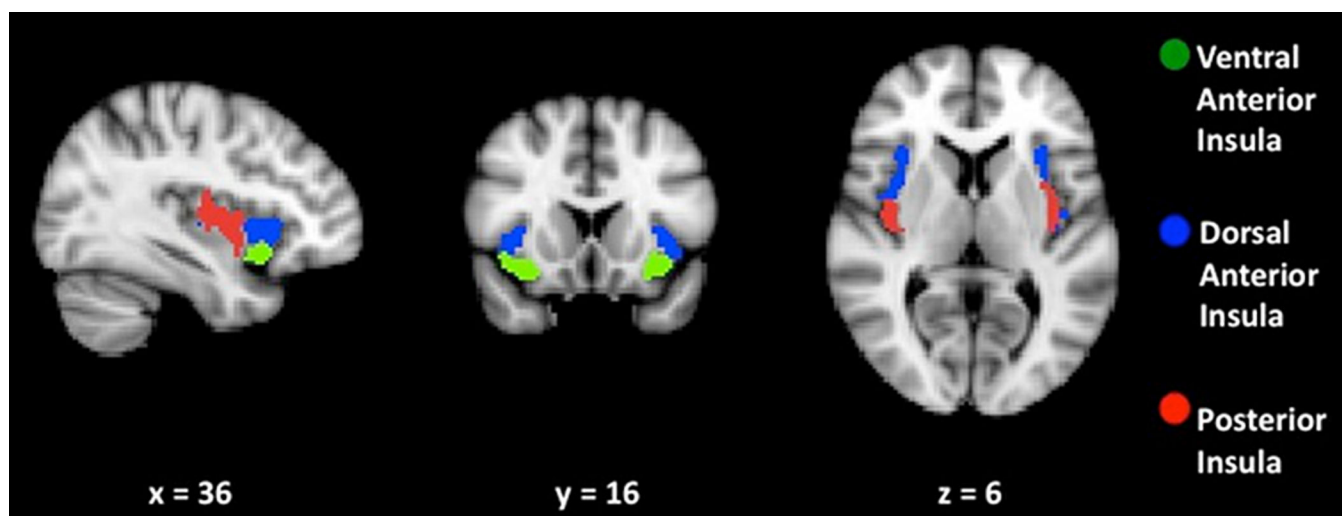
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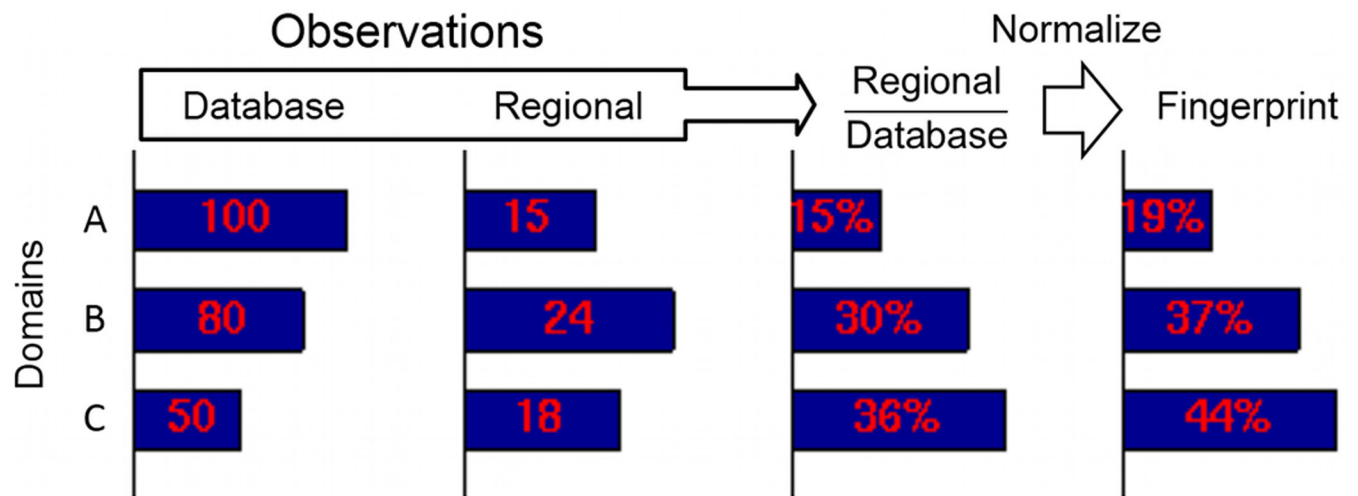


