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Clinical Magnetic Resonance Neuroimaging in Fibromyalgia

Nicolás Fayed* and Javier Garcia-Campayo**

*Department of Radiology, Quirón Hospital, Zaragoza, Spain**

*Somatoform Disorders and Fibromyalgia Unit, Miguel Servet Hospital, University of Zaragoza, Spain***

Key points

- Magnetic resonance spectroscopy (MRS) offers invaluable information about living tissues with special contribution to the diagnosis and prognosis of the central nervous system diseases.
- Diffusion tensor imaging (DTI) detects subtle degradation of white matter microstructure in fibromyalgia.
- Perfusion magnetic resonance imaging (MRI) offers higher spatial resolution than radionuclide techniques such as positron emission tomography and single-photon emission computed tomography.
- Voxel-based morphometry (VBM) is a recent methodology that can simultaneously visualize group differences or statistical effects on gray and white matter, throughout the whole brain.
- Functional magnetic resonance imaging (fMRI) studies regularly confirm that multiple brain regions are invoked to execute even ostensibly simple tasks.

1. Introduction

Imaging human internal organs with exact and non-invasive methods is very important in medicine for medical diagnosis, treatment and follow-up, as well as for clinical research. Today, one of the most important tools for this purpose is magnetic resonance imaging (MRI). MRI scanners are based on the nuclear magnetic resonance (NMR) phenomenon, which was detected independently by Bloch, Purcell et al. in 1946. The advent of neuroimaging techniques yielding neuropsychological data in addition to structural information was of particular interest for scientific and clinical research into fibromyalgia and psychiatric disorders. These are groups of conditions for which any structural changes evident in anatomical imaging sequences generally correlate poorly with clinical diagnostic categories, pointing to underlying pathophysiology and severity of disease. T1- and T2-dependent MR sequences, the mainstay of routine clinical neuroimaging, are frequently insensitive to the underlying pathological processes in these conditions. Focal or global atrophy due to associated neuronal loss is also frequently absent.

The remit of this section is an overview of some general issues concerning the application of spectroscopy, diffusion, perfusion, morphometry and functional techniques in fibromyalgia, and their clinical impact in the context of other available tests.

2. Magnetic Resonance Spectroscopy (MRS)

This technique enables us to study the chemical composition of living tissues. It is based on the chemical shift of atoms. The concentration of some metabolites is determined from spectra that may be acquired in several ways.

3. Voxel placement

Currently the spectra may be acquired with single-voxel (SV) or multivoxel techniques (MV). The SV technique is readily available on most scanners. Voxels must be positioned away from sources of susceptibility artifacts and lipids. For diffuse processes, a $2 \times 2 \times 2$ -cm (8 cm^3) voxel is routinely used. For local lesions, the SV can be reduced in volume. The SV technique offers the advantages of better spatial location, more homogeneity, better water suppression and speed. However, only one spectrum can be obtained per acquisition.

However, The MV technique makes it possible to obtain multiple spectra simultaneously per acquisition and to assess a greater area of the brain but with smaller spectral resolution. To date, the SV is still superior to MV on the grounds of reproducibility (Sauter et al., 1991; Hsu et al., 1999, 2001; Law et al., 2004). For both SV and MV, the MR scanner employs a process known as shimming to narrow peak linewidths within the spectra. For SV studies, improving field homogeneity is performed with basic, zero-ordered shimming on clinical MR scanners. For MV, the simultaneous production of uniform field homogeneity in multiple regions requires higher order shimming. To obtain high-quality spectra, blood products, air, fat, necrotic areas, cerebrospinal fluid, metal, calcification and bone should be avoided. In such areas differing magnetic susceptibility results in a non-homogenous field that hinders the production of diagnostic quality spectra.

4. MRS pulse sequence

Two different approaches are generally used for proton spectroscopy of the brain: a) single-voxel methods based on the stimulated echo acquisition mode (STEAM) and b) point resolved spectroscopy (PRESS) pulse sequences and spectroscopy imaging (SI), also known as chemical shift imaging (CSI). These latter studies are usually done in two dimensions, using a variety of different pulse sequences (spin-echo (SE), usually PRESS).

