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Mapping the functional connectivity of anterior cingulate cortex

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Anterior cingulate cortex (ACC) is a nexus of information processing and regulation in the brain. Reflecting this central role, ACC is structurally and functionally heterogeneous, a fact long appreciated in studies of non-human primates. Human neuroimaging studies also recognize this functional heterogeneity, with meta-analyses and task-based studies demonstrating the existence of motor, cognitive and affective subdivisions. In contrast to task-based approaches, examinations of resting-state functional connectivity enable the characterization of task-independent patterns of correlated activity. In a novel approach to understanding ACC functional segregation, we systematically mapped ACC functional connectivity during rest. We examined patterns of functional connectivity for 16 seed ROIs systematically placed throughout caudal, rostral, and subgenual ACC in each hemisphere. First, our data support the commonly observed rostral/caudal distinction, but also suggest the existence of a dorsal/ventral functional distinction. For each of these distinctions, more fine-grained patterns of differentiation were observed than commonly appreciated in human imaging studies. Second, we demonstrate the presence of negatively predicted relationships between distinct ACC functional networks. In particular, we highlight negative relationships between rostral ACC-based affective networks (including the "default mode network") and dorsal–caudal ACC-based frontoparietal attention networks. Finally, interhemispheric activations were more strongly correlated between homologous regions than in non-homologous regions. We discuss the implications of our work for understanding ACC function and potential applications to clinical populations.

Keywords: Brain mapping; Resting state networks; Intrinsic functional activity; Anticorrelation

Central to a broad array of cognitive, sensorimotor, affective and visceral functions, the anterior cingulate cortex (ACC) has emerged as a locus of information processing and regulation in the brain. These roles befit its central anatomic location and diverse cortical, limbic and paralimbic connections. Though classically designated as a single region, animal studies (Devinsky et al., 1995; Öngür et al., 2003; Paus et al., 1996), as well as human morphometric studies (Huster et al., 2007; Paus et al., 1996; Vogt et al., 1995), have long demonstrated that ACC can be differentiated into functionally and structurally distinct subregions. Neuroimaging and neuropsychological studies in humans are beginning to recognize these distinctions (Barch et al., 2001; Braver et al., 2001; Bush et al., 2000; Derbyshire et al., 1998; Gusnard et al., 2001a; Kiehl et al., 2000; Milham and Banich, 2005; Paus, 2001; Paus et al., 1998; Turken and Swick, 1999; van Veen and Carter, 2002a; Vogt et al., 1996).

In an early effort to delineate ACC functional subdivision in humans, Picard and Strick conducted a meta-analysis of human PET studies in light of findings of motor cortex segregation observed in animals (Picard and Strick, 1996). By defining as simple tasks those that were basic and rote, and as complex those that required additional cognitive or motor demands, the authors found that rostral ACC was activated in response to complex tasks and that caudal ACC was activated during simple tasks. Similar to the findings of animal studies (e.g., Devinsky et al., 1995), there was some evidence that the two divisions are somatotopically organized with respect to output modality. The authors also noted that rostral ACC was activated in conjunction with prefrontal cortex during complex tasks.

In a subsequent meta-analysis of human PET studies, Koski and Paus identified regions within the frontal cortex that were co-activated with distinct ACC subdivisions across a range of tasks (Koski and Paus, 2000). Consistent with a cognitive/affective distinction suggested by animal studies, they found that the middle frontal gyrus was more frequently co-activated with supracallosal ACC, while the medial orbitofrontal gyrus was more frequently co-activated with the subcallosal ACC. Dorsal portions of the supra-

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callosal ACC were consistently co-activated with dorsolateral prefrontal regions, suggesting a greater involvement in complex cognitive operations. Finally, the caudal ACC co-activated with primary and supplementary motor areas, suggesting the presence of cingulate motor areas.

The aforementioned meta-analyses have not been uniformly supported by task-related fMRI studies. Specifically, when Barch and colleagues compared activations related to vocal and manual responses in the spatial and verbal domains, they did not observe subdivisions in ACC corresponding to the different response domains (Barch et al., 2001). On the other hand, the segregation of ACC into affective and cognitive subdivisions has been largely supported by fMRI studies demonstrating the presence of rostral and caudal distinctions, respectively (Bush et al., 2000; Haas et al., 2006; Kiehl et al., 2000; Milham and Banich, 2005; Van Veen and Carter, 2002b).

While task-related fMRI has been useful in mapping these broad ACC subdivisions, it has been limited in affording greater regional specificity. Various cognitive processes have been ascribed to ACC, such as conflict monitoring (Botvinick et al., 2004; Carter et al., 1998), error monitoring and detection (Gehring and Fencsik, 2001; Gehring and Knight, 2000; Holroyd et al., 1998; Lorist et al., 2005), response selection (Awh and Gehring, 1999; Milham et al., 2001; Paus, 2001; Paus et al., 1993), and attention control (Crottaz-Herbette and Menon, 2006; Peterson et al., 1999; Posner and Dehaene, 1994; Posner et al., 1997). However, investigators have noted the sensitivity of ACC activations to task parameters such as stimulus presentation rate (Bench et al., 1993), stimulus novelty (Petersen et al., 1998) and practice effects (Kelly and Garavan, 2005; Milham et al., 2003).

