Exercise Training in patients with multiple sclerosis: status quo and prospect

Masterarbeit

zur Erlangung des akademischen Grades
Master of Science

an der Karl-Franzens-Universität Graz

vorgelegt von
Viktoria SCHMIDHUBER, Bsc

am Institut für Sportwissenschaften
bei Ao.Univ.-Prof. Mag.phil. Dr.rer.nat. Hofmann, Peter
Graz, 2016
Ehrenwörtliche Erklärung

Hiermit erkläre ich, dass ich die vorliegende Arbeit selbstständig und ohne fremde Hilfe verfasst, andere als die angegebenen Quellen nicht benützt und die den benutzen Quellen wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht habe. Die Arbeit wurde bisher in gleicher oder ähnlicher Form keiner anderen inländischen oder ausländischen Prüfungsbehörde vorgelegt und auch noch nicht veröffentlicht.

Graz, 11.02.2016

Viktoria Schmidhuber
Abstract

Multiple sclerosis (MS) is a chronic, immune-mediated and inflammatory disease of the central nervous system (CNS) that mostly occurs in young adults. MS susceptibility is influenced by many factors, such as environmental and genetic factors, but the precise etiology is still elusive. The disease causes multifocal demyelination and variable axonal loss in the brain and spine, leading to various symptoms, depending on the locality of neural damage or brain lesions. These symptoms often lead to the adaption of a physically inactive and sedentary lifestyle, which leads to deconditioning, a worsening of symptoms and further complications. Furthermore, physical activity and cardiorespiratory fitness have been linked to a decreased risk of relapse, fewer complications and a better quality of life. Recent literature shows a beneficial effect of physical activity and exercise in patients with MS. These beneficial effects include positive feelings triggered by exercise, improvements in strength, walking abilities, aerobic capacity and balance. Nonetheless, negative influences of exercise on the patients have to be taken into account, including perceived physical deterioration, feeling of failure, anxiety and loss of safety. Physical activity might lead to side effects or relapses, but these events have rarely been reported. Exercise training is generally considered safe and has a potential positive effect on patients with MS, but further research and better guidelines for patients, as well as training therapists, physicians and caretakers are needed.
4.6.3 Effects on Body structure (axonal damage/ loss and neuronal loss) ......... 61
4.7 Body function .............................................................................................................. 63
  4.7.1 Depression ............................................................................................................. 63
  4.7.2 Fatigue ................................................................................................................... 64
  4.7.3 Cognition ................................................................................................................ 66
  4.7.4 Cardiovascular ...................................................................................................... 67
  4.7.5 Aerobic power/cardiorespiratory fitness/ VO$_2$ ................................................. 69
  4.7.6 Spasticity and Paresis ........................................................................................... 70
  4.7.7 Gait parameters/ Walking performance ................................................................. 71
  4.7.8 Sensory and balance ............................................................................................. 73
  4.7.9 Muscle strength/ muscle endurance/ intramuscular ............................................. 74
  4.8. Quality of Life (QoL) ............................................................................................. 76
5. Exercise recommendations (so far published guidelines for persons with MS) ....... 77
6. Conclusion and outlook ................................................................................................. 80
7. References ..................................................................................................................... 83
8. Figures .......................................................................................................................... 90
9. Tables ............................................................................................................................ 90
1. Introduction

Multiple sclerosis (MS) is a chronic, immune-mediated and inflammatory disease of the central nervous system (CNS) that mostly occurs in young adults. MS susceptibility is influenced by many factors, such as environmental and genetic factors, but the precise etiology is still elusive. The disease causes multifocal demyelination and variable axonal loss in the brain and spine, leading to various symptoms, depending on the locality of neural damage or brain lesions. These symptoms often lead to the adaption of a physically inactive and sedentary lifestyle, which leads to deconditioning, a worsening of symptoms and further complications. Furthermore, physical activity and cardiorespiratory fitness have been linked to a decreased risk of relapse, fewer complications and a better quality of life (Döring et al., 2012; Motl & Pilutti, 2012; Motl & Sandroff, 2015).

Standard treatment of MS consists of drug-based immunomodulatory treatment and complementary therapy, such as physiotherapy and ergotherapy. Exercise training has not been included in standard MS treatment so far. For a long time exercise has even been considered harmful for patients with MS leading to the promotion of inactive lifestyles in patients with MS.

There is a need for an effective treatment method with less side effects than drug based treatment that approaches many symptoms at once, such as exercise training. Exercise training in other diseases and elderly has shown promising results. Throughout the last years the literature on exercise training in patients with MS has increased, with several trials investigating the effects of exercise on several aspects of the disease.

In the following recently published (since 2000) literature on the topic has been reviewed and the status quo has been investigated. A summary of what has been observed about the effects of physical exercise on specific MS symptoms and impairments will be given and the suitability of exercise training in patients with different disability levels explored. Further, current recommendations for appropriate exercise training will be discussed.

Finally, the question whether exercise training is a suitable standard therapy and to what extent it is suitable will be discussed, as well as the question, what still has to be done, to improve patient care, physical activity in patients with MS and exercise training in patients with MS.
2. Background of Multiple Sclerosis

2.1 Neuropathology
Multiple Sclerosis (MS) is a chronic inflammatory disease of the CNS, which causes multifocal demyelination along with astrocytic gliosis and variable axon loss in the brain and spine, as explained by Döring et al., (2012). More specific MS affects mainly the white and grey matter tissue producing demyelinated plaques or lesions in the brain and spinal cord (Zuvich et al., 2009; Lassmann, 2013).

MS is generally considered to be autoimmune and neurodegenerative in nature. Th1 cells recognize components of the myelin sheath and in consequence, initiate a self-propagating autodestructive process within the CNS. Additionally demyelinating amplification factors are required in this progress (Kornek & Lassmann, 2003). All the components linked to MS lead to the concept of MS as a heterogeneous disease with “respect to the pathogenetic mechanisms of demyelination. In fact profound heterogeneity with respect to clinical course, neuroradiological presentation and response to therapy is a characteristic feature of MS” explain Kornek and Lassmann (2003).

In contrast to other inflammatory diseases the formation of MS plaques is unique in patients with multiple sclerosis. Some studies consider the formation of MS plaques as the main pathological characteristic of MS (Hernandez-Pedro et al., 2013).

Through these processes scar tissues are formed (“sclerosis”) in various areas of the CNS (“multiple”), which defines the disease progress as “Multiple Sclerosis” (Zuvich et al., 2009; Lassmann, 2013).

Inflammation in the brain
As long as the disease process is active, inflammation is present at all stages of MS, but changes its characteristics throughout the progress of the disease (Lassmann, 2013).

Kornek and Lassmann (2013) explain the inflammation process stating that “it has been suggested that the initial event of induction of inflammation in the brain is the migration of activated Th1 cells through the blood-brain barrier (BBB). Activated Th1 cells may stimulate local or haematogenous macrophages that destroy myelin and lead to further release of potential CNS autoantigens” (p.1). This indicates that the inflammation during early stages of MS is associated with profound blood brain barrier leakage. Therefore inflammatory cells that infiltrate the brain enter the CNS from the circulation (Lassmann, 2013). The breakdown of the
BBB lasts for about a month before it resolves itself. Still the damage done to the BBB can later be shown by magnetic resonance imaging (Mirshafiey & Kianiaslani, 2013).

In advanced stages of the disease inflammation is more often seen around vessels with an intact blood brain barrier. This leads to the conclusion that the inflammatory process becomes at least on part trapped in within the CNS compartment with disease progression (Lassmann, 2013).

A typical feature seen in MS is the building of plaques. Pathologically these plaques are characterized by blood brain barrier leakage, destruction of myelin sheaths, oligodendrocyte damage and cell death, as well as axonal damage and loss, glial scar formation and presence of inflammatory infiltrates (Hernandez-Pedro et al., 2013).

**Demyelination**

Different mechanism may lead to myelin destruction. Most studies emphasize a close relation between inflammation and demyelination (Stadelmann et al., 2011; Hemmer et al., 2006; Kornek & Lassmann, 2003).

Some suggest that inflammatory mechanisms, such as antibodies, T cells and macrophages lead to demyelination (Stadelmann et al., 2011). Proof for such hypotheses could be that actively demyelinating lesions are heavily infiltrted by macrophages (Kornek & Lassmann, 2003). Other suggestions are that oligodecrocyte damage and myelin destruction are considered the primary events and only later inflammatory cells from the circulation invade (Stadelmann et al., 2011).

**Axonal loss**

Axonal damage and loss occurs even in the early stages of MS. Progressive and irreversible neurological disability in MS has been attributed to axonal damage and loss (Hauser & Oksenberg, 2006, Kornek & Lassmann, 2003, Nessler et al., 2006). Axonal damage appears to take place in every newly formed lesion. It has also been observed in inactive and remyelinating lesions, cortical tissues and the normal-appearing white matter in the brain and spinal cord (Hauser & Oksenberg, 2006).

