High-Resolution Cortical Imaging

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Structure of the cortex

The adult cerebral cortex is a complex convoluted multilayered structure averaging around 2.3mm thick, but thinner (≤ 2mm) in the depths of the sulcal folds and thicker (3-4mm) at the crown of the gyri. It is typically divided into 6 layers depending upon the constituent cell types. On examination a section of the cortex, it is seen to consist of alternating white and gray layers from the surface inward: (1) a thin layer of white substance; (2) a layer of gray substance; (3) a second white layer (outer band of Baillarger or band of Gennari); (4) a second gray layer; (5) a third white layer (inner band of Baillarger); (6) a third gray layer, which rests on the medullary substance of the gyrus (1). Cortical neurons form a highly organized laminar and radial structure with extensive efferents. Long association fibers connect to distant regions of the ipsilateral hemisphere, while short fibers connect to nearby ipsilateral regions. Commissural fibers connect to the cortical regions of the contralateral hemisphere, and projection fibers reach from the cortex into the subcortical structures e.g., corticothalamic/subthalamic projections, etc.

High resolution structural MRI of the cortex

Conventional diagnostic clinical MRI scans, with in plane resolution of ~1mm and slice thickness up to 5mm can define the gray-white interface of the cerebral cortex but cannot visualize structure within the cortex itself. Nevertheless, even the ability to define the cortical margin is valuable. High resolution T_1-weighted structural scans can accurately identify the gray-white interface as well as the cortical surface, and can therefore be used to map cortical thickness over the whole brain (2). Using this approach, cortical thickness changes have been demonstrated with normal aging (3) and regional changes have been observed with schizophrenia (4, 5), multiple sclerosis (6), Huntington's disease (7) and HIV/AIDS (8).

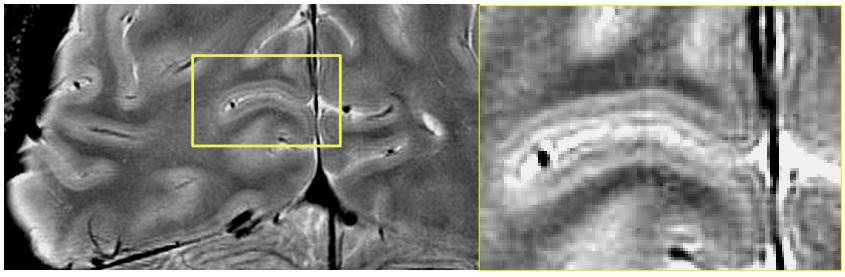

Figure 1. Proton density weighted, FSE image of the human primary visual cortex showing the line of Gennari (7T, 330μm in plane resolution). Courtesy, L. Wald, A. Pothast, G. Wiggins, MGH.

The additional SNR made available through the use of higher field (3T and above) magnets and multi-coil head arrays now allows the direct visualization of the cortical ribbon itself. For example at 7T, an in plane resolution of 330μm with a 2mm slice thickness is sufficient to detect the highly myelinated line of Gennari (cortical layer 4) (Figure 1). Such high resolution imaging of the cortex offers improved diagnosis of disease;

for example, the detection of subtle cortical neoplasms (not seen on conventional clinical scans) can identify an epileptogenic focus on patients who might not otherwise have an indication for epilepsy surgery.

