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Mapping anatomical correlations across cerebral cortex (MACACC) using cortical thickness from MRI

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We introduce MACACC-Mapping Anatomical Correlations Across Cerebral Cortex-to study correlated changes within and across different cortical networks. The principal topic of investigation is whether the thickness of one area of the cortex changes in a statistically correlated fashion with changes in thickness of other cortical regions. We further extend these methods by introducing techniques to test whether different population groupings exhibit significantly varying MACACC patterns. The methods are described in detail and applied to a normal childhood development population (n = 292), and show that association cortices have the highest correlation strengths. Taking Brodmann Area (BA) 44 as a seed region revealed MACACC patterns strikingly similar to tractography maps obtained from diffusion tensor imaging. Furthermore, the MACACC map of BA 44 changed with age, older subjects featuring tighter correlations with BA 44 in the anterior portions of the superior temporal gyri. Lastly, IQ-dependent MACACC differences were investigated, revealing steeper correlations between BA 44 and multiple frontal and parietal regions for the higher IQ group, most significantly (t = 4.0) in the anterior cingulate.

Introduction

The cerebral cortex is organized into networks of functionally complementary areas. Classic examples include the dorsal and ventral visual streams, the limbic system, and the language networks. These networks are traditionally studied using functional paradigms designed to reveal the particular role of a certain area. Examples of such studies include the role of Broca's Area in word repetition, synonym generation (Klein et al., 1997), verbal fluency (Frith et al., 1991), speech production (Buckner et al., 1995) and silent word production (Friedman et al., 1998).

Functional specialization can also lead to related anatomical change. A recent study investigated the size of the hippocampus, a structure involved in spatial navigation, in London taxi drivers and found increases in size correlating with increased experience in navigating the streets of London (Maguire et al., 2000, 2003). Similarly, faster phonetic learners were found to have greater white matter density in parietal regions than slower learners (Golestani et al., 2002). Trained musicians feature enlarged primary motor and sensorimotor areas, premotor areas, anterior superior parietal areas, and inferior temporal gyri (Schlaug, 2001; Gaser and Schlaug, 2003a,b). This last example involving musicians is particularly informative as it involves multiple cortical areas, including motor, sensorimotor, and multimodal sensory areas, collaborating. Increases in anterior corpus callosum size further suggests that the intra-hemispheric connectivity of the brain is enhanced in trained musicians (Schlaug, 2001).

We propose to address a related but less explored topic: as the anatomy of one cortical area changes, are there correlated morphological changes in other cortical areas? An example hypothesis from the language-processing domain might be that a population with thicker cortices in Broca's Area will have a correspondingly larger Wernicke's Area.

The connectivity of the human cerebral cortex is not a new topic of investigation. It has traditionally been studied using fiber tracing, wherein a seed region is injected with a retrograde tracer in order to determine which areas have direct fibre connections to the seed region (Romanski et al., 1999; Petrides and Pandya, 2002). More recently the notion of functional connectivity has been promoted, i.e. areas that are functionally related will feature correlated change in a fMRI or PET functional activation study (Friston, 2002; Friston et al., 1993, 1996, 2003; Koski and Paus, 2000; Horwitz, 2003; Lee et al., 2003; Ramnani et al., 2004).

We propose to study correlated anatomical changes using methods related to functional connectivity but employing morphometric data; we have dubbed this approach Mapping Anatomical Correlation Across Cerebral Cortex (MACACC). Of particular interest will be not just testing which areas of the cortex correlate with which other areas, but also whether the MACACC patterns vary across different categorical groupings based on demographical variables (age, gender, socio-economic status) or clinical diagnoses.

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The methods used in MACACC involve statistical analyses of data extracted from anatomical MRI using the metric of cortical thickness, which features several advantageous properties for MACACC:

1. It covers the entire cortex.
2. It provides a biologically meaningful measurement (cortical thickness).
3. It has a reduced number of points compared to volumetric data (40,962 vertices versus 1,000,000 voxels).

The methods developed herein should, however, also be applicable to other anatomical data such as, for example, voxel density measures from Voxel Based Morphometry (VBM) (Ashburner and Friston, 2000; Watkins et al., 2001). Some statistical issues have been explored in (Worsley et al., 2005).

