Quantitative brain MRI at 7T in healthy subjects and in metabolic diseases

7.1. | KNOWLEDGE VALORIZATION

Besides scientific merit, the experiments and their outcomes, presented in this thesis, also carry social and economic value and implications. In the following, we place the research approach and results into a broader perspective and indicate the valorization potential of the main findings.

Following the title of this thesis ("Quantitative 7T MRI in healthy subjects and in metabolic diseases"), the main findings can be approached from two perspectives, either from (i) the 7T MRI user's (Chapters 2 and 3) or (ii) a clinician's (Chapters 4 and 5) point of view. As such, in the following, we will discuss the socioeconomic benefits of the current work for each of them.

7.1.1. | Ultra-high field MRI user

MRI has become one of the major clinical diagnostic tools used worldwide. It allows non-invasive imaging and characterization of the human body, based on the principles described in Chapter 1, and thus, enables detection of changes and abnormalities due to development, aging or disease. Since its initial discovery (Lauterbur, 1973; Mansfield and Grannell, 1973), there has been tremendous developments related to almost every aspect of MRI, ranging from better hardware to optimized analysis strategies. Here, 7T MRI has been one of the most significant advances (Ugurbil, 2017). Although the technology has been in use for over 15 years with >70 7T scanners worldwide (see Fig. 7.1), the recent FDA and CE approval for the Terra system, manufactured by Siemens Healthineers, will make 7T MRI better accessible for non-MRI experts and pushing it towards a wider range of applications.

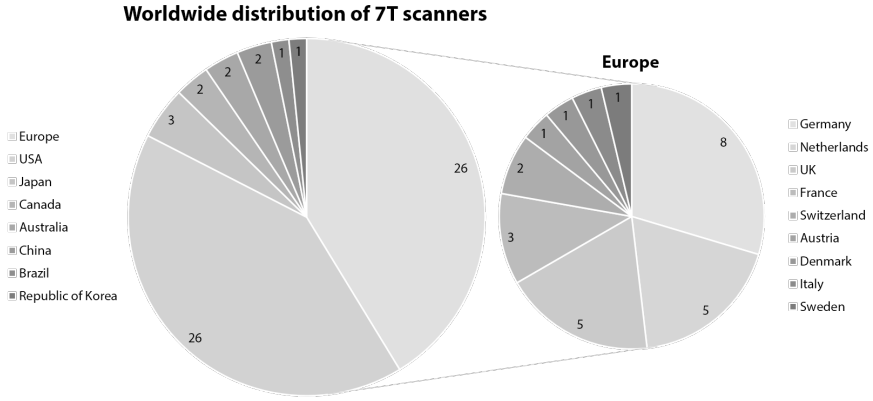

Fig. 7.1. | Overview of worldwide 7T MRI scanners. Please, note that this may not represent the actual status due to contineous installation of new machines.

While progress has plateaued at conventional field strengths (i.e. ≤ 3T), the increasingly availability of 7T scanners enables to continuate the growing potential of MRI as a diagnostic tool in, for example, neurodegenerative diseases. This is mainly driven by the higher field strength, leading to increased data quality (i.e. signal-to-noise) (Pohmann *et al.*, 2016), and higher spatial and temporal imaging resolutions (Pfeuffer *et al.*, 2002; Yacoub *et al.*, 2008). As such, subtle changes in brain anatomy and vasculature have shown to be better detectable compared to standard clinical MRI (i.e. due to improved contrast-to-noise) (Trattnig *et al.*, 2016).

However, clinical decision-making, as well as studies on disease-, aging- and/or development-related changes in the brain, using 7T MRI, requires reproducible (i.e. precise) and reliable data. The importance of this, mainly with respect to across studies, sites and manufacturer generalizability of (ultra-high field) MRI data, has been discussed previously in the general discussion. However, as summarized in the previous chapter, the results in Chapters 2 and 3 show the potential and relative performance of some of the commonly used quantitative anatomical (i.e. T_1 and T_2*) imaging approaches. These were evaluated, mostly with respect to in vivo myelin mapping, in terms of reproducibility (i.e. coefficient of variation) and quality (i.e. contrast-to-nose), as well as the effect of magnetic field (i.e. B_1^+) inhomogeneities on morphological measurements (i.e. cortical thickness). Especially the latter is of great importance for users working in a clinical setting and requires accurate measurements. As such, the work and results of the current thesis contributes to a better understanding of the relative performance of (quantitative) T_1 and T_2* imaging methods at 7T. It shows how they could be reliable acquired and analyzed by others that are interested in the use of these sequences, such as in patient populations, or in healthy subjects for similar applications (e.g. cortical parcellation and/or myelin mapping). Eventually and from a more business-type of perspective, standardized protocols, validated across different imaging sites and scanner vendors, as well as the workflows to analyze the acquired data, can be used as service products by MR imaging companies to improve accessibility of 7T MRI.