The application of correlational analyses to resting state fMRI data enables the characterization of task-independent patterns of functional connectivity during rest (Biswal et al., 1995). This analytic approach has demonstrated that functionally relevant patterns of activity, commonly observed during task performance, are intrinsically represented in spontaneous brain activity (Beckmann et al., 2005; Damoiseaux et al., 2006; De Luca et al., 2006; Fransson, 2005; Greicius et al., 2003). A recent study by Fox et al. (2006) demonstrated the utility of resting state approaches in mapping neural systems, successfully differentiating the dorsal and ventral attentional systems, two functionally related but distinct networks.

The present work extends this approach to the mapping of functionally distinct subregions of ACC, a functionally and structurally complex region. More specifically, we conducted an unbiased study of functional connectivity in ACC at rest using

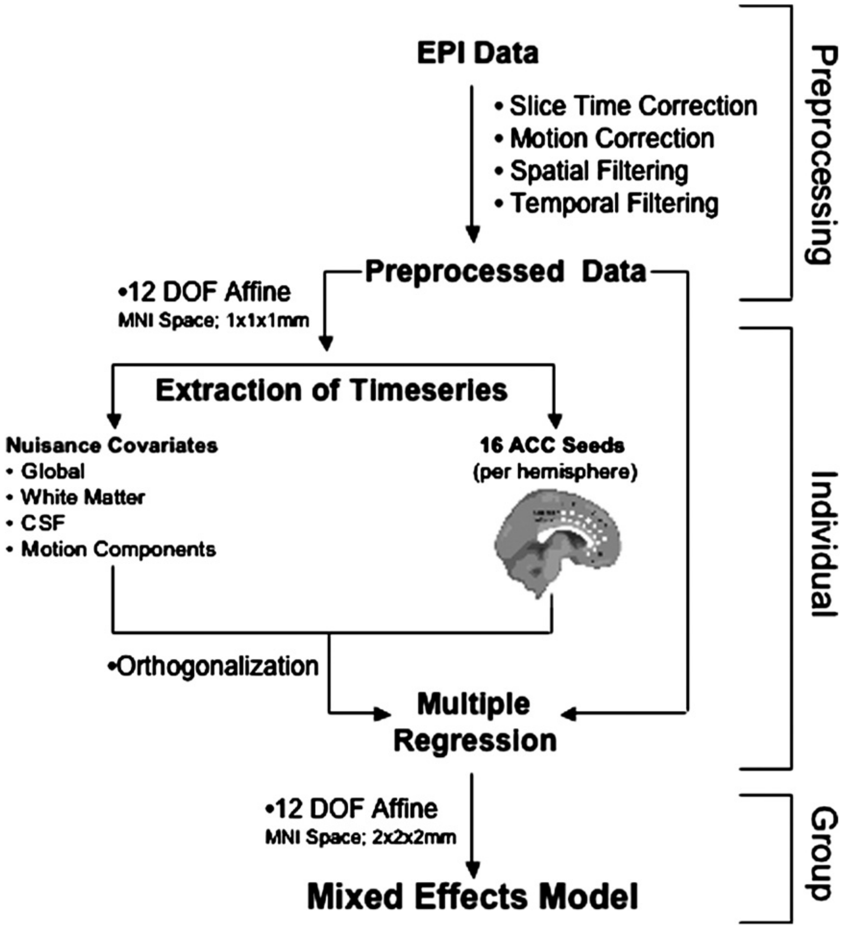

Fig. 1. Data analysis path. Overview of processing steps involved in preprocessing, time-series extraction, and statistical analyses. *Note:* preprocessed functional data interpolated to 1 × 1 × 1 mm in MNI space for time-series extraction in order to increase spatial accuracy of seed placement along inferior and superior ACC curves.

systematically spaced seeds throughout the caudal, rostral, and subgenual regions of ACC in each hemisphere. Prior efforts to provide a comprehensive examination of functional connectivity in ACC using the task-based approaches have required the synthesis of findings across multiple studies (e.g., meta-analyses). We hypothesized that in a single study, systematic examination of patterns of resting state connectivity would provide a more fine-grained understanding of the well established rostral/caudal distinction as well as more subtle regional differentiations (e.g., ventral/dorsal, supracallosal/subcallosal) than has been possible with task-based approaches.

Materials and methods

Participants

Twenty-four right-handed native English-speaking participants were included in our study (15 m; 9 f; mean age: 27.8±8.0). Subjects had no history of psychiatric or neurological illness as confirmed by psychiatric clinical assessment. Signed informed consent was obtained prior to participation. The study was approved by the institutional review boards of the NYU School of Medicine and New York University.

Data acquisition

A Siemens Allegra 3.0 T scanner equipped for echo planar imaging (EPI) was used for data acquisition. For each participant, we collected 197 contiguous EPI functional volumes (TR= 2000 ms; TE=30 ms; flip angle=90, 39 slices, matrix=64×64; FOV=192 mm; acquisition voxel size=3×3×3 mm). Complete cerebellar coverage was not possible for all subjects. During the scan, subjects were instructed to rest with eyes open while the word “Relax” was projected center-screen in white against a black background. For spatial normalization and localization, a high-resolution T1-weighted anatomical image was then acquired using a magnetization prepared gradient echo sequence (MPRAGE, TR=2500 ms; TE=4.35 ms; TI=900 ms; flip angle=8; 176 slices, FOV=256 mm).