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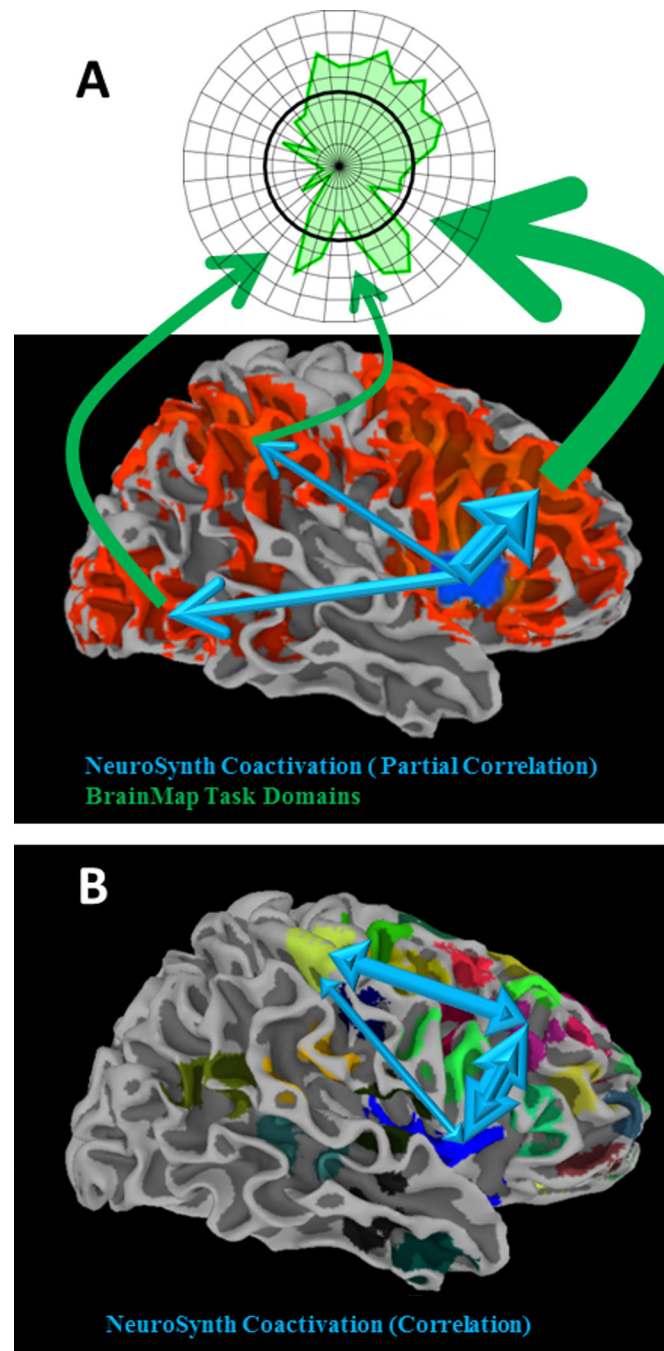
**Figure 1. Insula subdivisions**

The insula was divided following the parcellation scheme reported by (Deen et al., 2010) into three subdivisions: dorsal anterior (blue), ventral anterior (green), and posterior (red).