The basic principle underlying single-voxel localization techniques is to use three mutually orthogonal slice selective pulses and design the pulse sequence to collect only the echo signal from the point (voxel) in space where all three slices intersect. In STEAM, three 90° pulses are used and the stimulated echo is collected. All other signals (echoes) should be dephased by the large crusher gradient applied during the so-called mixing time. Crusher gradients are necessary for consistent formation of the stimulated echo and removal of unwanted coherences. In PRESS, the second and third pulses are refocusing (180°) pulses, and crusher gradients are applied around these pulses to select the desired SE signal arising

from all three RF pulses and dephasing unwanted coherences. STEAM and PRESS are generally similar but differ in a few key aspects.

With regard to the mode of acquisition, PRESS can be performed with short and long echo times (TEs) and there is complete recovery of signal. STEAM can be performed with very short TEs, but there is incomplete recovery of signal and a precise volume element (voxel) is formed. The PRESS mode is used more than STEAM because it increases the signal/noise ratio and is less sensitive to movement artifacts (Maheshwari et al. 2000). A short TE (20-40 ms) allows us to increase the signal/noise ratio and to visualize most metabolite peaks, with the inconvenience of some degree of peak overlapping. Time matters in clinical practice, so short TEs are preferable. In our experience with a 1.5T GE Signa Horizon-clinical scanner a TE of 30 ms and a TR of 2500 ms have proven valuable (Fayed et al., 2006). Recently, a TE-averaged PRESS technique has been yielding highly simplified spectra with better suppression of signals not pertaining to assessed metabolites, such as that of macromolecules. TE is increased from 35 ms to 355 ms in steps of 2.5 ms with two acquisitions per step (Hancu et al., 2005).

5. MR spectra quantification

The most commonly used spectroscopy is that originating from a Hydrogen nucleus (proton 1H-MRS). This technique is based on the differences in resonance obtained from hydrogen nuclei depending on the surrounding atoms (chemical shift). Each metabolite being assessed discloses a different hydrogen resonance frequency and appears in a different site in the spectrum. The most frequently evaluated metabolites are N-acetyl-aspartate (NAA), myo-inositol (mI), choline (Ch), creatine (Cr) and glutamate+glutamine (Glx). The position of the metabolite signal is identified on the horizontal axis by its chemical shift, scaled in units referred to as parts per million (ppm). With the appropriate factors considered, such as the number of protons, relaxation times and so forth, a signal can be converted into a metabolite concentration by measuring the area under the curve. Because water is the main component of living beings and its concentration is much higher than that of metabolites, it becomes necessary to suppress the resonance signal from the hydrogen of water (Maheshwari et al. 2000 and Bonavita et al. 1999). A plot showing peak amplitudes and frequencies is obtained. Each spectrum shows peaks corresponding to the different metabolite values: Myo-inositol (mI), 3.56 and 4.06 ppm; Choline compounds (Ch), 3.23 ppm; Creatine (Cr), 3.03 and 3.94 ppm; γ N-acetyl-aspartate (NAA), 2.02; 2.5 and 2.6 ppm; glutamine and glutamate (Glx), 2.1-2.55 ppm and 3.8 ppm. Ratios between metabolites and creatine are also of great value as they counteract the systematic errors of measurements.

6. Fitting of model spectra

A more recent program, called a linear combination model ("LCModel") (Provencher, 1993), fits in vivo spectra as a linear superposition of high-resolution "basis" spectra that are acquired from model solutions of the metabolites present in the organ of interest. Advantages of LCModel are that all pre-processing steps, automatic phase correction as well as modelling of a smooth baseline are included. Standardized basis sets are available for the most common clinical MR machines (both 1.5 and 3 T).

