General Introduction

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GENERAL INTRODUCTION

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Multiple sclerosis (MS) is a chronic inflammatory, demyelinating and neurodegenerative disorder of the central nervous system (CNS). According to the World Health Organization (WHO), MS is one of the most common causes of neurological disability in young adults. More than two million people worldwide suffer from MS with a higher incidence in women than in men, with ratios as high as 3:1. The disease can develop during childhood or at later stage in life, but MS mainly affects young people with a mean age of onset around 30 years. Although MS can occur throughout all parts of the world, the prevalence of MS varies geographically, ranging from 2 per 100,000 in sub-Saharan Africa to 250 per 100,000 in North America and Europe. In the Netherlands, the total number of patients with MS is estimated at 17,000 and 1,800 people are diagnosed with MS each year. Although the exact cause of MS is still largely unknown, several risk factors have been proposed, including genetic factors related to immune function and environmental factors related to the substantial geographical variation, such as vitamin D.

The clinical course of patients with MS is heterogeneous and characterized by a wide variety of neurological symptoms. Common presenting symptoms include visual disturbances, loss of coordination, motor weakness, sensory disturbances, gait disturbances, spasticity and more. Although MS is commonly viewed as a typical motor disease, cognitive deficits are also frequently present in patients with MS and can occur independently of physical disability. In fact, up to 70% of all patients experience some degree of cognitive impairment, which is more frequent in progressive phases than in early phases of the disease. Like physical symptoms, cognitive deficits can be highly heterogeneous in nature, although it seems that information processing speed and episodic memory deficits are most prominently affected. Cognitive dysfunction can influence the patients’ lives considerably, from impairments in daily living to social isolation and unemployment. Furthermore, patients with MS who experience cognitive impairment at disease onset have been reported to have a worse prognosis and/or a more rapid disease progression.

Most patients with MS initially develop a relapsing and remitting type of the disease (RRMS) with recurrent episodes (i.e. relapses) of neurological symptoms, followed by partial or complete recovery. After around ten years, fifty percent of RRMS patients will subsequently develop secondary progressive MS (SPMS). This SPMS phase is characterized by an unremitting progressive worsening of clinical symptoms, leading to a continuous and gradual accumulation of clinical deficits. Approximately 10-15% of all MS patients experience this unremitting progressive worsening of symptoms from the disease onset, which is called primary progressive MS (PPMS).

The classical view of the MS brain

Focal inflammatory demyelinating lesions in the white matter are considered as the classical pathological hallmark of MS. Myelin forms a fatty sheath around fibers called axons, long projections that extend from the neuron. The white matter is composed of bundles of myelinated axons, which create a network of nerves allowing the passage of electrical signals from and to grey matter regions in the cortex (i.e. neurons). Since the main function of myelin is to protect and insulate axons to enhance transmission of signals, the destruction of myelin in MS interferes with signal propagation, which in turn contributes to the emergence of clinical symptoms.

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These white matter MS lesions can occur throughout the brain, but known predilection sites are periventricular areas and areas with a high venous density.\textsuperscript{16} Early stages of RRMS are characterized by periods of strong neuro-inflammatory activity and new lesions are frequent,\textsuperscript{17} while the immune response seems to dampen down after the conversion to progressive MS.\textsuperscript{16,17}

Detecting and visualizing these white matter lesions in clinic is imperative for diagnostic purposes and has been a prominent focus of research using magnetic resonance imaging (MRI; Box A). With the advancement of MRI acquisition techniques, it has become possible to integrate information

\section*{BOX A - FROM MAGNET TO PICTURES}

To understand how the brain can be imaged, some basic physics need to be introduced. Protons are little particles that have a positive electrical charge, which is constantly spinning around an axis. A moving electrical charge is also called an electrical current, which induce a magnetic force, or magnetic field. Thus, each proton has its own magnetic field and can be seen as a little magnet. Therefore, these protons mainly align with their south and north poles in the direction of the external field (i.e. parallel to the magnet). This type of alignment needs the least energy and is therefore the preferred state, thus more protons are on the lower energy level (i.e. parallel to the external magnetic field) and only a few out of parallel. As there are more protons aligned parallel to the external field, there is a net magnetic moment aligned with, or longitudinal to, the external magnetic field. The protons do not just only align to the magnetic field lines, but they move around in a certain way (i.e. precession). During this precession, the axis of the spinning circles form a cone shape.

