

# Two Systems of Resting State Connectivity Between the Insula and Cingulate Cortex

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**Abstract:** The insula and cingulate cortices are implicated in emotional, homeostatic/allostatic, sensorimotor, and cognitive functions. Non-human primates have specific anatomical connections between sub-divisions of the insula and cingulate. Specifically, the anterior insula projects to the pregenual anterior cingulate cortex (pACC) and the anterior and posterior mid-cingulate cortex (aMCC and pMCC); the mid-posterior insula only projects to the posterior MCC (pMCC). In humans, functional neuroimaging studies implicate the anterior insula and pre/subgenual ACC in emotional processes, the mid-posterior insula with awareness and interoception, and the MCC with environmental monitoring, response selection, and skeletomotor body orientation. Here, we tested the hypothesis that distinct resting state functional connectivity could be identified between (1) the anterior insula and pACC/aMCC; and (2) the entire insula (anterior, middle, and posterior insula) and the pMCC. Functional connectivity was assessed from resting state fMRI scans in 19 healthy volunteers using seed regions of interest in the anterior, middle, and posterior insula. Highly correlated, low-frequency oscillations (< 0.05 Hz) were identified between specific insula and cingulate subdivisions. The anterior insula was shown to be functionally connected with the pACC/aMCC and the pMCC, while the mid/posterior insula was only connected with the pMCC. These data provide evidence for a resting state anterior insula–pACC/aMCC cingulate system that may integrate interoceptive information with emotional salience to form a subjective representation of the body; and another system that includes the entire insula and MCC, likely involved in environmental monitoring, response selection, and skeletomotor body orientation. *Hum Brain Mapp* 30:2731–2745, 2009. © 2008 Wiley-Liss, Inc.

**Key words:** functional connectivity; fMRI; resting state; salience; insula; cingulate

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## INTRODUCTION

The insula and cingulate cortex play key roles in integrating multimodal information important for sensorimotor, emotional, allostatic/homeostatic, and cognitive functions (Craig, 2002; Critchley, 2004; Devinsky et al., 1995; Pollatos et al., 2007). For example, the dorsal margin of the mid-posterior insula has been associated with interoception because it receives information regarding the physiological condition of the body (Craig, 2004), including pain, temperature, sensual touch, itch, visceral sensations, thirst, and hunger (Augustine, 1996; Brooks et al., 2005; Cole et al., 2006; Craig, 2003; Craig, 2004; Olausson et al., 2005;

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Ostrowsky et al., 2002; Schweinhardt et al., 2006). The anterior insular cortex is thought to form a global representation of the bodily state, because it is situated to integrate homeostatic afferent activity from the dorsal posterior insula with emotional salience (Craig, 2002).

The insular cortex lies in the depths of the lateral sulcus covered by the opercula of the frontal, parietal, and temporal lobes (Ture et al., 1999) and contains rostroventral agranular, middle dysgranular, and posterior granular regions (Augustine, 1985), each with connections to the frontal, parietal, and temporal lobes (Mesulam and Mufson, 1982a; Mesulam and Mufson, 1982b; Mufson and Mesulam, 1982) and the cingulate gyrus (Augustine, 1996). In the non-human primate, the anterior insula is connected to the rostral extent of Brodmann area 24 of the anterior cingulate cortex (ACC) and a dorsal transitional area between areas 24 and 6 (Mesulam and Mufson, 1982b; Vogt and Pandya, 1987). In contrast, the mid and posterior primate insula have connections with dorsal cingulate areas 23 and 24, and the upper banks of the cingulate sulcus and premotor cortex (Mesulam and Mufson, 1982b).

The cingulate cortex has been divided into four major regions based on cytoarchitectonics, electrophysiology, imaging, and lesion studies (Vogt et al., 2005). These four regions include the ACC, mid-cingulate cortex (MCC), posterior cingulate cortex (PCC), and retrosplenial cortex (RSC). The ACC has been subdivided into subgenual (sACC) and pregenual ACC (pACC) regions, whereas the MCC has been subdivided into anterior (aMCC) and posterior mid-cingulate (pMCC) regions (Vogt et al., 2005; Vogt, 2005). The sACC and pACC are primarily concerned with emotions and pain. The MCC includes regions involved in pain (Apkarian et al., 2005), and motor functions involved in response selection (aMCC) and skeleto-motor body orientation (pMCC) (Vogt, 2005). The MCC has also been implicated in cognitive processes including error detection, salience, attention to behaviorally relevant stimuli, anticipation, decision making, and task-set implementation (i.e., task initiation or task switching) (Bush et al., 2000; Davis et al., 1997; Davis et al., 2000; Dosenbach et al., 2006; Dosenbach et al., 2007; Dux et al., 2006; Fair et al., 2007; Rushworth et al., 2007).

To our knowledge, information exchange between the insula and cingulate cortex has never been directly shown. However, the distinct anatomical connections between these two brain regions identified in non-human primates combined with the evidence from numerous human functional imaging studies revealing coactivation within specific parts of the insula and cingulate cortex, suggests that multiple information processing pathways may exist between these two regions. Alternatively, these two brain regions could be part of multiple networks with common inputs. Therefore, the aim of this article was to examine functional connectivity between specific parts of the insula and subregions of the cingulate cortex.

Functional connectivity has been operationally defined to refer to temporal correlations across cortical regions and

can represent an index of brain function (Friston et al., 1993; Horwitz, 2003). Several imaging modalities have been utilized to record indices of brain function, such as electroencephalography (EEG), positron emission tomography (PET), magnetoencephalography (MEG), and functional magnetic resonance imaging (fMRI). Resting state functional connectivity analysis is a technique that identifies cortical areas that have strong temporally-correlated low-frequency (< 0.1 Hz) activity in a non-task (i.e., rest) state. Using this approach the relationship between anatomically distinct, but functionally connected, brain regions can be investigated. It is thought that these low-frequency fluctuations are functionally relevant indices of connectivity between brain regions subserving similar or related brain functions (Birn, 2007). To date this approach has identified multiple resting state networks, including the so called “default mode” or task-negative network, a network that is active during rest and is suppressed during the performance of a task (Fox et al., 2005; Raichle et al., 2001), and the task-positive network, which performs attention orienting operations (Fox et al., 2006). A recent study by DeLuca et al. (2006) established that these resting state networks are not artifacts produced by aliasing of cardiac and respiratory cycles, but are localized to gray matter of the cerebral cortex and are likely related to ongoing neuronal activity (DeLuca et al., 2006). In addition, Damoiseaux et al. (2006) demonstrated that these resting state networks display blood oxygen level dependent (BOLD) signal changes up to 3%, values that are comparable with task-related BOLD changes. Furthermore, the authors demonstrated that these networks were consistent across individuals and stable across repeated sessions (Damoiseaux et al., 2006).

Thus, in this study we used resting state functional connectivity analysis to determine if BOLD fluctuations within the anterior, middle, and posterior insula correlate with specific subregions of the cingulate cortex. Based on primate tracing studies and functional activation studies, we hypothesized that two distinct systems could be identified at rest: (1) a system linking the anterior insula with pACC/aMCC, potentially involved in integrating interoceptive information with emotional salience to form a subjective bodily representation; (2) a system that links the entire insula with the MCC, potentially involved in general salience, response selection, and action.

