Introduction to Advanced Techniques in MR Neuroimaging

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fMRI and DTI of a brain tumor: Function and structure

Functional MRI (fMRI)

Functional magnetic resonance imaging (fMRI) is based on the blood oxygenation level dependent (BOLD) effect. BOLD contrast rises with neural activation and depends on the variables blood flow and oxygenation. Augmentation of regional cerebral blood flow (CBF) is accompanied by a local increase in oxygen extraction due to a rise in the cerebral metabolic rate of oxygen consumption. The ferrous iron in deoxyhemoglobin adopts paramagnetic properties contrary to the diamagnetic effect in oxyhemoglobin. This results in a susceptibility induced field shift and leads to an increase in T2* value and a signal increase in T2* gradient echo or echo planar imaging (EPI) studies. The high sensitivity of EPI sequences enables real time visualization of activation of different parts of the brain in comparison to a resting state. In a functional MR paradigm the patient is asked to alternatively perform tasks or is stimulated to trigger several processes or emotions. Threshold functional MRI activation maps are spatially addressed (Fig. 1A) and therefore typically overlaid in colour on a high resolution anatomical T1 MPREAD or SPACE FLAIR MR image (Figs. 1B, C).

fMRI was first employed for mapping of neuronal activation during visual perception tasks and motor activation in the early nineties. Since then fMRI has evolved into an invaluable research tool e.g. in cognitive neuroscience or neuropharmacology as well as a routinely applied clinical MR technique. Clinical applications comprise mainly neurosurgical planning in order to determine resection margins in relation to functional ‘eloquent’ areas. With fMRI brain functional plasticity may also be visualized in recovery after stroke or surgery. Furthermore fMRI can be used to evaluate specific brain functions in a range of neuro-degenerative diseases. Despite existing limitations of fMRI, a significant increase in spatial and temporal resolution has been achieved in order to improve localization of specific brain function and individualized treatment.

Diffusion Tensor Tractography (Diffusion Tensor Imaging, DTI)

DTI is a non-invasive MR technique to study brain tissue composition and architecture in vivo. DTI is based on the concept that water diffusion is anisotropic in organized tissues. Cerebral white matter is composed of axons, myelin sheaths and neuroglia which are aligned to form fiber tracts. DTI provides information on water diffusion properties regarding the extent of diffusion anisotropy and its orientation. A pair of magnetic dephasing and refocusing field gradients is successively applied in distinct directions in 3D space. The resulting images exhibit signal attenuation in the direction of the applied gradient which is proportional to water diffusivity. The largest principal axis of the diffusion tensor aligns with the predominant fiber orientation in an MRI voxel. A diffusion tensor or the mean diffusivity may be estimated from as few as 6 diffusion-weighted images acquired along non-collinear directions and 1 minimally 1 T2-weighted (b0) image. From the diffusion tensor, the DTI indices derived include the mean diffusion coefficient (ADC), calculated eigenvalues and eigenvectors and an index of diffusion anisotropy, e.g. fractional anisotropy (FA). To achieve a high signal-to-noise ratio DTI employs more than the minimum of 6 diffusion-weighting angulations and/or acquires repeated measurements of diffusion directions. Despite substantial improvement in technique, spatial resolution of DTI in the order of 1–4 mm per dimension, reflects limitations imposed by using a macroscopic technique to visualize microscopic restrictions.

DTI is performed in combination with fMRI for preoperative localization of fiber tracts in proximity to a lesion (Figs. 1D–F), and for preoperative differentiation of white matter tract infiltration from displacement in patients with low grade glioma in particular. Following hemorrhagic or ischemic stroke and trauma DTI has become an important tool to assess white matter tract involvement beyond findings by morphologic imaging. This holds also true for white matter alterations in patients suffering from neurodegenerative and movement disorders, and to visualize secondary neurodegeneration in inflammatory conditions such as multiple sclerosis.