**Figure 2. Determination of functional fingerprints**

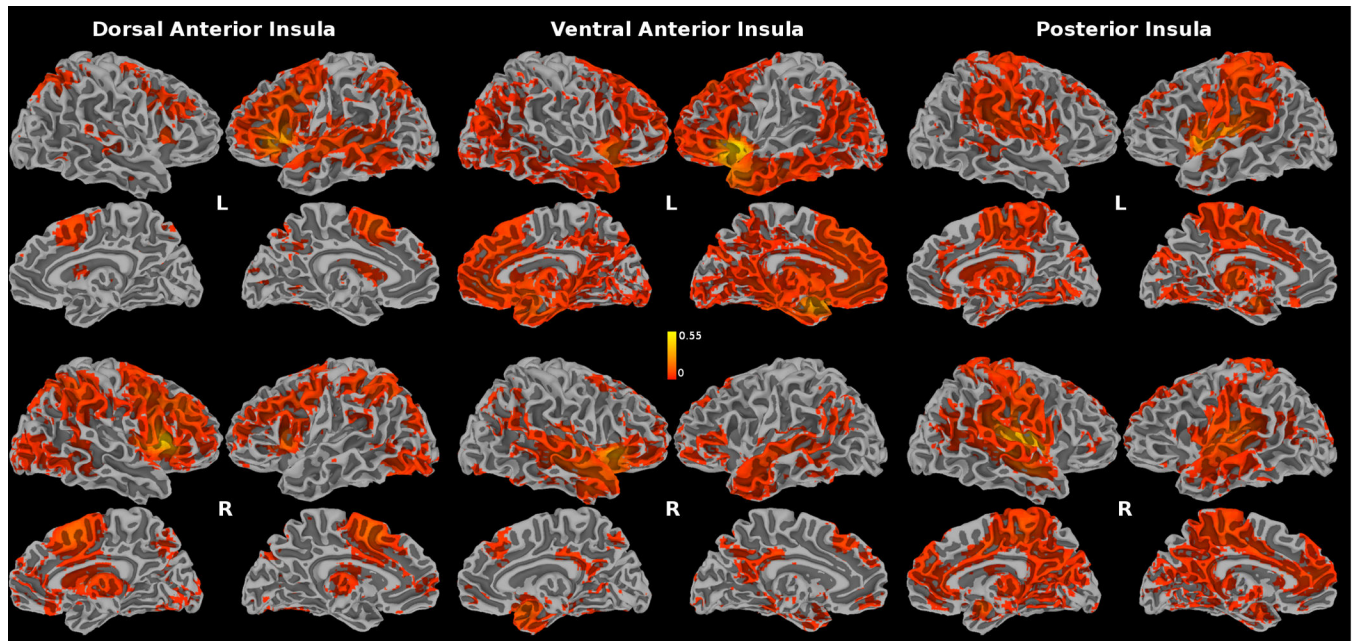
To illustrate the process, only three task domains are shown. The actual fingerprints used in the paper were 32-dimensional. The label “regional” refers to voxels (via the searchlight) or regions of interest. The final normalization step ensures that the fingerprint values all sum to 1.



**Figure 3. Schematic diagram of data analysis**

(A) Coactivation maps and functional fingerprints. Using data from the Neurosynth database, task-based coactivations were determined for each insular subdivision by moving a searchlight in a voxel-wise manner. The blue arrows denote the strength of partial correlation between an insular subdivision and specific voxels on the surface. All significant voxels contributed to the functional fingerprint of the “partner” regions that coactivated with the specific insular subregion. Their contribution was proportional to the value of the partial correlation (as indicated by the green arrow widths). To determine the fingerprints

