Phase maps reveal cortical architecture

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I n this issue of PNAS, Duyn *et al.* (1) present a magnetic resonance imaging (MRI) technique that reveals astonishing and hitherto unseen details of the architecture of the cerebral cortex of living human beings. The cortex (Latin for "bark" or "outer rind") is a thin layer of gray matter that is highly folded to attain a large surface area within the limited volume of the human skull, and it is thought to be the substrate for the vast majority of the cognitive skills that we possess. That the cortex has an interesting laminar structure, and that this structure may relate to its functional properties, has been known for more than 100 years (2, 3). Directly visualizing these laminar properties in living humans is one of the central goals of structural neuroimaging research. From a neuroscience standpoint, the importance of imaging cortical architecture stems from the fact that the human cortex can be parcellated into discrete regions based on changes in the laminar distributions of cell types and density, dating back to the classic work of Korbinian Brodmann a century ago, one of a number of famous cortical parcellations (3–7). These regions, frequently referred to as "cortical areas," are strongly tied to the functional properties of the brain, and hence being able to robustly and routinely delineate them *in vivo* would be a fundamental tool in research aimed at deepening our understanding of the human brain.

The challenge of visualization of cortical architecture is illustrated in Fig. 1, which shows a coronal section (a plane perpendicular to the line connecting the nose to the back of the head) through the human medial temporal lobe, one of the regions affected earliest by Alzheimer's disease (AD) (8). In MRI there is a direct relationship between resolution and signal-to-noise ratio (SNR). Specifically, the SNR varies with the third power of the linear dimension of a voxel (or linearly with the volume of a voxel). Fig. 1 *Left* shows a standard *in vivo* MRI scan obtained at ≈1-mm resolution, requiring 8.5 min to acquire. Fig. 1 *Center* is of a portion of a fixed *ex vivo* brain acquired at 100-µm isotropic resolution, and Fig. 1 *Right* is a standard Nissl stain, which marks cell bodies as dark spots. As can be seen, the *ex vivo* MRI scan in the center reveals much of the same laminar information as the
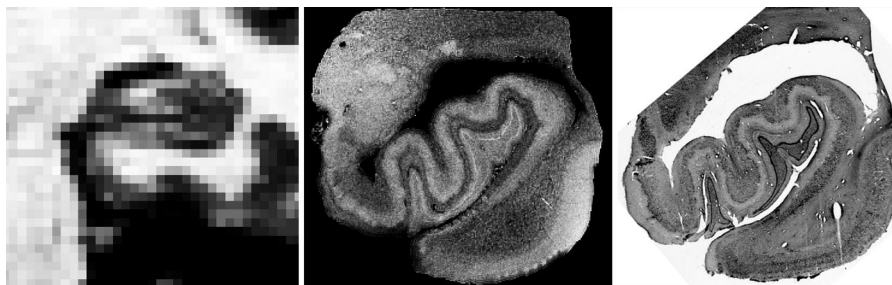

Fig. 1. Comparison of coronal sections through the medial temporal lobe *in vivo* (*Left*), *ex vivo* (*Center*), and histological images. (*Left*) Standard 1-mm *in vivo* image of a temporal lobe. (*Center*) A 100-µm isotropic *ex vivo* MRI image showing laminar structure in the cortex and the hippocampus. (*Right*) Nissl stain revealing distribution of cell bodies into layers. Neda Bernasconi and Jean Augustinack (Harvard Medical School, Boston, MA) provided these images.

histological image on the right, again showing that MRI has the potential to probe laminar architecture. The additional SNR required to obtain Fig. 1 *Center* relative to *Left* is approximately a factor of 1,000 or the ratio of the volume of the voxels in each image. This resolution is achievable in imaging *ex vivo* samples because of a number of factors that result in a dramatic increase in SNR, including scan times that would be prohibitively long *in vivo* (e.g., >12 h), the placement of small coils in close proximity to the sample with no intervening skull, and the absence of artifacts and image blurring due to respiratory and cardiac cycles. None of these factors are applicable *in vivo*, implying that the SNR needed to attain the image resolution to visualize these details *in vivo* must be obtained elsewhere.

The fundamental technique used by Duyn *et al.* (1), using phase changes in the MRI signal that arise from local variations in the magnetic susceptibility of brain tissue to reveal underlying anatomical structure, has been in use for some time (8, 9). The contributions of the present paper are in bringing this technique to the level where it can be used to study the internal structure of the cortex and the simply astonishing images that they have obtained. As always in MRI, the increase in resolution comes about because of an increase in SNR, which can then be traded off for smaller voxel sizes. The authors achieve the unprecedented SNR and resolution through advances on a number of fronts. First, they worked with state-of-the-art ultra-high-field magnetic resonance equipment and solved some of the con-

founds associated with imaging at this type of field strength, such as the modulations in the magnetic field induced by respiratory cycles. Second, they were quick to realize that by measuring phase changes rather than signal magnitude they were severalfold more sensitive to susceptibility-based contrast, a contrast that is enhanced at higher field. Finally, they realized that the internal structure of the cortex offers an attractive target for this contrast mechanism. The result is a convincing demonstration that these images can be useful for directly visualizing the underlying laminar architecture of the cortex.

The basic insight of using the signal phase to reveal anatomical and physiological details of the human brain was developed more than a decade ago (9) and has been dubbed susceptibility weighted imaging (SWI) (8). The technique allows the visualization of phase difference in the hydrogen protons precessing at a rate that is proportional to the local magnetic field. When brain structures magnetize to different degrees, the result is local variations in the magnetic fields in and around these structures, and changes in the phase thus reflect anatomical and physiological

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phenomena related to the source of the magnetization, such as the amount of iron in the tissue or blood. Originally this technique was applied to imaging of the vasculature by Haacke and colleagues (10), which resulted in significant clinical applications such as visualization of tumor neovasculature (11). More recently, it has been applied at ultra-high field by a group at Ohio State University to image brain structure with some success (12).

Several researchers have shown examples of being able to directly visualize laminar architecture both *in vivo* (13–16) and *ex vivo* (17–19), using signal magnitude. These studies have used exceedingly long scan sessions or extremely localized imaging to detect signatures of the cortical architecture, but none have been able to convincingly demonstrate the delineation of a entire cortical area *in vivo*. From a clinical standpoint, being able to detect the borders of cortical areas by using laminar properties would

be a critical advance in our ability to diagnose disorders such as AD earlier in

Signal phase has advantages over signal magnitude in imaging cortical architecture.

their course. In AD specifically, the earliest stage of the disease is thought to be confined to a small number of cortical areas (20, 21). Thus, detecting changes in brain structure in early AD can be decomposed into two separate problems: (*i*) localizing the regions where an effect is expected, and (*ii*) detecting the effect. The phase imaging technique has the potential to aid in each of these ar-

eas. Early detection would be vital because therapeutic intervention will likely be effective only before widespread cell death. The contribution of Duyn *et al.* (1) vividly demonstrates that signal phase has such significant advantages over signal magnitude in imaging cortical architecture, thus bringing neuroimaging one step closer to the *in vivo* delineation of cortical regions.

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