Image preprocessing

Data processing, as schematically shown in Fig. 1, was carried out using FSL (www.fmrib.ox.ac.uk). Image preprocessing consisted of: (1) slice time correction for interleaved acquisitions (using Fourier-space time-series phase-shifting), (2) motion correction (using a six parameter affine transformation implemented in FLIRT), (3) spatial smoothing (Gaussian kernel of FWHM 6 mm), (4) temporal high-pass filtering (Gaussian-weighted least-squares straight line fitting with sigma=100.0 s), and (5) low-pass temporal filtering (Gaussian filter with HWHM=2.8 s).

Functional connectivity: seed generation

The goal of the present study was to provide a systematic and unbiased survey of functional connectivity of the anterior cingulate. We created two parallel arrays of spherical seeds (123 voxels in 1×1×1 mm space, radius=3.5 mm) systematically distributed throughout the anterior cingulate cortex in the following manner: (1) the corpus callosum was traced on the standard 152 brain MNI template and fit with a quadratic function; (2) using the callosal curve as a reference, two parallel curves were created within cingulate cortex, one 5 mm above the callosal curve (referred to as “inferior”) and the other 15 mm above the callosal curve (referred to as “superior”); (3) 9 equidistant (10 mm distance) points were calculated along the inferior curve starting at $y = -10$ mm; and, (4) 7 points in the superior curve were calculated, such that each lay along a radial from the inferior points [see Table 1]. One set of seeds was created for each hemisphere at $x = \pm 5$ mm.

In order to obtain the time-series for each seed in each subject, we (1) transformed the subject’s time-series into MNI space using a 12 DOF linear affine transformation implemented in FLIRT (voxel size=1×1×1 mm) and (2) calculated the mean time-series for each of the 16 mask-spheres (in each hemisphere) centered around a seed coordinate.

Functional connectivity: statistical analysis

For each hemisphere, individual analyses were carried out on all 16 seeds for each participant using multiple regression (as implemented in FSL’s FEAT). The regression model included the 16 ACC seed time-series as predictors as well as the nuisance covariates (seed time-series for global signal, white matter, cerebrospinal fluid, and six motion parameters). In order to ensure that the time-series for each seed mask reflected its own unique variance, each seed’s time-series was orthogonalized with respect to each of the other 15 ACC seeds and the nuisance covariates using the Gram–Schmidt process ($A_{\mathrm{orth}} = A - B\ (A \cdot B)/(B \cdot B)$) as implemented in FEAT. The effectiveness of the orthogonalization strategy was verified by examination of correlation matrices before and after orthogonalization (see Fig. 2 for average before and after correlation matrices). The individual participant analysis produced subject-level maps of all positively and negatively predicted voxels for each regressor.

Group-level analyses were carried out using a mixed-effects model (FLAME) as implemented in FSL. Corrections for multiple comparisons were carried out at the cluster level using Gaussian random field theory (min $Z > 2.3$; cluster significance: $p < 0.05$, corrected). This group-level analysis produced threshold *z*-score maps of activity associated with each ACC seed.

Table 1
Coordinates for each of the right and left hemisphere seeds are given in coordinates defined by the Montreal Neurological Institute stereotaxic space

Seed	x	y	z
i1	±5	−10	37
i2	±5	0	36
i3	±5	10	33
i4	±5	19	28
i5	±5	27	21
i6	±5	34	14
i7	±5	38	6
i8	±5	34	−4
i9	±5	25	−10
s1	±5	−10	47
s2	±5	2	46
s3	±5	14	42
s4	±5	25	36
s5	±5	34	28
s6	±5	41	21
s7	±5	47	11

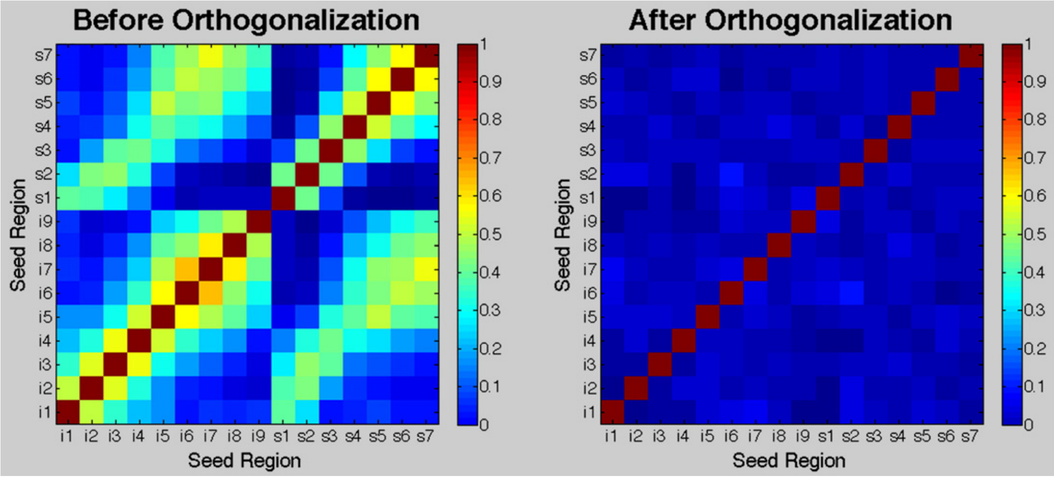

Fig. 2. Impact of orthogonalization on time-series correlations. Each seed's time-series was orthogonalized with respect to every other seed's time-series in a given hemisphere. The mean correlation matrix for right hemisphere seeds (averaged across participants) is depicted before and after orthogonalization.

