Application of quantitative MRI methods in central nervous system diseases

Ph.D. thesis

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1. Introduction

During the past couple of decades, conventional magnetic resonance imaging (MRI) techniques have been increasingly used to assess alterations in the central nervous system (CNS). Nowadays, a variety of conventional MRI protocols are also routinely used to detect therapeutic effects of different treatment strategies. These offer several important advantages, such as the definition of disability level, the association of blood brain barrier damage, spatial and temporal dissemination of brain lesions. In the past few years, a host of non-conventional quantitative MRI techniques have been introduced for the assessment of CNS diseases. These MRI techniques appear to be reliable markers in monitoring pathologic processes related to disease activity and clinical progression. They are able to reveal a range of tissue changes that include oedema, inflammation, demyelination, axonal loss, and degeneration. Therefore, in a disease with a high degree of longitudinal variability of clinical signs and with no current adequate biological markers of disease progression, non-conventional quantitative MRI techniques provide a powerful tool to non-invasively investigate not only the pathological substrates of overt lesions but also subtle global changes that may affect the entire brain. Additionally, conventional MR imaging gives only a cross-sectional qualitative information of different tissues, while quantitative approaches offer the advantage of absolute rather than relative characterization of the underlying biochemical composition of the tissue. The determination of quantitative MRI data requires more detailed approaches and a good understanding of basic MR phenomena. Generally, it is performed by using and analysing a set of qualitative images, where the signal intensity is controlled by the change of an MR imaging parameter: inversion time, flip angle or repetition time for T1

relaxometry; echo time for T2 relaxometry and b-value for diffusion-weighted data. Then quantitative MR data can be calculated by mono- or multi-exponentially fitting the signal change against these parameters. In clinical perspective, T1 and T2 relaxation times depend on structural characteristics such as local tissue density (i.e. water content), while quantitative diffusion data provides an indirect measure of tissue structure on a microscopic scale.

Taking the advantage of quantitative MRI techniques, a series of studies tested the usefulness of them in the CNS where conventional MR methods were insensitive. MR imaging of the CNS has great importance in the diagnostic evaluation and monitoring of treatment response in multiple sclerosis (MS). Also mild traumatic brain injury patients with negative computed tomography scans showed significant alterations on advanced quantitative MR images. Additionally, numerous studies of lesional and non-lesional epilepsy patients have demonstrated that advanced quantitative MRI methods can reliably improve surgical outcome and help the detection of seizure origin. Although white matter (WM) alterations with distinct lesions-tissue contrast are still the main radiological hallmark in many of CNS diseases, the detection of pathological WM without visible contrast changes is also important and even more challenging.

To date, numerous studies and books exist to study how to apply quantitative MRI techniques in the spinal cord, but fewer examined the quantitative MRI alterations in intervertebral disc diseases, although low back pain is one of the most prevalent and costly illness in today's society. T2 relaxation time evaluation provides a reliable correlation to detect changes in the molecular environment of the disc and the method is implemented on most clinical MR scanners. T2 relaxation time

measurements correlate with intervertebral disc tissue water content and have therefore been used to quantify the hydration of the disc which is essential for disease grading.

2. Objectives

Generally, the aim of our research was to examine molecular alterations of CNS diseases in vivo using quantitative MRI methods – like diffusion-weighted imaging and T2 relaxometry – and novel image processing algorithms such as segmentation, registration and mono- and bi-exponential data fitting supplemented by advanced statistical approaches.

Our first experiment targeted relapsing remitting MS patients and matched controls to characterize bi-exponential diffusion related signal changes in the normal appearing white matter areas. Unlike previous studies, this experiment provides deeper insights into the effects of age and lesion load on different water fractions.

Additionally, we wanted to shed additional light on WM diffusion changes with respect to epilepsy related diffusion parameters such as age at epilepsy onset and chronic seizure activity. Therefore, we investigated diffusion changes in the WM of mesial-temporal lobe epilepsy patients with unilateral hippocampal sclerosis (MTLE-HS) and compared them to an age- and sex-matched control group. We hypothesized that chronic WM damage occurs in both the early and late onset disease groups, but the extent of that is different according to the timing of epilepsy onset.