Diffusion tensor imaging of the cortex

DTI tractography studies have sought to characterize the connections between cortical regions (9, 10). Typically DTI tract tracing algorithms halt when the diffusion anisotropy index FA falls below a threshold value (~0.2) and thus fall short of penetrating into the cortex itself. It is well known that there is a significant orientational dependence of diffusion of water within the cerebral cortex in the early developing brain. This cortical anisotropy, which is mainly in a radial direction (i.e. perpendicular to the cortical surface), was observed in animal MRI studies (11). Serial DTI measurements in animals have shown a rapidly decreasing FA in the cortex as a function of increasing age (12-14). In extremely premature infants the cortical plate is largely unconvoluted and shows significant diffusion anisotropy (15). After birth, radial diffusion anisotropy is present in the human neonatal cortex which decreases with age as the cortex develops and the sulci become more pronounced (16) and is not typically seen at all in adults. Imaging the cortex with DTI in adult human presents a particular challenge because the thin cortical sheet is highly convoluted, and diffusion weighted images of this structure are often plagued by inadequate resolution, partial volume averaging with CSF (serving to reduce the apparent anisotropy (17)) and eddy current effects.. Even at a relatively high resolution (for DTI) of 2mm isotropic voxel size in the human brain, it is difficult to find pixels that contain only cortical gray matter (Fig. 2). As a result, the familiar FA map of an adult brain shows most of the cerebral cortex as dark and generally uninformative. Nevertheless there is some evidence that gray matter FA measured by conventional DTI may be sensitive to pathology such as stroke (18, 19) although the mechanisms are not yet clear. High b-value DTI acquisitions in adult cat brain have indicated the presence of radial fiber structure in the cortex (20). Using a multi-channel head coil (e.g. 22+ coils), it is possibly to acquire higher resolution DTI with a 1mm voxel size which begins to visualize the cortical strip and shows evidence of the radial orientational structure in gray matter. However this is still insufficient spatial resolution to see detail such as the layering with the gray matter itself.

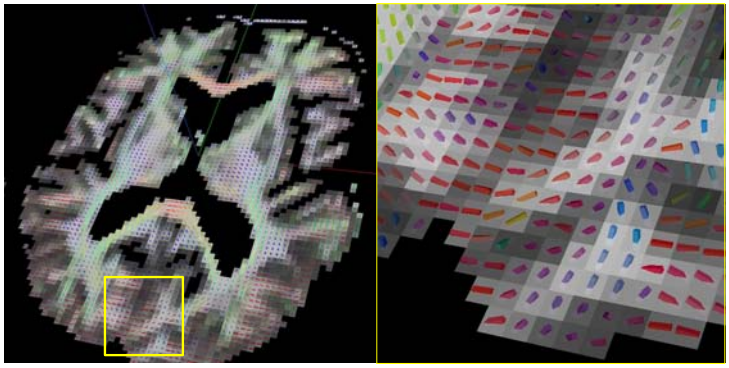

Figure 2. DTI at 2mm isotropic resolution at 3T. FA map with tensors superimposed. (courtesy, D. Tuch, J Wisco, MGH).

Imaging studies of fixed cortical samples

While advances in human MRI hardware continue to improve spatial resolution in the brain *in vivo*, there are some compelling reasons to carry out studies of fixed brain tissues; the most obvious being that the stability of such samples allows for extended scanning in high field magnets to achieve much greater spatial resolution than is currently possible *in vivo*. Noninvasive 'histology' using MRI and MR microscopy is an established methodology (21,

22). It can provide a way to relate macrostructure (seen on *in vivo* scans) to microstructure (seen on conventional histology), as well as to establish the spatial resolution needed to visualize various structures (e.g. cortical layering), as well as providing morphological phenotyping in model systems (23).

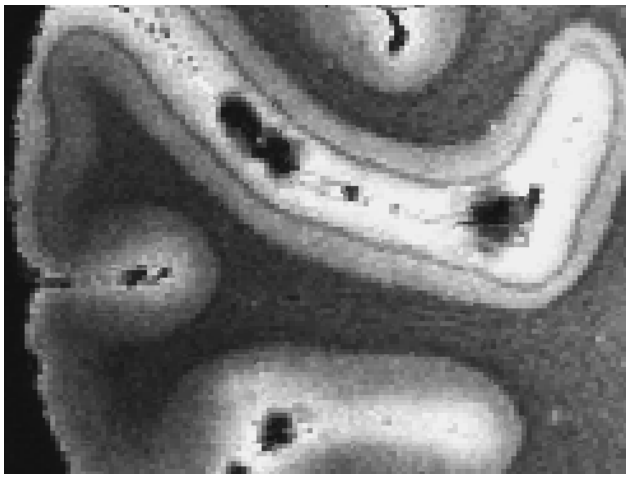

Figure 3: PD/T_2* weighted image of the V1/V2 boundary in human visual cortex (7T, 160μm isotropic resolution, TE 46.5ms).