## METHODS

### Subjects

Nineteen right-handed healthy subjects (11 male, 8 female;  $28.1 \pm 5.6$  years old) with no history of neurological injury, participated in the study. Handedness was determined using the Edinburgh handedness inventory (Oldfield, 1971). All subjects gave informed written consent to procedures approved by the University Health Network Research Ethics Board.

TABLE I. Insula regions of interest

	ROI centre of mass			ROI volume (mm <sup>3</sup> ), (mean ± SD)
	X	Y	Z	
R anterior insula (RaIC)	36	16	2	1,986 ± 600
R middle insula (RmIC)	38	1	6	1,219 ± 261
R posterior insula (RpIC)	38	-10	7	1,271 ± 217
L anterior insula (LaIC)	-34	14	2	1,834 ± 502
L middle insula (LmIC)	-38	-1	6	1,284 ± 269
L posterior insula (LpIC)	-38	-12	7	1,321 ± 407

Shown are the coordinates (Talairach space) and region of interest volumes for each insula subregion used in the connectivity analysis.

### Data Acquisition

All data were obtained using a 3T GE MRI system fitted with an eight channel phased array head coil. A three-dimensional high resolution anatomical scan of the whole brain (124 sagittal slices, 24 × 24 cm FOV, 256 × 256 matrix, 1.5 × 0.94 × 0.94 mm voxels) was acquired with a T1-weighted 3D spoiled gradient echo (SPGR) sequence (flip angle = 45°, TE = 5 ms, TR = 25 ms). Resting state fMRI data was acquired using T2\*-weighted echo planar imaging (EPI) (25 axial slices, FOV = 20 × 20 cm, 64 × 64 matrix, 3.125 × 3.125 × 4 mm voxels, TE = 40 ms, TR = 2000 ms). The scan time was 5 minutes and 8 seconds (154 frames). Subjects were instructed to relax, keep their eyes closed, and think of nothing in particular (Damoiseaux et al., 2006; Greicius et al., 2004). Greicius et al. (2003) investigated the default mode network during resting state and during a passive visual processing task (i.e., eyes open) and found almost identical patterns of activity, indicating that tasks that require minimal cognitive processing do not disrupt resting state networks (Greicius et al., 2003).

### Data Analysis

Data were preprocessed and analyzed using Brainvoyager QX v1.8 (Brain Innovation, Maastricht, Netherlands). Preprocessing included motion correction, slice timing correction, linear trend removal, and spatial smoothing with a 6 mm FWHM Gaussian kernel. fMRI datasets were interpolated to 3 × 3 × 3 mm voxels, registered to the high resolution anatomical image and normalized to standard Talairach space (Talairach and Tournoux, 1988). Voxels are reported as 1 × 1 × 1 mm.

Previous cytoarchitectonic studies performed in non-human primates have identified three distinct insular subregions which have different anatomical connections with the rest of the brain (rostroventral agranular, middle dysgranular, and posterior granular regions [Augustine, 1985]). As our main interest was to examine the functional connectivity with these three insular subregions and the cingulate cortex, six regions of interest (ROIs) were drawn for each subject within the anterior, middle, and posterior

insula (three left and three right) based on previous anatomical and MR imaging studies (Naidich et al., 2004; Ture et al., 1999; Varnavas and Grand, 1999) (Table I). Thus, the anterior insula included the anterior short gyrus, the middle insula included the middle and posterior short gyrus, and the posterior insula included the anterior long gyrus (Brooks et al., 2002; Brooks et al., 2005; Schweinhardt et al., 2006). Because our intention was to obtain an average time course for each major region of the insula that was as distinct as possible from the adjacent areas, each ROI was restricted to gray matter and carefully delineated to avoid overlap with other subregions (see Fig. 4A).

The average time course (averaged across all voxels within each insula region) was extracted for each ROI on a single subject basis. Frequency periodograms were calculated separately for each subject and ROI to ensure that the data were in the typical resting state frequency range (< 0.1 Hz). This was accomplished by performing Fourier transforms of the average time course extracted from each ROI using SPSS 12.0 (SPSS Inc., Chicago). Single subject average time courses were then used as predictors in a fixed effects multisubject general linear model (GLM). One multisubject GLM analysis was performed for each ROI for a total of six multisubject GLMs (i.e., anterior, mid, and posterior insula, bilaterally). A conjunction analysis was performed to identify brain regions highly correlated with the insular ROIs in all 19 subjects. This was done by searching across all subjects to identify the minimum statistical *t*-value for each voxel. Once this minimum was identified, it was assigned as the voxel value. These maps were then thresholded at a corrected value of  $P < 0.05$  (derived from an uncorrected  $P < 0.0001$  and 120 mm<sup>3</sup> contiguous clusters as previously reported by Downar et al. [2003] and validated by a Monte Carlo simulation implemented in the Analysis of Functional NeuroImages software with the AlphaSim application [<http://afni.nimh.nih.gov/afni/doc/manual/AlphaSim>]). To further identify the connectivity of each insula region, unthresholded average *t*-scores were extracted from 5 mm<sup>3</sup> cubes, which were placed within each of the group correlation maps, within four bilateral brain regions: ACC, MCC, primary (S1), and secondary (S2) somatosensory

cortices centered on the following  $x$ ,  $y$ ,  $z$  coordinates: pACC/aMCC,  $\pm 8, 38, 19$ ; pMCC,  $\pm 6, 9, 36$ ; S1,  $\pm 42, -22, 51$ ; S2,  $\pm 42, -22, 23$ . The strength of the resting state connectivity (i.e., the  $t$ -scores) between each insula region and the cingulate and somatosensory regions were then displayed visually as regional “fingerprints” from polar plots created with Sigma Plot 9.0. The somatosensory cortices were included in this analysis because anatomical pathways between the insula and somatosensory regions have been identified in non-human primates (Augustine, 1996), and because of our interest in nociception, during which it is common to observe activation within all four of these brain regions.

Random effects analyses were also performed to ascertain if there were significant differences in spatial spread and strength of connectivity of the insula ROIs within cingulate cortex subregions. The models included all 19 subjects and their predictors, derived from the anterior, middle, and posterior insula, for the left and right hemispheres separately. Six sets of contrasts were generated: (1) left anterior insula vs. left posterior insula; (2) left anterior vs. left mid-insula; (3) left mid vs. left posterior insula; (4) right anterior insula vs. right posterior insula; (5) right anterior vs. right mid-insula; (6) right mid vs. right posterior insula. All statistical maps were thresholded at a corrected  $P < 0.05$  (derived from an uncorrected  $P < 0.0001$  and  $120 \text{ mm}^3$  contiguous clusters).