Axonal injury and loss can be considered a consistent feature of MS but it’s extent is variable. This can be explained by the demyelinating activity within the plaque. It could also be due to an inter-individual heterogeneity in axonal pathology (Kornek & Lassmann, 2003).
As so often within this disease, the reasons for axonal loss and damage appear to be multifaceted. Some hypotheses might explain axonal loss and damage in patients with MS. On one hand the loss of myelin greatly enhances the propensity of axons for transport disturbances. On the other hand a link between an aberrant inflammatory response in the CNS and axonal damage can be seen. Even though these hypotheses exist, the molecular events underlying axonal damage remain unclear (Hemmer et al., 2006; Stadelmann et al., 2011).

**Lesions**

Different classification schemes for MS lesions are currently discussed. The most commonly used scheme is the classification of lesions in four different patterns of pathology resulting in demyelination. The first pattern, Type 1, is T-cell mediated and is characterized by demyelination and macrophage-related products. Type 2 is the most commonly observed pathology of lesions in MS: both T-cells and antibodies are involved and it is characterized by the presence of immunoglobulin and complement. Type 3 shows early loss of myelin associated glycoprotein and no remyelination. These lesions are related to distal oligodendropathy. The last pattern, Type 4, results in primary oligodendrocyte damage followed by secondary demyelination. These types of lesions can only be seen in a small subset of primary progressive MS patients. In patients with MS lesions can in fact obtain features of not only one pattern, but of more (Frohmann et al., 2006; Mirshafiey & Kianiaslani, 2013).

MS lesions occur when leukocytes are able to migrate into the brain and this migration is followed by inflammation. The migration of leukocytes into the brain is possible when a BBB leakage occurs (Hoglund & Maghazachi, 2014). Lesions in MS can be distinguished in white matter lesions and gray matter lesions.

Different types of white matter lesions can be seen in MS brains including classical active lesions, slowly expanding lesions, inactive lesions and remyelinated shadow plaques (Lassmann, 2013). Lassmann (2013) points out that “Classical active lesions are characterized by profound lymphocytic inflammation and massive infiltration by macrophages containing myelin debris. Classic active lesions are most frequent in patients with acute or relapsing MS, but become rare in patients with progressive MS” (p.2).

Largely overlooked throughout the last decades greater interest in gray matter lesions developed lately. Today demyelinated gray matter lesions are known to cover substantial areas of the cortical, deep and spinal gray matter (Stadelmann et al., 2011). Gray matter lesions are hard to detect and therefore only recently the impact of these lesions could be
detected. Imaging evidence suggests that cortical lesions may contribute to cognitive deficits and epileptic seizures (Stadelmann et al., 2011).

**Experimental autoimmune encephalomyelitis (EAE)**

The experimental autoimmune encephalomyelitis (EAE) is a complex animal model of neuroinflammatory diseases developed to study the role of the immune system in CNS diseases (Hemmer et al., 2006). In the EAE models CNS pathology similar to the MS pathology can be seen and it is possible to draw interferences from the interaction between various immunopathological and neuropathological mechanisms in EAE to the key pathological features of MS (Hemmer et al., 2006; Hernandez-Pedro, et al., 2013). EAE itself is a T-cell mediated inflammatory disease of the CNS with variable degrees of demyelination and axonal damage. It has been inducted in many animals such as monkeys, rodents and rats.

The EAE models have been helpful in developing, testing and validating therapies for MS and have been valuable for studying and understanding basic mechanisms of neuroinflammation and neurodegeneration. Still the extent of similarity between MS and EAE remains debatable as they cannot thoroughly display every aspect of a disease as complex as MS (Hemmer, et al., 2006; Hernandez-Pedro, et al., 2013). Some differences include the role of the B cells, which is dispensable in EAE, and the different treatment approaches in EAE and patients with MS (Hemmer et al., 2006).

**MS and immune system**

In attempting to understand the etiology of MS it is necessary to take a close look at the immune system.

The current state of research suggests that the immune system can either have a positive or a negative influence in MS. Positively it can prevent autoimmunity by differentiation of regulatory T cells and by secretion of neurotrophic growth factors. Negatively the innate immune system can promote the differentiation of Th1 and Th17 cells which drive acute inflammatory events associated with relapses in MS. "Furthermore, the progressive phase of MS is now believed to be mediated by innate immune system as reflected by their activated phenotype in periphery which might be directly responsible for neurodegenerative changes in secondary progressive MS" explain Gandhi et al., (2010) new insights on the role of the immune system in MS (p. 8).
Role of the T-cells

The central role of T-cells in MS pathogenesis has always been given attention due to findings in EAE and the strong association with HLA class II genes (Hoglund & Maghazachi, 2014). Myelin-specific T cells have a crucial role in the inflammatory process leading to CNS demyelination. Although the number of T-cells in the peripheral blood that react to myelin is the same in patients with MS and healthy persons those cells have substantial qualitative differences in responses mediated by circulating mononuclear-cell populations (Hemmer et al., 2006; Frohmann et al., 2006; Racke, 2009). While the myelin-reactive T-cells in healthy patients appear to have a naïve phenotype, the same antigens in patients with MS exhibit an activated phenotype. Furthermore, the myelin reactive T-cells from patients with multiple sclerosis are more inflammatory in nature (Frohmann et al., 2006). The activated phenotype of autoreactive T-cells in patients with MS are believed to upregulate adhesion molecules. These upregulated molecules allow the T-cells to interact with and cross the blood-brain barrier and establish an inflammatory response directed against myelin (Racke, 2009).

The activating process of autoreactive myelin-specific T-cells remains elusive. A potential mechanism by which these T-cells get activated could be molecular mimicry. Thereby T-cells respond to environmental antigens that resemble self-antigens (Racke, 2009).

Autoreactive T cells

Autoreactive T-cells such as CD4+ and CD8+ T-cells can be divided into effector subtypes which could be both pro- or anti-inflammatory depending on the cytokines they produce (Duffy et al., 2014). Both CD4+ and CD8+ T-cells can result in inflammatory demyelination of the CNS (Frohmann et al., 2006) and are present in MS lesions (Hemmer et al., 2006). CD4+ T-cells can be found predominantly in the perivascular cuff. CD8+ T-cells are more prevalent in the center and the border of lesions (Hemmer et al., 2006). In actively demyelinating lesions CD8+ T-cells may outnumber CD4+ T-cells and can even be found in the cerebrospinal fluid (CSF) and blood of patients for many years (Duffy et al., 2014). Both CD4+ and CD8+ cells express interleukin 17 in MS lesions (Hoglund & Maghazachi, 2014; Hernandez-Pedro et al., 2013). These high levels of IL 17 found in MS lesions induce a strong inflammatory response.

As the animal model of MS, experimental autoimmune encephalomyelitis (EAE), is considered to be a CD4+ T-cell induced disease these cells have been well studied in MS, and for a long time have been believed to be the main cause for inflammation (Holgrund & Maghazachi, 2014). CD4+ T-cells are described to carry out multiple functions. These functions include the regulation of the innate and adaptive immunity activation of other immune and non immune cells and suppression of immune reactions (Duffy et al., 2014).
CD8+ T-cells could play a part in the initiation of MS. This hypothesis is underlined by findings in biopsy samples of early stage MS patients, which revealed extensive CD8+ T-cell infiltration in the cortex. Moreover, CD8+ T-cells seem to be necessary for disease induction in the EAE model (Duffy et al., 2014).

Studies have shown that CD8+ T-cells recognize myelin antigens in MS patients and play a role in the breakdown of the BBB (Racke, 2009). Furthermore, it is believed that CD8+ T-cells are actively involved in the inflammatory process as they can be found in increased numbers proximal to demyelinated axons (Duffy et al., 2014). CD8+ T-cells appear to be more abundant in patients with RRMS which may suggest a prominent role in this stage of the disease (Frohmann et al., 2006).

The role of CD8+ T-cells in EAE has been topic of research for a long time, but further research is necessary to fully understand it. In mice with EAE CD8+ T-cells are known to be able to migrate to the CNS, but what happens after the migration is still elusive. Another finding in EAE that requires further research is the fact that CD8+ T-cells accumulate in the CNS of mice with EAE, yet their presence has shown no effect on the severity of the clinical disease (Duffy et al., 2014).

T helper cells

The most prominent T helper cells involved in neuroinflammation are Th1, Th2 and Th17. These myelin-specific auto-reactive lymphocytes are believed to be primed in periphery by unknown factors. Later they migrate to the CNS leading to demyelination and axonal loss later terminating in neurological disability (Gandhi et al., 2010).

