# Title: Imaging Micro-Structure: Applications in Neuroscience

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Highlights:

- New MRI frameworks provide new tools for the neuroscientists to investigate brain micro-anatomy and physiology
- Voxel-based morphometry and Diffusion MRI can highlight areas that underwent structural plasticity
- Diffusion MRI can infer axon diameter distribution and imply of tract-specific axonal conduction velocity
- T1 and diffusion MRI can differ between cortical layers

Target Audience: MRI experts with interest in applications in neuroscience

Outcome/Objective: Define the current cutting-edge MRI technology that can provide neuroscientists additional tools to investigate brain anatomy and physiology.

The talk will cover 3 topics: structural neuroplasticity, conduction velocity and cortical architecture. For these specific topics so far there was no non-invasive technology that could obtain such measures on the human brain. In recent years, MRI image acquisition and analysis framework enables investigation and characterization of these features in-vivo providing a unique tool for the neuroscientists to investigate the brain in an unprecedented way.

**Topic 1: Neuroplasticity**

Neuro-plasticity is one of the key processes in brain's physiology. While functional aspects of neuro-plasticity can be studied in-vivo using microscopy and electrophysiology as well as non-invasively with fMRI and EEG, investigation of the structural characteristics of neuro-plasticity requires histological or other invasive approaches .

In the last decade, structural MRI (mainly T1-weighted analysis via voxel based morphometry) studies of long-term brain plasticity revealed significant volumetric/regional changes following weeks of training (1-3). Yet, none of the known hallmark mechanism of neuroplasticity can explain these effects. As a consequence, the micro-structural and cellular correlates of these structural plasticity changes are not well understood. In addition, the mechanism in which these significant brain structural changes are built over time is still unexplored.

In the presentation, we will explore the origins of structural plasticity, as revealed by MRI, and it's evolution in time (from seconds to months). For that purpose we will utilize T1-weighted (VBM) and diffusion MRI to explore the macro- and micro-structural aspects of neuroplasticity. By demonstrating several plasticity studies performed in rodents and humans with VBM and diffusion MRI we will try to unravel the mechanism responsible for this phenomenon (1,4-10). We will discuss the impact of using MRI in studying neuroplasticity – the ability to localize and explore this basic process of brain physiology, in-vivo and for the whole brain both in rodents and humans.

**Topic 2: Axonal Conduction Velocity**

There are no in-vivo probes that can quantify white matter's physiology (e.g. conduction velocity). These features of white matter are traditionally measured by invasive procedures on excised tissue samples. However, since white matter physiology is correlated with its micro-structure one can elucidate on the one by measuring the other. DTI provided the first unique measure of white matter's micro-

structure: the diffusion anisotropy (11). Despite the fundamental new insights it provides, the DTI model is not specific to any of the underlying tissue micro-structural features. Therefore, in this presentation we will introduce and demonstrate the utility of using micro-structural directed measures such as AxCaliber, ActiveAx and CHARMED to study the white matter and its physiology (12-17).

Recent geometrical models of diffusion offers a more direct measure of microstructural features. AxCaliber, for example, is used to compute the axon diameter distribution (ADD) in each voxel through the measurement of diffusion weighted signals in various diffusion times (15). This model is based on the assumption that water diffusion within the axon is restricted while elsewhere it is only hindered. The idea behind AxCaliber is that each axon, depending on its diameter, will experience restricted diffusion at a different diffusion time.

The AxCaliber framework was verified on excised samples of optic and sciatic nerves and in-vivo on rat corpus callosum by comparison of the computed ADD with the histological analysis of the same samples. Moreover, the relation of ADD measures to neurophysiology (conduction velocity) and white matter plasticity will be presented (14).

With the geometrical model approach (as in CHARMED and AxCaliber) it is possible to use diffusion MRI to extract compartment specific information and thus turning it into a microstructural probe that actually serves as a virtual histological tool. These kinds of measures represent white matter more directly and thus may infer accurately on the physiology of white matter.

**Topic 3: Cortical Architecture**

The ability to characterize cortical sub-structures (i.e. the cortical layers) *in-vivo* is one of the holy-grails of neuroscience. The measurement of cortical sub-structures is limited today to post-mortem histological analysis.

T1 is one of the best MRI contrast mechanisms that allows visualization of different tissue types in the brain (e.g. gray matter vs. white matter). In recent years, several groups demonstrated that within the cortex, T1 has a unique fingerprint of relaxation variability that arranges in a laminar pattern (18-21). This laminar appearance of longitudinal relaxation, via T1 measurements, although not directly related to tissue architecture seem to enable the investigation of cortical lamination patterns for the whole brain, in 3D, *in-vivo* and non-invasively.

Preliminary data suggested that the cortex can be segmented based on its T1 composition. More recently, high resolution diffusion MRI was also shown to allow segmentation to the cortex based on anisotropy and tensor directionality (22). In this talk, we wish to describe the basic phenomena and discuss its main limitation: partial volume. We will discuss the relation between T1 and diffusion cortical composition and cyto- and myelo-architecture.