## RESULTS

The location and size of each insula ROI is shown in Table I. Single subject spectral analyses of the resting state BOLD activity within the insula ROIs identified low-frequency oscillations of  $0.04 \pm 0.002 \text{ Hz}$  (mean  $\pm$  SE). Examples of these oscillations in an individual subject can be seen in Figures 1–3A,D. Resting state connectivity analysis based on seeds within the three insula subdivisions revealed remarkably similar (between subjects) low-frequency oscillations in specific cingulate subdivisions (see Figs. 1–3 B,E).

The location of the cingulate subregions found to have tightly correlated resting state activity with the insula ROIs are shown in Figures 1–3. Activity in both the left and right anterior insula cortices was strongly correlated with the bilateral pACC/aMCC and bilateral pMCC (Fig. 1C,F). However, the fMRI signal in the mid and posterior insula cortices were strongly correlated with bilateral pMCC (Figs. 2 and 3, parts C,F), but not with the more rostral pACC/aMCC. A complete list of brain regions that displayed significant correlations with bilateral anterior, middle, or posterior insula in all 19 subjects is provided in Table II.

Insula connectivity “fingerprints” were constructed to illustrate patterns of connectivity of each insula subdivision with the cingulate cortex and also key somatosensory regions. Figure 4 shows these “fingerprints” as polar plots

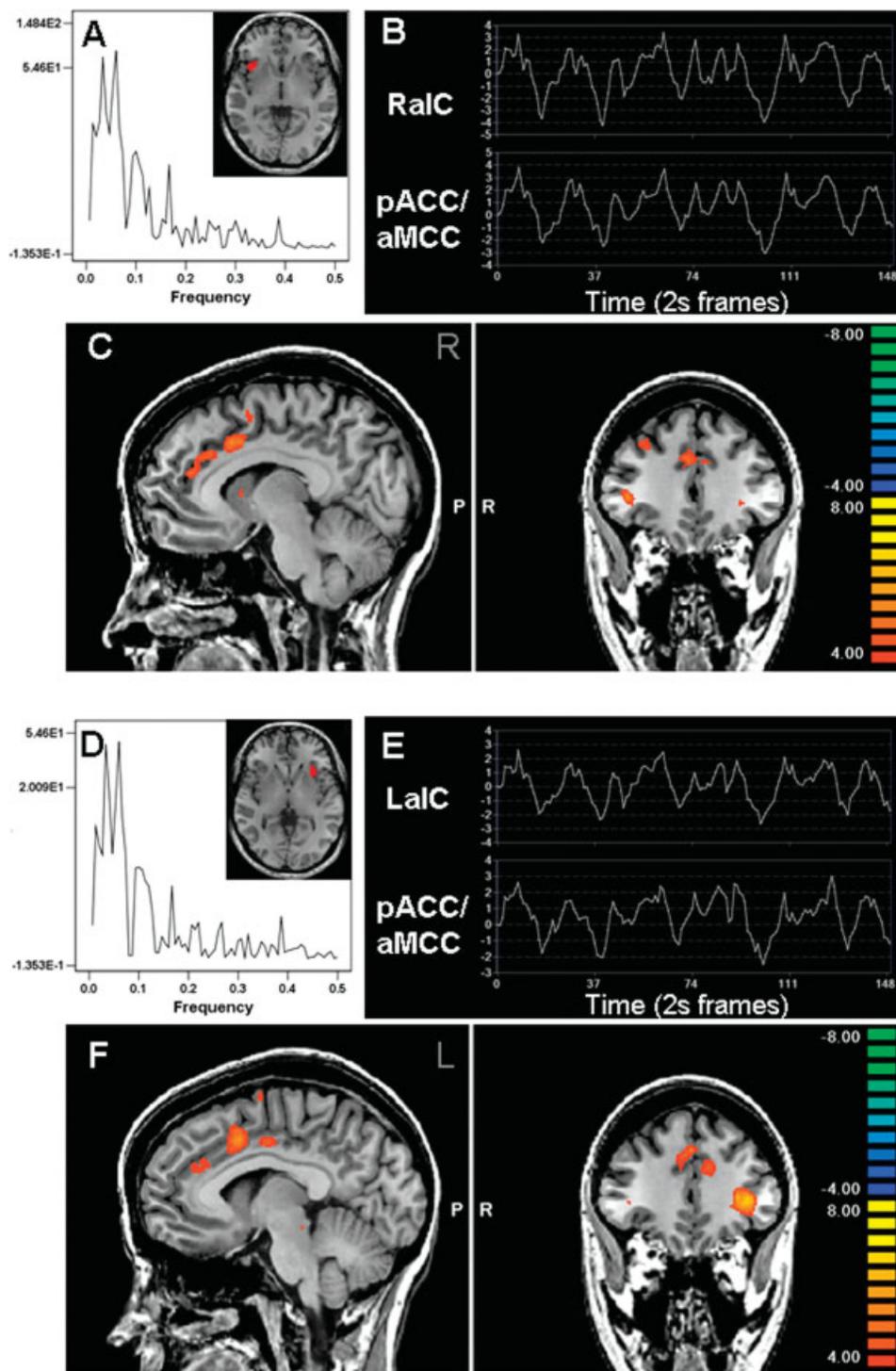
of the strength (average  $t$ -score) of correlated activity between the anterior, middle, and posterior insula and the cingulate, S1 and S2. The fingerprints illustrate that all insular ROIs, except the left posterior insula, had strongly correlated activity with pMCC, while only the anterior insular ROIs displayed significant correlations with pACC/aMCC. The left mid-insula and bilateral posterior insula were significantly correlated with activity within S1 and S2. However, there were no statistically significant correlations with S1 and S2 for the right middle insula and bilateral anterior insula ( $t < 4.0$ ) (see Fig. 4).

To determine if the strength of the identified connectivity patterns were significantly different between the anterior, middle, and posterior insula, a random effects group analysis was performed. Connectivity with S1 and S2 was not found to differ between sub-regions of the insula. Table III displays additional brain regions that demonstrated significantly different connectivity between insular subregions. However, there were significant differences within the cingulate cortex for the contrasts: (1) anterior IC vs. posterior IC; (2) anterior IC vs. mid-IC; (3) mid-IC vs. posterior IC, and these are highlighted in Figure 5. Interestingly, the anterior insula bilaterally showed stronger resting state connectivity with the pACC/aMCC than either the middle or posterior insula (see Fig. 5, first 2 columns). However, the mid-insula was more strongly connected with the pMCC than the posterior insula (Fig. 5, third column).

## DISCUSSION

We have used functional connectivity analysis to identify resting state systems between the insula and cingulate cortices. The anterior insula was shown to be functionally connected with the pACC/aMCC and the pMCC, while the mid/posterior insula was only connected with the pMCC. We propose that the system linking the anterior insula with the pACC/aMCC may be involved in emotional salience monitoring, while the system linking the entire insula with the pMCC could be a general salience and action system.

