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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

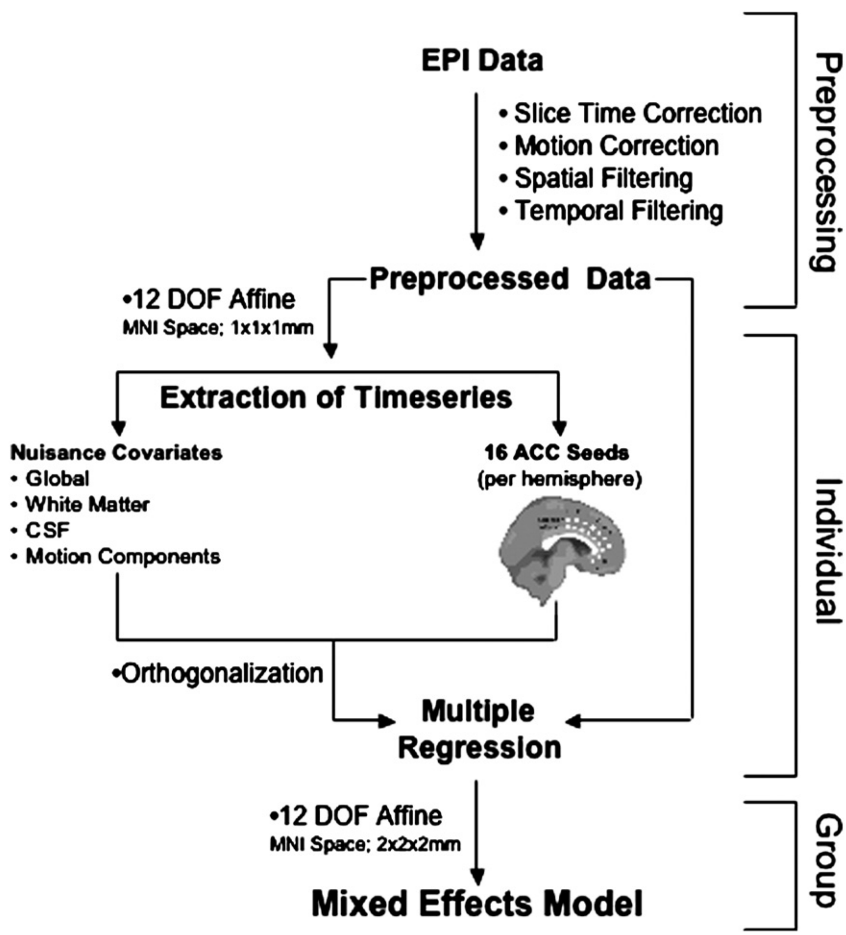

Fig. 1. Data analysis path. Overview of processing steps involved in preprocessing, time-series extraction, and statistical analyses. *Note:* preprocessed functional data interpolated to 1 × 1 × 1 mm in MNI space for time-series extraction in order to increase spatial accuracy of seed placement along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