Although both Th1 and Th2 cells are actively involved in the inflammatory milieu of multiple stages of the disease the role of Th1 cells is more prominent that this of Th2 cells (Duffy et al., 2014; Frohmann et al., 2006). Type 1 helper cells produce interferon - γ (IFN-γ) which greatly worsens MS (Frohmann et al., 2006). In patients with MS higher levels of interferon - γ can be found in the brain, cerebrospinal fluid and peripheral blood (Hoglund & Maghazachi, 2014; Duffy et al., 2014). In mice with EAE Th1 cells infiltrate the brain in increased numbers and the blocking of IFN-γ production inhibited the progression of EAE (Duffy et al., 2014). In patients with RRMS CD4+ T- cells have been collected, that show a more differential Th1 phenotype compared to those of healthy individuals. Additionally relapse is associated with increased production of IFN-γ (Duffy et al., 2014). Type 2 helper cells on the other hand are protective anti-inflammatory in nature and are believed to play a suppressive role in EAE (Duffy et al., 2014).
Studies have shown that Th17 cells are upregulated in patients with MS. Th17 cells generate inflammatory cytokines like IL 17, IL 21 and IL 22 (Hernandez-Pedro et al., 2013; Duffy et al., 2014; Hoglund & Maghazachi, 2014).

Cytokines produced by Th17-cells contribute to the inflammation in the brain. Inflammation mediated by Th17 cells is characterized by neurophil recruitment into the CNS and myelin loss (Hernandez-Pedro et al., 2013). It is believed that Th17 cells further increase the permeability of the BBB, as the endothelial tight junction is disrupted by the secretion of IL 17 and IL 22. Furthermore, the interactions with endothelium lead to further attraction of CD4+ subsets as well as other immune cells (Hoglund & Maghazachi, 2014).

Studies have shown that mice with fewer Th17 cells are less susceptible to EAE (Mirshafiey & Kianiaslani, 2013) and that more Th17 cells are necessary to develop EAE (Hoglund & Maghazachi, 2014).

Regulatory T cells
Regulatory T cells (Treg) are cells that prevent or suppress autoimmunity. In MS and other autoimmune diseases these cells are deficient (Constantinescu & Gran, 2014). Two types of Treg can be distinguished: natural Treg (nTreg) and induced Treg (iTreg). nTreg represent an independent population, such as β lymphocytes, and develop in the thymus. nTreg are involved in immunological tolerance and down regulate activities of autoreactiv T cells. iTreg develop during immune response and represent a subset of CD4+ Thelper cells. iTreg are active during the immune response of antigens, where they restrict the activities of effector T cells. nTreg and iTreg are non-interchangeable in their activities as they complement each other. Because of their beneficial suppressing activities Treg cells are considered for cellular therapy, in particular transplantation (Constantinescu & Gran, 2014; Buc, 2013).

B cells
Like other lymphocytes B cells function as a part of the adaptive immune response. Predominantly B cells mediate humoral immunity (Duffy et al., 2014). Involvement of B cell activity in MS pathogenesis can be explained by the presence of immunoglobulins in the CSF of patients with MS (Hoglund & Maghazachi, 2014). In 50-75% of MS patients immunoglobulins such as immunoglobulin G (IgG) and immunoglobulin M (IgM) have been found in acute, chronic active and chronic inactive lesions. These findings are independent of disease duration, clinical disease or staging (Duffy et al., 2014).
B cell activity may not be a primary inducer of MS but can be seen as a response to the autoimmune reaction (Hoglund & Maghazachi, 2014). The definite role of B cells in MS pathogenesis remains elusive but some hypothesis can be made.

B cells may have a role in the myelin breakdown. Studies have shown, that B cells in EAE contribute to demyelination, as they produce anti-myelin antibodies (Racke, 2009; Duffy et al., 2014). On the other hand B cells may as well have a protective function by downregulation of inflammation. This can either happen through a direct contact with target cells or by transforming growth factor – β (TGF-β) (Duffy et al., 2014; Buc, 2013). Some of the B cells had undergone editing and therefore are able to recognize the body’s misguided capability to manufacture auto-antibodies and subsequently remove this capacity (Frohmann, Racke & Raine, 2006).

Targeting the B cell component of the immune response could represent an attractive therapeutic strategy for patients with MS (Frohmann et al., 2006; Constantinescu & Gran, 2014). The response of B cells to exercise is discussed in chapter 4.

Natural killer cells (NK)

Natural killer cells (NK) are cells of the innate immunity that form the first line of defense. NK cells have the ability to spontaneously lyse target cells such as tumor cells without prior sensibilization (Hoglund & Maghazachi, 2014; Duffy et al., 2014). The role of NK cells in autoimmune diseases is highly debated, but it is suggested that they are somehow dysfunctional in these diseases. Still both positive and negative associations have been observed (Hoglund & Maghazachi, 2014; Duffy et al., 2014).

The EAE model provided evidence for positive impact of NK cells on the disease. The depletion of NK cells resulted in a severe relapsing EAE and the CNS pathology was more pronounced. Additionally the CD4+ T-cell activity was increased, which can be associated with a killing of these cells by NK cells (Hoglund & Maghazachi, 2014).

In patients with MS the frequency and functionality of NK cells is significantly decreased. Furthermore, these NK cells display an immature phenotype (Hoglund & Maghazachi, 2014; Duffy, Lees & Moalem-Tyler, 2014). In RRMS patients the functional of NK cells have been shown to be significantly lower (Duffy et al., 2014) and the reduced number of these cells was related to a higher relapse tendency (Hoglund & Maghazachi, 2014). There was also a correlation found between NK cell activity and lesions (Hoglund & Maghazachi, 2014; Duffy et al., 2014).
The successful immunomodulatory therapies provide additional evidence of a positive impact of NK cells in MS, as they correlate with a rescue of NK cell functions (Duffy et al., 2014).

For a long time the adaptive immune system was believed to cause MS. Recent research suggests that inflammation may follow initial axonal degeneration caused by a currently unknown factor. This hypothesis could be supported by the fact that disease progression is mainly caused by the amount of lost neurons (Hoglund & Maghazachi, 2014; Racke, 2009).

### 2.2 Epidemiology

MS affects approximately 2.5 million people around the world (Douglas et al., 2006; Döring et al., 2012).

MS usually manifests between the age of 20 to 40 years and is the most common cause of non-traumatic disability in young adults. (Döring et al., 2012). MS is also known to occur in prepubertal children and elder people, but such an early or late present of the disease is rather unlikely (Döring et al., 2012, Birnbaum, 2009,p.8). Lately the interest in and the knowledge of paediatric MS has been increasing (Douglas et al., 2006). Concurrent to the increased knowledge of paediatric MS patients the number of children diagnosed has risen, but the rates are still low affecting about 2-5% of the patients with MS (Birnbaum, 2009, p.124). Notably is, that the sexual bias given in adult MS is not as marked in paediatric MS, which “suggests, that, while the genetic implication of being female may influence MS risk, it appears to do so much more after puberty” (Douglas et al., 2006).

Women are more likely to develop the disease (Döring et al., 2012; White & Dressendorfer, 2004; Birnbaum, 2009, p.7). The sexual bias is most pronounced in patients with the relapsing-remitting form of MS, with a ratio of women to men at about 2-3:1. The difference is least pronounced in the primary-progressive form of MS (Birnbaum, 2009, p.8). These encountered differences between the genders suggest that “genetic and hormonal factors play a key role in defining susceptibility, especially genes on the X and the Y chromosomes” states Birnbaum (2009, p.8). Furthermore, hormonal factors and pregnancy can have an impact on the course of the disease, as well as it can be related to female-specific physiology (Ramagopalan et al., 2010). In females, menses and pregnancy also have an impact on the disease (Birnbaum, 2009, p.119). Males do not show gender unique aspects of MS but they seem to have more difficulties adapting to the diagnosis of MS than women (Birnbaum, 2009, p.120).
**Geographic distribution**

MS occurs worldwide, but the geographical distribution is uneven. There is data showing that the prevalence of MS varies with latitude. The rates rise as the distance from the equator increases (Birnbaum, 2009, p.9; Douglas et al., 2006; Zuvich et al., 2009). This uneven distribution might be related to a complex correlation between geography, genes and environment, which varies in the different latitudes.

Recent attempts to explain this geographical distribution state that the different environmental exposures occurring in different areas of the world affect the prevalence of MS essentially (Birnbaum, 2009, p.9; Douglas et al., 2006). Birnbaum (2009) outlines that “there are major differences in exposures to viral, bacterial, and parasitic agents in different geographic areas, as well as differences in the ages at which individuals are exposed to these agents” (p.7).