Since the disc degeneration and the associated changes are believed to be crucial factors in low back pain, the development of a classification system based on quantitative assessment would help to detect the degeneration grade independently of human bias or errors. Thus, we planned to

investigate the possible intra- and interobserver differences and to define quantitative T2 cut-off values with regard to two morphological classification systems – Pfirrmann and Schneiderman – in patients with intervertebral disc degeneration.

3. Materials and methods

Bi-exponential diffusion signal decay in normal appearing white matter of multiple sclerosis

Diffusion parameters were measured using mono-exponential (0–1000 s/mm^2) and bi-exponential (0–5000 s/mm^2) approaches from 14 relapsing-remitting subtype of MS patients and 14 age- and sex-matched controls after acquiring diffusion-weighted images on a 3T MRI system. The results were analyzed using parametric or nonparametric tests and multiple linear regression models.

Age at onset and seizure frequency affect white matter diffusion coefficient in patients with mesial temporal lobe epilepsy

Apparent diffusion coefficients (ADCs) were derived using mono-exponential approaches from 22 (11 early and 11 late age at onset) patients with unilateral MTLE-HS and 22 age- and sex-matched control subjects after acquiring diffusion-weighted images on a 3T MRI system. Data were analyzed using two-tailed t-tests and multiple linear regression models.

A Statistical Model for Intervertebral Disc Degeneration: Determination of the Optimal T2 Cut-Off Values

Lumbar MRI was performed on 21 subjects (a total of 104 lumbar disks). The T2 relaxation time was measured in the nucleus pulposus using a

sagittal multi-echo spin-echo sequence. The morphological classification of disc degeneration was assessed independently by three experienced neuroradiologists according to the Pfirrmann and Schneiderman classifications. Receiver operating characteristic analysis was performed among grades to determine T2 cut-off values in each classification. Intra- and interobserver differences were calculated using kappa statistics.

4. Results

Bi-exponential diffusion signal decay in normal appearing white matter of multiple sclerosis

Mono-exponential ADC slightly increased in controls (p=0.09), but decreased significantly in MS as a function of age, nonetheless an elevated ADC was observed with increasing lesion number in patients. Bi-exponential analyses showed that the increased ADC is the result of decreased relative volume fraction of slow diffusing component. However, the fast and slow diffusion components did not change as a function of either age in controls or lesion number and age in MS patients.

Age at onset and seizure frequency affect white matter diffusion coefficient in patients with mesial temporal lobe epilepsy

In the group with early onset MTLE-HS, ADC was significantly elevated in the ipsilateral hemispheric (p=0.04) and temporal lobe white matter (p=0.01) compared with that in controls. These differences were not detectable in late onset MTLE-HS patients. Apparent diffusion coefficient of the group with early onset MTLE-HS was negatively related to age at epilepsy onset in the ipsilateral hemispheric white matter (p=0.03) and the uncinate fasciculus (p=0.03), while in patients with late onset MTLE-HS,

ADC was no longer dependent on age at epilepsy onset itself but rather on the seizure frequency in the ipsilateral uncinate fasciculus ($p=0.03$).

A Statistical Model for Intervertebral Disc Degeneration: Determination of the Optimal T2 Cut-Off Values

Moderate overall interobserver agreement was found between observers in both the Pfirrmann and Schneiderman classification schemes (kappa 0.46 and 0.51), while intraobserver reliability was substantial to almost perfect. The interobserver reliability was only fair in Pfirrmann grades III and IV (kappa 0.33 and 0.36), but the T2 cut-off values still indicated a significant difference between grades ($p<0.05$).

5. Conclusions

Bi-exponential diffusion signal decay in normal appearing white matter of multiple sclerosis

We examined bi-exponential diffusion signal decay in normal appearing white matter of relapsing-remitting MS patients compared with an age- and sex-matched control group. According to our results and the literature, the decreased volume fraction of slow diffusing component may be the primary reason for the age-dependent increase of ADC in controls. In multiple sclerosis, the diffusion parameters are related to both age and total lesion number, in which the bi-exponential analysis indicated decreased relative volume fraction of slow diffusing component as a function of total lesion number while it increased with age, probably due to the reduction of myelin water fraction.