Diffusion-Weighted Imaging (DWI)

Diffusion-weighted MR imaging renders microscopic molecular motion of water visible within tissues. The anisotropic nature of diffusion in the brain can be visualized by comparing images obtained with DWI gradients applied in three orthogonal directions. DWI consists of an echo planar spin-echo T2w pulse sequence. Alternate DWI sequences are based on a single-shot gradient or single-shot fast spin-echo technique, ‘line-scan’ and spiral DWI technique. The signal intensity obtained by DWI correlates with the extent of cell damage decreased by a signal amount that is related to the rate of diffusion in the direction of the applied gradients. Pathology therefore is reflected by high signal on diffusion-weighted images and by decreased signal on apparent diffusion coefficient (ADC) maps. While DWI is highly sensitive in reflecting the physical properties of diffusion, the observation of restricted water diffusion is relatively non-specific for pathol- ogy. Restricted diffusion is the earliest detectable MR sign of ischemia. However diffusion changes are also seen with infection, inflammation and neoplasms. In an abscess restricted diffusion and low ADC values are attributed to increased fluid viscosity and higher cellularity present in pus. Metastases and tumors may have a similar appearance to an abscess on morphologic images but present with high ADC values in areas of necrosis. DWI is gaining increasing importance in oncology both for the initial diagnosis and as a sensitive tool to assess tumor response to treatment. Low ADC values in a lesion are an indicator for a malignant compression fracture in the spine as well as for malignant lymphadenopathy in the neck. In cerebral gliomas ADC values inversely correlate with the grading of gliomas, and low values indicate the higher grade component in a ‘mixed’ glioma. Lower ADC values in the edema of gliomas compared to metastases are an early sign of brain infiltration beyond macroscopic visible margins. Restricted diffusion in the early postoperative phase is more likely to correspond to ischemia and reparative changes, while after 6–8 weeks may indicate true progression or pseudoprogression. Increasing ADC values in a solid lesion like a glioma, lymphoma or metastasis are a more sensitive
Parameter to chemo-radiotherapy treatment response than the contrast enhanced T1 images. Metastases and glial tumors can be differentiated by low ADC due to their high grade cellularity (metastases) and by areas of high ADC due to necrosis (glial tumors) (Figs. 2A–D).

**Perfusion-MRI (PWI = Perfusion-weighted imaging)**

Perfusion MRI relies on two different techniques: dynamic contrast enhanced (DCE) perfusion MRI consists of a T1w 3D FLASH sequence which is used to depict cerebral microcirculation and is a direct measure of vascular permeability. On the other hand dynamic susceptibility contrast (DSC) MR perfusion is based on a gradient-echo echo planar sequence. DSC provides a measure of vascularity, microvascular density or relative cerebral blood volume (rCBV) and therefore is complementary to DCE perfusion. Both sequences require a bolus of contrast media injected into a peripheral vein.

**Perfusion MR in combination with diffusion-weighted imaging has been routinely applied in the setting of acute stroke.** The initial perfusion – diffusion mismatch correlates with the ischemic penumbra, the tissue at risk and the extent of the definitive infarct size. In brain neoplasms vascular proliferation and neoangiogenesis are hallmarks of differentiation to higher grades of malignancy. rCBV values as obtained by DSC show a significant correlation with tumor grade (Figs. 3A–C), microvascular density and in case of increase predict malignant transformation. Frequently, changes of these parameters during cytostatic, anti-angiogenic and radiation therapy (Figs. 4A–C) precede tumor volume reduction. DCE is applied to assess the degree of tumor angiogenesis and vessel permeability. Dynamic contrast enhanced perfusion (DCE) in combination with dynamic susceptibility contrast (DSC) perfusion (Fig. 5B) and MR spectroscopy (Fig. 6C) is applied to distinguish treatment related effects (pseudoprogression or pseudoresponse) from true progression and true response respectively.