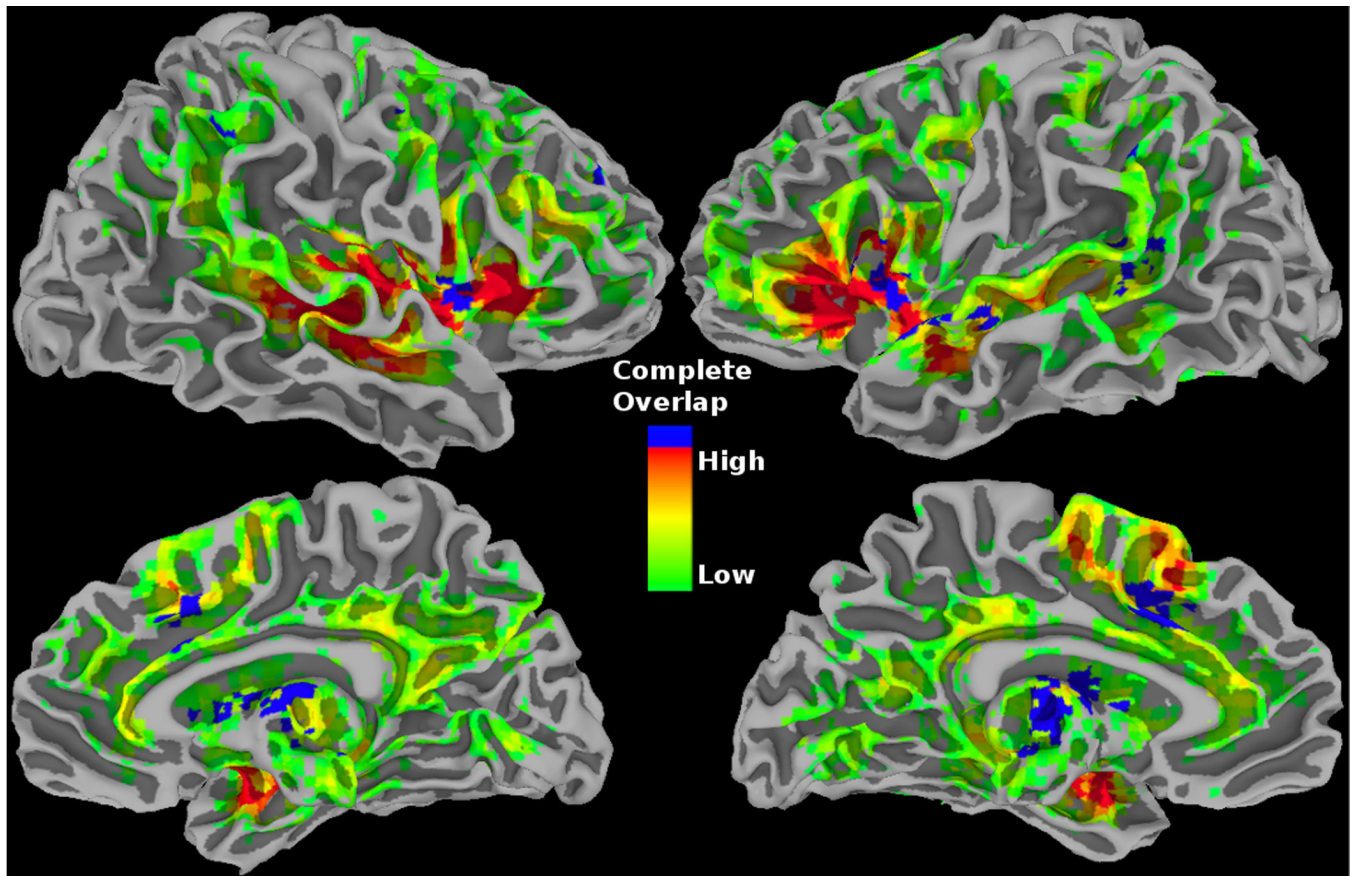
BrainMap data that includes task domain classification was used. (B) Network analysis. Using NeuroSynth data, pairwise correlations between a set of ROIs were computed and used in the graph-theoretic analysis.