We considered the possibility that orthogonalization of the time-series for each of the seeds with respect to each other may lead to underestimation of functional connectivity due to removal of common variation. Accordingly, we repeated our analyses, with each seed in a separate regression model (along with nuisance covariates), rather than orthogonalized and entered simultaneously into a single model as described above. Findings for analyses using orthogonalized and non-orthogonalized seeds were highly similar, with the most notable difference being higher degree of overlap in patterns of functional connectivity for neighboring seeds in the non-orthogonalized analyses (as would be expected given the presence of correlations) (see Supplementary Figs. 4 and 5 for examples of a single participant's data with and without orthogonalization). Data reported here are from the initial analyses for the right hemisphere, in which the seeds were modeled simultaneously in a single orthogonalized model. Left hemisphere results are presented as Supplementary Figs. 1–3.

Results

Rostral to caudal

Positively correlated networks

Consistent with prior work, our analyses revealed marked differences in functional connectivity along the rostral/caudal dimension, though with a more gradual and complex pattern of transition than commonly appreciated in human neuroimaging studies. At the extremes, the inferior rostral seeds i5–i9 exhibited consistent patterns of correlated activity with limbic and paralimbic regions implicated in affective processes (e.g., amygdala, hippocampus, ventromedial prefrontal cortex and posterior cingulate cortex), while caudal seeds (i1, i2, s1, s2) exhibited patterns of correlated activity with fronto-parietal regions commonly implicated in sensorimotor processes [see Figs. 3–5]. Intermediate seeds showed greater functional connectivity with lateral prefrontal regions associated with higher order cognitive functions (e.g., working memory, cognitive control), with superior seeds s3 and s4 correlating with dorsolateral and posterior inferior prefrontal cortices and inferior seeds i3–i5 correlating with ventrolateral prefrontal and lateral orbitofrontal regions.

Negatively correlated networks

Functional connectivity analyses also demonstrated marked distinctions in negative relationships ("anticorrelations") between ACC and other brain regions, which varied systematically from the rostral to caudal portions of ACC. The subgenual seeds i8 and i9, and superior rostral seeds s6 and s7 negatively predicted activity within a number of posterior brain regions linked to sensorimotor and attentional domains, including superior parietal regions, portions of extrastriate and striate visual cortices, and superior cerebellar regions (see Figs. 3–5). Centrally located superior seeds s4 and s5 negatively predicted activity within portions of the inferior temporal and medial temporal lobes (hippocampus and amygdala). Anticorrelations for centrally located inferior seeds were somewhat less extensive, primarily limited to inferior parietal regions and, to a lesser degree, to inferior temporal regions.

The extreme caudal seeds negatively predicted activity in many of the same regions positively predicted by extreme rostral seeds. More specifically, s1 and s2 negatively predicted activity in ventromedial prefrontal cortex, rostral ACC, and posterior cingulate cortex. In addition, they negatively predicted activity in medial, superior cerebellar, extrastriatal, and superior parietal regions. Finally, s1, which is correlated with motor cortices and generally implicated in complex motor tasks, negatively predicted superior cerebellar activity as well as portions of the basal ganglia and thalamus. It is worth noting that the extensive pattern of anticorrelated activity for seeds s1 and s2 was not noted in the inferior i1 and i2 seeds. In fact, seeds i1 and i2 actually show a pattern of positive co-activation extending through BA 24 into some of the same rostral regions negatively related with the superior seeds.

Subgenual

Examination of subgenual seeds i8 and i9 revealed an extensive pattern of connectivity with orbitofrontal and striatal regions. Connectivity for seed i9 was notably more extensive within orbitofrontal cortex than i8, reaching inferior lateral portions as well. In contrast to the supracallosal seeds, the subgenual seeds also showed greater connectivity with posterior cingulate.