**Diffusion in glioma and metastasis: Cellularity and tissue ultrastructure**

Contrast enhanced MRI does not reliably distinguish a glioblastoma multiforme (2A) from a metastasis (2B). Focal high ADC values (bright) indicate necrotic components in a glioma (arrow 2C). Low ADC values represent a solid metastasis (2B) as in this case or a lymphoma with dense cellularity (2D). ADC values are lower within the edema of a glioma due to microscopic infiltration which is usually not present within the edema of a metastasis.

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**Perfusion and diffusion in brain tumor imaging: Vascularisation, neo-angiogenesis, capillary permeability – cellularity vs. extracellular space**

Perfusion MR of a anaplastic glioma with high rCBV within the component of higher malignancy in the posterior part (arrow 3A) with restricted diffusion (3B) and low ADC values (3C) as additional signs of a highly cellular anaplastic component.

**Treatment monitoring: Decreased vascularity**

(4A) Cerebellar metastasis of renal cell carcinoma with subtle peripheral vessels indicated on the contrast enhanced T1w image. DSC perfusion MRI depicts markedly increased vascularity within the entire metastasis with high rCBV values before (4B) and with decreased rCBV values under radiotherapy (4C).
ASL Arterial Spin labelling
MR imaging with ASL is an alternative method to measure perfusion. Contrary to dynamic contrast enhanced (DCE) and dynamic susceptibility contrast (DSC) perfusion MRI, ASL uses electromagnetically labelled arterial blood water as a freely diffusible intrinsic tracer. In clinical applications, the ASL technique proved reproducible and reliable to assess cerebral blood flow (CBF) despite a relatively low signal intensity-to-noise ratio. ASL has been evaluated in various pathological states including cerebrovascular and neurodegenerative disease and for the assessment of glioma grading and tumor angiogenesis. Quantitative assessment of blood flow in gliomas by ASL yielded results and reproducibility comparable to DSC perfusion MR imaging.

MR Spectroscopy (MRS)
MR Spectroscopy provides a measure of brain metabolic composition or chemistry. Each metabolite appears at a specific ppm (Fig. 6A–C), and each one reflects specific cellular and biochemical processes. N-Acetyl-Aspartat (NAA) is a neuronal marker and decreases with any disease that adversely affects neuronal integrity. Creatine provides a measure of energy stores. Choline is a measure of increased cellular turnover and is elevated in tumors and inflammatory processes. Lactate is a marker of oxygen deficiency, lipids of tissue necrosis and myoinositol of granulation tissue (gliosis).

Indication of MRS:
- Differential diagnosis of low-grade and high-grade tumors
- Monitoring under radio-chemotherapy
- Differentiation of recurrent tumors from secondary necrosis due to therapy

Susceptibility-Weighted Imaging (SWI)
SWI is a modified 3D gradient-echo technique which exploits the susceptibility differences between tissues and uses the phase image to detect these differences. The magnitude and phase data are combined to produce an enhanced contrast magnitude image which is exquisitely sensitive to products of blood-deterioration (DeoxyHb, MethHb and Hemosiderin) (Fig. 7A–D).

Iron deposition can be the result of an untreated high blood pressure and accompanied by a gliosis could be a sign of a brain damage. Residual blood after a stroke, amyloid angiopathy or brain injury can be easily detected with gradient-echo sequences, such as SWI or T2*. Indications of SWI:
- Micro-bleedings in hypertension and vascular dementia
- Superficial bleedings in amyloid angiopathy
- Hemorrhagic contusion and diffuse axonal injury after brain trauma
- Iron deposition in neurodegenerative diseases

Advanced imaging in cerebrovascular diseases and vascular lesions
Contrast enhanced MR Angiography (MRA) is a well established complementary examination to Doppler sonography and in most cases replacement for digital subtraction angiography by producing high-quality static images.

Time resolved MR Angiography
The latest MRA technique is time resolved or 4D MRA with a time resolution of <0.7 s. This method is capable of capturing the dynamic filling of vessels, thus demonstrating the arterial, capillary and the venous phase of the cerebral circulation, similar to digital subtraction angiography (DSA). Hemodynamic changes caused by arterial stenoses and occlusions can be well

Iron deposition after trauma, in hypertension and in amyloid angiopathy

Spectrum of an Oligodendroglioma with high Cholin as a marker of a high proliferation-rate (thick arrow) and high Lactate as a sign of oxygen deficiency (thick arrow).