**Figure 4. Coactivation of insula subdivisions**

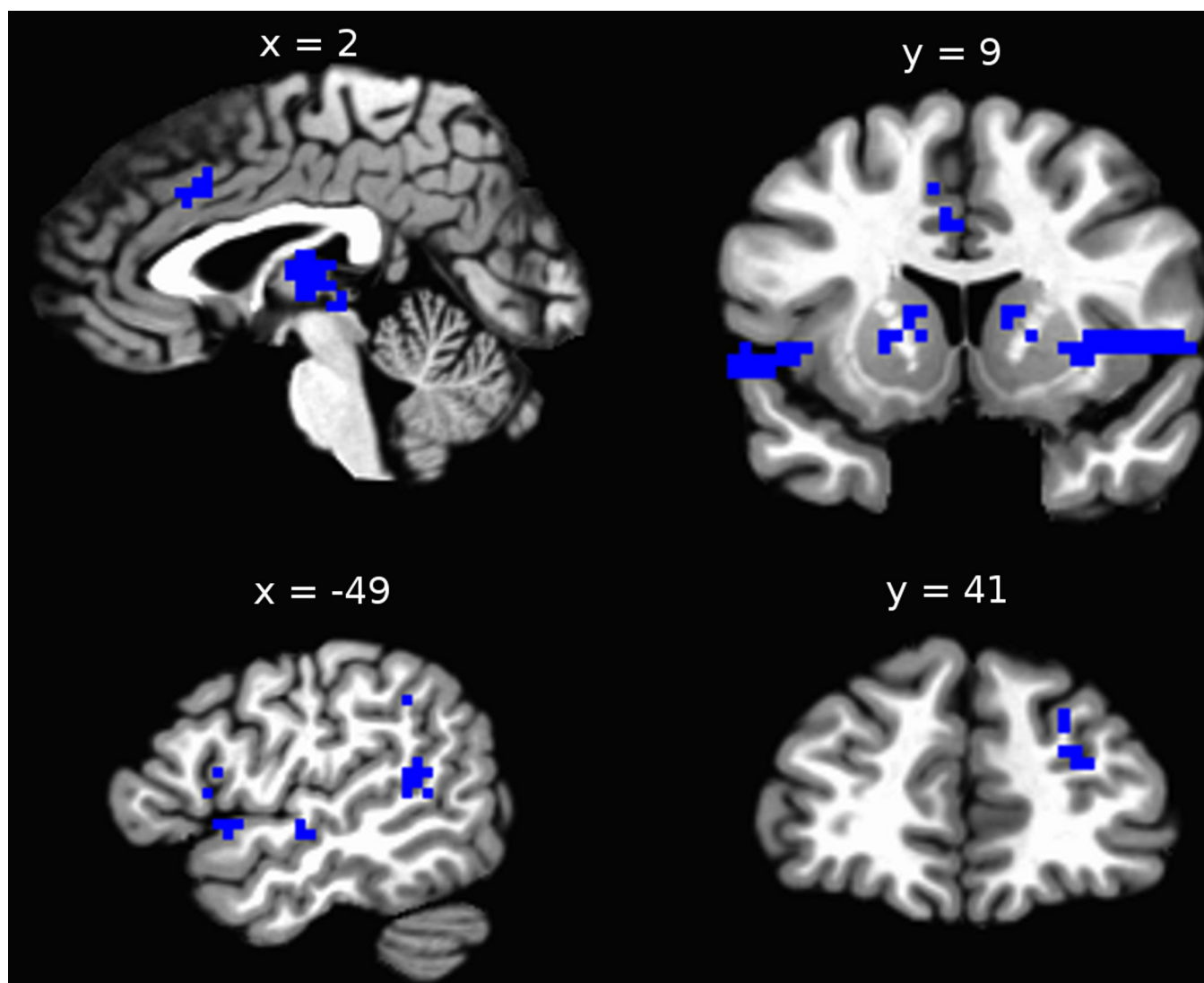
Using data from the Neurosynth database, task-based coactivation profiles were determined for each insular subdivision by moving a searchlight in a voxel-wise manner. The color bar indicates the partial correlation value with the specific insular subregion “seed” when all other subdivisions were also considered.