Within a MRI scanner, a short burst of electromagnetic waves can be sent in, which is called a radio frequency (RF) pulse. This RF pulse can disturb the protons by exchanging energy with the protons to change their alignment, and go from a lower (i.e. parallel) to a higher energy level (i.e. not in parallel). Only when the RF pulse and the protons have the same frequency, protons can pick up some energy from the radio wave, a phenomenon called resonance. This results in more protons being out of parallel and thus the longitudinal magnetization decreases. When the RF pulse is switched off, longitudinal magnetization increases again (i.e. relaxation). Due to differences in tissue characteristics, this rate of relaxation differs in each part of the brain and thus sends a slightly different signal back to the receiver coil. Decoding where the signal came from, forms the basis of constructing images of brain structures.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{magnet_to_pictures}
\caption{From magnet to pictures}
\end{figure}
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FROM PATHOLOGY TO CLINICAL SYMPTOMS

Soon after the emergence of MRI techniques sensitive to detect disseminated white matter lesions (Figure 1), imaging has become a major diagnostic tool for MS. However, attempts to associate the occurrence of focal white matter lesions to clinical measures have revealed a clinico-radiological paradox,21 showing that the volume and number of white matter lesions only relate relatively poorly with clinical and cognitive functioning.22,23 The weak relation between white matter lesions and patient functioning has led to the question whether other histopathological processes that are less easily visualized might better explain cognitive and clinical deterioration. Nowadays, several advanced imaging techniques offer opportunities to further quantify such pathological processes, which has improved our understanding of patient functioning.

Although MS has traditionally been considered primarily as a white matter disorder, advanced imaging and histopathological techniques have revealed extensive demyelination in the grey matter as well.24 Grey matter lesions can already be seen in early stages of the disease.25,26 Accumulate with disease duration and are most prominent in progressive phenotypes.26 Additionally, grey matter lesions have a much stronger relationship with cognitive dysfunction27–29 than white matter lesions. In general, grey matter lesions are more frequent and larger in deep invaginations of the brain surface, such as the cingulate gyrus and insular cortex.30 In the most severe cases, more than 70% of the cortex can be demyelinated.24 The pathology of grey matter lesions differs from that of white matter lesions in that many of the pathological signatures of white matter lesions, including infiltration of immune cells, complement activation and disruption of the blood-brain barrier, are mostly absent in grey matter lesions.31,32 Furthermore, grey matter lesions can occur independently of white matter demyelination.33

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Apart from the focal grey and white matter lesions, neurodegeneration is another important pathological feature of MS. Brain atrophy (Box B) is a commonly used marker of neurodegeneration and explains clinical and cognitive functioning of patients with MS to a larger extent than focal lesions. Brain atrophy can occur very early and while white matter atrophy rates appear to remain relatively constant, grey matter atrophy is thought to accelerate after converting to secondary progressive MS. Annual whole-brain atrophy rates in the MS population have been reported to be 4 to 8 times higher than in the healthy population, with estimates ranging from 0.4–0.8% of brain tissue loss each year. For a long time it was debated what the histopathological substrate of grey matter atrophy in MS could be, but recently it was shown that grey matter atrophy observed on MRI is mainly related to a decrease in neuronal density, neuronal size and axonal density.

**MOVING FORWARD - ADVANCED IMAGING TECHNIQUES**

Over the last years impressive progress has been made in the development of more advanced imaging techniques to visualize the widespread pathological features of MS. Diffusion tensor imaging, for example, is a technique which allows a researcher to visualize the microstructural organization of the white matter, which cannot be detected with conventional MRI (DTI; Box C). DTI is able to provide rich anatomical information about the white matter and is sensitive to variances in the integrity of this tissue. In patients with MS, DTI has not only revealed reduced integrity in white matter lesions, but also in regions adjacent to white matter lesions, the so-called normal appearing white matter. Intriguingly, it turns out that especially damage to

**BOX B – MEASURING BRAIN VOLUMES**

3D T1-weighted images are most suitable to measure all kind of brain volumes, including whole-brain volume, cortical grey matter volume, deep grey matter volume and white matter volume (Figure B). To extract these volumetric measures, different FSL toolboxes are used. SIENAX performs segmentation of the brain from non-brain tissue and provides whole-brain, grey matter and white matter volume normalized for head size. FIRST can be used to accurately outline the deep grey matter structures, such as the thalamus and hippocampus. The volumes of all deep grey matter structure can be estimated.