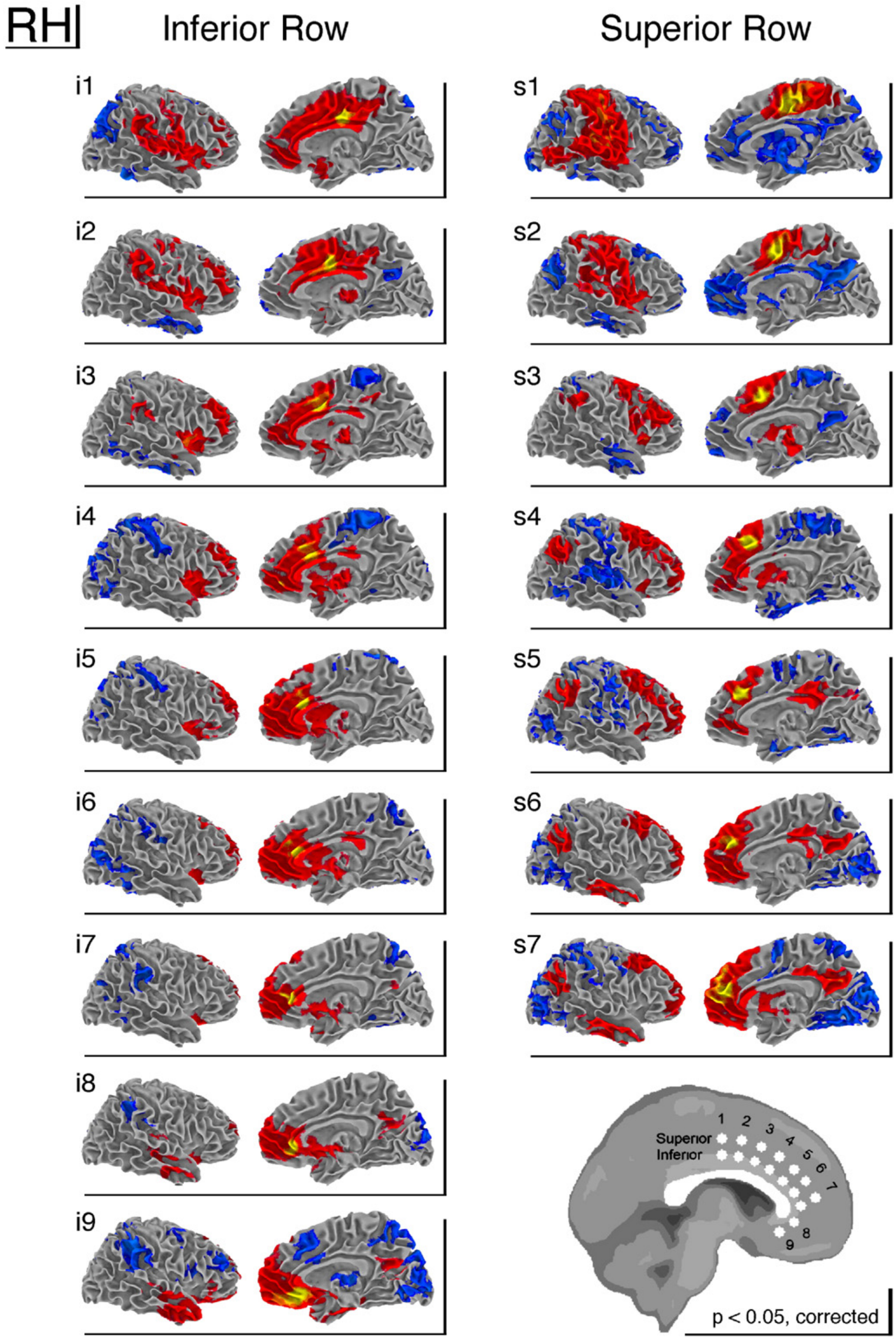

Fig. 3. Functional connectivity in right anterior cingulate cortex (surface maps). Bottom right corner: anterior cingulate cortex (ACC) was seeded at 16 coordinates along two separate rows. Inferior seeds (i1–i9) are located 5 mm from the corpus callosum starting at $y = -10$ mm and spaced 10 mm apart along the curve parallel to the corpus callosum. Superior seeds (s1–s7) are located 15 mm from the corpus callosum along the radial axis from each of the first seven inferior seeds. *Main:* cortical surface maps were created using the 16 right hemisphere seeds of the positively (red) and negatively (blue) predicted voxels for each inferior (left column) and superior (right column) seed ($p < 0.05$, corrected).

Right versus left hemispheres

Right and left hemispheres showed highly similar patterns of anterior cingulate connectivity [for left hemisphere connectivity maps, see Supplementary Figs. 1–3]. Correlation analyses examining the relationships between right and left hemisphere seeds suggest that the similarity in patterns of functional connectivity is a reflection of the highly similar spontaneous activity