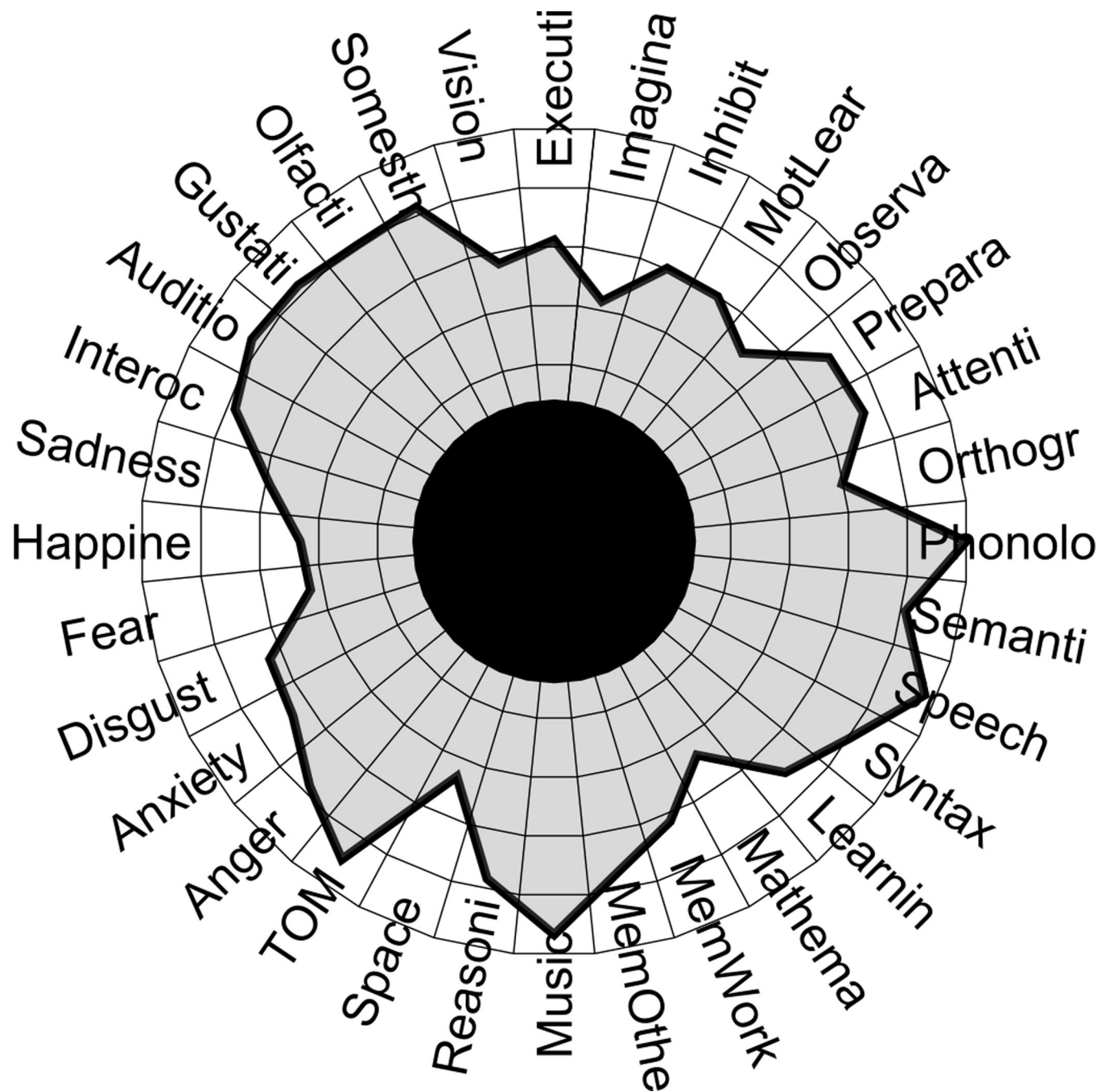
**Figure 5. Overlap between connection partners of each insular subdivision**

To facilitate displaying overlap, the corresponding right and left insular subregions were pooled together resulting in three insular subregions (dorsal anterior, ventral anterior, posterior insula). Voxels shown in green-to-red colors were coactive with two out of the three subregions (the color bar indicates the strength of overlap, specifically, the smallest value of the two strongest partial correlations). Voxels in blue were coactive across all three subdivisions.



**Figure 6. Overlap between connection partners of each insular subdivision**

As in Figure 5, voxels in blue were coactive across all three subdivisions. The slices shown highlight several notable brain regions, including thalamus, caudate, putamen, anterior cingulate cortex, left temporo-parietal junction, and right lateral PFC.

