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Limited relationships between two-year changes in sulcal morphology and other common neuroimaging indices in the elderly

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ABSTRACT

Measuring the geometry or morphology of sulcal folds has recently become an important approach to investigating neuroanatomy. However, relationships between cortical sulci and other brain structures are poorly understood. The present study investigates how age-related changes in sulcal width are associated with age-related changes in traditional indices of brain structure such as cortical thickness, and cortical gray matter (GM), white matter (WM), subcortical, and white matter hyperintensity (WMH) volumes. These indices and sulcal width were measured at baseline and at two-year follow up in 185 community-dwelling individuals (91 men) aged 70–89 years. There were significant increases in sulcal width and WMH volume, and significant decreases in all other indices between baseline and follow-up. Sulcal widening was associated with decreases in cortical GM, subcortical and WM volumes. A further association between sulcal width and cortical thickness became non-significant when cortical GM volume was controlled for. Our findings give insights into the mechanisms responsible for cortical sulcal morphology. The relationships between sulcal morphology and other common measures suggest that it could be a more comprehensive measure for clinical classifications than traditional neuroimaging metrics, such as cortical thickness.

Introduction

Sulcal folds are the principal surface landmarks of the human cerebral cortex, and exhibit structurally complex patterns (Welker, 1988). Measuring the geometry or morphology of sulcal folds has become an important approach to investigating neuroanatomy. Recent studies have identified distinguishing sulcal patterns in patients with psychiatric and neurological conditions like schizophrenia (Cachia et al., 2008) and bipolar disorder (Penttila et al., 2009), individuals with cerebral small vessel disease (Jouvent et al., 2011), and some professional groups, including musicians (Li et al., 2010b). Evidence also suggests that sulcal morphology changes with normal aging (Liu et al., 2010; Rettmann et al., 2006), is associated with cognitive functioning in the elderly (Liu et al., 2011), and is abnormal in Alzheimer's disease (AD) (Im et al., 2008; Liu et al., 2012; Reiner et al., 2012).

Measures of sulcal folding can provide insights into structural brain changes beyond those of traditional indices like cortical thickness (Kochunov et al., 2012; Mangin et al., 2010). It has also been shown that sulcal width, but not cortical thickness, is associated with cognitive function in elderly individuals (Liu et al., 2011) and with apathy in patients with CADASIL syndrome (Jouvent et al., 2011).

The reasons why behavioral measures are more associated with sulcal width than cortical thickness are unclear. Investigations of relationships between sulcal width and cortical thickness have produced mixed results, with associations reported by some studies (Im et al., 2008; Kochunov et al., 2008) but not others (Jouvent et al., 2011; Liu et al., 2011). It is also unclear if changes in sulcal morphology are associated with other changes in traditional neuroimaging metrics of cortical gray matter (GM), white matter (WM) and subcortical structures. Age-related structural changes in these traditional measures have been reported widely and underlying mechanisms proposed. It is thought that age-related decreases in GM volume and cortical thickness arise from decreases in regional neuronal density and the loss of cortical neurons (Harding et al., 1998; Peters et al., 1998; Prothero, 1997; Sowell et al., 2003), and that age-related WM changes are associated with a

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loss of myelin and axons (Bronge et al., 2002; Prothero, 1997). Age-related shrinkage of subcortical structures, including the hippocampus, is considered to be caused by a loss of regional neurons (Harding et al., 1998).

In contrast to traditional neuroimaging indices, the mechanisms underlying changes in sulcal folding are unknown (Mangin et al., 2010). It is possible that age-related changes in sulcal width reflect the combined effects of age-related changes in GM, WM and subcortical volumes. Previous relevant studies have been cross-sectional and unable to represent fully the trajectory of age-related changes because of methodological influences that include cohort effects (Kraemer et al., 2000).The present study of elderly individuals used a longitudinal approach to overcome these limitations of earlier designs. We also extend upon previous studies by investigating neuroimaging indices commonly used in aging and disease research for which relationships with cortical folding have received little attention. Our full range of traditional indices included cortical thickness, and volumes relating to GM, WM, WM hyperintensities (WMH) and subcortical structures. We quantified 2-year changes in these indices and investigated their relationships with 2-year changes in sulcal width.

Methods

A flowchart of the present study is illustrated in Fig. 1 and is described below.

Participants

Participants were members of the Sydney Memory and Ageing Study (MAS), a longitudinal study of community-dwelling individuals aged 70 to 90 years recruited via the electoral roll for two regions of Sydney, Australia (Sachdev et al., 2010). Individuals were excluded if they had a previous diagnosis of dementia, mental retardation, psychotic disorder including schizophrenia or bipolar disorder, multiple sclerosis, motor neuron disease, developmental disability, or progressive malignancy. For the current study, we included 185 MAS participants with MRI scans at both baseline and a 2-year follow-up. All participants were from an English speaking background, with further demographic characteristics detailed in Table 1. The study was approved by the Ethics Committees of the University of New South Wales and the South Eastern Sydney and Illawarra Area Health Service. Written informed consent was obtained from each participant.