![Figure B | To determine the level of atrophy, white matter, gray matter and deep grey matter regions can be segmented, and subsequently the volumes of these segmentations can be computed.](image-url)
the normal appearing white matter, rather than lesional damage, is correlated to the clinical functioning of patients with MS.\textsuperscript{41-45} In addition, cognitively impaired patients displayed more extensive and severe loss of white matter integrity in cognitively relevant white matter tracts compared to cognitively preserved patients with MS, highlighting the value of studying the normal appearing white matter.\textsuperscript{41-45}

To examine the impact of disease-related tissue damage on brain function, advanced functional neuroimaging techniques can be used. The structural architecture of the brain is relatively constant over short time ranges, whereas the functional network can be very dynamic over time. Therefore the wide repertoire of flexible functional patterns, upon the more solid structural backbone, is likely to support all kinds of human behavior and gives rise to complex cognitive functions.\textsuperscript{44} Within the functional neuroimaging field, brain function can be investigated either during the performance of certain tasks (i.e. task-related fMRI) or in a so-called rest condition (i.e. resting-state fMRI). A commonly used task-related fMRI study design features a chosen paradigm that alternates between periods of performing a particular task and a control state, such as performing a memory task. The two different states are then contrasted to identify brain regions associated with this task, and activation levels are then compared between groups. In MS, two typical phenomena are commonly seen during a task: 1) increased activation of regions also activated in healthy subjects in response to the task and 2) activation of additional areas that are not recruited in healthy subjects.\textsuperscript{45-49} Apart from the mapping of regional brain activity,
it is also possible to measure how well brain regions are connected to each other, i.e. how strongly they are communicating (Box D). This functional connectivity between regions is typically assessed during rest. Resting-state fMRI studies have taught us that the connectivity between brain regions is disturbed in patients with MS, which is associated with cognitive and clinical dysfunction.48–50

To summarize, while conventional structural imaging modalities have revealed the typical MS lesions, especially used to diagnose and monitor the disease, more subtle measures of atrophy and normal-appearing brain tissue changes relate more closely with patient functioning. Newer studies have identified the impact of these types of damage using functional imaging modalities, which have disclosed how the brain responds to damage. However, since the brain is a complex system consisting of regions that are either directly or indirectly connected to each other, all these local structural and functional changes are likely to affect regions elsewhere in the brain.

To better understand cognitive and clinical functioning of patients with MS, there is now growing consensus about the need to move from studies focusing on particular single regions to investigate the brain in its entirety.51,52 Investigating the brain as a network endorses the possibility to investigate the brain as a complex system.

THE BRAIN AS A NETWORK

In the latter half of the 19th century the concepts of brain networks emerged with the advent of the "disconnection syndrome" hypothesis propounded by Wernicke, Lichtheim, Liepmann, Dejerine and others.53 This hypothesis was based on neuroanatomical research showing that the brain...
was neither uniform nor composed of identical modules, but rather a heterogeneous mosaic of interconnected regions. Therefore this concept can be seen as the precursor of network models as we know it today and as the first biologically plausible account of mental phenomena, based on neuroanatomy and empirical clinical observations rather than philosophy. Nevertheless, this hypothesis competed with many other theories of brain organization in the mid-20th century and lost ground. The concept of a brain network organized to efficiently integrate information was reintroduced by Norman Geschwind in the 1960s. The emergence of advanced MRI modalities, including diffusion tensor imaging (DTI; Box C) and resting-state functional MRI (rs-fMRI; Box D), together with new computational approaches to network analysis, have taught us a lot about the architecture of the brain. Building on the well-established mathematical framework of graph theory developed in computer science, the brain network can be described as a graph (Figure 2) with nodes representing neural elements and edges their structural or functional relations. Without exception, network studies conducted across neural data sets from a variety of species have revealed characteristic non-random features, including high clustering, short path length, as well as modules and highly central hub nodes. It is thought that these patterns of brain-organization are of high functional importance since they facilitate an optimal integration and segregation of information flows. Nowadays, we know that the brain network organization is changed in MS and other neurological disorders and to better understand patient functioning graph based analysis is applied to examine the influence of pathology on the communication between regions on the network level.