Next to different exposures the various amount of sun exposure may be a potential risk factor. While sunlight alone cannot be associated with risk, but interaction between sunlight and other factors, such as diet, may be so. Recent studies have focused on the connection between sun exposure and vitamin D deficiency (Zuvich et al., 2009).

Migration studies provided substantial information on the prevalence and incidence of MS in different geographic regions. Moving from a high-risk area to a low-risk area, or vice versa, has shown that living in a particular risk area before puberty establishes the risk for that individual. Moving to another risk area after puberty does not make a difference. These findings suggest that an early environmental event is important in determining susceptibility to MS (Birnbaum, 2009, p.7). Other studies suggest that the risk is not restricted to childhood and adolescent but can happen over many years (Gilden, 2005).

Gilden (2005) gives two possible explanations to the controversial epidemiological data: “The ‘prevalence’ hypothesis of MS suggests that the disease is most common where the causative agent is most widespread. By contrast, the ‘polio’ hypothesis suggests that acquisition of MS early in life […] reduces the likelihood that the agent will ever reach the CNS, but that primary infection after puberty or in adult life results in a small incidence of CNS infection, leading to MS” (p.196).

**Ethnic origin**

Although MS occurs worldwide it predominantly affects white-populations (Birnbaum, 2009, p.8; Douglas et al., 2006). Areas at medium or high risk for MS have mostly white population and in countries with both white and non-white populations, the MS rates are lower in the non-
Some ethnic groups, [such as Native American Indians, Inuit and African American,] are relatively resistant to developing MS, states Birnbaum (2009) and adds that “relatively segregated ethnic groups, such as the Hutterites, also are resistant to MS, even though they live in high-risk geographic areas” (p.8). Observing these race-specific differences provide strong evidence for the role of genes in determining susceptibility to MS (Birnbaum, 2009, p.8).

2.3 Causes of MS
The etiology of MS is still unclear. There are presumptions, that MS “may be a syndrome and not a disease, with different pathogenic pathways leading to CNS demyelination and axonal loss” explains Birnbaum (2009, p.8). Various factors, such as genes, genetic infectious, environmental and/or autoimmune factors, and combinations of these factors are believed to contribute to disease onset (White & Dressendorfer, 2004).

The hypotheses that received most attention throughout the past years that could explain the development of MS are discussed below.

Genetics

Recent studies emphasize the assumption that genes have a major role in determining susceptibility to MS (Birnbaum, 2009, p.9).

Some of the geographic variations of MS may occur due to a genetic predisposition. To follow those hypotheses family and twin studies have been conducted and have shown that there is a strong genetic component underlying the etiology of multiple sclerosis (Zuvich et al., 2009). About 25% of patients diagnosed with MS have family members with the disease (Birnbaum, 2009, p.9), with the highest risk for those genetically identical (Zuvich et al., 2009). The concordance rates for identical twins (30-40%) are higher than those in non-identical twins (3-4%) and other siblings (Birnbaum, 2009, p9; Zuvich et al., 2009; Compston & Coles; 2008).

Specific studies of the genetic typing have shown that particular genes of the major histocompatibility complex (MHC genes) are associated with the development of MS (Zuvich et al., 2009; Birnbaum, 2009, p9). Birnbaum (2009) outlines the coherence of genes and the immune system in patients with MS as following: “the common thread is that class II MHC genes play a major role in immune system functioning, supporting the hypotheses that MS is associated with a particular pattern of the immune responses […] These in turn, lead to CNS tissue destruction.”

Further investigations have shown that the HLA types seem to have the strongest genetic effect in MS (Ramagopalan et al., 2010; Zuvich, McCauley et al., 2009; Hauser & Oksenberg,
Recent studies suggest that the HLA-DRB1 gene may have the strongest influence and furthermore that “trans HLA-DRB1 allelic interactions may determine the balance between susceptibility and resistance” explained Hauser and Oksenberg (2006) the association of MS with HLA – DRB1 genes (p.64). But the exact mechanisms by which the HLA - DRB1 gene influences susceptibility to MS remain undefined (Hauser & Oksenberg, 2006). It is likely that more complexity at the HLA region exists than has been described to date and that further research will show more associations (Ramagopalan et al., 2010). Since the HLA-DR1 genes alone cannot be responsible for the genetic influence on MS the search for additional influencing genes has been given a lot of attention, but has yet leaked to be successful especially due to the small sample sizes used (Zuvich et al., 2009).

**Environmental Factors**

The geographic distribution of MS leads to the conclusion that environmental factors play a significant role in determining susceptibility to MS.

Studies have shown a broad range of environmental exposures that could influence the susceptibility to MS. These exposures include viral and bacterial infections, nutritional and dietary factors, well water consumption, exposure to animals, trauma due to accident or surgery, pollution, solar radiation, temperature, chemical agents and organic solvents among others (Hauser & Oksenberg, 2006). The many exposures identified underline the heterogeneity of factors involved in the process of developing MS.

One of the most frequently studied hypothesis deals with viral influences on MS. Viruses are said to be the biologically most plausible infectious agents related to MS pathogenesis (Hauser & Oksenberg, 2006). At one time or another viruses like measles, rubella, mumps and the herpes virus, including Epstein Barr virus (EBV) have been proposed as a causative MS agent (Hauser & Oksenberg, 2006). The strong suggestion of a significant role of infectious agents in the literature is encouraged by the fact that the exposure to infectious agents varies with latitude (the coherence between geographic distribution and the prevalence of MS that lead to this hypotheses is described above). But the most important evidence supporting the hypothesis of infections causing MS is that the brain and the cerebrospinal fluid of patients have high concentrations of Immunoglobulin G (IgG) (Gilden, 2005). Other findings showed that viral infections frequently precede relapses in patients with MS. The possibility of IFN-γ production during infections may trigger immunopathological events leading to demyelination (Buc, 2013).
**Herpesvirus**

Two human herpesviruses have been associated with MS: human herpesvirus 6 (HHV-6) and Epstein-Barr virus (EBV) (Gilden, 2005). The seroconversion to both herpesviruses happens before or during puberty into adult life – matching the “polio” hypothesis for the time of exposure to the disease causing agent of MS (Gilden, 2005).

**Epstein-Barr virus**

Among all viral agents related to susceptibility of MS EBV has gained most notable scientific interest (Kakalacheva & Lünemann, 2011). Gilden (2005) quotes that “all patients with MS have antibody against EBV, compared with 86-95% of controls. Whether infection with EBV is a prerequisite for the development of MS or whether 100% seropositivity for EBV is a consequence of MS is not known" (p.199). The difference in seropositivity is even more pronounced in pediatric MS: patients with pediatric MS carry 83% seroprevalence compared to 42% in controls. In contrast a substantial fraction of children with MS is seronegative for EBV (Kakalacheva & Lünemann, 2011). Antibodies against the EBV nuclear antigen 1 increase several years before the onset of neurological symptoms of MS (Ramagopalan et al., 2010). Although the findings suggest a strong relationship between the EBV and MS the IgG in brain and CSF in MS patients cannot be directly linked to EBV (Gilden, 2005). It can be said that there is “strong epidemiological evidence linking symptomatic EBV infection with MS development rendering the virus a major candidate for MS initiation” conclude Kakalacheva and Lünemann (2011) and add that further experiments are needed.

**Human - Herpesvirus 6**

Another herpesvirus that has been connected to MS is the human-herpesvirus 6 (HHV-6). Studies demonstrated the presence of HHV-6 in serum, CSF, brain tissue and in MS lesions (Milo & Kahana, 2009; Kakalacheva & Lünemann, 2011). The hypothesis that HHV-6 is related to MS is strengthened by the fact that the virus leads to severe neurological complications and leads to infections in T lymphocytes (Kakalacheva & Lünemann, 2011). Some studies also suggest that the frequency of reactivation of this virus in MS patients is greater than in healthy individuals (Milo & Kahana, 2009). Even though the hypothesis suggests an influence of HHV-6 on MS there is no epidemiological evidence of an HHV-6 infection increasing the risk for developing MS. Nonetheless there are suggestions that bystander reactivation of HHV-6 could potentially augment CNS inflammation (Kakalacheva & Lünemann, 2011).
**Chlamydia pneumoniae**

Chlamydia pneumoniae is very common among neurological diseases. In patients with MS 97% have positive PCR for the virus. The high titres of antibodies found in the serum of MS patients indicate that MS patients might be less able to clear the organism from the CNS (Kakalacheva & Lünemann, 2011). However those antibodies could not be significantly correlated with disease duration, disease course, clinical or MRI disease activity, disability, or presence of oligoclonal IgG (Gilden, 2005). Overall many studies examined the relationship between Chlamydia pneumoniae but the exact correlation could not be determined.

