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Diffusion-weighted MRS and MRI : methods and neuro applications

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General Discussion: DW-MRS current state, major challenges and future directions

7.1 Introduction

WITHIN the realm of MRI microstructural tools DW-MRS has a unique role, due to its compartment specificity. In this thesis, metabolite diffusion values in *in vivo* human brain white matter were linked to tissue neuroanatomical properties, new methods were proposed for the acquisition and analysis of DW-MRS data, and DW-MRS was evaluated and optimized for basic neuroscience and clinical research studies. In contrast tothe proliferation of applications of DWI and DTI, DW-MRS has so far found only few applications in human brain [1–19]. In this thesis, some of the challenges preventing the DW-MRS method from being more frequently applied were addressed. The results presented in this thesis point towards the use of the DW-MRS method for both basic neuroanatomical research and for research in clinical settings. Some challenges related to DW-MRS still remain unmet. This chapter focuses on the current state of DW-MRS and DW-CSI, discusses some of most salient challenges, and indicates potential future directions.

7.2 Variability of metabolite diffusivity measures across sites: implications on diagnostic and research DW-MRS

The DW-MRS literature shows a high variability of metabolite diffusivity measures across studies and sites. For instance, ADC(tNAA) values obtained from brain white matter of healthy control subjects varied between 0.14 mm^2/s and 0.26 mm^2/s across studies [1–3, 6, 7, 10, 13, 18, 19]. The main reason for this variability is the differences in acquisition parameters such as echo time, diffusion time, number of diffusion directions, size and the location of VOI, and maximum b-value used in different studies. All these parameters influence the resulting ADC value in different ways. Echo time has been shown to correlate with the ADC(tNAA) values measured in human brain white matter [12]. ADC(tNAA) values decrease with increasing diffusion time [20]. Calculating ADC with one diffusion direction results in rotationally variant ADC(tNAA) values which can be influenced by the axonal orientation within the VOI. This causes variability in the results since ADC(tNAA) can change depending on the choice of gradient direction orientation. The size of the VOI can impact the SNR and consequently deteriorate the accuracy of the obtained ADC values. The inclusion of gray matter tissue in a predominantly white matter VOI volume can result in decreased ADC(tNAA) depending on the extent of the partial volume effect from the gray matter since gray matter ADC(tNAA) is significantly lower than white matter ADC(tNAA) values [6]. A large effect on ADC is also observed based on the choice of b-value since relatively low b-values ($b << 1/ADC$) leads to error propagation [4], and non-monoexponentiality of the diffusion-weighted signal decay needs to be taken account when higher b-values are used [20].

Where clinical studies are concerned, it is important to choose adequate DW-MRS acquisition parameters to prevent unnecessary source of errors (resulting from insufficient number of diffusion directions or low b-values) which can impact the reliability of the DW-MRS results. In the DW-MRS reproducibility study presented in chapter 3 of this thesis, an optimized acquisition scheme is proposed to obtain robust diffusivity values. In this work, a high degree of reproducibility was achieved in a DW-MRS protocol applied at two different sites and two different field strengths. Such an optimized protocol can help resolving inconsistencies in acquisition and post-processing of the DW-MRS across sites. For future clinical studies, it is recommended to establish a baseline clinical DW-MRS

protocol which can enable obtaining reliable results and comparable metabolite diffusivity values across different clinical sites. Moreover, since many diseases also affect the gray matter, exploration of suitable protocols and evaluation of metabolite diffusion properties in gray matter tissue is also needed for future clinical applications of DW-MRS. While conducting such investigations, one should be careful about taking partial volume effect from white matter into account due to the difficulty of planning a VOI that consists of only gray matter tissue, since the cortical volume is relatively small compared to VOI sizes used in DW-MRS.

7.3 Diffusion-weighted CSI: promises and challenges

A reproducible and robust implementation of 2D DW-CSI has been shown in this thesis, within a supra-callosal axial slice. 2D DW-CSI provides spatially-resolved information from a large field-of-view and increases the amount of information obtained from a single scan. This allows simultaneous investigation of multiple brain regions and can subsequently lead to direct comparison of regions with visible disease-effects, such as brain tumors, to regions with normal appearing brain tissue from the same subject. This is advantageous for clinical research since it can help understand intracellular changes leading to visible lesions in various diseases including brain tumors, MS, ischemia and many others. Moreover, since these visible effects are often heterogeneous, investigation of metabolite diffusivity values from different voxels within these visible lesions could help surgery or treatment planning.

Another potential advantage of DW-CSI is that it can be co-analyzed with imaging methods such as FLAIR, DTI and MTI, which provide complementary information to that of DW-MRS. Co-analysis of DW-CSI with T_2-weighted and/or FLAIR images can help to explore cell-specific microstructural differences between normal appearing white matter, lesions and non-affected tissue, as mentioned above. Co-analysis of DW-CSI with DTI can provide a more comprehensive microstructural exploration of white matter tracts. By applying DW-CSI with at least six non-collinear diffusion directions, it is possible to calculate diffusion tensor for different metabolites. Combining the information from water and tNAA diffusion tensors can give more complete information about both intraneuronal and extracellular space. This, in turn, can provide better insight about disease-related changes in the brain. For instance, correlating water and metabolite diffusivities along white matter tracts can help differentiating axonal damage from extracellular edema and demyelination which occur in disease that specifically affect these tracts. This can have an impact on the treatment strategies as well as improve the understanding of the relation these disease processes have with specific white matter tracts.