THE EARLY DAYS OF FUNCTIONAL CONNECTIVITY STUDIES IN MS

Early functional connectivity studies found increased connectivity in clinically isolated syndrome (CIS) patients and decreased connectivity in progressive MS, which was related to cognitive impairment. Together with task-related fMRI findings of hyperactivation of task-involved regions and recruitment of additional brain regions, all these increases in brain function (i.e. activity and connectivity) together were interpreted as a compensatory mechanism to sustain clinical and cognitive functions. These findings led to the functional reorganization hypothesis, which asserted that increasing structural damage, in combination with an optimum curve of functional reorganization, results in a delayed development of cognitive dysfunction. Based on this hypothesis, it was proposed that an increase in brain function, both in terms of activity and connectivity, reflects a functional reorganization mechanism which compensates for accumulating structural damage, resulting in maintaining cognitive dysfunction. However, at that point in time, the functional connectivity field was still in its infancy, and the conclusion of compensation was purely based on the direction of the effect, i.e. increases were seen as good, and decreases as bad. Soon after this hypothesis was coined, the field expanded enormously with findings that did not fit the previously stated functional reorganization hypothesis, and showed this model to be incomplete and overly simplistic. Nevertheless, these studies have taught us that the observed changes in the level of functional connectivity are able to discriminate cognitive and MS phenotypes. Since the efficiency of a network strongly depends on the topological organization of a brain network, it is likely that changes in functional connectivity, either increases or decreases, which influence the functional network topology, reduce the global network efficiency. In the healthy brain, the functional network is constructed in a cost-

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An efficient way characterized by both scale-free and small-world properties, which make efficient information flow throughout the brain feasible. In short, this means that brain regions are not randomly or evenly connected, and that most brain regions are not neighbours of one another, but can be reached in a small number of steps. There is now growing consensus that optimal brain functioning requires regional specialization with efficient global information transfer and integration. A wide variety of topological characteristics among brain regions are necessary to support both processes of information integration and segregation.

ADVANCES IN THE FUNCTIONAL NETWORK FIELD

The reason why some studies mainly identified increases and others mainly decreases in functional connectivity remains unclear and could be numerous, including different patient groups, a variety of methodological approaches and changes could be region specific. In addition, the observed high between-subject variability of the functional network in both patients and controls makes it even more complicated. Despite that the composition and strength of individual functional networks varies considerably between individuals, functional MRI studies typically collapse data from many subjects in order to draw inferences about differences in fMRI connectivity patterns between groups. To become more sensitive to specific topological changes and to enhance the between-subject comparability, it is necessary to consider the variability of these individual network properties when comparing functional networks across groups. This provides the possibility to investigate which connections are the strongest and which are the weakest within an individual functional network and could provide insight in the underlying functional scaffold. In this thesis, we aim to investigate changes in the functional network of patients.

Figure 2 | Graphical representation of the brain. Network measures are shown in a graph with nodes (grey dots) and edges (grey lines). Some of the nodes are characterized by a high level of clustering (red) and others by a low level of clustering (blue). The distance between two nodes is referred to as the path length (green dotted line).
with MS, while taking the individual scaling of connectivity levels within the brain network into account. This measure would then allow for a more sensitive investigation of changes in the functional network topology, by looking at connectivity shifts between different parts of the brain network. In other words, it provides the possibility to investigate shifts in the network balance, which connections become stronger or weaker in relation to clinical deficits.

As a small change in the make-up of the functional scaffold is likely to change the optimal efficiency, we expected that these changes are closely related to clinical functions. Furthermore, we expected that changes in the functional network are not random but follow certain patterns instead. For example, it could be that functional connectivity changes follow the apparent pattern of atrophy, from deep grey matter structures to cortical regions. Eventually, the accumulating structural damage and the resulting pressure on the functional network may lead to a functional “network collapse”, i.e. a sudden drop in efficiency. Furthermore, we expected that some functional changes have more severe network (and clinical) consequences than others. For example, changes in regions that are highly connected, the so-called hub regions, which are highly responsible for the network efficiency. This high grade of efficiency can be achieved via long-distance connections of these hubs to other brain regions and their strong interconnectedness to each other, forming the so-called rich club.14 Their topological centrality and embedding within the network support efficient processing of signals throughout the brain making them functionally valuable and relevant. In neurological disorders like MS, it could be that clinical and cognitive dysfunction can be related to disturbances of hub regions.23,48

