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Anterior cingulate activation relates to local cortical thickness

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Abstract

Few studies have examined the relationship between local anatomic thickness of the cortex and the activation signals arising from it. Using structural and functional magnetic resonance imaging, we examined whether a relationship exists between cortical thickness and brain activation. Twenty-eight subjects were asked to perform the Go/NoGo response inhibition task known to activate the anterior cingulate and prefrontal cortex. Structural data of the same regions were simultaneously collected. We hypothesized that cortical thickness in these brain regions would positively correlate with brain activation. Data from the structural MRI were aligned with the functional MRI activation data. There was a positive linear correlation between cortical thickness and activation during response inhibition in the right anterior cingulate cortex [Brodmann's Area (BA) 24]. No significant thickness-activation correlations were found in the prefrontal cortex. Correlations between cortical thickness and activation may occur only in certain brain regions.

Keywords

Anterior cingulate cortex; Magnetic Resonance Imaging; cortical thickness; fMRI; response inhibition

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Introduction

Few studies have examined whether there is a relationship between regional cortical thickness and brain function. The dearth of studies using multiple imaging techniques can be partly attributed to the complexity of aligning, or registering, data sets of structure (thickness) and function (activation) within and across subjects. In fact, to our knowledge only two studies have directly correlated functional magnetic resonance imaging (fMRI) signals [blood oxygen level dependent (BOLD) signal response] to the underlying anatomy (cortical thickness) obtained from structural MRI [1,2].

A technique known as cortical pattern matching (CPM) allows for anatomy across participants to be aligned in the same coordinate space as fMRI data, making it easier to align the activation patterns [3]. In this study we collected structural MRI data and functional MRI (fMRI) data and used CPM to align brain images obtained from each technique. For fMRI we used the Go/NoGo response inhibition task, which is known to reliably and robustly elicit activation in the anterior cingulate cortex [4,5] and prefrontal cortex [4–6]. We examined associations at the voxel level (that is, a volume of measurement equal to .33 mm cubed) between cortical gray matter thickness and the BOLD signal arising from the same region or voxel. We hypothesized that cortical gray matter thickness would be strongly correlated with BOLD signal response in the anterior cingulate cortex and prefrontal cortex.

Methods

Participants

The study was approved by the University of California, Los Angeles (UCLA) Institutional Review Board, and all participants provided written informed consent. Participants were recruited through advertisement and were excluded if they met SCID [7] criteria for any current or past psychiatric diagnosis, had a history of substance abuse, were left-handed, had untreated hypertension, neurological illness, metal implants, or a history of skull fracture or head trauma with a loss of consciousness exceeding 5 minutes. Twenty-eight adult participants (15 males/13 females), with an average age of 35.61 ± 12.32 years, met study criteria.

Image acquisition

High-resolution structural data for use in cortical thickness analyses were acquired for all subjects on a 1.5 Tesla (T) Siemens Sonata MRI scanner. We obtained contiguous sagittal high-resolution three-dimensional magnetization-prepared rapid gradient echo (MP-RAGE) T1-weighted images (TR=1,900 ms; TE=4.38 ms, Flip-angle: 15°, FOV=256mm; slice thickness=1mm; 160 slices). Functional MRI data were collected for all subjects on a 3 Tesla (T) Siemens Allegra MRI scanner. Functional series used to evaluate the BOLD signal used a T2*-weighted EPI gradient-echo pulse sequence [repetition time (TR)=2,500ms; echo time (TE)=35ms; Flip-angle=90° field of view (FOV)=24cm; slice thickness = 3mm; 28 slices]. EPI structural images were obtained co-planar to the functional scans (TR=5000, TE=33 ms, 3 mm thick, matrix 128², FOV=24 cm, 28 slices) for use in registration.

Activation task paradigm

The Go/NoGo task began and ended with 30-second rest blocks, with eight alternating 30.5-second blocks of “Go” and “NoGo” conditions. During the “Go” (control) condition, subjects viewed a series of random letters and were instructed to press a button on a response box for each letter. In the “NoGo” (experimental) condition, subjects were also shown a series of random letters, but were instructed to withhold responses to the letter “X.”

In the “NoGo” subjects saw the letter “X” in 25% of trials and the order of the appearance of the letter “X” in the experimental block was random. Stimulus presentation lasted 0.5 sec, with an interstimulus interval of 1.5 sec.