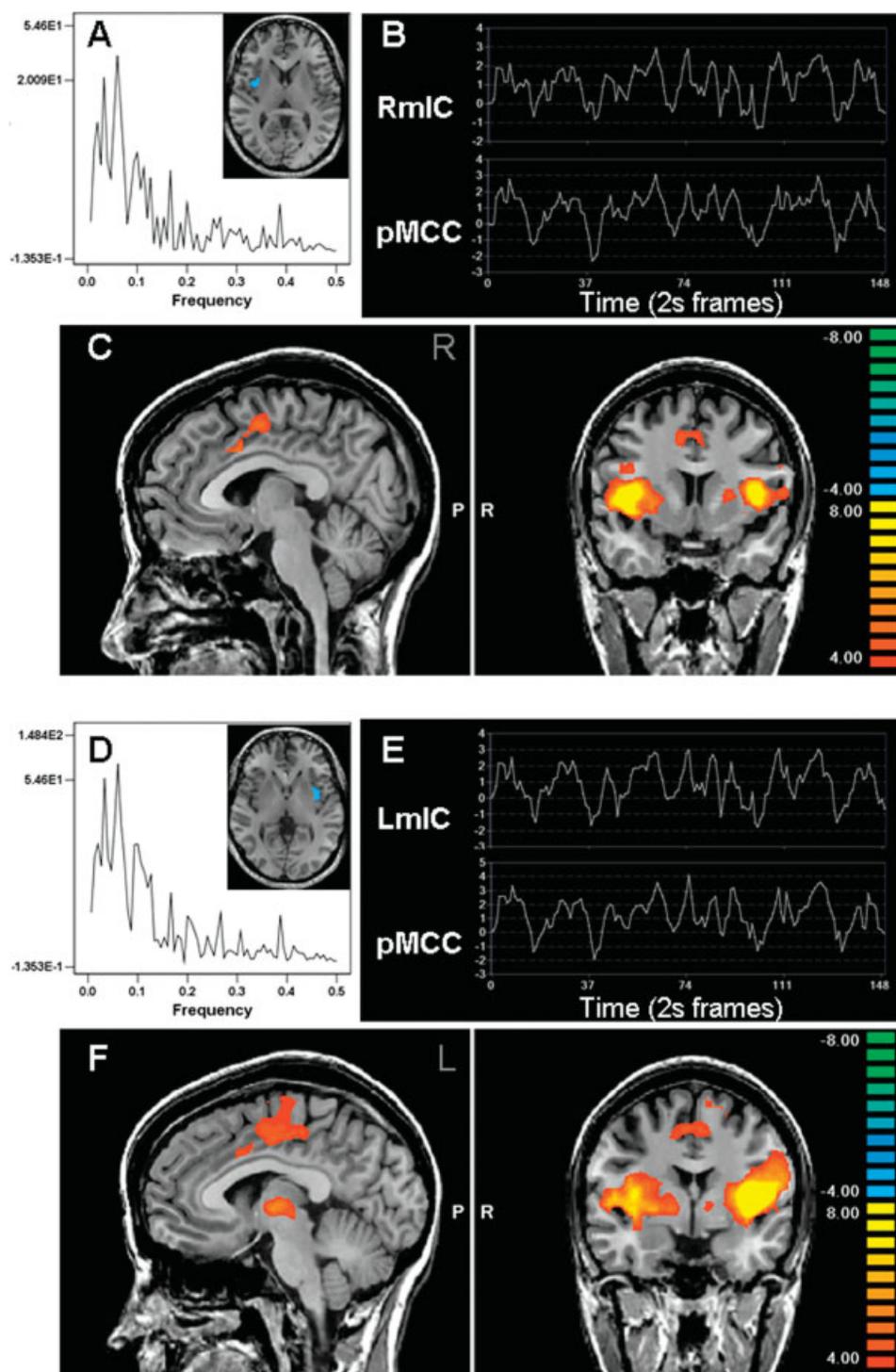
The identification of a general salience system stems from a large body of converging evidence, including Downar et al. (2000, 2002, 2003) who identified a set of brain regions, including the anterior insula and MCC, that detects salient environmental changes regardless of the modality of the task employed (i.e., visual, auditory, tactile, pain). Furthermore, using single cell electrophysiological recordings in the human brain our group has identified neurons within the MCC that respond to pain (Hutchison et al., 1999) and neurons that respond to cognitively-demanding tasks proposed to be involved in general salience detection (Davis et al., 2005). In contrast, functional activation studies in healthy individuals and patients with abnormal emotional processing (e.g., depression) strongly implicate more rostral areas of the cingulate cortex (i.e., ACC) in emotional salience (Bush et al., 2000; Etkin et al., 2006; Mayberg et al., 2000; Phan et al., 2002).



**Figure 1.**

Whole brain multisubject conjunction analysis showing anterior insula connectivity with the cingulate cortex. The spectral analysis and ROI time course from a single subject is shown for the

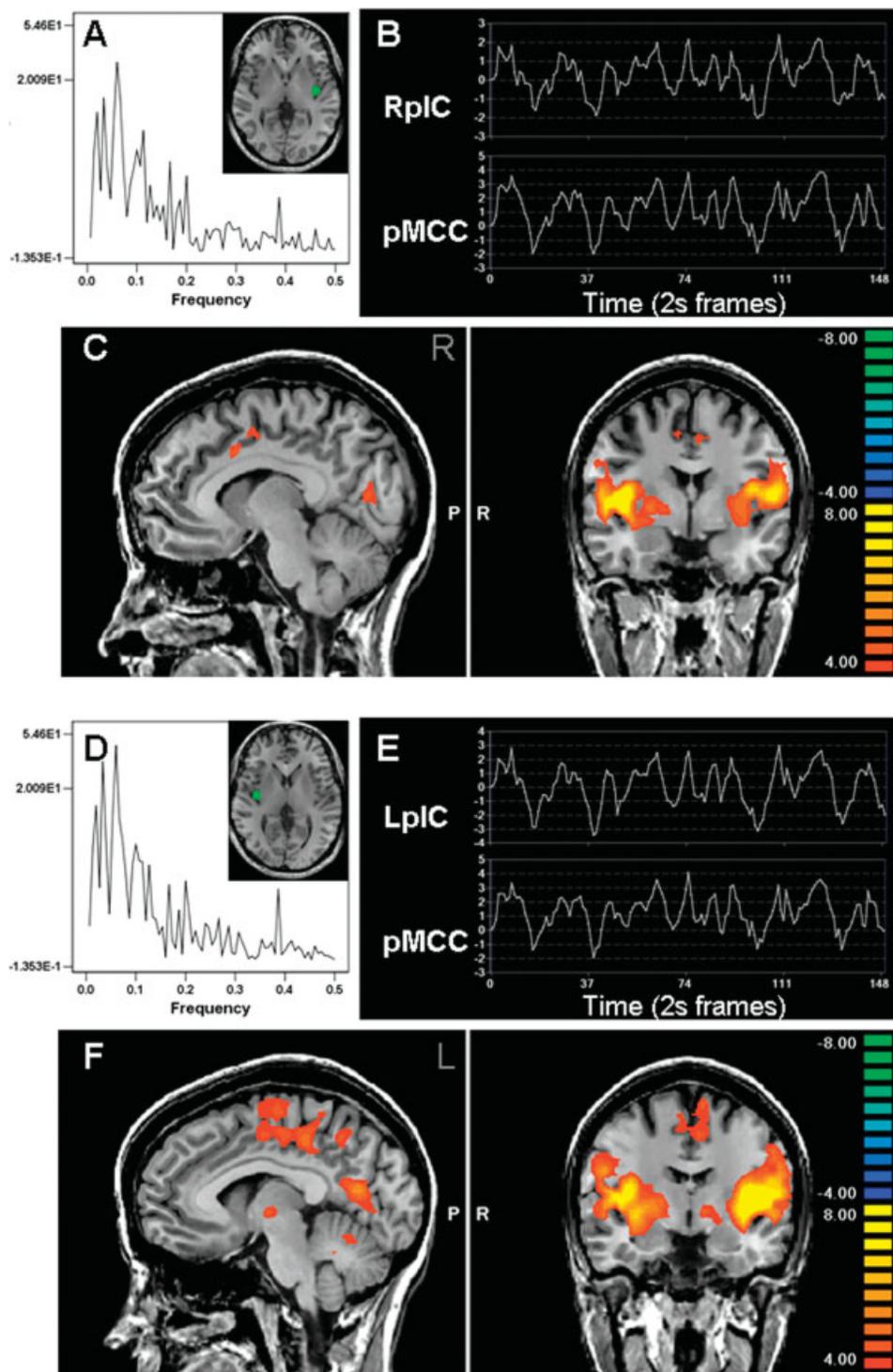
left (A, B) and right (D, E) anterior insula (aIC). These regions had tight correlations of low-frequency oscillations (B, E) with the pregenu and mid-cingulate cortex (C, F).