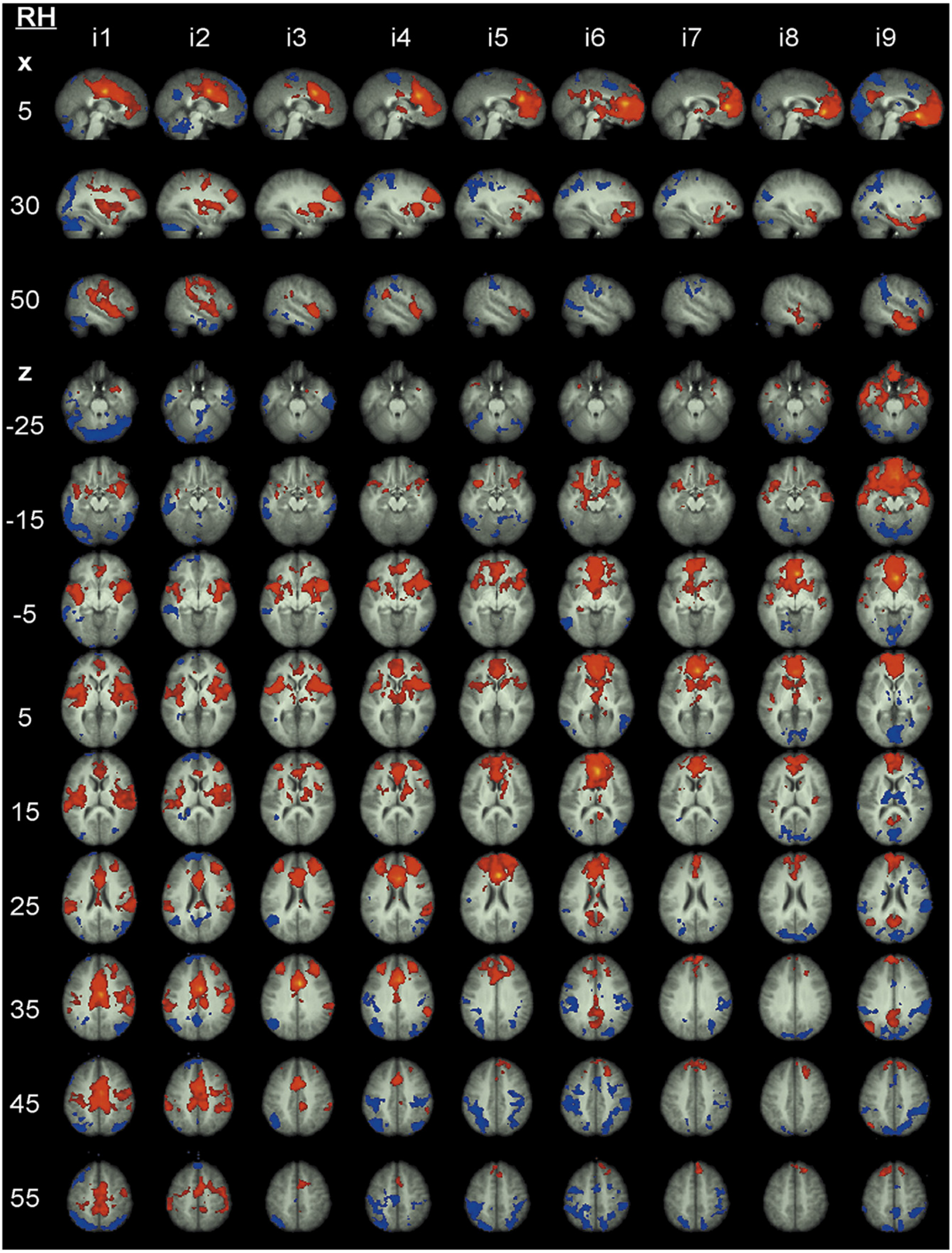

Fig. 4. Functional connectivity in right anterior cingulate cortex (inferior seeds). Inferior right hemisphere (RH) maps of seeds i1–i9 are presented with positive and negative correlations superimposed on three sagittal slices located at $x = 5$, 30, and 50 mm, and nine axial slices at $z = -25$, -15, -5, 5, 15, 25, 35, 45, 55 mm ($p < 0.05$, corrected).

