

Novel methods for the detection of functional brain activity using 17O MRI

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Appendix B

Valorisation

Researchers at Maastricht University are expected to discuss the social and economic value of the knowledge developed during their doctoral studies. This chapter addresses the current and potential impact of this thesis.

B.1 Social and Economic Relevance

In this work an enhanced method for quantitative and non-invasive measurements of the $CMRO_2$ in healthy volunteers is presented. Aging and, more importantly, healthy aging is becoming a focus of clinical research since the life expectancies are on the rise. In prosperous countries, Alzheimer's disease is one of the most prevalent neurodegenerative diseases. Novel methods for identifying disease onsets and tracking severity are highly desired for preclinical and clinical testing of disease-modifying therapies. It has been shown that neurodegenerative and metabolic diseases associated with aging and pathologies such as Alzheimer's disease indicate altered values for $CMRO_2$ [71–73] even before anatomical changes are detectable; this makes $CMRO_2$ a perfect molecular imaging candidate for tracking the disease and its severity, and perhaps its early identification.

In the past, $CMRO_2$ was measured by means of radioactive and invasive PET measurements and thus these are not practical on large cohorts of healthy or apparently healthy volunteers. New non-invasive methods such as those presented in section 3.1 pave the way for easier patient handling and clinical acceptance, this is of large impact for social relevance. Shorter measurement times are of economic relevance since the costs of MRI measurement time are a crucial factor in clinical applications.

Quantitative imaging methods such as relaxation time mapping or quantification of absolute water content are of great interest in clinical applications since standard clinical MR images cannot be directly compared. Most methods for imaging anatomical details in high resolution are relaxation-time weighted, T_1 -weighted for example, and the results differ for the same patient at different field strengths or when acquired with MRI machines from different vendors or in longitudinal studies. Thus, a quantitative long-term evaluation of patient treatment is not easily feasible. Utilising the quantitative imaging methods, which are shown in this work in section 3.3, it is possible to acquire quantitative relaxation times, on a voxelwise basis, of the longitudinal relaxation time, T_1 , and the absolute water content within clinically acceptable measurement times of 11:18 min in total. The *in vivo* precision of the mean values and the accuracy, which is referenced to the gold standard spectroscopic inversion recovery experiment of WM and GM are approximately 2% and 1%, respectively.

B.2 Target Group

This work is of interest not only for academic and basic researchers but also for medical personnel and financial decision makers in clinics. First it enables an easier patient handling compared to ^{15}O -based radioactive PET measurements, which decreases corrupted measurement data due to e.g. motion. Second, measurement time and thus running costs of MRI and PET machines can be reduced.

Quantitative imaging techniques are already used by various research sites potentially leading to a better understanding of different diseases and their treatments.

B.3 Products and Services

The presented quantitative imaging methods and the developments of TAPIR, shown in section 3.3.2.2, already led to various partnerships in research. For example, the developments of this work and a software package for evaluation were used for permeability measurements of the blood brain barrier [142]. Further studies could pave the way for quantitative imaging methods in clinical environments to support diagnostic evaluation processes.

Accessing CMRO_2 by non-invasive imaging methods or combining it with simultaneous measurements of other relevant molecular parameters could lead to a deeper knowledge and better understanding of various diseases and their possible treatments. Since ultra-high magnetic field strength MRI is a growing field of current research and the first *clinical* 7 T machines are about to be introduced, studies of other nuclei than ^1H approaches clinical practice and thus, ^{17}O -based measurements become more attractive. ^1H -based measurements of CMRO_2 , as they are presented in this work, are the method of choice, whenever ultra-high magnetic field strength is not available. The developments presented in this work have the potential to lead to clinical utility.

B.4 Innovation

As Albert Einstein already mentioned

"Life is like riding a bicycle. To keep your balance, you must keep moving."

which implies a continuous and ongoing innovation process in life and absolutely in research. Innovative research is of fundamental importance. The work presented in this thesis is yet another step that enhances existing methods.

Ultra-high magnetic field strength MRI with 7 T and above is a growing topic in research and this is also the case for higher field strength such as 9.4 T, as used in this.

The measurements presented in section 4.1.2 for quantifying absolute water content in the living human brain use state-of-the-art methodologies including adiabatic inversion radiofrequency pulses, parallel imaging techniques, and multi-channel receive RF coils to overcome inhomogeneity effects in B_1^+ fields which are a negative side-effect caused by high magnetic field strengths. The method for correcting the B_1^- receive field inhomogeneity, described briefly in section 3.3.3.3, was developed in our group and is completely new and innovative. Prior to the availability of that method either corrections based on the reciprocity theorem, which does not hold for high field strength, or just simple bias field corrections by homogenisation of the resulted quantitative measurement were used.

The essential *in vivo* and phantom measurements of the natural abundance of ^{17}O signal at ultra-high field strength (9.4 T) presented in section 4.2.1 and thereafter are one of the first presented at that high field strength using a state-of-the-art prototype UHF scanner.

The use of SAR-reduced adiabatic pulses in a T2prep module is an innovative method. Previously, mostly normal adiabatic pulses, which have the negative side-effect of high SAR values or non-adiabatic pulses which in turn have a poor B_1^+ RF profile were used.

B.5 Shedule and Implementation

First, all necessary imaging sequences were implemented for Siemens MRI scanner systems (Siemens AG, Erlangen, Germany) and tested extensively. The good agreement of TAPIR T_1 measurement results with spectroscopically measured ones triggered great interest in the community, leading to international cooperations with various partners who are using the sequence (e.g. University of New Mexico, Albuquerque, NM; University of Cambridge, UK) or plan future usage (e.g. University of Hawaii, HI).

Second, not only did sequence implementation lead to cooperations but also the evaluation software package in which all used fitting routines and all described B_1^- corrections were implemented. The software package is called "Juqebox" and is freely available upon request from our research group.

Evaluation of $CMRO_2$ based on ^{17}O imaging data is complex and patient comfort is reduced for this imaging modality. Firstly by special safety issues due to ultra-high field MRI (see section 2.4) and secondly due to the need of a breathing / rebreathing system [81], which has to be used inside of the RF head coil in the scanner bore.

Evaluation of $CMRO_2$ data based on 1H imaging is much easier with simple exponential fitting and basic mathematics as described in section 3.1.4.1 and in the literature [14, 77, 88]. Furthermore, no additional breathing devices are needed paving the way to easier patient handling in clinical applications.