NeuroImage 49 (2010) 3075–3085

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

A multiple-plane approach to measure the structural properties of functionally active regions in the human cortex

Xin Wang [a,b,c,d], Sarah N. Garfinkel [a], Anthony P. King [a], Mike Angstadt [a], Michael J. Dennis [c], Hong Xie [d], Robert C. Welsh [e], Marijo B. Tamburrino [b], Israel Liberzon [a,*]

[a] Department of Psychiatry, University of Michigan, Ann Arbor, MI 48109, USA
[b] Department of Psychiatry, University of Toledo, Toledo, OH 43614, USA
[c] Department of Radiology, University of Toledo, Toledo, OH 43614, USA
[d] Department of Neuroscience, University of Toledo, Toledo, OH 43614, USA
[e] Department of Radiology, University of Michigan, Ann Arbor, MI 48109, USA

ARTICLE INFO

Article history:
Received 2 July 2009
Revised 4 November 2009
Accepted 10 November 2009
Available online 14 November 2009

ABSTRACT

Advanced magnetic resonance imaging (MRI) techniques provide the means of studying both the structural and the functional properties of various brain regions, allowing us to address the relationship between the structural changes in human brain regions and the activity of these regions. However, analytical approaches combining functional (fMRI) and structural (sMRI) information are still far from optimal. In order to improve the accuracy of measurement of structural properties in active regions, the current study tested a new analytical approach that repeated a surface-based analysis at multiple planes crossing different depths of cortex. Twelve subjects underwent a fear conditioning study. During these tasks, fMRI and sMRI scans were acquired. The fMRI images were carefully registered to the sMRI images with an additional correction for cortical borders. The fMRI images were then analyzed with the new multiple-plane surface-based approach as compared to the volume-based approach, and the cortical thickness and volume of an active region were measured. The results suggested (1) using an additional correction for cortical borders and an intermediate template image produced an acceptable registration of fMRI and sMRI images; (2) surface-based analysis at multiple depths of cortex revealed more activity than the same analysis at any single depth; (3) projection of active surface vertices in a ribbon fashion improved active volume estimates; and (4) correction with gray matter segmentation removed non-cortical regions from the volumetric measurement of active regions. In conclusion, the new multiple-plane surface-based analysis approaches produce improved measurement of cortical thickness and volume of active brain regions. These results support the use of novel approaches for combined analysis of functional and structural neuroimaging.

Published by Elsevier Inc.

Introduction

One of the fundamental questions in neuroscience is the relationship between neural activity and structural properties of different brain regions. Investigation of this relationship will enrich our understanding of neuro-substrates involved in biological or pathological brain function. During decades of research, many invasive procedures have been used to study this question in animals (Martin, 2008; Miyawaki, 2005; Niell et al., 2004; Niell and Smith, 2004; Rhoades et al., 1993). None of these techniques, however, can be applied to humans, leading to a knowledge gap regarding the relationship between human brain activity and its substrates. The development of non-invasive magnetic resonance imaging (MRI) techniques provides the opportunity to study the relationship of brain activity with structural substrates in humans *in vivo*. Structural MRI (sMRI) images of the brain allow the study of volume, voxel-based morphometry (VBM), cortical thickness, and cortical surface shape and folding of brain regions (Ashburner and Friston, 2000; Caviness et al., 1999; Fischl et al., 1999; Good et al., 2001; Karl et al., 2006; Kasai et al., 2008; Lerch and Evans, 2005; Pienaar et al., 2008; Sallet et al., 2003). Correlating sMRI with functional MRI (fMRI), magnetoencephalography (MEG), positron emission tomography (PET), or event-related potentials (ERP) advances knowledge of the structure–activity relationship (Araki et al., 2005; Bremner et al., 2003; Schneider et al., 2002; Schuff et al., 2001). Functional MRI is more often combined with sMRI because its superior spatial and temporal resolutions improve detection of brain activity as compared to other functional neuroimaging techniques. Combining functional and structural MRI scanning is also an efficient use of laboratory resources. However, the few pioneering studies to employ this promising technique have used different analytical approaches in relating the fMRI and sMRI data (DaSilva et al., 2008; Hadjikhani et al., 2007; Milad et al., 2007a;

* Corresponding author. 2756 Rachel Upjohn Building, 4250 Plymouth Road, Ann Arbor, MI 48109-2700, USA. Fax: +1 734 936 7868.
E-mail address: liberzon@umich.edu (I. Liberzon).