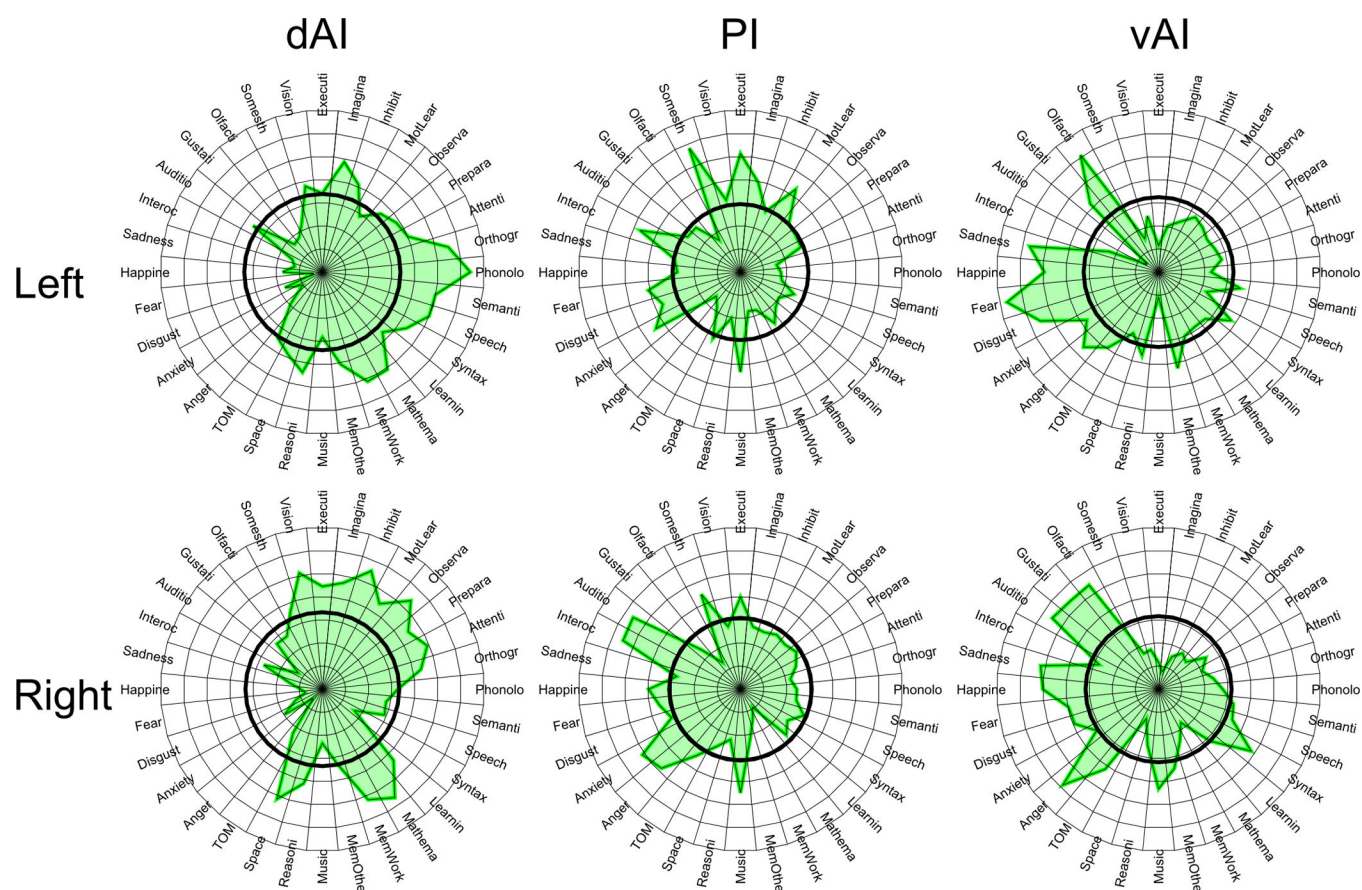


**Figure 7. “Common” functional fingerprint of insular subdivisions**

The common fingerprint was determined by combining all six insular subregion (see text).

All task domains were engaged by each subregion at least some of the time. TOM: theory of mind; MemWork: working memory; MemOther: long-term memory.





**Figure 8. “Specific” functional fingerprints of insular subdivisions**

When the “average profile” (not shown) is subtracted out, particular features are observed in the fingerprints. L: left; R: right; d: dorsal; v: ventral; P: posterior; AI: anterior insula; I: insula. The black circle represents zero, with points outside representing features found more in the given subdivision than the overall insula, and points within the black circle representing features found less in the given subdivision than the overall insula. Other abbreviations as in Figure 7.

**Table 1**

Insula subdivision coordinates (from Deen, 2010).

Insular Subdivision	Mean Talairach Coordinates		
	X	Y	Z
Left dorsal AI	−38	6	2
Left posterior insula	−38	−6	5
Left ventral AI	−33	13	−7
Right dorsal AI	35	7	3
Right posterior insula	35	−11	6
Right ventral AI	32	10	−6

**Table 2**

Graph metrics for insula subdivisions in each hemisphere.

Insular Subdivision	Degree	Strength *	Betweenness centrality
Left dorsal AI	100	100	86
Left posterior insula	89	92	74
Left ventral AI	1	4	13
Right dorsal AI	84	93	67
Right posterior insula	84	81	52
Right ventral AI	46	43	34

\* percentile calculated within own hemisphere