The opportunity to measure cortical sub-structures *in vivo* opens a vast of research opportunities. From studying the sub-cortical correlates of inter-subject behavioral and functional variability to understanding the mechanisms of neurological and psychiatric diseases.

**References:**


1. Draganski B, Gaser C, Busch V, Schuierer G, Bogdahn U, May A. Neuroplasticity: changes in grey matter induced by training. Nature 2004;427(6972):311-312.
2. Munte TF, Altenmuller E, Jancke L. The musician's brain as a model of neuroplasticity. Nat Rev Neurosci 2002;3(6):473-478.
3. Maguire EA, Gadian DG, Johnsrude IS, Good CD, Ashburner J, Frackowiak RS, Frith CD. Navigation-related structural change in the hippocampi of taxi drivers. Proc Natl Acad Sci U S A 2000;97(8):4398-4403.
4. Lerch JP, Yiu AP, Martinez-Canabal A, Pekar T, Bohbot VD, Frankland PW, Henkelman RM, Josselyn SA, Sled JG. Maze training in mice induces MRI-detectable brain shape changes specific to the type of learning. Neuroimage 2011;54(3):2086-2095.
5. Thomas AG, Dennis A, Bandettini PA, Johansen-Berg H. The effects of aerobic activity on brain structure. Front Psychol 2012;3:86.
6. Zatorre RJ, Fields RD, Johansen-Berg H. Plasticity in gray and white: neuroimaging changes in brain structure during learning. Nat Neurosci 2012;15(4):528-536.
7. Scholtz J, Johansen-Berg H. White matter microstructure changes in response to training. Proc Human Brain Mapping 2009;15:362.
8. Tavor I, Hofstetter S, Assaf Y. Micro-structural assessment of short term plasticity dynamics. Neuroimage 2013;81C:1-7.

9. Hofstetter S, Tavor I, Tzur Moryosef S, Assaf Y. Short-term learning induces white matter plasticity in the fornix. J Neurosci 2013;33(31):12844-12850.
10. Sagi Y, Tavor I, Hofstetter S, Tzur Moryosef S, Blumenfeld-Katzir T, Y. A. Learning in the fast lane: new insights into neuroplasticity. Neuron 2012;73:1195-1203.
11. Jones DK. Diffusion MRI : theory, methods, and application. New York: Oxford University Press. xvi, 767 p. p.
12. Assaf Y, Alexander DC, Jones DK, Bizzi A, Behrens TE, Clark CA, Cohen Y, Dyrby TB, Huppi PS, Knoesche TR, Le-Bihan D, Parker GJ. The CONNECT project: Combining macro- and micro-structure. Neuroimage 2013.
13. Assaf Y, Basser PJ. Composite hindered and restricted model of diffusion (CHARMED) MR imaging of the human brain. Neuroimage 2005;27(1):48-58.
14. Horowitz A, Barazany D, Tavor I, Bernstein M, Yovel G, Assaf Y. In vivo correlation between axon diameter and conduction velocity in the human brain. Brain Struct Funct 2014.
15. Barazany D, Basser PJ, Assaf Y. In vivo measurement of axon diameter distribution in the corpus callosum of rat brain. Brain 2009;132(Pt 5):1210-1220.
16. Dyrby TB, Sogaard LV, Hall MG, Ptito M, Alexander DC. Contrast and stability of the axon diameter index from microstructure imaging with diffusion MRI. Magn Reson Med 2012.
17. Alexander DC. A general framework for experiment design in diffusion MRI and its application in measuring direct tissue-microstructure features. Magn Reson Med 2008;60(2):439-448.
18. Barazany D, Assaf Y. Visualization of Cortical Lamination Patterns with Magnetic Resonance Imaging. Cereb Cortex 2011;Accepted.
19. Turner R, Oros-Peusquens AM, Romanzetti S, Zilles K, Shah NJ. Optimised in vivo visualisation of cortical structures in the human brain at 3 T using IR-TSE. Magn Reson Imaging 2008;26(7):935-942.
20. Geyer S, Weiss M, Reimann K, Lohmann G, Turner R. Microstructural Parcellation of the Human Cerebral Cortex - From Brodmann's Post-Mortem Map to in vivo Mapping with High-Field Magnetic Resonance Imaging. Front Hum Neurosci 2011;5:19.
21. Eickhoff S, Walters NB, Schleicher A, Kril J, Egan GF, Zilles K, Watson JD, Amunts K. High-resolution MRI reflects myeloarchitecture and cytoarchitecture of human cerebral cortex. Hum Brain Mapp 2005;24(3):206-215.
22. Leuze CW, Anwander A, Bazin PL, Dhital B, Stuber C, Reimann K, Geyer S, Turner R. Layer-Specific Intracortical Connectivity Revealed with Diffusion MRI. Cereb Cortex 2012.