**Figure 2.**

Whole brain multisubject conjunction analysis showing mid-insula connectivity with the cingulate cortex. The spectral analysis and ROI time course from a single subject is shown for the

left (A, B) and right (D, E) mid-insula (mIC). These regions had tight correlations of low frequency oscillations (B, E) with the mid-cingulate cortex (C, F).



**Figure 3.**

Whole brain multisubject conjunction analysis showing posterior insula connectivity with the cingulate cortex. The spectral analysis and ROI time course from a single subject is shown for the

left (**A, B**) and right (**D, E**) posterior insula (pIC). These regions had tight correlations of low frequency oscillations (**B, E**) with the mid-cingulate cortex (**C, F**).

**TABLE II. Anatomical locations and center of gravity coordinates (in Talairach space) displayed for brain regions that demonstrated significant correlations with each of the six insula ROIs**

ROI	Anatomical location (center of gravity)	Talairach coordinates			Voxels
		x	y	z	
LaIC	Left insula	-37	14	1	24,023
	Left cingulate gyrus BA 24/32 (pACC/aMCC)	-7	33	26	580
	Left cingulate gyrus/BA 24 (pMCC)	-6	6	41	1,419
	Left cerebellum	-4	-29	-15	125
	Left inferior frontal gyrus/BA 9	-34	8	28	189
	Right insula	33	-26	-12	14,420
	Right inferior parietal lobule/BA 40	51	-41	34	825
	Right fusiform gyrus/BA 37	42	-40	-13	840
	Right angular gyrus/BA 39	39	-57	37	143
	Right paracentral/inferior parietal gyrus/BA 2/40	21	-41	58	631
	Right cerebellum	3	-68	-24	472
	Right cingulate gyrus BA 24/32 (pACC/aMCC)	4	31	31	856
	Right cingulate gyrus/BA 24 (pMCC)	5	5	40	608
Right cingulate gyrus/BA31 (pMCC)	6	-41	43	147	
LmIC	Left insula	-36	-7	12	31,545
	Left postcentral gyrus/BA 2/BA 40 (S2)	-46	-18	27	2,834
	Left postcentral gyrus/BA 1, 2, 3 (S1)	-16	-39	62	1,314
	Left cingulate gyrus/BA 24 (pMCC)	-7	-9	46	1,479
	Left precentral gyrus/BA 4	-44	-14	43	1,892
	Left lingual gyrus/BA 18	-9	-71	6	210
	Left middle frontal gyrus/BA 10	-31	38	7	151
	Right insula	32	-6	10	16,793
	Right inferior parietal/postcentral gyrus/BA 40 (S2)	42	-23	27	3,033
	Right postcentral gyrus/BA 2/40	28	-42	47	4,023
	Right cingulate gyrus/BA 24 (pMCC)	7	-2	47	702
	Right precentral gyrus/BA 4	38	-18	46	2,344
	Right fusiform gyrus/BA 37	42	-41	-9	234
	Right inferior frontal gyrus/BA9	36	8	22	138
	Right fusiform gyrus/BA 37	36	-53	-3	310
	Right cuneus/BA 30	21	-71	7	566
	LpIC	Left insula	-37	-17	10
Left inferior parietal gyrus/BA 2/BA 40 (S2)		-40	-23	25	3,257
Left medial frontal gyrus/BA 6		-10	-11	67	338
Left cingulate gyrus/BA 31 (pMCC)		-10	-11	46	806
Left precuneus/BA 7		-10	-56	46	252
Left cuneus/BA 18		-16	-83	16	520
Left inferior parietal lobule/BA 40		-22	-35	52	371
Left postcentral gyrus/BA 2		-41	-29	45	1,240
Left precentral gyrus/BA 4		-36	-16	53	471
Left middle temporal gyrus/BA 37		-43	-59	-3	324
Right insula		36	-14	10	29,659
Right inferior parietal gyrus/BA 2/BA 40 (S2)		42	-23	25	2,319
Right precentral gyrus/BA 1, 2, 3 (S1)		36	-20	37	272
Right occipital lobe, sub-gyral, white matter		36	-59	-3	226
Right cingulate gyrus/BA 24 (pMCC)		2	-7	49	330
Right postcentral gyrus/BA 1, 2, 3 (S1)		25	-38	52	1,121
Right precuneus/BA 31		30	-71	16	1,724
Right insula		39	17	4	12,460
Right middle frontal gyrus/BA 9		30	32	37	308
Right/left cingulate gyrus/BA 24/32 (pACC/aMCC)	5	32	27	1,118	
Right cingulate gyrus (GC)/BA 24 (pMCC)	6	13	38	672	
RaIC	Left insula	-40	14	1	8,075
	Left cingulate gyrus/BA 24 (pACC/aMCC)	-6	36	26	128
	Left cingulate gyrus/BA 24 (pMCC)	-4	9	40	325
	Right insula	39	2	4	42,546
RmIC	Right postcentral gyrus/BA 1, 2, 3 (S1)	36	-19	25	371
	Right precentral gyrus/BA 6	36	5	22	134
	Right inferior frontal gyrus/BA 46	33	35	10	199
	Right fusiform gyrus/BA 19	36	-53	-6	139
	Right parahippocampal gyrus/BA 27	24	-32	-3	139
	Right cuneus/BA 31/17	12	-71	10	260
	Right cingulate gyrus/BA 24 (pMCC)	1	-2	48	978

TABLE II. (continued)