Hauser and Oksenberg (2006) sum up that the “attempts to isolate the causative environmental trigger(s) in MS have been largely unproductive and have failed to provide breakthrough insights into mechanisms of disease susceptibility and pathogenesis”. This again provides evidence for heterogeneity operating at the level of causative factors. Although “the expectation that any single agent would have enough specificity and universality to account for all cases of this disease seems unlikely” the possibility exists that “a previously undetected agent could be responsible for MS” (p.66).

**Vitamin D**

The effects of vitamin D levels on MS pathogenesis have lately gained scientific notice. Kakalacheva and Lünemann (2011) explained that “vitamin D is a potent immunomodulator affecting proinflammatory pathways as well as the number and activity of regulatory T cells” and therefore has an possible influence on the susceptibility of MS (p.3726).

Findings from epidemiological studies showed that the MS prevalence rises with an increased distance to the equator indicate a correlation to sunlight exposure. Further investigations on the topic have revealed that populations situated at high latitudes but having high consumptions of vitamin D rich food seemed to have reduced MS prevalence. Furthermore, the risk of MS incidence decreases with movement from high to low altitudes (Kakalacheva & Lünemann, 2011).

Studies also have shown that there is a possible link between prenatal sun exposure and the risk of MS. A study revealed that significantly fewer MS patients were born in November, while the incidence of MS was way higher for people born in May (Kakalacheva & Lünemann, 2011; Ramagopalan et al., 2010).

Vitamin D was also linked with T cells. Kakalacheva and Lünemann (2011) explain that T cells are described to carry vitamin D receptors and therefore “direct T cell inhibition is another
hypothesized molecular mechanism of vitamin D effect on MS pathology” (p.3726). Another connection that was drawn between MS and vitamin D is that seasonal variations in vitamin D levels inversely correlate with relapse rate. A low level of vitamin D was associated with relapses and degree of disability as measured by EDSS (Kakalacheva & Lünemann, 2011).

Ramagopalan et al., (2010) suggest that vitamin D supplementation might have the greatest effect on prevention of MS, due to the large number of people suffering from vitamin D deficiency (p.731). Nonetheless, the exact molecular mechanisms underlying the effect of vitamin D in MS remain unclear and require further investigations (Kakalacheva & Lünemann, 2011).

2.4 Pathophysiology

2.4.1 Course
The course of the disease varies strongly and even if some patients experience little disability during their lifetime, up to 60% are no longer fully ambulatory 20 years after onset (Douglas et al, 2006). Although the course of MS varies there are some general patterns of MS that must be identified, “since they imply certain pathophysiologic processes and indicate the use of particular disease-modifying therapies” (Birnbaum, 2009, p.15). The following categories are not clean and often overlap. Additionally the clinical patterns only tell part of the story and are based almost completely on the recollections of the patients and the skill of the neurologic examiner (Birnbaum, 2009, p.15). Ramagopalan et al., (2010) describe that “the current understanding of MS development is that RIS [radiologically isolated syndrome] leads to CIS [clinically isolated syndrome] and then eventually to MS (p. 733).

Relapse

Birnbaum (2009) defines a relapse as following: “Biologically, an MS relapse […] is defined as a clinical worsening due to a new or expanding area of CNS inflammation. Clinically, the change in neurologic symptoms and signs should persist for more than 48 hours” (p.71). A more specific definition of an attack or relapse is given by McDonald (2010) and further discussed in chapter 2.5.
**Radiologically isolated syndrome**

Some patients showing pathological features of MS at post mortem or having an MRI scan that is highly suggestive of MS never show signs or symptoms of the disease and therefore are never diagnosed with MS (Ramagopalan et al., 2010). These patients have radiologically isolated syndrome (RIS) and are at a higher risk of developing CIS and MS.

Some sources reported that 30-40% of patients diagnosed with RIS have another clinical events and therefore are diagnosed with CIS or MS (Miller et al., 2012).

**Clinically isolated syndrome**

The clinically isolated syndrome (CIS) is the earliest accessible timepoint for MS studies (Ramagopalan et al., 2010). CIS is defined as the first clinical episode in which the patient has symptoms and signs suggestive of an inflammatory demyelinating disorder of the CNS (Miller et al., 2012). In order to be able to make a diagnosis of CIS some criteria must be met. The episode should last at least 24 hours and should not show signs of fever or infection. Typically, CIS has an acute or sub-acute onset, which reaches a peak within 2-3 weeks. CIS is isolated in time as well as in space. Another characterization is the presence of a lesion that can be located in the optic nerve, spinal cord, brainstem, cerebellum or cerebral hemisphere (Miller et al., 2012; Ramagopalan et al., 2010).

The rate of patients with CIS converting to MS varies between the location of the lesions. Studies suggest that the chance of developing MS when there are lesions present in CIS is 60-80%. Factors that influence the presenting of a second attack are the number of lesions as well as the Barkhof criteria, which takes the number of lesions as well as the location of these lesions into account (Miller et al., 2012).

At the time of CIS presentation it is possible to diagnose MS in some patients, if the clinical features of the CIS are characteristic of MS. MRI alone is not a predictive factor as similar MRI results can be seen in other disorders (Miller et al., 2012).

**Relapsing-remitting MS**

The relapsing-remitting MS is the most common clinical pattern in patients with MS affecting approximately 80% of the patients at least once in their lifetime (Douglas et al., 2006; Birnbaum, 2009, p.15; Zuvich et al., 2009). The characteristics of this course are unpredictable relapses, during which new symptoms appear or existing symptoms become more severe. The
onset of these neurological changes can be rapid. The symptoms can appear over several hours or last for days, weeks and even months. The relapses can resolve completely (total recovery appears early in the disease = remitting) or only partial (as the disease progresses recovery to baseline becomes less common). Symptoms can also affect the patients permanently. The frequency of attacks varies considerably and may appear inactive for months or years (fig. 1). In the relapsing-remitting phase of the disease patients are usually younger at onset. Predominantly those patients are women and they respond well to both acute anti-inflammatory treatments and long-term immune-modulating therapies (Douglas et al., 2006; Birnbaum, 2009, p.15; Zuvich et al., 2009).

If the recovery of the relapses decreases patients may enter a progressive phase. The progressive phase can be distinguished in a secondary progressive phase and a primary progressive phase.

**Secondary progressive MS**

More over 50% of the individuals with relapsing-remitting MS have a change in patterns within 10 years and 80% within 20 years of disease onset (Douglas et al., 2006; Birnbaum, 2009, p.16). The frequency of relapses decreases and eventually stops. But as contrasted to the relapsing-remitting course of MS the relapse does not resolve, but is followed by an insidious, gradual progression of their disabilities. Characteristically for a secondary progressive course relapses still occur. In many cases the transition, which can be rapid or gradual, cannot be separated clearly (fig. 1). Patients who show characteristics of both relapsing-remitting and
Secondary progressive phase can be classified as having “transitional disease”. In the secondary progressive phase patients have less inflammatory changes on their MRIs. Consequently anti-inflammatory drugs are much less effective in this phase of the disease. Also long-term immune-modulating therapies have shown to be ineffective (Douglas et al, 2006; Birnbaum, 2009, p.16).

*Primary progressive MS*

The main characteristic of primary progressive MS is a lack of distinct attacks. Instead a primary progressive pattern shows a slow onset and steadily worsening of symptoms. Primary progressive MS affects 10-15% of all MS patients (Douglas et al., 2006; Birnbaum, 2009, p.16). As contrasted to the two phases described before the symptoms in primary progressive MS appear gradually, over months to years (fig. 1). The intensity of these symptoms may vary and depends on fatigue, hot weather or infections. Relapses, as can be seen in the relapsing-remitting and secondary progressive phase, do not, by definition, precede the onset of neurological difficulties, neither do acute changes in neurologic function (Birnbaum, 2009, p.17). The primary progressive MS is characterized by later onset with patients aged between 40-60 and a gender distribution of 50:50. “The most common symptoms at onset reflect spinal cord dysfunction. Most commonly there is a progressive lower extremity weakness [...]. In addition, changes in bowel, bladder, and sexual function are common” is the symptom specification provided by Birnbaum (2009, p.17). The course of disease varies greatly between the individual patients. Some experience significant disability within 1-2 years, whereas others progression is indolent (Douglas et al., 2006; Birnbaum, 2009, p.16).

*Progressive-relapsing MS*

Progressive-relapsing MS occurs in about 5% of the cases and features characteristics from both progressive and relapsing forms of MS. This course is characterized by progressive disability from onset of symptoms but also involves acute attacks and relapses (Birnbaum, 2009, p.17; Zuvich et al., 2009).