STRUCTURAL NETWORKS – MIND THE GAP

Apart from constituting functional networks based on resting-state fMRI data, it is also possible to map structural networks. However, there is less known about the impact of MS pathology on the structural network, partly due to methodological challenges of current algorithms that are used to map white matter tracts in the healthy brain and across neurodegenerative diseases. In MS, these tracing algorithms are hampered by the presence of focal white matter lesions making it complicated to map the white matter tracts.31,72 For this reason, most of the MS studies that have addressed the quality of the white matter tracts have applied Tract Bases Spatial Statistics (TBSS),71 which allows to investigate voxel-based changes in whole brain white matter integrity. Although studies have observed loss of white matter integrity throughout the brain, it is not known whether loss of white matter integrity occurs randomly throughout the brain or whether there are patterns to the white matter damage, nor whether these patterns could be clinically relevant. If we assume that individual white matter tracts are not isolated but are embedded within a network of white matter tracts and thus connected to each other, it would be likely that changes anywhere in the white matter leads to changes in other, most likely connected, white matter tracts as well. To mimic a network-based approach that allows us to examine white matter changes in relation to each other, it could be investigated whether patterns in white matter integrity loss occur. Eventually, it would be of interest to investigate structural networks in MS. Nowadays, alternative methods, such as correlating measures of cortical thickness, have been used to map the structural network in patients with MS.29,71 These studies have shown that especially the extent of white matter lesions seem to proportionally disrupt the efficiency of the structural network.21 To be able to apply tractography algorithms to perform structural network
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analyses in MS studies, consensus on how to estimate the best possible structural network is first needed. In this thesis, different methodological choices that have to be made along the construction of structural networks are evaluated and recommendation for future studies are provided.

FUNCTIONAL VERSUS STRUCTURAL CHANGES

The two paragraphs before describe the state of the art of the functional and structural MRI field in MS separately. However, when we engage a certain task, the brains’ functional and structural architecture together enable efficient processing of information across different brain regions which give rise to complex behavior, including cognitive functions.45,73 However, the exact interaction between the functional and structural connectivity is far from simple. Mapping the interplay between functional and structural brain could potentially better explain complex behavior than studying one or the other, especially because previous studies have suggested that there is no simple one-to-one relation between structural and functional properties of the brain. Functional connections are observed between two brain regions without a direct structural link, indicating that these regions can only reach each other through indirect structural pathways. Despite previous imaging studies have taught us that both functional and structural measures could be affected in MS,35,45,74,75 studies integrating functional and structural measures are missing. Although structural and functional brain characteristics are intertwined to a certain extent, structural damage can occur in the presence of minor functional changes, but may also involve severe functional changes.35 This emphasizes the necessity to investigate both in relation to each other. Without structural measures, information about the integrity and quality of the structural brain architecture is missing. In absence of functional measures, we most likely miss information regarding the functionality of the structural brain architecture. Until now, it is unclear whether different severities of functional and structural damage are associated with different clinical and/or cognitive phenotypes. In the MS field, a first step could be to individually map the level of structural and functional changes, and investigate whether a disparity in the level of structural and functional exist in patients with MS.

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AIM OF THIS THESIS

The general aim of the studies presented in this thesis is to expand our understanding of MS as a network disease by deciphering patterns in structural and functional brain changes in relation to the clinical picture of MS. To achieve this, we used advanced multi-model MRI techniques and both existing as well as innovative analyzing methods. This thesis is divided into three different chapters each covering a more specific research question while supporting the general aim:

1. Which shifts in the functional network balance can we observe in MS and what is the clinical relevance of these shifts?
2. Can we provide a better explanation of the clinical picture of MS using advanced diffusion tensor imaging at a voxel- and network-based level, and which are the best methodological approaches to map structural networks?
3. What is the interplay between functional and structural brain changes, and would studying the brain by combining both measures help to understand cognitive function better than studying either in isolation?

In CHAPTER 2 functional network shifts are not only investigated in relation with cognitive deficits, but also in relation with different phases of MS and treatment. The role of advanced DTI methods is addressed in CHAPTER 3. In this chapter, we not only investigate voxel-based changes in WM integrity and their cognitive relevance in SPMS, but also whether we can detect non-random patterns of damage in the WM. Finally, different methodological approaches to map structural networks are compared and evaluated. After studying functional and structural changes separately, in CHAPTER 4 we investigate the interplay between structural and functional changes in order to understand the mechanism underlying cognitive deficits better, for example by studying groups of patients with severe structural damage but few functional changes, and vice versa. In CHAPTER 5 the findings of the performed studies are summarized, integrated and discussed.
REFERENCES


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