

Mapping of cortical area 46 laminar boundaries in MRI volumes: A method developed to study the prenatally irradiated macaque

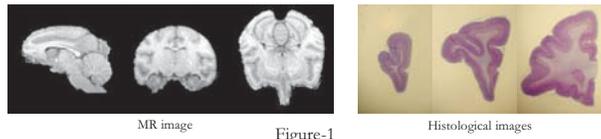
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Introduction

We have previously developed a multistep registration process to align high resolution photographic images of histological sections to ante-mortem magnetic resonance (MR) subvolumes of the same brain [1]. In this work, we utilize the same calculated transformations to transfer laminar boundaries from area 46, as identified in the histological sections, to the MR subvolumes of macaque brains. Our approach capitalizes on the advantages of both methods: postmortem analysis of Nissl-stained sections allows precise localization of layer boundaries, and transformation of the layers to the MR subvolume permits morphometric analysis of the layers that are not shrunken or distorted by postmortem fixation and processing.

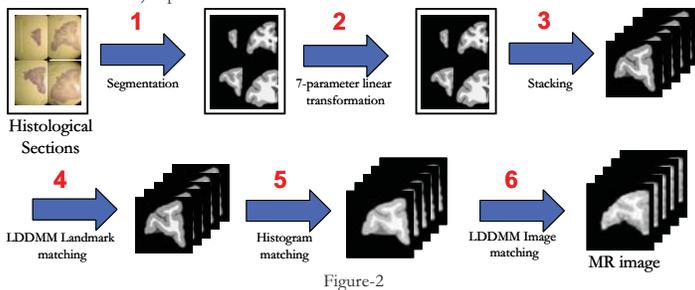
Data

We acquired MR in vivo volumetric scans of 9 adult macaque brains with a resolution of 0.625x0.7x0.625 mm/voxel (Figure-1 left). A series of celloidin-embedded, 40µm thick Nissl-stained sections (approximately stereotactic) through the frontal lobe was generated from these same animals postmortem. High resolution digital photographic images (0.005534x0.005534 mm²/pixel) were acquired without any external reference point for 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).

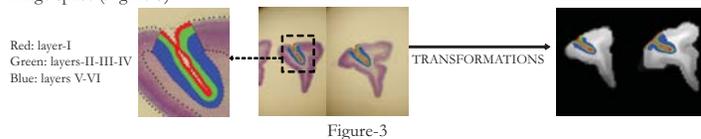


Methods

1) 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.



2) 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 into the MR image space (Figure-3).



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3) These transformations allowed us to construct the area 46 surface at the interface of the grey matter/white matter boundary of MR images (Figure-4).

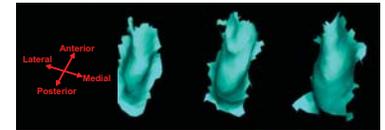


Figure-4

4) In figure 5, 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.

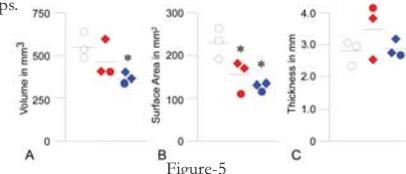


Figure-5

5) In figure 6, graphs show that both the (A) A-P and (C) M-L expanse of area 46, as schematically illustrated in (B), were reduced in eFIM (red) and mFIM (blue) groups compared to CONs (white). (Circles = females; diamonds = males; * = $p < 0.05$, Mann-Whitney U).

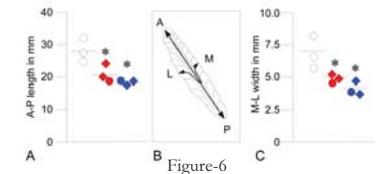


Figure-6

6) 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; * = $p < 0.05$, Mann-Whitney U).

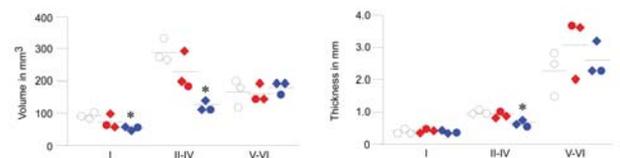


Figure-7

Conclusion

- 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.
- With this method, structural alterations in a single, cytoarchitectonically defined cortical area (Walker's area 46) 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.
- 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.
- 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.
- 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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