Age at onset and seizure frequency affect white matter diffusion coefficient in patients with mesial temporal lobe epilepsy

Taken together, ADC was higher in MTLE-HS, especially in the cerebral hemisphere ipsilateral to the seizure onset. Such diffusivity pattern has been associated with chronic WM degeneration, reflecting myelin and axonal loss, gliosis, and higher extracellular volume which are more pronounced in the frontotemporal regions, and also depends on clinical features like age at epilepsy onset and chronic seizure activity. In the group with early onset MTLE-HS, the timing of epilepsy seems to be the major origin of WM abnormalities while it should be assumed as a secondary effect provoking diffusion changes in the patients with late onset MTLE-HS. The combination of clinical data and novel MR methods used in our study has led to valuable insights into epilepsy-associated changes in the white matter and has increased our understanding of the pathophysiology of MTLE-HS.

A Statistical Model for Intervertebral Disc Degeneration: Determination of the Optimal T2 Cut-Off Values

This study reflected that T2 values tended to decrease with increasing age or grade in the nucleus pulposus possibly due to the decrease in water and proteoglycan content. Interobserver agreement of the morphological evaluation in patients with intervertebral disc degeneration was only fair between Pfirrmann III and IV. Based on our results, quantitative T2 cut-off values seem to be a more reliable method to define the degree of disc degeneration, even though the definitions of intervertebral disc degeneration in MRI are still not uniform.

6. Publications

Articles related to the thesis

Nagy S.A.[*], Horvath R.[*], Perlaki G., Orsi G., Barsi P., John F., Horvath A., Kovacs N., Bogner P., Abraham H., Bone B., Gyimesi C., Doczi T., Janszky J. Age at onset and seizure frequency affect white matter diffusion coefficient in patients with mesial temporal lobe epilepsy (2016). Epilepsy Behav 61:14-20. **IF: 2.332**
[*]Equal contribution in first authorship

Nagy S.A.[*], Juhasz I.[*], Komaromy H., Pozsar K., Zsigmond I., Perlaki G., Orsi G., Schwarcz A., Walter N., Doczi T., Bogner P. A statistical model for intervertebral disc degeneration: determination of the optimal T2 cut-off values (2014). Clin Neuroradiol 24:355-63. **IF: 2.250**
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Nagy S.A., Aradi M., Orsi G., Perlaki G., Kamson D.O., Mike A., Komaromy H., Schwarcz A., Kovacs A., Janszky J., Pfund Z., Illes Z., Bogner P. Bi-exponential diffusion signal decay in normal appearing white matter of multiple sclerosis (2013). Magn Reson Imaging 31:286-95. **IF: 2.022**

Articles unrelated to the thesis

Khan M.I.H., Wellard R.M., **Nagy S.A.**, Joardder M.U.H., Karim M.A. Experimental investigation of bound and free water transport process during drying of hygroscopic food material (2017). Int J Therm Sci. 117:266-273. **IF: 2.769**

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Nagy S.A., Horvath R., John F., Janszky J., Perlaki G., Doczi T., Bogner P. Age at onset effect on white matter diffusion coefficient of temporal lobe epilepsy patients. ESMRMB Congress (2015.10.01-03.). Edinburgh, UK, (Poster and oral presentation)

Nagy S.A., John F., Horvath R., Janszky J., Perlaki G., Orsi G., Barsi P., Bogner P. Age at onset effect on white matter diffusion coefficient of temporal lobe epilepsy patients. Neuroimaging workshop (2015.04.17-18.). Szeged, Hungary

Nagy S.A., Horvath R., John F., Janszky J., Perlaki G., Horvath A., Bogner P. Legújabb MR módszerek és alkalmazási területeik különböző intracraniális betegségekben. X. IME Jubileumi Képalkotó Diagnosztikai Továbbképzés és Konferencia (2015.03.26.). Budapest, Hungary