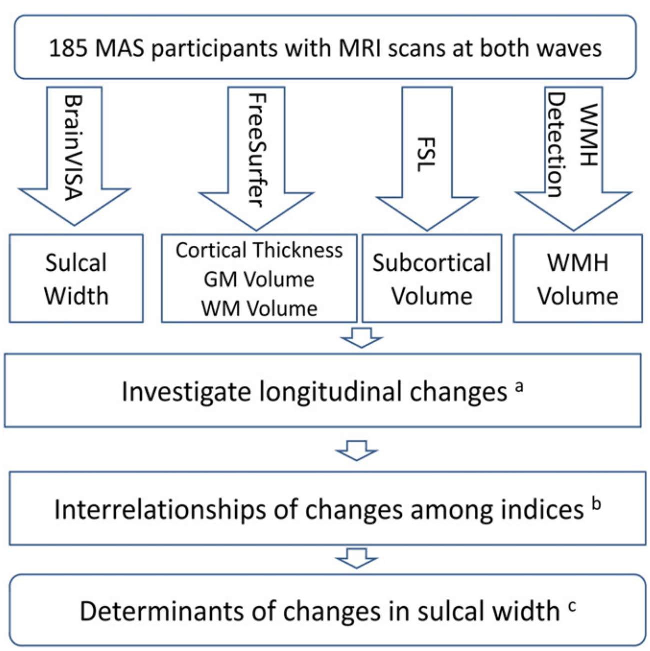

Fig. 1. Flowchart of investigating relationships between two-year changes in sulcal morphology and other common neuroimaging indices in the elderly. [a]Using repeated-measures analysis of variance.| [b]Using Pearson's correlations. [c]Using multiple regression.

Table 1
Demographic characteristics (mean ± SD) of the sample.

	N = 185
Age at baseline (years)	77.47 (4.39)[a]
Education at baseline (years)	11.76 (3.60)
MMSE[a] score at baseline	28.15 (1.32)
MMSE score at 2-year follow-up	28.37 (1.46)

[a] Mini–mental state examination (Folstein et al., 1975).

Image acquisition

MRI scans were obtained with a 3-T system (Philips Medical Systems, Best, The Netherlands) using the same sequence for both baseline and follow-up scans: TR = 6.39 ms, TE = 2.9 ms, flip angle = 8°, matrix size = 256 × 256, FOV = 256 × 256 × 190 mm, and slice thickness = 1 mm with no gap, yielding 1 × 1 × 1 mm^3 isotropic voxels.

Image processing

Sulcal width

Cortical sulci were extracted from the images via the following steps. First, non-brain tissue was removed to produce images containing GM, WM and cerebrospinal fluid (CSF). This was done by warping a brain mask defined in the standard space back to the T1-weighted structural MRI scan. The brain mask was obtained with an automated skull stripping procedure based on the SPM5 skull-cleanup tool (Ashburner, 2009). Second, images were segmented into GM, WM and CSF using histogram scale-space analysis and mathematical morphology (Mangin et al., 2004). Third, individual sulci were identified and extracted using the BrainVisa (BV) sulcal identification pipeline (version 4.1.1; http://brainvisa.info/). The medial surface of cortical folds was calculated using a homotopic erosion technique, and a crevasse detector was used to reconstruct sulcal structure as the medial surface from the two opposing gyral banks that spanned from the most internal point of the sulcal fold to the convex hull of the cortex (Mangin et al., 2004). A sulcal labeling tool incorporating 500 artificial neural network-based pattern classifiers (Riviere et al., 2002; Sun et al., 2007) was used to label sulci. Sulci that were mislabeled by BV were manually corrected. For each hemisphere, we determined the average sulcal width for five sulci: superior frontal, intra-parietal, superior temporal, central, and the Sylvian fissure (see Fig. 2). Sulcal width was defined as the average 3D distance between opposing gyral banks along the normal projections to the medial sulcal mesh (Kochunov et al., 2012). The five sulci investigated in the present study were chosen because they are present in all individuals, large and relatively easy to identify (facilitating error detection), and located on different cerebral lobes.

Cortical thickness, GM volume and WM volume

We computed average regional GM volume, average regional cortical thickness and total WM volume using the longitudinal stream in FreeSurfer 5.1 (http://surfer.nmr.mgh.harvard.edu/) (Reuter et al., 2012). This stream specifically creates an unbiased within-subject template space and image using robust, inverse consistent registration (Reuter and Fischl, 2011; Reuter et al., 2012). Briefly, this pipeline included several processing steps, including skull stripping, Talairach transforms, atlas registration, spherical surface maps, and parcellation of cerebral cortex (Desikan et al., 2006; Reuter et al., 2012). The pipeline modeled the cortical surface after detecting the gray/white boundary and then 'growing' the pial surface of GM. This yielded an estimate of cerebral cortical surface GM volume in addition to providing direct measures of cortical thickness, calculated as the