*Bening MS*

Bening MS is a relapsing-remitting type of MS pattern, that is either mild or non existing after a long period. Even though the patients are clinically diagnosed with MS, they experience no disability from their CNS disease (Birnbaum, 2009, p.16; Douglas et al., 2006).
2.4.2 Prognostic factors
Even though MS is an unpredictable condition, some factors can provide a better outlook. For example are long intervals between attacks and good recoveries from attacks in the relapsing-remitting phase better prognostic indicators (Birnbaum, 2009, p.15). On the other hand, multisite symptoms and poor recovery from an initial episode may indicate a worse outcome (Douglas et al., 2006). Studies on sexual biases additionally have observed that males experience a more severe course than females (Douglas et al., 2006). Experience also has shown that the development of a large number of lesions during the initial year is strongly associated with a greater risk of disability occurring years later (Hauser & Oksenberg, 2006).

2.5 Diagnosis and Classification
Although the phenotype of MS has been carefully defined, a diagnosis remains difficult as there are no reliable specific laboratory tests for MS (Zuvich et al., 2009). Therefore clinical and paraclinical evidence supported by many tests such as magnetic resonance imaging (MRI) is essential for diagnosis (Douglas et al., 2006; Zuvich et al, 2009).

The definition of MS diagnosis states that “a definite diagnosis of MS requires two different areas of the CNS being affected by inflammation in the form of lesion or plaque formation with two separate occurrences of an “attack” […]” (Zuvich et al., 2009).

Additionally to the definition the International Panel on MS Diagnosis presented revised diagnostic criteria for MS, which became known as the McDonald criteria (McDonald et al., 2010).

2.5.1 McDonald criteria
The McDonald criteria are a worldwide accepted and most commonly used system of classification that incorporates clinical and laboratory elements. The McDonald criteria allow an earlier confirmation of the diagnosis and therefore make an earlier decision about starting disease modifying therapies possible (Murray, 2006; Birnbaum, 2009, p.54).

The panel clarified terms for future diagnostic purposes. Most important the broad definition of an attack was clarified and defined as “an episode of neurological disturbance of the kind seen in MS, when clinicopathological studies have established that the causative lesions are inflammatory and demyelinating in nature. […] An attack, defined either by subjective report or by objective observation, should last for at least 24 hours.” (McDonald et al., 2001).

The most important criteria from the Panel were summarized by Zuvich et al. (2009): “
1) Objective abnormalities must be present causing dysfunction in the CNS
2) These abnormalities must involve the white matter long tracts
3) Two or more areas of the CNS must be affected
4) The clinical pattern must either involve two or more separate episodes, each lasting 24h and at least 30 days apart, or a slow or step-wise progression of disability over 6 months and an abnormal spinal fluid screen, in which the CSF would contain oligoclonal bands and increased production of immunoglobulin (IgG)
5) The age of onset should be between the ages of 10 and 60
6) The symptoms experienced cannot be attributed to another neurological disease.” (p.330).

Table 1: McDonald criteria for MS diagnosis (McDonald et al., 2010)

<table>
<thead>
<tr>
<th>Clinical (Attacks)</th>
<th>Lesions</th>
<th>Additional Criteria to Make DX</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 or more</td>
<td>Objective clinical evidence of 2 or more lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack</td>
<td>None. Clinical evidence alone will suffice; additional evidence desirable but must be consistent with MS</td>
</tr>
<tr>
<td>2 or more</td>
<td>Objective clinical evidence of 1 lesion</td>
<td>Dissemination in space, demonstrated by ➢ ≥1 T2 lesion in at least two MS typical CNS regions (periventricular, juxtacortical, infratentorial, spinal cord) OR ➢ Await further clinical attack implicating in a different CNS site</td>
</tr>
<tr>
<td>1</td>
<td>Objective clinical evidence of 2 or more lesions</td>
<td>Dissemination in time, demonstrated by ➢ Simultaneous asymptomatic contrast-enhancing and non-enhancing lesions at any time; OR ➢ A new T2 and/or contrast-enhancing lesion(s) on follow-up MRI, irrespective of its timing; OR ➢ Await a second clinical attack</td>
</tr>
<tr>
<td>1</td>
<td>Objective clinical evidence of 1 lesion</td>
<td>Dissemination in space, demonstrated by ➢ ≥1 T2 lesion in at least two MS typical CNS regions (periventricular, juxtacortical, infratentorial, spinal cord); OR ➢ Await further clinical attack implicating in a different CNS site AND Dissemination in time, demonstrated by ➢ A new T2 and/or contrast-enhancing lesion(s) on follow-up MRI, irrespective of its timing; OR ➢ Await a second clinical attack</td>
</tr>
<tr>
<td>0 (progression from onset)</td>
<td>One year of disease progression (retrospective or prospective) AND at least 2 out of 3 criteria: ➢ Dissemination in space in the brain based on ≥T2 lesion in periventricular, juxtacortical or infratentorial regions; ➢ Dissemination in space in the spinal cord based on ≥2 T2 lesions OR ➢ Positive CSF</td>
<td></td>
</tr>
</tbody>
</table>
The McDonald criteria also integrate magnetic resonance imaging to demonstrate multiple areas of involvement and also involvement over time with the appearance of new enhancing lesions to the diagnostic scheme (Zuvich et al., 2009; Murray, 2006). The McDonald criteria are revised on a regular basis (latest update 2010- table 1).

Various test are used to provide accurate diagnosis of MS. Up to date there is no single test that could provide an accurate diagnosis of MS.

*Magnetic resonance imagining (MRI)*

Magnetic resonance imagining (MRI) technology had a big impact on the diagnosis of MS. The MRI scans are used to examine the brain and spinal cord for multiple, asymmetrically located lesions, both active and old (Zuvich et al., 2009; Hauser & Oksenberg, 2006). The changes seen on MRI are based on changes in the proton density, which are caused by multiple reasons such as aging, migraine, high blood pressure, infections and head injuries to name a few. The “spots” seen on MRI are often mistaken for lesions and therefore no MS diagnosis should be based only on MRI results (Birnbaum, 2009, p.21 & 40). Important for establishing a diagnosis is not the presence of “spots”, but their shape and location (as many inflammatory lesions form around veins they are often oval shaped and oriented perpendicular to the axes of the ventricles) (Birnbaum, 2009, p.29). Overall, MRI has greatly increased the ability to diagnose MS and to follow the course of the disease as well as it helps determining an individual’s response to disease-modifying therapy (Birnbaum, 2009, p.24).

### 2.5.2 Neurological exams

*Evoked potentials*

Evoked potentials are used to measure the rate of conduction and the amplitude of the nerve impulse of the visual, sensory posterior column and motor systems (Palace, 2001). For the diagnosis of MS visual evoked potentials are most conclusive. Delay is indicative of demyelination and a reduction in amplitude can occur due to conduction block and dispersion, as well as from axonal damage (Palace, 2001). Furthermore evoked potentials can help to indentify silent lesions (Hauser & Oksenberg, 2006).
**Lumbar puncture**

Typically for inflammatory diseases the oligoclonal banding (OCB) in the CSF of up to 90% of MS patients will show changes. The lumbar puncture or spinal test is performed to identify these abnormalities and mostly these changes include the number and type of white blood cells, glucose levels and the levels of various proteins (Zuvich et al, 2009). This phenomena can be seen in many inflammatory diseases. But it has been shown that OCB patterns are remarkably stable within patients with MS over many years, although the absolute concentrations of IgG may decrease. It therefore can be assumed, that the OCBs are representing a specific immunological reaction within the CSF (Palace, 2001).

Early in the course of disease, when CSF changes can be of greatest value in supporting a diagnosis of MS, the CSF can be normal. (Birnbaum, 2009, p.44).

### 2.5.3 Expanded Disability Status Scale

Once diagnosed with MS the severity of the disease is quantified with the Expanded Disability Status Scale (EDSS). The EDSS is the most widely applied classification of neurological impairment in MS (White & Dressendorfer, 2004) and measures disability in eight functional systems: pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral, and other (Zuvich et al., 2009).

Zuvich et al. (2009) described the EDSS as following: “the scale ranges from 0.0 (normal neurological exam) to 10.0 (death due to MS). Measurements 1.0-4.5 indicate a person who is fully ambulatory, while 6.0-9.5 range indicates significant impairment.” Furthermore they explain that “this scale is not linear, some of the important landmarks include: 6.0, requires unilateral assistance; 6.5, requires bilateral assistance; and 7.0, restricted to a wheelchair” (fig. 2) (p.330).

![The Expanded Disability Status Scale (EDSS)](http://www.msatrium.com/evolutions-in-care/goals-of-therapy)
Although the EDSS is a very good attempt at quantifying MS disability it has also been criticized. Points of criticism include that it is a subjective measurement that can change frequently and the measurements do not include disease duration or the difference in rates of disease progression (Zuvich et al., 2009). Moreover the absence of adequate cognitive and visual components, the emphasis on ambulation status and the relatively reduced sensitivity in the middle and upper ranges of the score have been criticized (White & Dressendorfer, 2004).