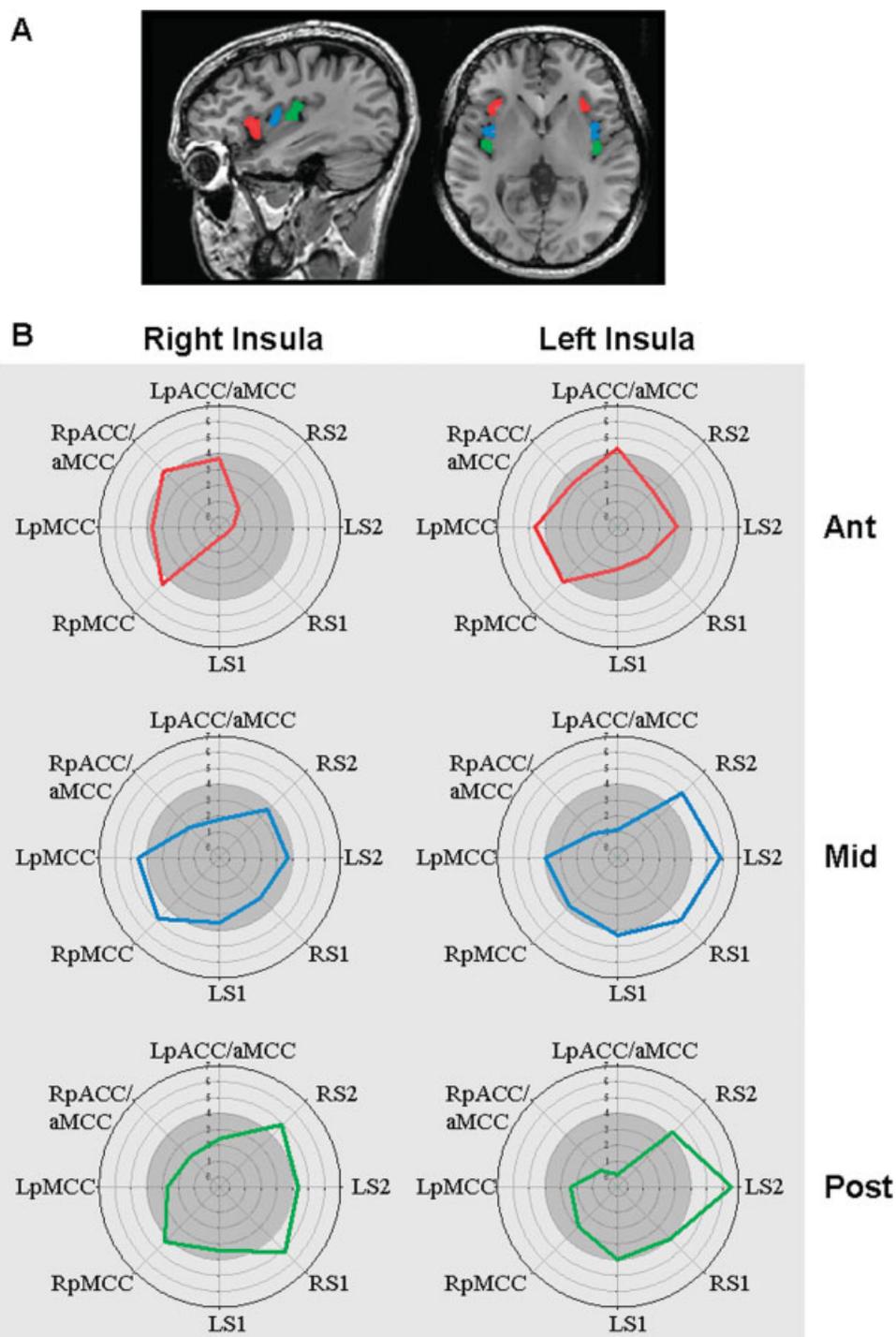
ROI	Anatomical location (center of gravity)	Talairach coordinates			Voxels
		x	y	z	
	Left insula	-37	2	10	27,661
	Left cingulated gyrus/BA 24 (pMCC)	-4	-2	46	981
	Left cuneus/BA 31/17	-13	-68	10	347
	Left postcentral gyrus/BA 40/42 (S2)	-40	-19	18	460
	Left cuneus/BA 18	-19	-80	25	155
RpIC	Right insula	36	-14	10	40,701
	Right postcentral gyrus/BA 40 (S2)	40	-20	20	901
	Right precentral gyrus/BA 4	42	-19	44	1,539
	Right medial temporal gyrus/BA 37	42	-62	10	149
	Left cuneus/BA 30	-13	-68	10	2,776
	Right postcentral gyrus/BA 1, 2, 3 (S1)	18	-35	61	277
	Right cingulate gyrus/BA 24/32 (pMCC)	6	-1	46	330
	Left insula	-40	-8	10	24,915
	Left paracentral/cingulate gyrus/BA 24 (pMCC/aPCC)	-7	-26	43	1,371
	Left superior frontal gyrus/BA 6	-10	-14	67	329
	Left cuneus/BA 17	-16	-83	10	367
	Left postcentral gyrus/BA 40 (S2)	-40	-18	19	726

Brain areas were derived from the multisubject conjunction analyses, thresholded at a corrected  $P < 0.05$ . Voxels are reported as  $1 \times 1 \times 1 \text{ mm}^3$ . aIC, anterior insula; mIC, mid-insula; pIC, posterior insula; pACC, pregenual anterior cingulate cortex; aMCC, anterior mid-cingulate cortex; pMCC, posterior mid-cingulate cortex; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; R, right; L, left.

The insular and cingulate cortices have both been implicated in emotional, homeostatic/allostatic, sensorimotor, and cognitive functions (Craig, 2002; Craig, 2008; Critchley et al., 2003; Critchley, 2004; Critchley et al., 2005; Devinsky et al., 1995). For example, the anterior insula has been shown to be activated in studies of emotional aspects of pain (Rainville et al., 1997), empathy relating to pain (Singer et al., 2004), temperature (Craig et al., 2000; Davis et al., 2004; Olausson et al., 2005), emotion (Buchel et al., 1998; Phillips et al., 1998), salience (Downar et al., 2000; Downar et al., 2002; Downar et al., 2003), and during subjective evaluation of autonomic function (i.e., heart beat detection) (Critchley et al., 2004). Interestingly, the right anterior insula is activated during painful rectal distention in healthy individuals but not in patients with irritable bowel syndrome (Kwan et al., 2005) and these patients also had cortical thinning of the anterior insula and pMCC (Davis et al., 2008). These findings suggest that the anterior insula normally works to monitor internal body functions. According to Craig (2002), interoceptive information regarding the physiological condition of the entire body is received by the posterior insula which is then projected to the anterior insula for subjective evaluation of internal conditions (Craig, 2002; Critchley et al., 2004). The sACC and pACC have also been implicated in autonomic and emotional processing, while the aMCC and the pMCC have been implicated in cognitive and sensorimotor functions (Bush et al., 2000; Critchley, 2004; Devinsky et al., 1995; Vogt, 2005).