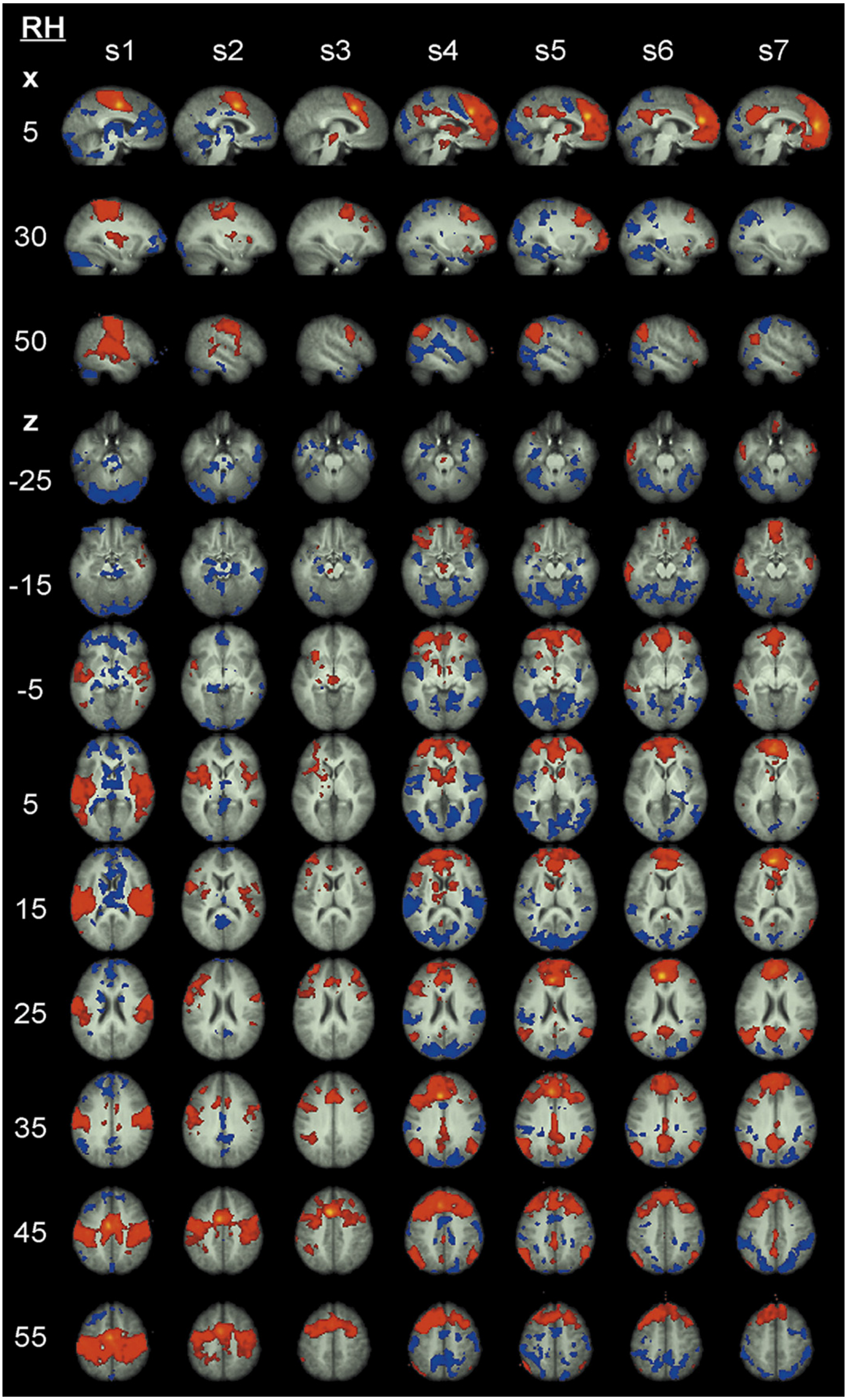

Fig. 5. Functional connectivity in right anterior cingulate cortex (superior seeds). Superior right hemisphere (RH) maps of seeds s1–s7 are presented with positive and negative correlations superimposed on three sagittal slices at $x=5$, 30, and 50 mm; and nine axial slices at $z=-25$, -15, -5, 5, 15, 25, 35, 45, 55 mm ($p<0.05$, corrected).

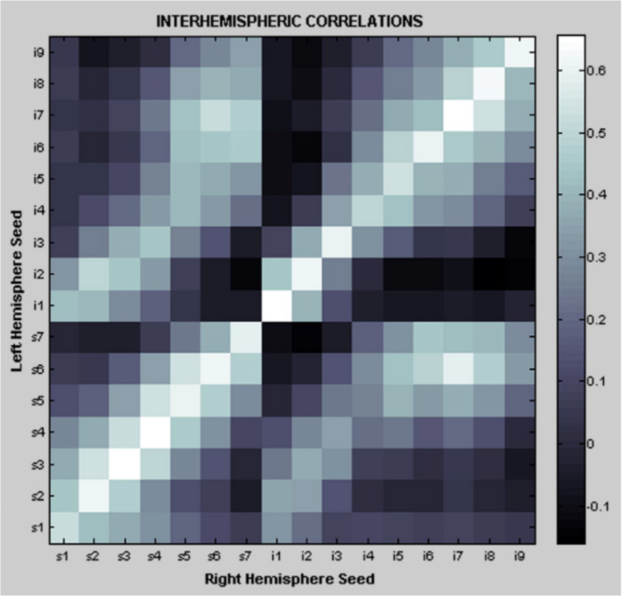

Fig. 6. Correlations among contralateral seeds. Correlation analyses were conducted between the time-series for right and left hemisphere seeds for each participant (correlation for each right–left hemisphere seed pair, averaged across participants, is depicted in figure). Maximal correlations were noted for homologous right–left seed pairs. Of note, correlations depicted in this figure were calculated using non-orthogonalized data.

present in both hemispheres. As Fig. 6 shows, spontaneous activity between contralateral (i.e., homologous) seeds was significantly more highly correlated than between any other seed pairs.

Despite the high degree of hemispheric similarity, our analyses do reveal some noteworthy distinctions. Negative relationships were, in general, more dominant in the left hemisphere. Specifically, the superior caudal-most seed of the left hemisphere [see s1, Supplementary Figs. 1 and 3] had more robust anticorrelations with basal ganglia and medial prefrontal regions. The right hemisphere had more anticorrelated activity in the rostral seeds, specifically with thalamus and occipital cortices.

Discussion

Here we present the first attempt to systematically map functional connectivity of ACC during the resting state. We examined ACC connectivity at 10 mm intervals along two parallel curves aligned with the corpus callosum and found progressive shifts in ACC connectivity from point to point. This is one of the first demonstrations of marked differences in the patterns of functional connectivity over such small distances (Fox et al., 2006; Vincent et al., 2006) within a functionally heterogeneous region such as anterior cingulate cortex.

Although numerous functional imaging studies have drawn attention to a rostral/caudal distinction in ACC function, our findings revealed more fine-grained variations. Activity in the caudal division of ACC was correlated with activity in sensorimotor circuits, while more rostral portions were correlated with prefrontal regions. This distinction is in line with the findings of previous studies that have suggested that anterior cingulate organization takes into account “task complexity” with sensorimotor circuits being represented in the posterior portion of the “caudal division” and higher order executive function circuits being located in the more anterior aspects of the division. Between rostral and caudal zones we observed transition regions, which appear to be associated with a combination of ventral and dorsal brain systems, possibly allowing for the integration of affective and sensorimotor processes required for processes such as conflict detection (Botvinick et al., 2004) and error monitoring (Gehring and Knight, 2000).