Spectrum of a therapy-induced necrosis with low Cholin and NAA and with low NAA as a marker of lost neuronal integrity (thin arrow)
Advanced MR imaging of inflammatory demyelinating diseases of the central nervous system

Advanced MR techniques have revolutionized the recognition and characterization of white matter disease. MR imaging is required to depict the presence and location of inflammatory lesions within the optic nerve, the brain and spinal cord. The morphology and distribution of lesions along the ventricular lining and perimedullary veins, in juxtacortical and infratentorial location may permit a tentative diagnosis. The acuity of lesions is assessed based on the presence of contrast enhancement or by alterations in the composition of neurometabolites in MR spectroscopy when large and unusual lesions or diffuse white matter changes are present. Follow-up examinations by high resolution MR sequences are of major importance to depict ‘dissemination in time’.

3D Fluid-Attenuated Inversion Recovery Sequence (FLAIR SPACE)

provides a higher spatial resolution with 0.8 to 1 mm isotropic slices and inherent contrast resolution in comparison to T2-weighted (Fig. 10A) and proton density-weighted images (Fig. 10B) and 2D standard FLAIR sequences. Higher resolution is beneficial due to better recognition of small demyelinating lesions on the initial examination: This holds particularly true in locations such as the brainstem, at the temporal horns, corpus callosum and in juxtacortical and infratentorial location. On follow-up examinations, isotropic 3D multiplanar reconstructions facilitate comparison and increase sensitivity to recognize new lesions. High inherent contrast allows to better differentiate cortical and juxtacortical lesions (Fig. 10C) similar to the 3D DIR sequence. Furthermore 3D FLAIR permits to differentiate acute and old lesions and to distinguish demyelination from perilesional edema and concomitant neurodegeneration of white matter tracts.

3D T1 MPRAGE sequence

provides isotropic resolution (0.8 to 1 mm) and thus sensitivity in recognition of small contrast enhancing lesions. High accuracy in detecting focal axonal destruction requires reassessment of the current concept of the frequency and distribution of “dark holes” which are a common finding with this new sequence.

4D MR Angiography

■ hemodynamic changes due to an arterial stenosis or occlusion
■ dural arteriovenous fistulas
■ vascular malformations of the brain, face or neck

4D MRA of a dural arteriovenous fistula – high temporal resolution

Contrast enhanced MRI shows a filling defect of the right sigmoid sinus (arrow). The 4D MRA depicts the arterial filling of the sinus as sign of a dural arteriovenous fistula (arrow) with origin from the branches of the external carotid artery.

The similar location, morphology and signal intensity of a paraganglioma (glomus tumor) and neurinoma (arrows: 9A, C) makes the differentiation sometimes challenging. The 4D MRA however, demonstrates the difference clearly: a paraganglioma shows an early and strong tumor filling (9B), and early washout in the venous phase (9C) whereas a vagal neurinoma (9D) exhibits no macroscopic vascularization in the arterial (9E) and venous (9F) phase.

3D Double Inversion-Recovery (DIR) sequence

is characterized by a high sensitivity to depict cortical (Fig. 10D) and deep grey matter involvement due to high signal of the lesions relative to the low white and grey matter signal intensity. 3D SPACE DIR sequence is equivalent to 3D FLAIR SPACE to depict white matter infra- and supratentorial lesions. The sequence appears slightly superior to recognize focal and generalized cortical grey matter volume loss in the vicinity of subcortical lesions and as a sign of neurodegeneration respectively.
Inflammatory demyelinating disease: new 3D sequences yield higher diagnostic accuracy, improved clinical and imaging correlation, and more precise follow-up assessment.

New sequences: increased sensitivity to gray and white matter involvement by demyelination