7. Fibromyalgia

Fibromyalgia is a chronic and disabling musculoskeletal pain disorder of unknown, characterized by a history of widespread pain for at least three months and patients reporting of tenderness in at least 11 of 18 defined tender points when digitally palpated with about 4 kg per unit area of force. Other frequent accompanying symptoms are fatigue, sleep disturbance and depressed mood (Wolfe et al, 1990; Giesecke et al, 2003). With an estimated lifetime prevalence of 2% in community samples (Wolfe et al, 1995), it accounts for 15% of outpatient rheumatology visits and 5% of primary care visits (Wolfe 1989). The prognosis for symptomatic recovery is generally poor (Wolfe et al., 1997). Recent meta-analysis (Garcia Campayo et al., 2008) demonstrates that both pharmacological and psychological treatments show moderate effectiveness with a mean effect size of 0.49. The variables that related most with improvement in outcome were younger age of the patients and shorter duration of the disorder. On the contrary, gender and type of treatment (pharmacological or psychological) did not affect outcome (Garcia Campayo et al., 2008).

8. Usefulness of different neuroimaging techniques in Fibromyalgia

a) 1H MRS in Fibromyalgia patients

Glutamate has been implicated as an important mediator in the neurotransmission, potentiation, and negative affect associated with pain, and it has been related to chronic pain sensitization (Dickenson et al., 2002). Experimental pain models for fibromyalgia have revealed elevated glutamate levels in the posterior insula. MRS spectroscopy studies have shown that dynamic changes in glutamate and glutamine levels in the insula were associated with improvements in clinical and experimental pain in fibromyalgia (Harris et al., 2008). Also, a recent MR spectroscopy study concludes with the involvement of the posterior insula in pain (Harris et al., 2009)

A previous MRS study by our group demonstrated the differences in metabolites between FM patients and controls. (A)

Our data suggest that Glx plays a role in this augmented pain processing in those individuals who have elevated Glx levels, which is entirely consistent with the literature and knowledge regarding FM. In our study there is a significant correlation in the posterior cingulate gyrus between Glu+Gln (Glx) and Glx/Cr with depression, pain measured in an objective way, such as by sphygmomanometer, and global function assessed with the Fibromyalgia Impact Questionnaire (FIQ). Since astrocytes participate in the uptake, metabolism, and recycling of glutamate, we hypothesize that an astrocyte deficit may account for the alterations in glutamate/GABA neurotransmission in depression. Factors such as stress, excess glucocorticoids, altered gene expression of neurotrophic factors and glial transporters, and changes in extracellular levels of neurotransmitters released by neurons may modify glial cell numbers and affect the neurophysiology of depression (Rajkowska et al., 2007). Other studies found that absolute concentrations of Glx, Glu, and creatine+phosphocreatine (Cr) were significantly higher in adult bipolar patients in all mood states compared to healthy controls (Yildiz-Yesiloglu et al. 2006).

Elevated Glx inside the astrocyte leads to increased cellular osmolarity in the brain. Within 30 minutes of glutamate administration, electron microscopy reveals massive acute swelling of neuronal cell bodies and dendrites. Consequently, water shifts from the extracellular fluid space to the intracellular fluid space resulting in edema of the astrocytes. Relevant clinical

manifestations are thought to be secondary to this edema (Häussinger et al., 2000). To compensate for the increased cellular osmolarity, myo-inositol shifts to the extracellular fluids space, leading to a reduction in its concentration inside the astrocyte. In consequence, Glx is an excitatory amino acid, and its increase indicates that the metabolic function of patients with fibromyalgia differs from controls. Elevation of Gln levels may result in permanent cerebral damage.

In addition, high correlations were found between some clinical variables and certain brain metabolites, for instance: ratios of myo-Inositol/Creatine and NAA + *N*-acetyl aspartyl glutamate (NAA+NAAG) in the left hippocampus with pain; myo-Inositol in the right hippocampus and myo-Inositol in the posterior cingulate gyrus with catastrophization.

A recent HMRS study, showed decreased NAA levels within the hippocampus of individuals with FM (Wood et al., 2009). In another study, a reduction in the absolute concentration of NAA in the right and left hippocampi was reported in a sample of 15 patients with fibromyalgia (Emad et al. 2008). Lower hippocampal NAA levels suggest neuronal or axonal metabolic dysfunction, or some combination of these processes. Neuronal loss in the hippocampus has not yet been studied in our series. This should be assessed in further studies, in order to gauge atrophic changes within the hippocampus. Some studies found that the persistence of elevated Ca²⁺ in hippocampal neurons exposed to glutamate correlated with the extent of neuronal death, and that a large rise in Ca²⁺ in cultured hippocampal neurons, following glutamate application, predicted cell death (Mattson et al., 1989). Hippocampal dysfunction may be partly responsible for some of the phenomena associated with FM. Blocking NMDA receptors in the hippocampal formation reduces nociceptive behaviours; this in turn supports the hypothesis that the hippocampal formation is involved in pain-related neural processing and expression of pain-related behaviours (McKenna et al. 2001).