1053-8119/$ – see front matter. Published by Elsevier Inc.
doi:10.1016/j.neuroimage.2009.11.018

Rasser et al., 2005; Remy et al., 2005; Schaechter et al., 2006; Siegle et al., 2003; Siok et al., 2008). As summarized below, these approaches could clearly benefit from further development.

Numerous studies have approached this question by measuring the volume or mean cortical thickness of anatomically defined brain regions where activity was detected with the fMRI (Remy et al., 2005; Siegle et al., 2003; Siok et al., 2008). However, the activity only occurred in part of the anatomical region; therefore, the volume or the mean cortical thickness of the anatomical region may not reflect the subtle differences in active regions. Other studies selected theoretically more sensitive approach by examining differences in cortical thickness or volume of the functionally active regions and a correlation between thickness and the regional activity (DaSilva et al., 2008; Hadjikhani et al., 2007; Rasser et al., 2005; Schaechter et al., 2006). However, these studies employed a range of analytical approaches to define the activity, differing in the normalization, smoothing, and definition of active regions. These differences may affect localization of fMRI activity, as well as the statistical power of the analysis (Hagler et al., 2006; Hayasaka et al., 2004).

Some studies used volume-based group analysis that is characterized by three-dimensional (3-D) smoothing in Euclidean space and 3-D cross-subject normalization according to a standard space (DaSilva et al., 2008; Milad et al., 2007a; VanEssen, 1997). Volume-based analyses encompass the whole brain at once, but have a number of intrinsic problems. For example, the 3-D smoothing may dilute the activity in gray matter with adjacent white matter or CSF. It may also extend active regions beyond the cortex since the 3-D smoothing of fMRI images is not restricted within the cortical boundary (e.g., Fig. 1A). Furthermore, the 3-D smoothing may extend the activity in a gyrus onto a part of an adjacent gyrus in Euclidean spaces that are not biologically connected (e.g., Fig. 1B). 3-D normalization in volume-based group analysis does not intend to match the gyri and sulci as surface-based normalization does (see below) (VanEssen and Drury, 1997). However, a number of studies ignore the differences in two normalization approaches by using 3-D normalization in defining group activity in the standard space, but then using surface-based normalization parameters created by programs of cortical thickness measurement to convert these active regions from the standard space back to individual spaces for cortical thickness or volume measures (DaSilva et al., 2008; Milad et al., 2007a). These inconsistencies between two types of normalizations could contribute to observed differences. In short, the 3-D normalization method is less than ideal for defining active regions and measuring their structural properties.

Surface-based analysis is a recently developed method to overcome the shortcomings of volume-based analysis. Surface-based analysis is characterized by two-dimensional (2-D) smoothing along the cortical surface and cross-subject normalization according to the gyri and sulci. In surface-based analysis, the activity of individual subjects is identified in non-smoothed fMRI images, and the coefficient image of a contrast is registered on the sMRI image of this subject (Anticevic et al., 2008; Desai et al., 2005; Greve and Fischl, 2009; Spiridon et al., 2006). The cortical surface is reconstructed from the sMRI images. The coefficient image is smoothed along the cortical surface to restrain the smoothing in the cortex and to avoid expanding the activity onto unconnected gyri (e.g., Figs. 1A′, B′). The cortical surface of each subject is registered using gyri and sulci as landmarks to reduce the mismatch of gyri (Desai et al., 2005; Fischl et al., 1999; Jo et al., 2007). The active vertices on the surface of standard space are individualized according to the same parameters as surface-based normalization to avoid any inconsistence in normalization and individualization (Anticevic et al., 2008; Schaechter et al., 2006). This approach theoretically allows to overcome some of the shortcomings of a volume-based analysis. However, the initial implementation of a surface-based analysis has not been error free. First, a