The concept that at rest, a network of cortical areas exists with tightly correlated activity was introduced by Biswal et al. (1995) who described a network of temporally

correlated motor-related brain areas. Functional connectivity analyses of resting state activity has identified low-frequency ( $< 0.1 \text{ Hz}$ ) fluctuations of BOLD fMRI signals (Biswal et al., 1995; Fox et al., 2005; Raichle et al., 2001). Examination of low-frequency fluctuations has revealed spatiotemporal synchrony (correlations) between distinct anatomical brain regions, which have been attributed to spontaneous neuronal activity (Xiong et al., 1999). Using this technique, multiple networks of temporally correlated brain regions have been identified that are related to specific types of sensory, motor, and cognitive functions (DeLuca et al., 2006; Margulies et al., 2007; Seeley et al., 2007). Indeed, these intrinsic networks include both the task negative network (i.e., the “default” mode resting state) that shows task-related deactivations, and anticorrelated task-positive networks (DeLuca et al., 2006; Fox et al., 2005; Fox et al., 2006) that are activated during specific tasks or by salient stimuli such as a painful event (Seminowicz and Davis, 2007). It has been proposed that the task-negative intrinsic network acts to monitor the environment to prepare for perception and/or action to salient information (Seminowicz and Davis, 2007). The intrinsic task-positive network includes the dorsolateral prefrontal cortex, insula, supplementary motor area, inferior parietal sulcus, and frontal eye fields (Fox et al., 2005). In a recent functional connectivity study, Seeley et al. (2007) suggested that this task-positive network is actually composed of a “salience network” that includes dorsal ACC, orbitofrontal-insular cortices, and subcortical limbic structures, and an “executive-control network,” connecting the dorsolateral frontal cortex with the parietal cortex. The authors propose that the “salience network” is responding



**Figure 4.**

Insula connectivity fingerprints. **(A)** ROI's placed in the anterior (red), mid (blue), and posterior (green) insula are shown for a single subject. **(B)** Polar plots illustrating patterns of connectivity of each insula subdivision with the cingulate cortex and also key somatosensory brain areas. These fingerprints are based on the correlations between pairs of brain areas. Concentric circles

represent increasing  $t$ -values of the correlation between resting activity of an insula ROI and the pregenual/anterior mid-cingulate (pACC/aMCC), posterior mid-cingulate cortex (pMCC), primary somatosensory (S1), and secondary somatosensory (S2) cortex. The lighter outer circle denotes the region of statistical significance at  $t > 4$ . R, right; L, left.

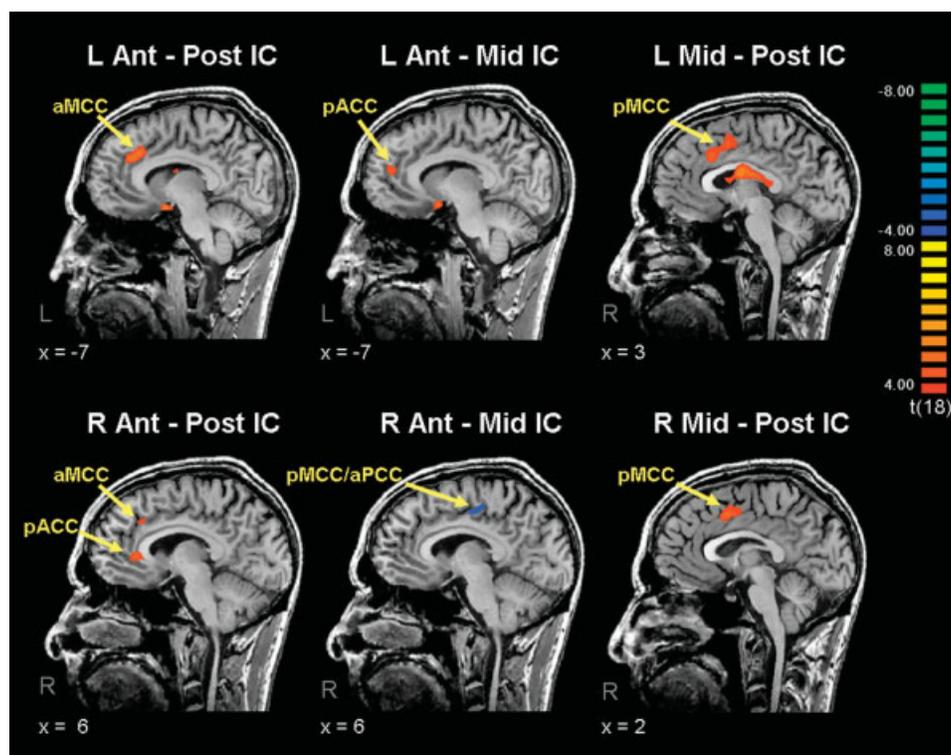
**TABLE III. Contrasts between insula sub-regions in a random effects group analysis of connectivity**

Contrast	Anatomical location (center of gravity)	Talairach coordinates			voxels
		x	y	z	
LaIC >	Left anterior insula	-29	16	-1	15,644
LpIC	Left cingulate gyrus/BA 32 (aMCC)	-1	23	38	4,190
	Left caudate	-12	-4	18	506
	Left middle frontal gyrus/BA 46	-26	48	15	1,075
	Right anterior insula	40	18	6	5,063
	Right middle frontal gyrus/BA 9	37	23	28	223
	Right caudate	7	-5	13	2,132
LaIC >	Left anterior insula	-32	17	-4	2,501
LmIC	Left medial frontal gyrus/BA 9	-1	50	25	200
	Left cingulate/medial frontal gyrus/BA 32 (pACC/aMCC)	-8	45	18	306
	Left superior frontal gyrus/BA 9	-22	58	20	523
	Left inferior frontal gyrus/BA 47	-20	30	-7	171
	Right superior frontal gyrus/BA 10	21	63	2	148
LmIC >	Left mid-posterior insula	-38	-9	12	1,193
LaIC					
LmIC >	Left mid-insula	-20	5	13	34,221
LpIC	Left middle frontal gyrus/BA 9	-37	31	32	168
	Left supramarginal gyrus/BA 40	-56	-43	37	153
	Left inferior frontal gyrus/BA 47	-60	23	-13	245
	Right inferior parietal lobule/supramarginal gyrus/BA 40	54	-40	33	3,730
	Right inferior frontal gyrus/BA 45/45	40	21	15	14,981
	Right inferior parietal gyrus/BA 40	56	-39	50	128
	Right fusiform/inferior temporal gyrus/BA 37	46	-48	-12	167
	Right precentral gyrus/BA 4	36	-7	54	1,154
	Right precuneus/BA 7	10	-66	52	263
	Right cingulate gyrus/BA 32 (aMCC/pMCC)	1	11	40	2,872
RaIC >	Right anterior insula/inferior frontal gyrus/BA 45/44	31	32	6	24,900
RpIC	Right cingulate gyrus/BA 32 (aMCC)	3	24	37	334
	Right cingulate gyrus/BA 24 (pACC)	7	35	6	316
	Left anterior insula	-37	18	-3	1,627
	Left superior frontal gyrus/BA 9	-25	47	27	418
	Left middle frontal gyrus/BA 10	-32	46	-4	188
RaIC >	Right inferior frontal gyrus/BA 47	37	23	-6	649
RmIC					
RmIC >	Right mid-posterior insula	38	-12	15	8,069
RaIC	Right paracentral/cingulate gyrus/BA 31 (pMCC/aPCC)	6	-20	45	752
	Left mid-posterior insula	-36	-16	12	4,872
	Left paracentral/cingulate gyrus/BA 31(pMCC/aPCC)	-10	-18	45	311
RmIC >	Right anterior mid-insula	36	18	14	45,219
RpIC	Right middle frontal gyrus/BA 9	53	-38	33	8,999
	Right middle-inferior temporal gyrus/BA 21/20	46	-32	-14	1,589
	Right superior frontal gyrus/BA 6	20	-5	64	191
	Right cingulate gyrus/BA 32/24 (aMCC/pMCC)	1	4	44	1,319
	Left anterior mid-insula	-40	5	8	13,289
	Left middle frontal gyrus/BA 46/9	-35	38	26	6,001
	Left inferior parietal lobule/BA 40	-56	-39	29	4,589
	Left inferior temporal gyrus/BA37	-57	-55	-5	749