Finally, our study confirms the reduction in myo-Inositol levels in both hippocampi and reduction in myo-Inositol/Cr ratios in the left hippocampus and sensitivomotrice area. In all cases, brain metabolites were lower in the patient group compared to controls. Changes in myo-Inositol have previously been described in patients suffering from bipolar disorder (Silverstone et al. 2005). Research suggests that lithium functions primarily by decreasing myo-inositol concentrations in bipolar patients (Harwood et al., 2005).

Patients suffering from clinical depression generally have decreased levels of inositol in their cerebrospinal fluid (Barkai et al., 1978). This deficiency could be explained by a reduced synthesis or more interestingly by an increased consumption of the compound (Lentner, 1986). We speculate that myo-Inositol might, via its conversion to glucuronic acid, be consumed in protective detoxification reactions of the brain and could be associated with depression.

b) Diffusion Tensor Imaging (DTI)

White matter structure

Neuroimaging reveals changes in the white matter (WM) structure in the human brain. White matter comprises half of the human brain and consists of bundles of myelinated axons connecting neurons in different brain regions (Fields, 2008). Grey matter is composed of neuronal cell bodies and dendrites concentrated in the outer layers of the cortex. Microstructural changes in white matter can be revealed by specialized MRI brain imaging techniques such as diffusion tensor imaging (DTI). This method analyses the of proton

diffusion in tissue, which is more restricted in white matter than in grey matter. The anisotropy increases with increased myelination, diameter and axon compaction.

DTI measurement

Water molecules in the brain are in constant Brownian motion, and although the movement of these protons affects conventional structural imaging, diffusion weighted imaging (DWI) and diffusion tensor imaging (DTI) allow quantification of this microscopic movement within each voxel. The main advantage of using DTI, rather than DWI, is that DTI reflects the underlying diffusion properties of the sample, independently of the orientation of the tissue with respect to the direction of measurements. DTI is thus a robust quantitative technique that is independent of how the subject has been oriented inside the scanner magnet and gradient coils. In regions with few or no constraints imposed by physical boundaries, such as CSF in the ventricles, water movement is random in every direction and is isotropic. In contrast to CSF, the path of a water molecule in a WM fibre is constrained by physical boundaries, such as the axon sheath, causing the movement along the long axis of a fibre to be greater than radial diffusion across the.

These data can be used to calculate the probable anatomy of white matter bundles in living brain, a process called tractography. Orientation is calculated from the eigenvectors defining proton diffusion in three dimensions in each voxel. Using algorithms, the principal eigenvalue vector is connected to the next voxel to trace the fibre structure and orientation in white matter tracts (Jones et al., 2002)

Diffusion tensor imaging (DTI) yields quantitative measures for tissue water mobility as a function of the direction of water motion and is probed by application of diffusion-sensitization gradients in multiple directions (Basser et al., 1996). Basser et al. describe the use of multivariate linear regression to calculate D from a non-diffusion-weighted image plus six or more diffusion-weighted measurements in a non-collinear direction. The diffusion weighting is obtained by simultaneously applying diffusion gradients along combinations of the three physical axes.

The appropriate mathematical combination of the directional diffusion-weighted images provides quantitative measures of water diffusion for each voxel via the apparent diffusion coefficient (ADC), as well as the degree of diffusion directionality, or anisotropy (Sundgren et al. 2004). Myelin is a major diffusion barrier for water, and gives white matter its high anisotropy. Demyelinating diseases are characterized by partial or total loss of myelin, with consequent loss of neuronal function.