Despite the given criticism of the scale the EDSS is used in this paper as an indicator of disability in patients with MS, as it is the most wildly applied classification of impairment and it is used in most papers.

2.6 Symptoms in Multiple Sclerosis
Symptoms in MS vary between individuals and change during the progression of the disease. The symptoms depend on the localization and the characteristics of the CNS pathology. Most of the symptoms occurring in MS can be modified but only a few can be eliminated. Important variables that have to be considered when dealing with symptoms are the severity of symptoms, the duration and the ability to tolerate pain-relieving medications (Birnbaum, 2009, p. 97; Döring et al., 2012). As mentioned before MS is a heterogenic disease and the wide variety of symptoms occurring underline the heterogeneous of MS character once more.

*Initial Symptoms*

Initial symptoms vary wildly and their onset can be severe or as trivial that patients won’t seek medical attention for a long period of time. One or more of the following can be presenting symptoms: numbness, weakness, tremors, a sensory disturbance, monocular visual loss (optic neuritis), double vision (diplopia), gait instability, ataxia and changes of function, like increased difficulty with handwriting or doing up buttons, increased difficulty with walking, running or leg coordination, or difficulty tracking while reading (Hauser & Oksenberg, 2006; Birnbaum, 2009, p.37).

*Frequent Symptoms*

The symptoms of MS result from the interruption of myelinated tracts in the CNS and therefore, depending on where the interruption is located, can appear in multiple manifestations (Hauser & Oksenberg, 2006). Some of the most frequent Symptoms are discussed below.
**Fatigue**

Fatigue is a common symptom in MS. It affects 75-90% of the patients during disease progression (Döring et al., 2012) and 45% even describe it as the most disabling symptom (White & Dressendorfer, 2004). Although Fatigue is experienced in different ways, most commonly it is described as “an extreme general feeling of tiredness or lassitude inadequate to the preceding demand or as a muscle fatigue without exercise” (Döring et al., 2012, White & Dressendorfer, 2004). MS patients may experience fatigue during different activities at home or work. Next to systematic fatigue cognitive fatigue, as indicated by reduced attention, memory and information processing have also been reported.

As MS-related fatigue differs between the patients the pathophysiology remains unclear. The causes can only be suggested and the investigations range from immune and neuromuscular mechanisms to brain metabolism (White & Dressendorfer, 2004). One suggestion is that fatigue is a symptom that is not directly connected to the inflammation of the CNS. It can be the result from intrinsic CNS inflammation, but other confounding variables such as drug side effects, mood alterations, obesity, lack of restorative sleep and many more can lead to the development of fatigue (Birnbaum, 2009, p.98). What can be taken as guaranteed is the fact that fatigue worsens throughout the day and environmental heat and humidity can dramatically increase both systemic fatigue and exercise-related fatigue, whereas cooling typically alleviates symptoms (White & Dressendorfer, 2004).

Physiologically muscle fatigue in patients with MS can be explained by dysfunction of the motor system or because the central nervous system fails to drive the motor neurons sufficiently. Andreason et al. (2011) explained that “patients with MS have reduced muscle performance, and their muscles show characteristics of disuse such as reduced muscle fibre size and a shift in proportion of fibre types from type 1 fibres towards a greater proportion of type 2a and 2ax fibres”. Furthermore, a relationship between peripheral muscle fatigue and suboptimal output from the motor cortex has been established (Andreason et al., 2011).

**Depression**

More than 50% of MS patients are known to suffer from depression and one study showed, that there is a 7.5 times higher risk of suicide among patients with MS than the general population (White & Dressendorfer, 2005; Hauser & Oksenberg, 2006). The depression may develop from the initial MS diagnosis and the realization that the disease may progress to permanent disability. Another possible explanation of depression may be the progression of MS and the neuroendocrine changes may influence brain centers responsible for emotion and
contribute to emotional lability (White & Dressendorfer, 2004). Some medications used to treat MS can also lead to depressive episodes.

Spasticity

Spasticity significantly reduces the quality of life of individuals with MS, as it leads to limitations in the range of movements and results in malpositioning of the joints, as well as bowel emptying (White & Dressendorfer, 2004; Henze et al., 2006). MS specific spasticity is caused by axonal degeneration or malfunction within specific descending spinal tracts. This leads predominantly in weakness of physiological flexor muscles, usually with increased muscle tone (=spastic) (Henze et al., 2006). "Spastic paresis is an upper motor neuron impairment that involves exaggerated reflexes, resistance to passive stretch and muscle weakness" explained White and Dressendorfer (2004, p.1084). Henze et al. (2006) also mentioned that a possible positive effect of spasticity in MS is the enhancement of muscle weakness, which reduces stability of lower limbs (p.80).

Bladder and bowel symptoms

During their lifetime 80% of the patients will suffer from neurogenic bladder dysfunction (NBD). NBD can even be the presenting symptom of MS (Henze et al., 2006). The most common types of NBD include restricted storage capacity, urgency, increased frequency of micturition and incontinence.

Even though 70% of MS patients suffer from disturbances of bowel function, the connection to MS is often questionable, as it is very common in healthy individuals as well (Henze et al., 2006).

Sexual dysfunction

Sexual dysfunction is a problem patients often do not talk about and only confess if directly asked. 80% of patients will experience sexual dysfunction throughout the course of their disease. Sexual dysfunction affects men more frequently than women and is usually combined with bladder dysfunction (Henze et al., 2006). Sexual dysfunction in patients with MS can be divided in primary and secondary sexual dysfunction. Primary sexual dysfunction is caused directly by MS- related demyelination. Secondary sexual dysfunctions are the consequences of MS- specific symptoms such as fatigue, spasticity or bladder dysfunction (Henze et al., 2006). Sexual dysfunction can also be caused by drugs used to treat specific MS symptoms (Birnbaum, 2009, p.64).
2.7 Complications and comorbidities in MS
Complications and comorbidities can occur due to effects of the disease progress on organs. These consequences are often related to increasing disability in patients with MS. Some of the most common and challenging complications and comorbidities in patients with MS are discussed below.

Osteopenia/ Osteoporosis
A loss of bone density is common among patients with MS. MS patients often have problems ambulating and bearing weight and have difficulty walking. Therefore, they are at a higher risk of falling and with suffering from a loss of bone density, the risk of fractures increases (Birnbaum, 2009, p.59).

Altered Sleep Patterns
Sleep disturbances can be caused by weight gain due to decreased physical activity, nocturnal spasms, myoclonus, periodic limb movements, nocturia, MS-related medications and mood disturbances. The lack of sleep can contribute greatly to MS related fatigue (Birnbaum, 2009, p.61).

Mood Disturbances
Perhaps one of the most common comorbidities among people with chronic, maybe even disabling disease are mood disturbances. The disturbances range from depression, to anxiety, to stress, to panic attacks and any combination of those (Birnbaum, 2009, p.63). Reasons for mood disturbances are multiple and some can be a direct result of the disease process. Suicide rates are higher in MS patients than in the general population and therefore mood disturbances should be given adequate attention (Birnbaum, 2009, p.63).

Obesity
As seen with many other chronic diseases with decreased mobility obesity is a big problem in patients with MS.
3. Multiple Sclerosis treatment

3.1. Disease modifying Treatment (DMT)
Although MS is not curable several pharmacological treatments with immunomodulatory properties were developed to treat MS and modify its natural history. These are referred to as disease modifying therapies (DMT) and represent a major step in the control of the disease (Mendes & Sa, 2010; Finkelsztejn, 2014).

DMT should be initiated earliest. Some factors challenge the attempt to start treatment as soon as possible: Before the treatment can be started a correct diagnosis must be present. Furthermore, the right patients must be selected for the right treatment procedure based on disease activity and severity of the initial symptoms (Rieckmann et al., 2008; Kamm et al., 2014). Currently ten different disease modifying agents have been approved for MS treatment either by the US Food and Drug Administration (FDA) or by the European Medicines Agency (EMA). These DMT include four forms of interferon-β, glatiramer acetate, natalizumab, fingolimod, alemtuzumab, teriflunomide and dimethyl fumarate (Finkelsztejn, 2014; Castro-Borrero et al., 2012). Currently approved drugs for patients with MS are only available if the disease course is dominated by relapses. Therefore, approved drugs are only available for patients with CIS, RRMS and occasionally SPMS. Currently no approved treatment is available for PPMS (Kamm et al., 2014).

Drug based treatments can be distinguished in relapse treatment, symptomatic treatment as well as disease-modifying treatment consisting of basic treatment and escalating treatment (Kamm et al., 2014; Döring et al., 2012). Typically treatment is started with basic therapeutics, although escalating therapeutics can also be considered as first-line therapy in patients with very active MS. After treatment start the patient is monitored clinically with subsequent MRI and if the disease is stable and the treatment well-tolerated by the patient the chosen therapy is continued. If the course of the disease worsens escalation therapy can be started. It is well established to take patients into account for a treatment shift if they have more than one relapse per year, complete recovery from relapses are absent, the EDSS worsens and the MRI shows progression. These patients are considered “treatment nonresponders” (Kamm et al., 2014).

