Myelin and networks

Valorization

Relevance

Magnetic resonance imaging (MRI) is a valuable tool to non-invasively gain information on cerebral abnormalities in patients with various neurological disorders. Anatomical MR images can potentially aid in diagnosis and/or treatment of the disorder [1]. However, the brain often has other, more subtle abnormalities which are not directly visible at radiological inspection of anatomical images obtained by MRI. This thesis focussed on cerebral abnormalities in patients with epilepsy, by employing advanced MRI techniques.

Epilepsy is one of the most common serious neurological disorders. The most characteristic feature of epilepsy is recurrent epileptic seizures, which can cause a wide range of outward effects from uncontrolled movement of (part of the) body to temporary losses of awareness. Besides the epileptic seizures, epilepsy is often accompanied by neurocognitive comorbidities [2]. In rare and very severe cases epilepsy can result in death. Epilepsy has a world-wide prevalence of about 6 to 9 per 1000 persons [3]. More specific, in the Netherlands 51.678 people were estimated to have epilepsy in 2016 of which 268 died as a result of the disorder [4].

Since the neuronal cell bodies that discharge synchronously during an epileptic seizure reside mainly in the gray matter of the brain, epilepsy was traditionally thought to be mainly a disorder of the gray matter [5]. However, recent research has shown that the disruptions of brain tissue in epilepsy affect the complex interactions of different brain regions connected by via the fiber bundles of the white matter. Therefore, epilepsy is currently regarded as a brain network disorder, for which the white matter also plays an important role [6].

A possible underlying factor of a hyper-excitable state of the epileptic brain is the temporal summation of several synchronous subthreshold excitatory stimuli [7]. This summation could be a direct consequence of axons with poorly distributed conduction velocities that result in the synchronous firing of action potentials. The conduction velocity of an axon is mainly related to its diameter and the myelin sheath. Therefore, a direct relation might exist between epileptic seizure susceptibility and an abnormal myelin content.

Main Findings

The main clinical finding of this thesis is the involvement of the myelin sheath in patients with epilepsy. Numerous studies have already hinted towards myelin abnormalities in preclinical epilepsy models and patients with epilepsy (chapter 2). Furthermore, a disrupted myelin content and myelin development was observed in children with epilepsy (chapters 5 and 6). Besides the clinical findings, this thesis also provided technical advances. First, an alternative analysis method to quantify the myelin content is proposed. The presented method provides more measures of myelin content compared to a widely-used alternative (chapter 3). In chapter 4 of this thesis, we introduced an adapted myelin imaging acquisition that is less

prone to head movement and has an acquisition time that is roughly twice as short compared to previous versions.

Target group

The new clinical insights of this thesis could potentially, in the long run, be beneficial to patients with epilepsy. New treatment regimens aimed towards the myelin sheath could have a positive effect on the disorder. However, it should be noted that from this thesis alone it cannot be concluded that abnormalities of the myelin sheath are a cause or consequence of epilepsy and/or epileptic seizures. Therefore, first, further research on the involvement of the myelin sheath in epilepsy is warranted.

The technical advances presented in this thesis can also benefit patients suffering from other myelin related neurological disorders, such as Alzheimer's disease [8], multiple sclerosis [9], Parkinson's disease [10], major depressive disorder [11] and schizophrenia [12]. The faster myelin acquisition method can reduce the total scanning time of future clinical studies, which is mainly beneficial for patients that cannot sustain long MRI scanning times, such as elderly patients, patients with movement disorders, young children and infants. Furthermore, the available MRI scanning time can be used more cost efficiently by hospitals.

The algorithm used to quantify the myelin content (chapter 3) is made publicly available as an open-source project on GitHub (https://github.com/GSDrenthen/Non-Negative-OMP). Therefore, other researches that are interested in the myelin content can easily implement the analysis.

Products and activities

Since myelin underlies several neurological and neuropsychiatric disorders, insights into the cerebral myelination could aid in the diagnostic and therapeutic strategies on an individual level. As such, the myelin content of an individual can be compared with measures from a large population to identify whether individual maps fall within the population distribution, or whether they constitute abnormal values. This approach of personalized medicine can be incorporated as a software application on a clinical scanner. Like this, undergoing a brain MRI exam, a myelin map can be acquired, and subsequently relevant deviations in myelination will be visualized. This could ultimately be used to determine the optimal therapeutic strategy and/or disease progression precisely tailored per individual.

Innovation and future directions

The research in this thesis indicates that epilepsy is related to abnormalities of the myelin sheath. However, the current evidence from advanced MRI methods is relatively scarce. Therefore, myelin-specific imaging methods should be employed in other (preferably larger) epilepsy studies. Furthermore, to explore whether myelin abnormalities are a cause or consequence of epilepsy longitudinal studies are required. Like this, it can for example be established whether the myelin abnormalities worsen over time. While this does not provide concluding causal evidence, it does provide new insights into the myelin-epilepsy relation.

Furthermore, this thesis shows that the acquisition of myelin-specific content can be accelerated by using multi-slice 2D scanning methods. Recently, under-sampling methods such as compressed sensing are used to decrease scanning times [13]. Therefore, further advances to reduce the acquisition time of the 2D pulse sequence can still be made.

Moreover, in the future, the acquisition of myelin-specific scans could be omitted entirely. Anatomical and diffusion MRI techniques relate to the myelin content and are already acquired in most clinical research studies. Although these techniques are not suitable for absolute quantification of myelin, combined they might exhibit an underlying (complex and non-linear) relation to the myelin content. Therefore, machine learning approaches can be employed to extract myelin-specific information from anatomical and diffusion MRI data.

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