We use this technique to address two core developmental issues. Firstly, several strands of evidence suggest that anatomical and functional interconnections between Broca's and Wernicke's areas may increase with age (Paus et al., 1999). Language becomes more lateralized (Holland et al., 2001) and DTI studies of the white matter tract connecting Broca's and Wernickes' areas shows changes in indirect measures of integrity (fractional anisotropy) (Schmithorst et al., 2002). Moreover, in an adult population, functional imaging studies demonstrate increased activity of Brodmann Area 44 (BA 44) during language processing (Amunts et al., 2004). We thus predict that the correlation in cortical thickness of these two language processing regions would show a developmental gradient, increasing with age. Secondly, intelligence is linked to brain activity. Greater brain activity during intellectually demanding activity has been shown using fMRI in individuals of greater general intelligence in an extensive network comprising lateral frontal and parietal regions (Gray et al., 2003). Others report similar alterations in functional connectivity linked to intelligence (Haier et al., 2004) which may be underpinned by enhanced structural connectivity. We hypothesize that, as seen in the motor learning examples given above, the functional enhancements are mirrored by concomitant change in the underlying neural substrate which can be detected by MRI-based morphometry, e.g. MACACC. The population used herein comes from a study of normal childhood brain development (Giedd, 2004; Gogtay et al., 2004). The purpose is not to provide a definitive account of these latter two questions but rather to illustrate the concept of MACACC, leaving more detailed study of brain development for future work.

Methods

The methods used to study MACACC can be subdivided into: (1) the extraction of the morphometric data and, (2) the statistical techniques used to ascertain the correlations. A summary of all the definitions used throughout is included in Table 1.

Extraction of morphometric data

The input metric for MACACC studies is cortical thickness as measured from MRI. The choice of MR sequence is immaterial as long as sufficient resolution and grey/white matter contrast are provided and subject groups to be compared were not acquired using different sequences. The native MR image is corrected for non-uniformity artefacts (Sled et al., 1998) and registered into stereotaxic space using a nine parameter linear transformation (Collins et al., 1994). Cerebral tissue is classified into white matter, gray matter, spinal fluid and background using a neural net classifier (Zijdenbos et al., 2002). The inner and outer cortical surfaces are then extracted using deformable surface-mesh models (MacDonald et al., 2000; Kim et al., 2005) and non-linearly aligned towards a standard template surface (Robbins et al., 2004). Cortical thickness is measured in native-space millimetres using the linked distance between the white and pial surfaces, tlink (MacDonald et al., 2000; Lerch and Evans, 2005). The thickness map is blurred using a 30 mm surface based diffusion smoothing kernel (Chung et al., 2003). These methods have been validated using both manual measurements (Kabani et al., 2001) and a population simulation (Lerch and Evans, 2005), and used in an Alzheimer's Disease population study (Lerch et al., 2005). Closely related methods have also been applied to Huntington's (Rosas et al., 2002) and normal ageing (Salat et al., 2004) among others. Example output can be seen in Fig. 1.

Table 1
Definition of terms: a list of the definitions used throughout the paper

Name	Definition
Correlation	Measured using Pearson's r, relates to the strength of the correlation between a seed region and the rest of the cortex.
MACACC-strength	The average correlation coefficient when every vertex is correlated with every other vertex.
MACACC-slope	Shows a group difference in the estimated slope between the seed region and target vertex.
MACACC-variance	Shows a group difference in the variance around the estimated slope between the seed region and target vertex.

Statistical techniques

Measuring MACACC can be subdivided into two main components: assessing cross-cortical correlations as well as quantifying differences in MACACC maps across groups.

MACACC methods—correlations

Cortical cross-correlations are obtained using simple linear correlations whose strength is measured using Pearson's r.

$$r = \frac{\sum T_{\mathrm{i}} T_{\mathrm{j}} - \frac{\sum T_{\mathrm{i}} \sum T_{\mathrm{j}}}{N_{\mathrm{s}}}}{\sqrt{\left(\sum T_{\mathrm{i}}^2 - \frac{\left(\sum T_i\right)^2}{N_{\mathrm{s}}}\right)\left(\sum T_{\mathrm{j}}^2 - \frac{\left(\sum T_{\mathrm{j}}\right)^2}{N_{\mathrm{s}}}\right)}} \quad (1)$$

Eq. (1) Pearson's r. Where T_{i} and T_{j} represent cortical thickness at the two vertices to be correlated with each other and Ns is the total number of subjects. Summations are performed over Ns.

Pearson's r takes on a value between 1 and −1, the sign referring to whether the correlation is positive or negative, and the closer to 1 or −1 the more significant the correlation. Equivalently, though slower computationally, is the use of a linear model wherein the seed region T_{i} (the area whose MACACC one is