Fibromyalgia

DTI allows in vivo mapping of the anatomic connections in the human brain; previous studies have identified and confirmed the existence of an anatomic circuitry for the functionally characterized top-down influences on pain processing via brainstem structures in humans (Hadjipavlou et al., 2006) Fractional anisotropy (FA) is a measure of the portion of the diffusion tensor from anisotropy.

Previous studies with diffusion tensor imaging in FM patients showed alterations in the right thalamus and significantly lower fractionated anisotropy in comparison with controls. A negative correlation was seen between the FA values in the right thalamus and clinical pain in the FM group (Sundgren et al., 2007). Other authors confirmed that DTI in the brain

of patients with FM appears to be more sensitive than volumetric imaging of voxel-based morphometry (VBM) and increased pain intensity scores were correlated with changes in DTI measurements in the right superior frontal gyrus. Increased fatigue was correlated with changes in the left superior frontal and left anterior cingulate gyrus, and self-perceived physical impairment was correlated with changes in the left postcentral gyrus. Higher intensity scores for stress symptoms were correlated negatively with diffusivity in the thalamus and FA in the left insular cortex (Lutz et al., 2008).

In a previous study by our group, DWI and DTI were not sensitive enough to detect changes in fibromyalgia patients. This may be explained because intraparenchymal injection of glutamate or other excitatory aminoacids cause neuronal cell bodies and dendrites to be predominantly affected, whereas axons and terminal boutons, originating from cell bodies outside of the affected region, remain largely intact (Coyle et al., 1981).

c) Perfusion MRI

Positron emission tomography (PET) (Jones et al., 1991) and single-photon emission computed tomography (SPECT) (Kwiatek et al., 2000) have been used to identify focal changes in regional cerebral blood flow (CBF) in patients with fibromyalgia. However, the low spatial resolution of PET and SPECT, and the ionizing radiation emitted from the nuclear medicine tracers are major concerns. MR perfusion techniques have also been developed and offer higher spatial resolution without the use of ionizing radiation (Rosen et al., 1990; Belliveau et al., 1990; Detre et al., 1992).

MR perfusion techniques are based on exogenous or endogenous tracers. In the method based on exogenous tracers, a paramagnetic agent such as gadolinium dimeglumine gadopentate (Gd-DTPA) is injected, and the resulting decrease and subsequent recovery of the MR signal is used to estimate perfusion (Ostergaard et al., 1996; Liu et al., 1999). In the method using endogenous tracers, the magnetization of the spins of arterial water are non-invasively labelled using radiofrequency (RF) pulses, and the regional accumulation of the label is measured in the tissues by comparison with an image acquired without labelling (Edelman et al., 1994; Kim, 1995; Kwong et al., 1995).

d) Voxel-based morphometry (VBM)

Tissue volumes in the CNS, and in particular changes in volume over time, are sensitive markers of a range of neurological disease states and disease progression. Measurement of brain volume requires segmentation of the brain from the rest of the tissues in the head and neck. Whilst this can be performed manually or in a semiautomated fashion (see for example Harris et al., 1999; Bokde et al., 2002), automated procedures are likely to be more reproducible and rapid. This is understandable as the size of the structures involved is usually relatively small, making the analysis less tedious than a manual segmentation of the whole brain. Additionally, many structures, such as the hippocampus, are difficult to segment in an automated fashion, but are relatively easily identified and manually or semiautomatically outlined, given appropriate software. Some progress has been made in automating segmentation procedures, with methods including the use of deformable shape models.

Tensor-based morphometry (TBM) is a relatively new image analysis technique that identifies regional structural differences in the brain, across groups or over time, from the

gradients of the deformation fields that warp images to a common anatomical template. The anatomical information is encoded in the spatial transformation. Therefore, accurate inter-subject non-rigid registration is an essential tool. With the new advent of recent and powerful non-rigid registration algorithms based on the large deformation paradigm, TBM is being increasingly used (Lepore et al., 2008; Chiang et al., 2007; Lee et al., 2007).

