Large Deformation Diffeomorphic Metric Mapping Registration of in-vivo MR Images and Reconstructed 3D Images of Histological Sections

Can Ceritoglu*, Lei Wang†, Matt Trachtenberg*, Lynn D. Selemon**, John G. Csernansky†, Michael I. Miller*, John T. Ratnanather*

Introduction

MR imaging technology enables the acquisition of in vivo brain structure and has therefore found widespread application in studies of anatomic changes associated with brain disorders. However, the cytoarchitectural boundaries that define individual functional units in the brain, as for example the borders between neighboring cortical areas, cannot be captured at the resolution of MR images. Such cellular detail is available from postmortem microscopic analysis of histologically processed brains. We propose a multistep method for registering reconstructed 3D volumes derived from histological sections to corresponding in vivo MR image volumes from the same subjects. As a demonstration, we used the method in analyzing prefrontal cortical area-46 in adult macaque brains (Figure-1 left).

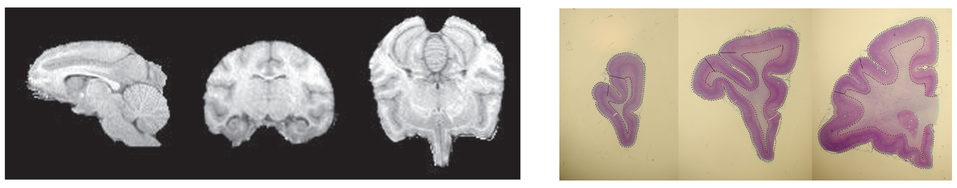

Figure-1

Methods

We acquired 3 in vivo MR scans of three adult macaque brains with a resolution of 0.625x0.7x0.625 mm/voxel (Figure-1 left). We also generated a series of celloidin-embedded, 40μm thick Nissl-stained sections through the frontal lobe for the same subject postmortem. Afterwards, we acquired high resolution digital photographic images (0.005534x0.005534 mm2/pixel) of each histological section (Figure-1 right). Three of the subjects were fetally irradiated in early gestation (eFIM), 3 were fetally irradiated in midgestation (mFIM), and 3 were non-irradiated controls (CON).

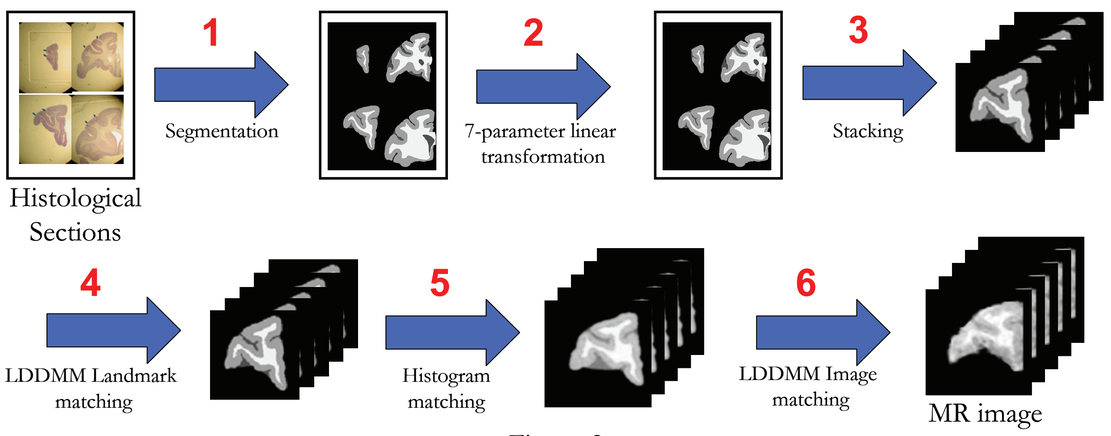

Figure-2

In the registration process, the MR scans were first reoriented to AC-PC orientation. Each histological section and its proximal MR section were landmarked to reconstruct a 3D histological image based on low dimensional affine transformations of the landmarks. LDDMM (large deformation diffeomorphic metric mapping) landmark matching [2] was used to further align the reconstructed 3D histological volume to the 3D MR image subvolume and to overcome the difference in brain slicing orientation. LDDMM image matching [3] was used to complete the registration (Figure-2). The LDDMM framework, in which the transformations are constrained as diffeomorphisms, is a highly suitable choice for anatomical studies. In LDDMM, the transformations are smooth and invertible with smooth inverses;, therefore, connected sets remain connected, disjoint sets remain disjoint and smoothness of anatomical features (such as curves and surfaces) is preserved.

The boundaries of prefrontal area 46, the boundaries between cortical layers I/II and IV/V defined in histological sections were then carried through these transformations onto the MR image space (Figure-3).

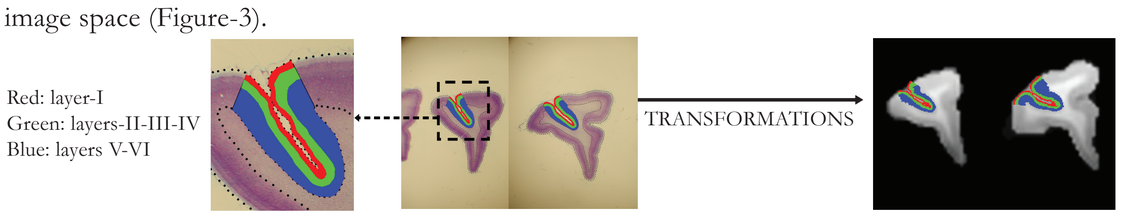

Figure-3

References:

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* Center for Imaging Science, The Whiting School of Engineering, The Johns Hopkins University, 301 Clark Hall, Baltimore, MD, USA
† Department of Psychiatry and Behavioral Sciences, Northwestern University, Feinberg School of Medicine, Chicago, IL, USA.
** Department of Neurobiology, School of Medicine, Yale University, New Haven, CT, USA

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Results

1) To measure the registration accuracy, we calculated errors between the 3D histological images and 3D MR images before and after registration. The image mismatch error decreased after registration to 25.6 % on average (Figure-4)

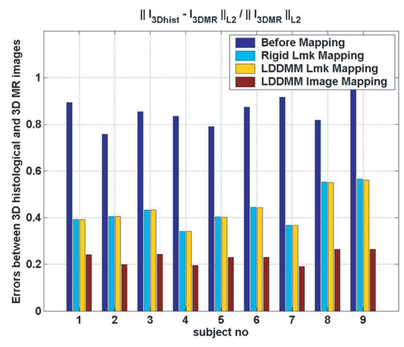

Figure-4

2) These transformations allowed us to construct the area 46 surface at the interface of the grey matter/white matter boundary of MR images (Figure-5 left) and area 46 grey matter 3D volume (Figure-5 right).

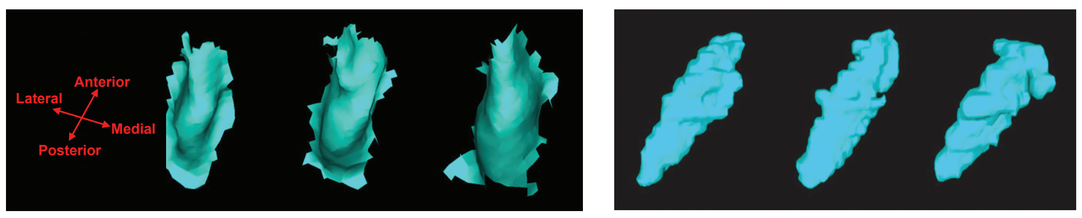

Figure-5

4) In figure 6, graphs show cortical volume, grey matter/white matter surface area, and thickness [4] of prefrontal area 46 in 3 macaques irradiated in early gestation (eFIM, red), 3 irradiated in midgestation (mFIM, blue), and 3 non-irradiated controls (white). All three groups consisted of both males (diamonds) and females (circles). Trend reductions (p= 0.05 based on paired Mann-Whitney U tests) were observed for surface area in eFIM vs. CON and for volume and surface area in mFIM vs. CON. Cortical thickness as measured across all six layers did not differ among the three groups.

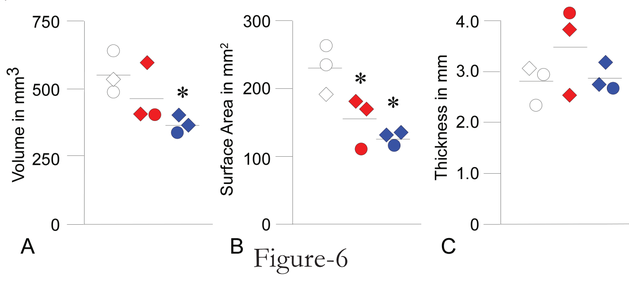

Figure-6

5) In figure 7, measurement of volume (left) and cortical thickness (right) of the three layers indicate that volume was reduced in mFIMs in layers I and II-IV and cortical thickness was reduced in layers II-IV compared to CONs. No significant differences in laminar volume or thickness were found between eFIMs and CONs (White = CONs; Red = eFIMs; Blue = mFIMs; circles = females; diamonds = males; * = p.05, Mann-Whitney U).

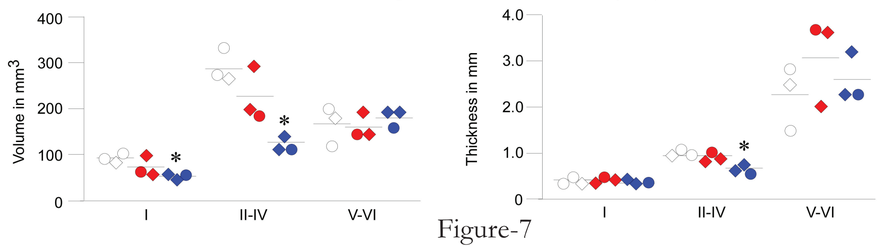

Figure-7

Conclusions

1) A novel method is described for the transfer of cortical and laminar borders, as defined by cytoarchitectonic analysis of postmortem histology sections, to in vivo MR subvolumes of the same brains.

2) With this method, structural alterations in a single, cytoarchitectonically defined cortical area were analyzed in adult macaques that had been exposed to x-irradiation in early gestation, i.e. before the onset of corticogenesis, or in mid-gestation, during the period of corticogenesis, in comparison to non-irradiated controls.

3) The two irradiated groups exhibited distinct patterns of cortical pathology. Monkeys exposed to irradiation in early gestation exhibited a reduction in cortical surface area but did not differ from controls in volume or cortical thickness of area 46. In contrast, monkeys irradiated in midgestation showed deficits in area 46 volume as well as surface area.

4) Analysis of laminar volume and thickness indicated that supragranular layers were selectively reduced in volume and thickness in the midgestationally irradiated group. This pattern of pathology is consistent with exposure to irradiation in mid-gestation when neurons in layers II and III are generated. It is noteworthy that differences in overall cortical thickness were not detected in these animals.

5) **The transfer of laminar boundaries revealed pathology that otherwise would not have been detected in the MR analysis.** The use of postmortem histology to define region of interests in the MR scans is a method that could be adapted to study of human brains in the study of neurodevelopmental diseases like schizophrenia.

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