The protein cross linking that occurs upon tissue fixation significantly reduces both T_1 and T_2 (24, 25) and has the effect of flattening image contrast in the brain. However proton density contrast is maintained and even increases slightly upon tissue fixation (26). Therefore, a mixed contrast imaging protocol has proved useful for delineating cortical layering structure (27) and entorhinal islands in the hippocampal cortex (28). In addition to proton density contrast, T_2* provides excellent tissue contrast at high field, Figure 3. Both contrast mechanisms seem to be related to differences in the tissue myelination and correspond well to contrast seen on Nissl stains (28).

DTI studies of fixed brain tissue indicate that while the trace ADC values are significantly reduced, the diffusion anisotropy is well preserved (12, 29). This is true of both FA from DTI scans and also higher order orientational structure (e.g. from DSI scans (30)) (31). High resolution DTI scans of human cortical samples show laminar structure and tractography results show white matter fibers inserting into the cortical gray matter, and also short range U-fibers connecting nearby cortical regions (32), see Figure 4. This approach shows promise for detecting changes in complex fiber 'connectivity' patterns in conditions such as stroke, and for characterizing developmental and other abnormalities of the cortex (33).

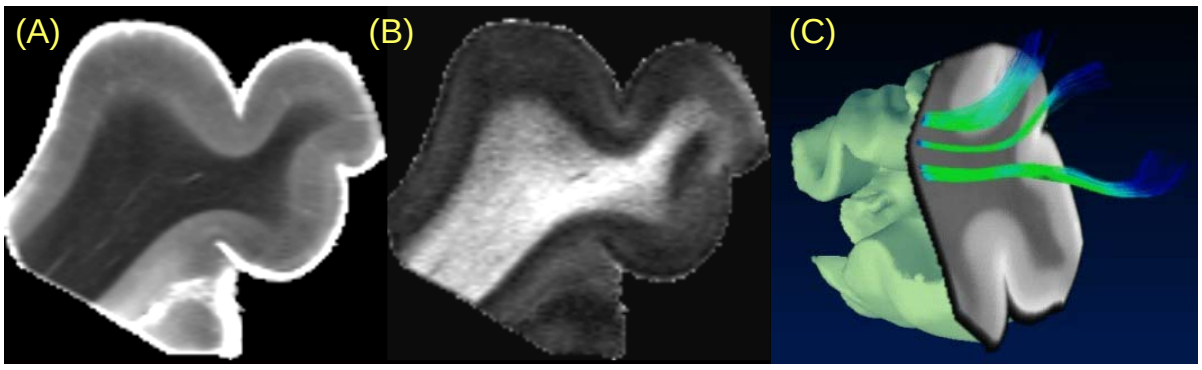

Figure 4: High resolution 3D DTI scans of fixed human premotor cortex (4.7T, 220μm isotropic resolution). (A) ADC (trace), (B) FA, (C) DTI tractography.

Summary
Current clinical MRI scans do not yet typically resolve structure within the cerebral cortex, however high resolution 3D scanning allows accurate measurements of the thickness of the cortical ribbon, which may be a valuable indicator of various disease states. Very high resolution structural scans of fixed brain specimens reveals detailed structure consistent with histological sections and points the way for further developments in *in vivo* MRI of the cortex. DTI scans in human neonates have showed strong diffusion anisotropy in the cerebral cortex which declines rapidly with age. DTI data from animal and *in vitr*o human experiments confirm the presence of diffusion anisotropy in adult cortex, a weaker form of that present in infant brain. *Ex vivo* DTI tractography shows complex structure in the cortex which is markedly perturbed in several disease states. The keys to successfully implementing such methods in the living human cortex are high spatial resolution, high SNR and high b-values. Continued improvements in multi-coil technology, high field MRI scanners and pulse sequence design will allow us to meet this challenge. Given the tremendous yield from studies of diffusion anisotropy in cerebral white matter, there is every reason to expect that extending the methodology to cortical gray matter would be well worth the effort.

Acknowledgements
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