In FM, Valet et al. (2009) found significant grey-matter decreases in the prefrontal, cingulate, and insular cortex. These regions are known to be critically involved in the modulation of subjective pain experiences. Patients presented a decrease in grey matter volume in the prefrontal cortex, the amygdala, and the anterior cingulate cortex (ACC). The duration of pain or functional pain disability did not correlate with grey matter volumes. A trend of inverse correlation of grey matter volume reduction in the ACC with the duration of pain medication intake has been detected. Some authors (Burgmer et al., 2009) suggest that structural changes in the pain system are associated with FM. As disease factors do not correlate with reduced grey matter volume in areas of the cingulo-frontal cortex and the amygdala in patients, one possible interpretation is that volume reductions might be a precondition for central sensitization in fibromyalgia.

e) Functional MR imaging (fMRI)

Another more recent imaging method is functional MRI (fMRI) for the mapping of activation patterns in the brain. This is an important technique for better understanding of brain function. When a brain region is activated, new energy must be transported to this region, which leads to increased blood flow to that part of the brain. This can be imaged by repetitive MR scans and detected by appropriate signal processing methods.

Over the years, many have viewed Fibromyalgia syndrome (FMS) as a so-called "functional disorder" and patients have experienced a concomitant lack of interest and legitimacy from the medical profession. The symptoms have not been explained by peripheral mechanisms alone or by specific central nervous system mechanisms.

Functional MRI blood oxygenation level dependent activation studies on patients who have FM have demonstrated augmented sensitivity to painful pressure and the association of this augmentation with variables such as depression and catastrophizing, and have also been used to evaluate the symptoms of cognitive dysfunction.

The fMRI-analysis by Jensen et al. (2009), revealed no differences in activity in brain regions related with attention and affection or regions with sensory projections from the stimulated body area. However, when there is a primary lesion in the descending pain regulating system (the rostral anterior cingulate cortex), the patients failed to respond to pain provocation. The attenuated response to pain in these cases is the first demonstration of a specific brain region where the impairment of pain inhibition in FMS patients is expressed. These results validate previous reports of dysfunctional endogenous pain inhibition in FM, and advance the understanding of the central pathophysiologic mechanisms, providing a new direction for the development of successful treatments in FM.

Fibromyalgia is the prototypical functional chronic pain condition, and it affects 2-4% of individuals. Although the aetiology of this disorder remains largely unknown, emerging data suggest that FM arises through augmentation of central pain processing pathways. This hypothesis is largely based upon findings of previous functional neuroimaging studies showing that FM patients display augmented neuronal responses to both innocuous and

painful stimuli (Gracely et al., 2002; Cook et al., 2004), confirming the allodynia and hyperalgesia seen in this condition (Petzke et al., 2003).

Studies with functional neuroimaging support the hypothesis of central pain augmentation in FMS. Differences of activation in the fronto-cingulate cortex, the supplemental motor areas and the thalamus were found between both groups with distinct differences in BOLD-signals changes over the time course of pain stimulation, even during anticipation of pain. These results support the hypothesis that central mechanisms of pain processing in the medial pain system, favourable cognitive/affective factors even during the anticipation of pain, may play an important role for pain processing in patients with FMS (Burgmer et al., 2009).

9. Summary, conclusions and future directions

In this chapter, several techniques used for the diagnosis of fibromyalgia are discussed. At present, there are no other non-invasive techniques that can provide equivalent information and, as a consequence, MRS, DTI tractography and functional MRI are expected to be a powerful combined technique for researching brain anatomy and disease *in situ* in human beings.

Diffusion tensor imaging (DTI) in combination with magnetic resonance spectroscopy (MRS) and functional MRI (fMRI) may provide clinicians with information about ongoing pathological changes in FM. Future studies may investigate whether DTI can detect Many factors may influence the ability of DTI to discriminate patients with FM from healthy individuals. These factors include the field strength of the magnet, spatial resolution, signal-to-noise ratio, contrast-to-noise ratio and image artifacts. DTI and MRS are non-invasive and do not require the use of radioactive tracers, suggesting its potential safe application for longitudinal follow-up and repeated assessments.

Continued improvements in the design of imaging equipment and analysis algorithms are progressively improving the specificity of the biological parameters that can be calculated, allowing detailed quantitative characterization of microvascular structure in a wide range of pathological tissues, including fibromyalgia.