Cortical thickness analysis

Image pre-processing consisted of (1) adjustment for head position and transformation of data into a common stereotaxic coordinate system without scaling using a 6-parameter transformation (<http://www.bic.mni.mcgill.ca/ServicesSoftware/>); (2) automated exclusion of non-brain tissue and cerebellum [8]; (3) correction for magnetic field inhomogeneity artifacts [9]; (4) resampling using isotropic voxels of size 0.33 mm to estimate cortical thickness with voxel accuracy and (5) partial volume classification to classify voxels as gray matter, white matter, CSF, or a non-brain class [10]. After preprocessing, cortical thickness was computed separately for each participant from preprocessed MR images. Thickness was defined as the shortest 3D distance from the cortical white-gray matter boundary to the hemispheric surface without crossing voxels classified as CSF. Specifically, an implementation of the Eikonal equation was applied to voxels segmenting as cortical gray matter to compute these distances (in millimeters) in a fully automated manner at each point along the cortical surface [3]. A uniform spatial filter of a radius of 15 mm was applied. These methods produce thickness measurements that agree with those in post mortem samples [11] and are stable over time in validation studies using short-interval repeat scans of multiple subjects [12].

fMRI data analysis

Processing of functional neuroimaging data was performed using FEAT (FMRI Expert Analysis Tool) Version 5.91, part of FSL 4.0 (www.fmrib.ox.ac.uk/fsl). The following pre-processing methods were applied: motion correction using MCFLIRT [13]; removal of non-brain matter using Brain Extraction Tool (BET) [14]; spatial smoothing using a Gaussian kernel of FWHM 5mm; grand-mean intensity normalization of the entire functional data set by a single multiplicative factor; and high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with $\sigma=65.0$ -sec) [15]. Subjects showing head motion greater than 1.5mm were excluded from further analysis. A first-level analysis was performed for each subject for the “NoGo” minus “Go” contrast to evaluate which regions demonstrated increased activation during response inhibition (cluster threshold of $Z>2.3$, $p=0.05$, corrected for multiple comparisons) and to generate unthresholded t -maps for use in subsequent steps.

Relating structural and functional MRI data

For the precise mapping of structure-function correlations within each subject, structural MR images were co-registered with functional MR images in the following manner. First, the low-resolution 3T structural scan was registered to the subject's high resolution 1.5T structural scan using a rigid-body transformation. This transformation was applied to the unthresholded t -map for each subject representing the “NoGo” minus “Go” contrast, to register the functional activation map to the high resolution structural data. The unthresholded t -map for each individual was then smoothed using a spatial spherical smoothing kernel with a 15 mm radius.

To allow for the registration of individual cortical thickness and functional activation maps to the study-specific anatomical template, cortical pattern matching methods were applied [3]. Each participant's T1-weighted image was processed to create a 3D surface model of the cortex using automated software that deforms a spherical mesh surface to fit cortical surface tissue using a threshold intensity value that differentiates extracortical CSF from brain tissue [16]. Thirty-one separate sulci, per hemisphere, were manually delineated on each

participant's surface model. Sulcal tracing was performed by a trained researcher blind to participant characteristics, using the MNI-Display software (<http://www.bic.mni.mcgill.ca/ServicesSoftware>), in conjunction with a previously validated surface-based anatomical protocol [12]. Tracer reliability was confirmed using the three-dimensional root mean square difference (in millimeters) between sulci in a set of six test brains and those of a gold standard set. A disparity of less than 2 mm between the test and gold standard brains was used as the reliability threshold for all landmarks.

To align sulcal/gyral anatomy, warping algorithms were used to compute the amount of shift in the x, y, and z directions needed to explicitly match each sulcus in every participant to that of the average anatomical study template [3]. CPM algorithms were then used to associate the same parameter space coordinates across participants, without actually changing the dimensions of the cortical surface models so that corresponding anatomy across participants bore the same coordinate locations.

Correlations between activation occurring during the “NoGo” minus “Go” contrast and cortical gray matter thickness were examined by calculating Pearson's r correlation coefficients at each cortical surface point. Correlation results were thresholded at $p < 0.05$, using Fisher's z-transform. False Discovery Rate (FDR) correction was used to control for multiple comparisons [17] within the prefrontal cortex (BA 44–47, and 8–11) and anterior cingulate cortex (BA 24, 32 and 33). These regions of interest were defined using the deformable Brodmann Area Atlas [18]. After revealing a significant correlation within the anterior cingulate cortex, we repeated FDR correction on individual Brodmann's Areas (BA) to determine which specific subregions of the anterior cingulate cortex were driving the significant effect.

Results

Behavioral responses

All subjects had high accuracy across both the Go and NoGo conditions. The mean accuracy was 99.7% (± 0.39) during Go trials and 99.9% (± 0.003) during NoGo trials.

Cortical thickness and fMRI activation maps

Maps of average cortical thickness across all subjects revealed greater cortical thickness in the cingulate cortex relative to the prefrontal cortex (Figure 1a). Relative to the overall cortex, there was greater cortical thickness in temporal regions and cortical thinning in the medial occipital regions. Analysis of fMRI BOLD signal during the response inhibition contrast of “NoGo” minus “Go” revealed activation in the inferior frontal gyrus, anterior cingulate cortex and striatum in both hemispheres. These results are also consistent with prior fMRI studies such as Horn et al. [19].