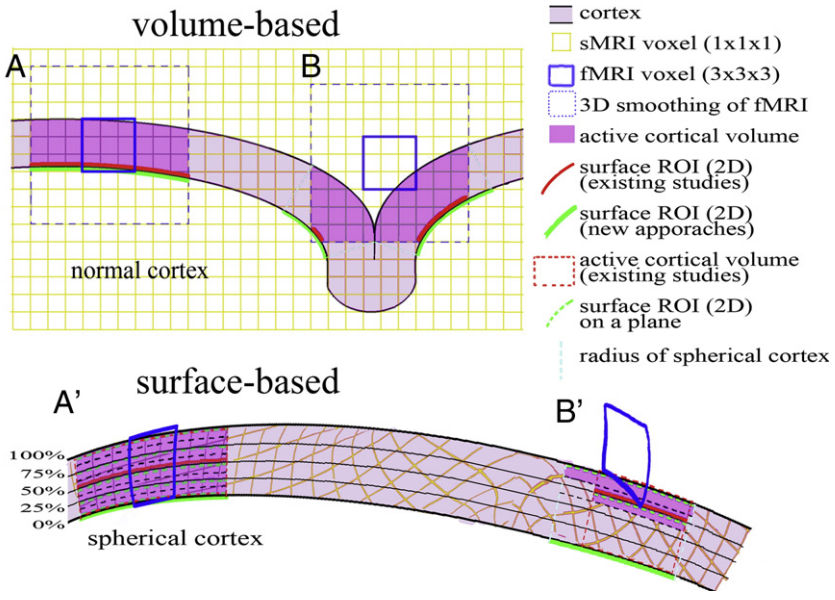

Fig. 1. Illustration of analytical approaches. A part of *normal cortex* with curvature is at the top and the same part of the cortex on the spherical model of cortex (*spherical cortex*) is at the bottom. The small yellow squares are sMRI voxels and the large blue boxes are fMRI voxels. Note that the voxels are transformed in the *spherical cortex* during the inflation of cortex to sphere. In the *Volume-based analysis*, (A) a fMRI voxel (blue line box) was smoothed to 1 voxel length in 3-D in Euclidean space (blue dash line box), and occupies the active cortical volume (purple shaded). The intersection of the smoothed voxel and a cortical surface is defined as a surface ROI in existing studies (red line) or in the volume-based analysis of the current study (green line). Two surface ROIs are similar if the smoothed voxel occupies the entire cortical depth. (B) A fMRI voxel is registered in part of cortical depth, and 3-D smoothing expends the active volume to an adjacent gyrus. The surface ROI is split on both gryi. The current study defined a larger surface ROI (green line) than existing studies (red line). (A′) The A is transformed in the spherical cortical model. Previous studies defined active vertices on one depth at surface ROI (red line) and projected the surface ROI to the entire cortex as active volume (red dash box). The new multiple-plane approach defined the active vertices on five planes at 0, 25%, 50%, 75%, and 100% of cortical thickness from white matter border (black lines), and projected the active vertices of each plane to sMRI voxels (yellow) in a ribbon of 12.5% of cortical thickness above and below the plane within cortex (black dash line). Active vertices on all planes are summed on one surface as a surface ROI (green line) for thickness measurement, and hit voxels in all ribbons are assembled together as a volume ROI to estimate the active volume (purple). (B′) The B is transformed in the spherical cortical model. The multiple-plane approach defines a larger surface-ROI (green line) than existing studies (red line) because it summed activity on two planes. In contrast, this approach estimates a smaller active volume (purple) than existing studies (red dash line box).