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11. Annex. Some examples of new neuroimaging techniques in fibromyalgia.

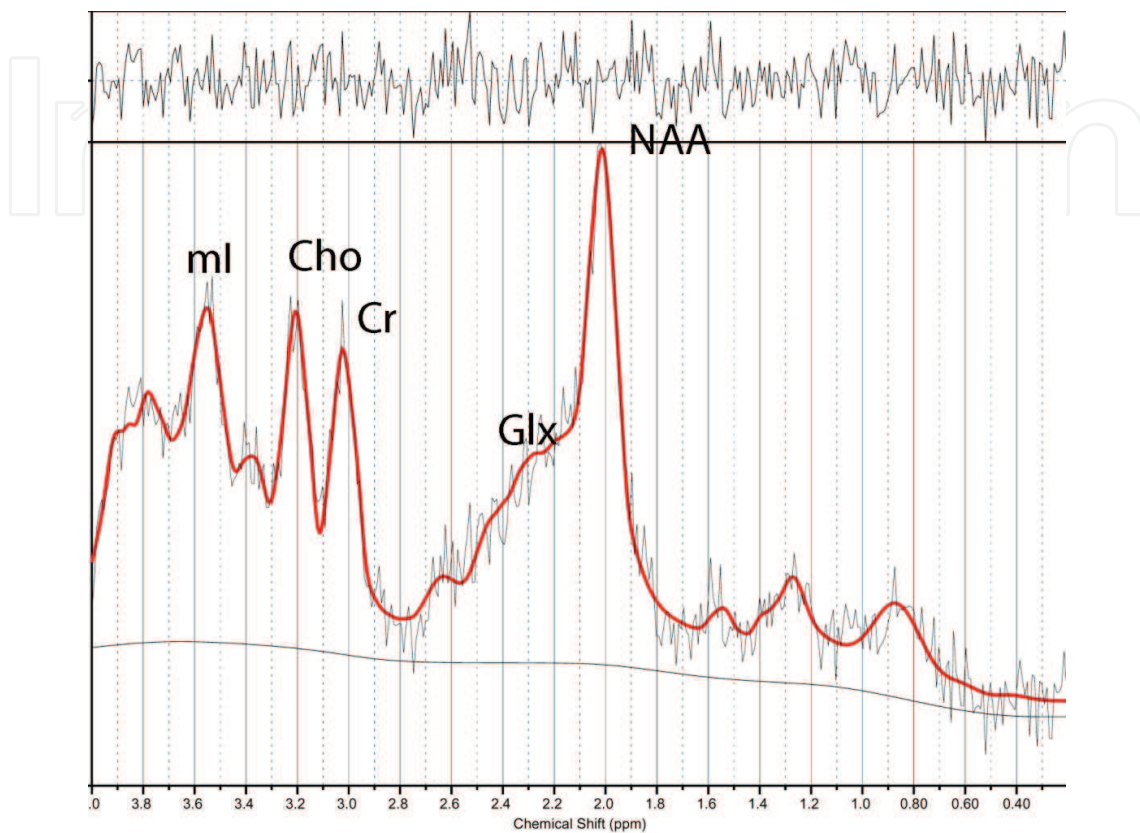


Fig. 1. Magnetic Resonance Spectroscopy

Typical in-vivo proton magnetic resonance spectrum depicts the localization of major peaks for *N*-acetylaspartate (2.02 ppm), creatine/phosphocreatine complex (3.02 ppm), choline (3.22 ppm), glutamine and glutamate (2.1 to 2.55 ppm); and myo-inositol (3.56 ppm)