Correlations between cortical thickness and function

Significant positive correlations between cortical thickness (at the voxel level) and fMRI BOLD signal were found within subjects in the right anterior cingulate cortex ($p = 0.008$; Figure 1c). Exploratory analyses using smaller Brodmann's Area regions of interest revealed that this effect was driven by the correlation in BA 24 ($p = 0.006$). Participants showed no significant structure-function correlations in the left anterior cingulate cortex, nor any correlations within prefrontal cortex regions (all p 's > 0.10).

Discussion

This is the first study, to our knowledge, to show a significant positive, linear association between cortical gray matter thickness with fMRI BOLD signal response in the right anterior cingulate cortex during a task known to activate this brain region (response inhibition task). By aligning structural and functional datasets using cortical pattern matching registration methods [3], we were able to demonstrate correlations at each 3D point on the cortical surface. No structure-function correlations were detected in other subregions of the frontal lobe, including the lateral prefrontal cortex and left anterior cingulate cortex.

The anterior cingulate cortex is involved in performance monitoring and response conflict [20]. During response inhibition, the anterior cingulate cortex functions as a relay station between the ipsilateral inferior frontal cortex and subthalamic nuclei, activating the globus pallidus, which in turn suppresses the thalamus and primary motor response [4]. Our findings of activation in this region are consistent with existing literature on activation patterns in the inferior frontal and anterior cingulate cortices during tasks that require inhibiting responses [4,21]. We expand on these prior fMRI studies by linking the BOLD signal response with the thickness of the cortical gray matter in this region. The lack of significant structure-function correlations in the prefrontal cortex is consistent with one previous study [22], although a second study of healthy adults revealed a negative correlation between thickness and activation in this region [2]. Few prior studies have used CPM to relate cortical thickness to measures from other imaging modalities. Foland-Ross et al. found amygdala activity in response to an emotional task was inversely correlated with left prefrontal cortex cortical thickness in healthy adults [23], suggesting that the inhibitory role of the prefrontal cortex on amygdala activation might be mediated by prefrontal cortex gray matter thickness. A second study used CPM to relate gray matter thickness to the cortical distribution of a PET ligand associated with the presence of plaques and tangles in normal aging and Alzheimer's disease [22]. No significant correlations were detected. If there is indeed a direct relationship between the structure and function of a given brain area, then examining that relationship at each cortical surface point (as in this study) as opposed to examinations of average activation and structural measurements across a region, may offer a more spatially detailed and accurate way of measuring the relationship between cortical structure and function.

This study has two limitations. First, while our findings reveal a strong positive association of right anterior cingulate function with the thickness of the right anterior cingulate structure, we cannot be certain of a causal relationship between structure and function: the correlations revealed may be due to an unknown effect of another brain factor. For example, both the BOLD signal and the gray matter may be influenced by the microvasculature of the cortex. Second, in some brain regions the relationship between cortical thickness and function might be non-linear, such that at a certain point increases in cortical thickness may not result in a corresponding proportional increase in functional activation [2].

Conclusion

While existing studies have employed the combination of several imaging approaches in an attempt to understand how brain structure relates to function, this is the first study, to our knowledge, that has successfully identified a linear, positive relationship in locations across the cortical surface, between gray matter thickness and activation in the right anterior cingulate cortex of healthy subjects. Application of this technique to other focal regions of interest in larger samples will help untangle the complex relationship of brain function and structure. Existing cortical thickness measurement tools do not allow for the identification of

whether cortical thickness measurements reflect differences in the number or density of neurons, glia, or variations in intra-cortical myelination levels. Future studies that employ high-resolution images of the cortex, attainable perhaps by use of local coils and higher field strengths (7 or 8T), could address these issues.