Raichle and colleagues have drawn attention to a negative relationship between areas supporting performance of a variety of attentional functions (such as dorsolateral prefrontal cortex, caudal ACC and superior parietal cortex) and rostral regions associated with non-goal directed, stimulus-independent processes (a default mode network, comprising ventromedial prefrontal, posterior cingulate and lateral parietal cortices) (Gusnard et al., 2001a,b). The present work provides further support for the existence of such negative relationships, albeit with greater specificity. We observed that the dorsal aspect of caudal ACC, which was positively correlated with regions typically implicated in attentional processes (e.g., dorsolateral and posterior inferior prefrontal cortices), was negatively correlated with rostral ACC and other regions of the default mode network including ventromedial prefrontal and posterior cingulate cortices. Based upon prior anatomical and functional studies, Koski and Paus (2000) suggested that the rostral and caudal divisions can be delineated by the plane $y=10$. Our analyses also suggested the presence of a delineation in proximity of $y=10$, a portion of ACC which showed virtually no negative correlations within or outside of ACC. Of note, the antagonistic relationship between caudal and rostral ACC regions was limited to the dorsal aspect of caudal ACC (s1 and s2). The i1 and i2 seeds in caudal ACC actually showed a positive relationship with more rostral portions of ACC, extending through BA 24 and into subgenual cingulate. This positive link between caudal and rostral divisions suggests the existence of a more complex relationship than is commonly appreciated in discussions of the rostral/caudal distinction. It also draws attention to a possible dorsal/ventral functional distinction in supracallosal ACC, one which follows the structural distinction between BA 32 and 24.

Several additional meaningful negative relationships were noted between ACC subregions and a variety of other distributed brain systems. Seed s1, which primarily correlated positively with motor cortex, negatively correlated with subcortical circuits including basal ganglia, thalamus, and cerebellum, possibly reflecting its hypothesized role in the inhibition of prepotent stereotyped responses (Paus, 2001; Paus et al., 1993). Rostral seeds i4, i5, i6, i9, s6 and s7, while positively correlated with limbic and paralimbic regions implicated in affective processing (Davidson and Irwin, 1999), were negatively correlated with superior parietal regions, which are involved in higher order cognitive processes such as attentional control and working memory (Banich et al., 2000; Carlson et al., 1998; Coull et al., 2003). These relationships may delineate some of the circuits through which emotional and cognitive processes interact.

Our findings also provide insights into the patterns of functionally coordinated activity between the two cerebral hemispheres. While some models of interhemispheric interaction suggest that the cerebral hemispheres act independently of one another (Zaidel and Clarke, 1990), we demonstrated the presence of coherent fluctuations in homologous regions between hemispheres. This finding is more consistent with models of interhemispheric interaction that emphasize the parallel distributed nature of interhemispheric processing (Banich, 1998; Banich and Belger, 1990). Ongoing work is examining factors capable of modulating such connectivity.

Beyond the potential benefits of examining functional connectivity in ACC and other heterogeneous regions, our approach provides a systematic method for examining neural connectivity in various clinical disorders. The mapping of functional connectivity may help reveal the circuitry underlying deficits in cognitive and affective control processes. Functional imaging during resting states also has the advantage of bypassing potentially confounding issues relating to ceiling, floor, and practice effects, which can be particularly problematic for studies of psychopathology and development.

Though intriguing, examination of resting-state data alone does have a notable limitation: multiple studies have shown that functional connectivity can change during task performance (e.g., De Luca et al., 2005; Fransson, 2006). Additional work is needed to further delineate the impact of task performance on patterns of activity observed at rest. Furthermore, there is no reason to believe that resting-state analysis does not face the same potential limitations as task-related fMRI studies attempting to spatially differentiate the ACC, namely, that of high inter-individual variability in ACC organization and connectivity (Paus et al., 1996). However, as demonstrated in Supplementary Fig. 4, the patterns of functional differentiation observed in our group analyses using our seeding approach are relatively robust and detectable at the individual participant level.

While we acknowledge that further subdivisions in ACC beyond those identified in the present study may exist, our selection of 10 mm spacing between seeds was based on the commonly accepted notion that resolving brain regions beyond 8–10 mm with fMRI can be difficult. Similarly, different schemes for distributing seeds throughout ACC can be derived—the one used in the present study was designed to provide an objective, unbiased survey, but was not intended to be definitive. An additional limitation of the present study was that incomplete coverage of the inferior portions of cerebellum prevented us from potentially appreciating even more robust cingulate–cerebellar interactions, which were clearly present for superior regions of the cerebellum. Finally, it is worth noting that these results do not address causality or hierarchy within any of the circuits identified. Future work using methods such as path analysis or Granger causality (Goebel et al., 2003) may serve to elucidate such relationships.

In summary, the present study yielded a number of notable findings: (1) patterns of ACC functional connectivity commonly observed in neuroimaging studies were intrinsically represented in resting state brain activity, (2) the functional connectivity maps supported the commonly cited rostral/caudal functional distinction and the need to appreciate a more fine-grained pattern of differentiation in future studies, and (3) intricate negatively correlated relationships between networks provide unique insights into the functional segregation of ACC. Future work will focus on similarly systematic examination of other brain regions and the application of these systematic approaches to clinical populations.

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Appendix A. Supplementary Data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2007.05.019.

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