Anatomical locations and center of gravity coordinates (in Talairach space) are provided for the brain areas where the strength of connectivity was found to be significantly different between insular sub-regions at  $P < 0.05$  (corrected). Voxels are reported as  $1 \times 1 \times 1 \text{ mm}^3$ . aIC, anterior insula; mIC, mid-insula; pIC, posterior insula; pACC, pregenual anterior cingulate cortex; aMCC, anterior mid-cingulate cortex; pMCC, posterior mid-cingulate cortex; S2, secondary somatosensory cortex; R, right; L, left.

to the amount of personal salience and not specifically to the stimuli's specific nature (i.e., homeostatic, emotional, or cognitive). Dosenbach et al. (2007) also separated this task-positive network into cingulo-opercular and frontoparietal components using resting state functional connectivity analysis. While these authors propose slightly different functional roles for these two networks, their study also

highlights the tight coupling of resting state activity between parts of the insula and cingulate cortex. Interestingly, these networks were reported to be incomplete in children ( $< 9$  years) with strengthening and maturation of long range connections occurring throughout adolescence; a process that may be related to increased myelination or strengthening of connections through coactivation (Fair et al., 2007).



**Figure 5.**

Random effects contrast maps. All 19 subjects and their insula ROIs were included in the statistical model. Contrasts were made between: (1) bilateral anterior IC minus bilateral posterior (first column); (2) bilateral anterior IC minus bilateral mid-IC (second column); (3) bilateral mid-IC minus bilateral posterior

IC (third column). Maps were thresholded at corrected  $P < 0.05$ . Anterior insula demonstrates stronger connectivity with the pACC/aMCC than either the mid or posterior insular cortex. No significant differences were identified for the pMCC, S1 or S2. IC = insular cortex.

Using an ROI approach based on insula anatomy, we identified this anterior insula/pMCC or “salience network” and additionally found strong correlations between the mid/posterior insula and the MCC. If indeed this network is involved in general salience to internal and externally generated stimuli, the involvement of a brain region that has been termed the “primary interoceptive cortex” is not surprising. Finally, ROIs placed in the mid/posterior insula also revealed strong correlations with the primary and secondary somatosensory cortices, supporting our hypothesis that this system may play a role in skeletomotor body orientation and response selection.

Although there is a growing body of evidence supporting the existence of resting state functional connectivity networks, some studies have shown that in some situations, some of the low-frequency fluctuations are due to non-neuronal physiological fluctuations, such as cardiac, respiratory, and blood CO<sub>2</sub> fluctuations, or scanner instability (Birn et al., 2006; Birn et al., 2008a; Birn et al., 2008b; Fox and Raichle, 2007; Shmueli et al., 2007; Wise et al., 2004). Recent studies suggested that removal of these artifacts (by recording these parameters at the time of scanning and including them as regressors in the statistical

model) can clean the data and improve statistical significance (Birn et al., 2006; Shmueli et al., 2007). Here, we did not collect these physiological parameters, and therefore we cannot access the impact of these artifacts on our data. However, these potential sources of noise are unlikely to have been a significant factor in our study since the major frequencies produced through the cardiac and respiratory processes are in the range of 0.6–1.2 Hz and 0.1–0.5 Hz, respectively (Cordes et al., 2001) and most of our data was in the 0.02–0.1 Hz band. However, it is also possible that high frequency data could be aliased into a lower frequency range. Furthermore, although our data may include some physiological noise, the use of seed regions that are anatomically close, and therefore likely to contain similar amounts of physiological noise, combined with the fact that distinct resting state networks were still identified, leads us to believe that these noise sources were not a major factor.

Tracing studies in the monkey delineate anterior insula connections with the rostral extent of ACC area 24 and a dorsal area between areas 24 and 6 (Mesulam and Mufson, 1982b; Vogt and Pandya, 1987); and mid and posterior insula connections with dorsal areas 23 and 24 (Mesulam

and Mufson, 1982b). Although functional connectivity alone cannot demonstrate direct monosynaptic connections, our functional connectivity findings do support the anatomical evidence that in the human brain these areas are connected. Alternatively, sub-regions of the insula and cingulate could have common inputs driving the synchronous BOLD fluctuations. The thalamus is the most likely candidate as direct projections from the thalamus to the insula and cingulate have been demonstrated in non-human primates (Augustine, 1996; Craig, 2008; Hatanaka et al., 2003; Mufson and Mesulam, 1984; Vogt et al., 1979). Specifically, thalamic nuclei that project to both the cingulate and the insula include the parafascicularis, submedial, reuniens, limitans, and mediodorsal nucleus (Hatanaka et al., 2003; Mufson and Mesulam, 1984; Vogt et al., 1979). In our study, strong connectivity with the thalamus was not found in either the conjunction or the random effect contrast analyses, likely due to the strict statistical requirements combined with the minimum cluster size.

We have identified two systems between the insula and cingulate cortices and used functional fingerprints as a means to convey the connectivity of insular subregions with other brain areas. Previous studies have used the concept of “fingerprints” to display specific patterns of brain activity as polar plot displays of measures ranging from power spectrum peaks to descriptive measures of shape (DeMartino et al., 2007). In addition, Passingham et al. (2002) used fingerprints to display cytoarchitectonic and functional connectivity (Passingham et al., 2002). We now introduce a new application of functional fingerprinting to highlight the strength of resting state connectivity (i.e., correlation of oscillatory activity) between brain areas and conceptualize functional networks based on low-frequency resting state oscillations.

Taken together, the known anatomical projections in the primate brain, combined with the functional connectivity analysis performed in our study and previous functional imaging data indicate two distinct systems between the insula and the cingulate in the adult human brain, for which we suggest the following possible functions: (1) an emotional salience monitoring system linking the anterior insula with the pACC/aMCC, a system responsible for integrating interoceptive information with emotional salience forming a subjective image of our bodily state; and (2) a general salience and action system that links the entire insula and MCC, a system involved in environmental monitoring, response selection and skeletomotor body orientation.

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