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References

- [1]. Lu LH, Dapretto M, O'Hare ED, Kan E, McCourt ST, Thompson PM, et al. Relationships between brain activation and brain structure in normally developing children. *Cereb Cortex*. 2009; 19:2595–2604. [PubMed: 19240138]
- [2]. Rasser PE, Johnston P, Lagopoulos J, Ward PB, Schall U, Thienel R, et al. Functional MRI BOLD response to Tower of London performance of first-episode schizophrenia patients using cortical pattern matching. *Neuroimage*. 2005; 26:941–951. [PubMed: 15955504]
- [3]. Thompson PM, Hayashi KM, Sowell ER, Gogtay N, Giedd JN, Rapoport JL, et al. Mapping cortical change in Alzheimer's disease, brain development, and schizophrenia. *Neuroimage*. 2004; 23(Suppl 1):S2–18. [PubMed: 15501091]
- [4]. Aron AR. The neural basis of inhibition in cognitive control. *Neuroscientist*. 2007; 13:214–228. [PubMed: 17519365]
- [5]. Rubia K, Russell T, Overmeyer S, Brammer MJ, Bullmore ET, Sharma T, et al. Mapping motor inhibition: conjunctive brain activations across different versions of go/no-go and stop tasks. *Neuroimage*. 2001; 13:250–261. [PubMed: 11162266]
- [6]. Forstmann BU, Jahfari S, Scholte HS, Wolfensteller U, van den Wildenberg WP, Ridderinkhof KR. Function and structure of the right inferior frontal cortex predict individual differences in response inhibition: a model-based approach. *J Neurosci*. 2008; 28:9790–9796. [PubMed: 18815263]
- [7]. Spitzer, RL.; Williams, JB.; Gibbon, M.; First, MB. Structured clinical interview for DSM-IV. Biometrics Research Dept., NYC Psychiatric Institute; New York: 1996.
- [8]. Shattuck DW, Leahy RM. BrainSuite: an automated cortical surface identification tool. *Med Image Anal*. 2002; 6:129–142. [PubMed: 12045000]
- [9]. Zijdenbos AP, Dawant BM. Brain segmentation and white matter lesion detection in MR images. *Crit Rev Biomed Eng*. 1994; 22:401–465. [PubMed: 8631195]
- [10]. Shattuck DW, Sandor-Leahy SR, Schaper KA, Rottenberg DA, Leahy RM. Magnetic resonance image tissue classification using a partial volume model. *Neuroimage*. 2001; 13:856–876. [PubMed: 11304082]
- [11]. Von Economo, C. *The Cytoarchitectonics of the Human Cerebral Cortex*. Oxford Medical Publications; London: 1929.
- [12]. Sowell ER, Thompson PM, Leonard CM, Welcome SE, Kan E, Toga AW. Longitudinal mapping of cortical thickness and brain growth in normal children. *J Neurosci*. 2004; 24:8223–8231. [PubMed: 15385605]
- [13]. Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage*. 2002; 17:825–841. [PubMed: 12377157]
- [14]. Smith SM. Fast robust automated brain extraction. *Human Brain Mapping*. 2002; 17(3):143–155. [PubMed: 12391568]

- [15]. Woolrich MW, Ripley BD, Brady JM, Smith SM. Temporal autocorrelation in univariate modelling of FMRI data. *Neuroimage*. 2001; 14(6):1370–1386. [PubMed: 11707093]
- [16]. MacDonald, D. School of Computer Science. McGill University; Montreal: 1998. A method for identifying geometrically simple surfaces from three dimensional images (doctoral dissertation).
- [17]. Storey J. A direct approach to false discovery rates. *Journal of the Royal Statistical Society*. 2002; 64:479–496.
- [18]. Rasser, P.; Johnston, P.; Lagopoulos, J.; Ward, P.; Schall, U.; Thienel, R., et al. A deformable brodmann area atlas. In: Leahy, R., editor. *Proc IEEE International Symposium on Biomedical Imaging*. 2004. p. 400–403.
- [19]. Horn NR, Dolan M, Elliott R, Deakin JF, Woodruff PW. Response inhibition and impulsivity: an fMRI study. *Neuropsychologia*. 2003; 41:1959–1966. [PubMed: 14572528]
- [20]. Purves, D.; Brannon, EM.; Cabeza, R.; Huettel, SA.; Labar, KS.; Platt, ML., et al. *Principles of Cognitive Neuroscience*. Sinauer Associates, Inc; Sunderland, MA: 2008.
- [21]. Aron AR, Durston S, Eagle DM, Logan GD, Stinear CM, Stuphorn V. Converging evidence for a fronto-basal-ganglia network for inhibitory control of action and cognition. *J Neurosci*. 2007; 27:11860–11864. [PubMed: 17978025]
- [22]. Braskie MN, Klunder AD, Hayashi KM, Protas H, Kepe V, Miller KJ, et al. Plaque and tangle imaging and cognition in normal aging and Alzheimer's disease. *Neurobiol Aging*. 2010; 31:1669–1678. [PubMed: 19004525]
- [23]. Foland LC, Altschuler LL, Bookheimer SY, Eisenberger N, Townsend J, Thompson PM. Evidence for deficient modulation of amygdala response by prefrontal cortex in bipolar mania. *Psychiatry Res*. 2008; 162:27–37. [PubMed: 18063349]

Figure 1.

a. Average cortical thickness (mm) maps across all 28 subjects, b. activation maps of the “NoGo” minus “Go” comparison, c. statistical maps showing correlations of cortical thickness and activation at the voxel level.