7.1.2. | Clinical perspective

While Chapters 2 and 3 are mainly useful for (future) 7T MRI users, the experiments in Chapters 4 and 5 are especially important for clinicians involved in the treatment of individuals affected by the m.3243A>G mutation or with Type 2 Diabetes Mellitus (T2DM), respectively. The impact of the current research on each of them will be discussed in the following paragraphs.

The m.3243A>G mutation is one of the most common mitochondrial mutations with a carrier rate of 1 in 400 people (Elliott *et al.*, 2008). It can induce a wide-range of clinical symptoms leading to a diverse phenotypic spectrum (Nesbitt *et al.*, 2013). Better knowledge of the genotype (e.g. mutation load) – phenotype (e.g. brain) relationship may potentially enhance patient prognosis. We showed that the m.3243A>G mutation load (i.e. percentage of affected mitochondria in a single cell) in blood (as well as urine) correlated significantly with the brain phenotype: the patients with a higher mutation load were characterized by a lower brain volume. Especially cortical gray matter thickness, but also T_1, T_2* and CBF, were affected. This was predominantly restricted to (e.g. auditory or frontal lobe) regions that can be linked to the observed symptoms (e.g. impaired hearing) and/or cognitive performance (e.g. Stroop task). Although mutation load may not be the only contributor to disease severity, it may provide an initial scale for clinical geneticists and neurologists, working with m.3243A>G patients, to estimate the patient's prognosis, in terms of the brain phenotype and cognitive performance. In addition, these results can guide future pathobiological studies towards more targeted experiments to disentangle the underlying biochemical changes. Alternatively, it may facilitate testing the effect of possible intervention strategies, such as arginine supplementation, on the progression of brain atrophy (El-Hattab *et al.*, 2012). Eventually, improved follow-up and management of patients harboring the m.3243A>G, may improve their quality-of-life. Finally, while both the m.3243A>G and T2DM affect specific metabolic pathways, T2DM is much more prevalent and therefore carries a higher socioeconomic burden. As a result, much more studies focus on T2DM-related pathologies and little work is done to systematically characterize the neurodegenerative changes induced by the m.3243A>G genotype. Therefore, the current work may have significant impact on the respective field due to the relatively large number of m.3243A>G patients that was recruited.

T2DM is a metabolic disease and, in contrast to patients affected by the m.3243A>G genotype, characterized by high global prevalence. The total number of people with T2DM was estimated at 171 million individuals world-wide in 2000 and is projected to rise to 366 million in 2030 (Wild *et al.*, 2004). Patients with T2DM have an increased risk to develop dementia (Biessels *et al.*, 2006), which may eventually result in significant impairment of daily life and quality-of-life. Early identification of (pre-)diabetic subjects at risk for cognitive decline, as a result of neurodegenerative changes, is vital to keep the economic and emotional burden at a minimum level. In the current thesis, we have combined genetic, metabolomic and MR imaging with extensive phenotypical (e.g. clinical and cognitive) data to put together a unique dataset. This dataset allows extensive phenotyping by genetics, metabolomics, MRI, but also "systems biology" ex-

perts to highlight features that differ between controls without diabetes, pre-diabetic and diabetic subjects, or find novel subgroups. Eventually, identification of biomarkers that are able to characterize the subjects with an increased risk of cognitive decline and/or dementia will improve diabetes care, for example, through personalized medicine, next to standard diabetes treatment strategies, and significantly impact the socioeconomic burden of T2DM. At the same time, this will also provide possibilities for the pharmaceutical industry to improve the impact of their products due to more effective treatment.

7.1.3. | References

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