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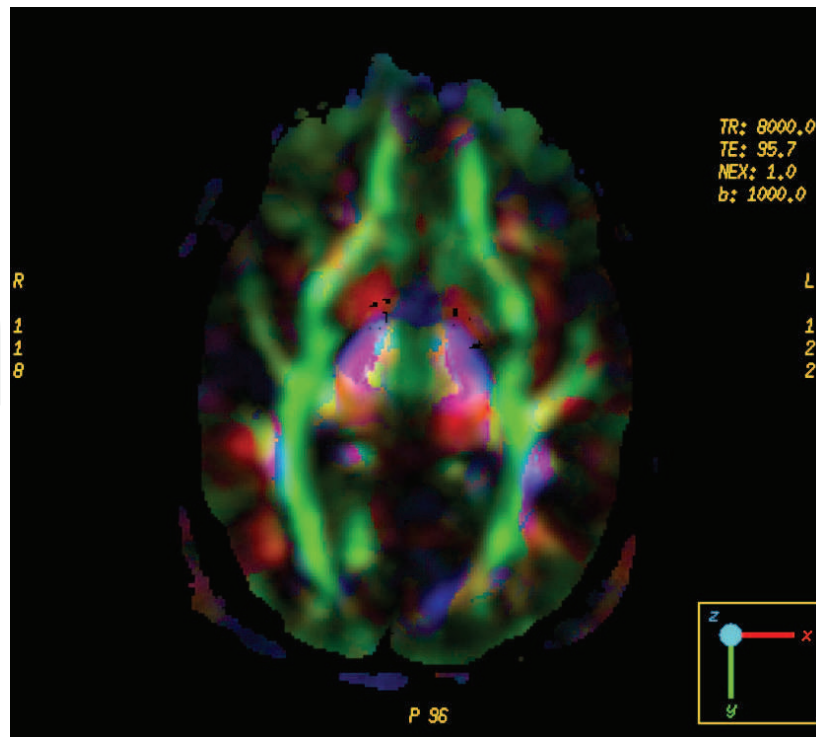


Fig. 2. Diffusion Tensor Imaging

Example of color-encoded fiber orientation maps. Fibers that are predominantly oriented left-right are shown in red, anterior-posterior fibers are shown in green, and superior-inferior fibers are shown in blue.

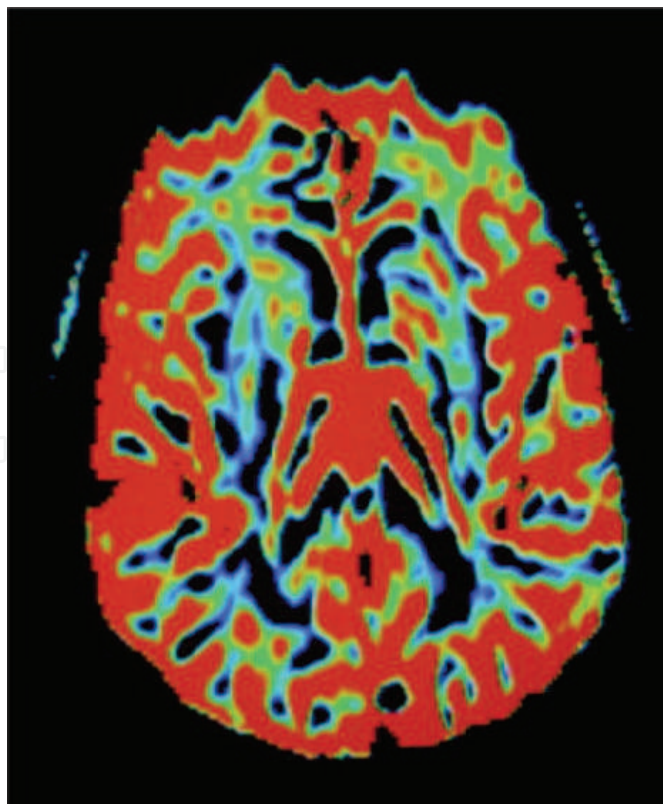
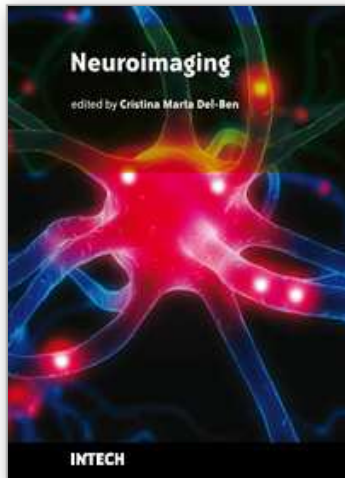


Fig. 3. Perfusion study



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InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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