A major challenge of DW-CSI is the long acquisition time. This is detrimental for clinical applications, where longer scan times cause discomfort to vulnerable clinical populations. Moreover longer scan times can also lead to subject motion and subsequently result in increase in the variance of data across subjects. Longer acquisition times limit the possibility of including more diffusion directions, or a separate acquisition with water as the planned metabolite, which can subsequently be used for a more efficient eddy-current correction than the one shown in this thesis. Several strategies for accelerating the acquisition of DW-CSI data can be explored. Past studies show that the acquisition time of MR spectroscopic imaging can be reduced by an acceleration factor of 7 by employing information from different coil elements [21, 22]. By integrating parallel imaging in DW-CSI, it is possible to accelerate future DW-CSI applications and reduce the scan time of a

regular DW-CSI scan (with 4 conditions: one without and three with diffusion-weighting) down to about 3 minutes from the current scan time of about 20 minutes. It should be noted that this reduction in time is accompanied by a loss in SNR, and so a suitable compromise must be found. Compressed sensing is another recent technique used to reduce the acquisition time [23]. A recent study showed the possibility to preserve spectral resolution with a six-fold reduction of the acquisition time by implementing compressed sensing in MR spectroscopic imaging. Implementing this technique can therefore further accelerate the scan time of DW-CSI. With such reductions in the acquisition time, clinical applications of DW-CSI method can be facilitated.

7.4 DW-MRS at ultrahigh field: advantages, challenges and proposed future directions

The advent of ultrahigh field (7 Tesla and beyond) for human MRI scanners provides higher SNR and increased spectral resolution in *in vivo* MRS, both of which positively affect spectral quality in DW-MRS. A particularly relevant example is shown in the reproducibility study presented in chapter 3 of this thesis, where ADC values obtained at 7 Tesla had significantly smaller variability compared to those obtained at 3 Tesla.

Besides the advantages of ultrahigh field, there are also some significant drawbacks and challenges. A major drawback of ultrahigh field for brain research is the B_1 transmit field inhomogeneity across the brain. This is mainly caused by the shortened electromagnetic wavelength of the radio frequency (RF) signal at the higher field strengths, where the wavelength is roughly the size of the imaged object. The B_1 inhomogeneity at 7 Tesla is shown to be about 42% across the brain, causing variations in the tip angle at the lateral regions of the brain compared to the medial parts [24]. B_1 inhomogeneity can cause severe reduction of the acquired signal intensity [24], especially in spectroscopic sequences, where at least 3 pulses are consecutively applied with large tip angles (of 90°-180°-180° for PRESS sequence and 90°-90°-90° for STEAM sequence). In most of the DW-MRS studies presented in this thesis, the corpus callosum was chosen as the region of interest. This choice avoided most of the B_1-related issues since the central location of this structure does not suffer significant B_1 inhomogeneity. Single volume DW-MRS applications in other brain regions can significantly suffer from degradation of B_1 in that region. For DW-CSI acquisitions, non-uniformity of the B_1 field is more detrimental since the aim is to cover as large an area as possible. B_1 inhomogeneity across a large field of view was the reason for the preselection of a relatively small VOI for the DW-CSI study presented in chapter 4 of this thesis. Various approaches exist to resolve the B_1 inhomogeneity. These approaches include using pads with dielectric material that can increase the B_1 homogeneity [24], implementation of adiabatic RF pulses that are intrinsically less sensitive to the strength of the B_1 transmit field [25, 26] and optimizing the phase and magnitude of individual elements of multi-transmit RF coils to obtain more homogeneous B_1 [27].

The PRESS sequence used for DW-MRS and DW-CSI measurements suffers from large chemical shift displacement at 7T. This is caused by the small bandwidth of the refocusing 180° pulses used in the sequence for slab selection in two directions. In the typical diffusion-weighted PRESS sequence that we used for 7T experiments, a 54% overlap had been observed between tNAA and water resonances due to chemical shift displacement. For single volume DW-MRS this effect can result, for example, in different gray/white matter fractions in the VOI, and add a confound to the ADC values of different metabolites.

In the DW-CSI implementation shown in chapter 4, chemical shift displacement leads to a more challenging situation, since in addition to the shift among metabolites, the water peak is used for eddy current correction. In the regions where the VOI of water did not overlap with the metabolite VOI eddy current correction could not be applied, the metabolite peaks could not be estimated properly and thus metabolite ADC values could not be calculated. This results in unnecessary loss of information from a significant portion of the field of view. Implementing a DW-CSI with adiabatic pulses can resolve some of these problems in the future applications of the method [26], but may result in an increase in SAR and thus require longer TR values, resulting in a longer scan time.

7.5 Dependence of the performance of DW-MRS on gradient coil hardware specifications

The maximum gradient strength of the system is an intrinsic limiting factor for DW-MRS experiments. This, in turn, imposes a limit on the minimum TE value for a given b value in a DW-MRS experiment. For example, the gradients of the 7 Tesla system used in this thesis are limited to a maximum gradient strength of 40 mT/m. In order to obtain high b-values (on the order of b = 8000 s/mm^2), it was therefore necessary to use long gradient durations (~37 ms). This in turn resulted in long echo times (~121 ms) and subsequently resulted in lower SNR at such b-values, limiting the quantification of metabolites such as myo-inositol, glutamate and other unique intracellular markers. By using stronger gradient systems, such as those used for the human Connectome project [28] (with a maximum gradient strength of 300 mT/m), one can could reach similar b values with much shorter TE values of about 60 ms. Assuming a typical T_2 for brain metabolites at 7T to be of the order of 150 ms in human brain [29, 30], the expected gain in signal in this case is given by,

$$\frac{e^{-\frac{0.060}{0.150}}}{e^{-\frac{0.121}{0.150}}}$$

and is equivalent to an increase in 50% in SNR.

7.6 References

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