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Nagy S.A., Juhasz I., Komaromy H., Pozsar K., Zsigmond I., Perlaki G., Orsi G., Schwarcz A., Janszky J., Bogner P. A statistical model for intervertebral disc degeneration: determination of the optimal T2 cut-off values. Neuroimaging Workshop (2013.04.19-20.). Pécs, Hungary

Nagy S.A., Juhasz I., Komaromy H., Pozsar K., Zsigmond I., Perlaki G., Orsi G., Aradi M., Perlaki G., Orsi G., Bogner P. Classification of intervertebral disk degeneration using quantitative T2 relaxation time measurements. European Congress of Radiology (2013.03.07-11.).Vienna, Austria (Electronic poster)

Nagy S.A., Bogner P., Aradi M., Orsi G., Perlaki G., Komaromy H., Schwarcz A., Janszky J. Bi-exponential diffusion signal decay in normal appearing white matter of multiple sclerosis. 16th EFNS Congress (2012.09.08-11.). Stockholm, Sweden (Poster presentation with oral discussion)

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Nagy S.A. Az agyszöveti vízdiffúzió életkori változása egészséges és sclerosis multiplexes csoportokban. XVI. Kari Tudományos Diákköri Konferencia (2010.04.23-24.). Szombathely, Hungary (First place and special award)

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Nemeth N., **Nagy S.A.**, Czeh B., Doczi T., Bogner P., Miseta A., Tenyi T., Simon M. Agyi funkcionális MR eltérések kori traumán átesett depressziós betegekben. A Magyar Pszichiátriai Társaság XXI. Vándorgyűlése (2017.01.26-28.). Siófok, Hungary (Poster presentation)

Nemeth N., **Nagy S.A.**, Bogner P., Doczi T., Miseta A., Czeh B., Simon M. A face-emotion fMRI paradigm to activate the amygdala in early traumatized adults with depression. IBRO Workshop, Hungarian Academy of Science (2016.01.21-22.). Budapest, Hungary (Poster presentation)

Nagy S.A., Nemeth N., Bogner P., Miseta A., Doczi T., Czeh B., Simon M. Resting-state functional connectivity alterations in depressed subjects with childhood trauma. A pilot study. IBRO Workshop, Hungarian Academy of Science (2016.01.21-22.). Budapest, Hungary (Poster presentation)

Orsi G., Perlaki G., Horvath R., **Nagy S.A.**, Toth A., Horvath A., Doczi T., Bogner P., Janszky J. Comparison of accuracy between FSL's FIRST and Freesurfer for caudate nucleus and putamen segmentation. ESMRMB Congress (2015.10.01-03.). Edinburgh, UK, (Poster and oral presentation)

Orsi G., Perlaki G., Horvath R., **Nagy S.A.**, Horvath A., Bogner P., Janszky J. Comparison of accuracy between FSL's FIRST and Freesurfer for caudate nucleus and putamen segmentation. Neuroimaging workshop (2015.04.17-18.). Szeged, Hungary

Hetenyi Sz., **Nagy S.A.**, Horvath F., Toth K., Vaczi M., Illes Zs., Bogner P. Volumetric changes of hamstring muscles after exercise in patients with Pompe disease. European Society of Musculoskeletal Radiology (2015.06.18-20.). York, UK. (Poster presentation)

Horvath A., Perlaki G., Toth A., Orsi G., **Nagy S.A.**, Doczi T., Horvath Zs., Bogner P. Diffusion alterations in the normal appearing white matter of glioma and meningioma patients. Neuroimaging workshop (2015.04.17-18.). Szeged, Hungary

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Horvath A., **Nagy S.A.**, Perlaki G., Orsi G., Aradi M., Horvath Zs., Bogner P. Perfusion MRI methods in different neoplasms. A Magyar Neuroradiológiai Társaság XXI. Kongresszusa (2013.11.07-09.). Visegrád, Hungary

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