The EAE model has been extremely valuable for the development and testing of drugs, even though some treatment strategies are effective only in EAE and could even exacerbate MS in patients (Hemmer et al., 2006).

As for the inflammatory characteristics of the disease an immune response targeting treatment approach is most wildly used in patients with MS (Hemmer et al., 2006).
The following description of the most common pharmacological treatments in MS is included into my thesis as there can occur possible negative interactions between the drugs and the training routine chosen as exercise therapy. This should not be considered a complete list of DMT, but should provide additional information on standards in MS treatment.

Table 2: Current DMD in MS care (Kamm et al., 2014, p. 137)

<table>
<thead>
<tr>
<th>Drug (brand name)</th>
<th>Approval</th>
<th>Indication</th>
<th>Dosage/application</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Basic therapeutics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFN-β- 1b</td>
<td>1995</td>
<td>CIS, RRMS, SPMS</td>
<td>250 μg s.c. every other day</td>
<td>Flu-like symptoms, injection site reactions, elevated liver enzymes</td>
</tr>
<tr>
<td>(Betaferon/ Betaseron)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFN- β- 1a</td>
<td>1997</td>
<td>CIS, RRMS</td>
<td>30 μg i.m. once weekly</td>
<td>Flu-like symptoms, injection site reactions, elevated liver enzymes</td>
</tr>
<tr>
<td>(Avonex)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>1997</td>
<td>CIS, RRMS</td>
<td>20 mg s.c. daily</td>
<td>Injection site reactions, immediate postinjection systemic reaction</td>
</tr>
<tr>
<td>(Copaxone)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFN- β- 1a</td>
<td>2002</td>
<td>CIS, RRMS, SPMS</td>
<td>44 μg s.c. three times weekly</td>
<td>Flu-like symptoms, injection site reactions, elevated liver enzymes</td>
</tr>
<tr>
<td>(Rebif)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Escalation therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Natalizumab</td>
<td>2007</td>
<td>Highly active RRMS</td>
<td>300 mg i.v. every 4 weeks</td>
<td>Allergic infusion reactions, PML</td>
</tr>
<tr>
<td>(Tysabri)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fingolimod</td>
<td>2011</td>
<td>RRMS</td>
<td>0.5 mg p.o. once daily</td>
<td>(Brady-) arrhythmias, FEV&lt;sub&gt;1&lt;/sub&gt; reduction, macular edema</td>
</tr>
<tr>
<td>(Gilenya)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>2002</td>
<td>Highly active RRMS or SPMS</td>
<td>12mg/m² BS i.v. every 3 months; maximum lifetime cumulative dose 140 mg/m² BS</td>
<td>Nausea, vomiting, alopecia, therapy-related leukemia, cardiotoxicity</td>
</tr>
<tr>
<td>(Novantron, Mitoxantrone Ebewew)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CIS= Clinically isolated syndrome; FEV<sub>1</sub>= forced expiratory volume in 1 s; BS= body surface.

3.1.1. Relapse treatments
Relapse treatment aims to shorten the duration of a relapse and to allow better healing. Relapse duration can usually be controlled whereas it is uncertain whether a healing process with little to none residua remaining can be achieved. Most commonly, exacerbations in patients with MS are treated with corticosteroids. Corticosteroids can be administered orally or intravenously and may lead to a variety of side effects like insomnia, abdominal discomfort, fluid retention, mood changes, elevated blood sugar levels, elevated blood pressure and heart rate and muscle soreness. If corticosteroid treatment fails second – line treatments like IV IgG and plasmapheresis can be considered (Birnbaum, 2009, p.72-74).

3.1.2 Symptomatic Treatment
The specific treatment of symptoms in patients with MS is an essential component of the overall management of the disease. The aim of symptomatic treatment in patients with MS is to eliminate or reduce the symptoms that lead to impairment of functional abilities and quality
of life. Secondary impairment or disability is to be avoided (Henze et al., 2006; Correia de Sa et al., 2011).

As MS related symptoms are only recently getting more recognition many drugs and treatment methods that are widely used in MS symptomatic treatment are still off-label in most countries. Many treatment regimes and drugs are lacking a proper clinical trial and are therefore not approved by the respective American or European health authorities (Henze et al., 2006; Correia de Sa et al. 2011). Consensus guidelines for the treatment of MS symptoms are needed in order to ensure optimal treatment for affected patients (Henze et al., 2006).

Treatment strategies include physiotherapy, drug treatment and in some severe cases surgery. Exercise training is currently not an acknowledged treatment strategy for MS patients.

3.1.3. Basic treatments
Immunomodulatory therapy is commonly used as first-line therapeutics in patients with MS and has more than 20 years of experience in some countries. Four IFN-β and one glatiramer acetate preparation belong to this group of drugs. Because of the reduction of the annualized relapse rate (ARR) by approximately 30%, the reduction of inflammatory activity and lesion load (measured by MRI) as well as favorable long-term safety profiles and no severe side effects these drugs are the first choice treatment for most (Finkelsztejn, 2014; Kamm et al., 2014; Hemmer et al., 2006; Mendes & Sa, 2011). The position of the first-line therapeutics in their current form (injections) is challenged by the development of oral drugs, which would increase the quality of life for many patients significantly (Finkelsztejn, 2014).

*Interferon β (IFN-β)*
Interferons are proteins secreted by cells and are involved in self defense to viral infections, the regulation of cell growth and the modulation of immune responses (Mendes & Sa, 2011). IFN-β was the first therapy (established 1993 in the USA and 1995 in Europe) to have proven beneficial effects on the natural course of MS and remains the most wildly used treatment in patients with MS (Mendes & Sa, 2011; Buc, 2013).

IFN-β has multiple immunomodulatory effects mostly targeting T- and B-cells and is used as first-line agents in MS treatment. Generally, two molecules of IFN-β are beneficial for patients with MS: INF-β 1a and IFN-β 1b (Mendes & Sa, 2011). IFN-β 1b is self injected by patients every other day with a dosage of 250 μg. The dosage of IFN-β 1a depends on the brand: Avonex is dosed in 30 μg once a week and Rebif in 44 μg three times a week. IFN-β 1b and IFN-β 1a (Rebif) are indicated for patients with RRMS, SPMS and CIS, whereas IFN-β 1a
(Avonex) is indicated for CIS and RRMS only (Mendes & Sa, 2011; Kamm et al., 2014). The treatment with IFN-β leads to a reduced clinical relapse rate and to a confirmed one point EDSS rate decrease.

As mentioned above IFN-β has an impact on the immune system by producing effects on T- and B-cells and influence on the BBB permeability (Mendes & Sa, 2011). IFNs are believed to inhibit antigen presentation. In patients with MS IFN-β decreases T-cell production of IFN-γ and/or counteracts effects of IFN-γ (Finkelsztejn, 2014; Mendes & Sa, 2011). IFN-β further has an impact on the activation of autoreactive T-cells. The T-cell activation is reduced by the downregulation of the expression of MHC class II, which leads to a decreased peptide presentation to T-cells (Buc, 2013; Mendes & Sa, 2011). T-cell trafficking is reduced by IFN-β treatment. On one hand the transmigration of activated T-cells into the CNS is decreased by interaction with VLA4 adhesive molecules (Buc, 2013; Finkelsztejn, 2014). On the other hand the trespassing of T-cells into the brain through the BBB is inhibited (Mendes & Sa, 2011).

Some authors also suggested an influence on T-helper cells. IFN-β is by some believed to cause a shift from Th1 to Th2 cells, specifically in cytokine production (Finkelsztejn, 2014; Hemmer et al., 2006). Another suggestion that has been made is the influence of IFN-β on the activities of Treg-cells (Buc, 2013; Mendes & Sa, 2011).

The investigation of blood in patients with MS also showed antiviral properties of IFN-β. MS duration was directly linked to the viral load found in the blood and within 3 months of IFN-β treatment the levels of viral load fell below detection limits (Mendes & Sa, 2011; Hemmer et al., 2006). Some studies issued more positive effects of IFN-β. For example they promote potential neuroprotective effects of IFN-β (stimulation of self-protection of neurons, release of nerve growth factors) and partially reversion of axonal injury (Mendes & Sa, 2011).

IFN-β is also known for the upregulation of B-cell survival factors. This could effect some patients negatively and therefore might explain controversial therapeutic responses from patients (Mendes & Sa, 2011).

Generally IFN-β is well tolerated by patients. Most common reactions shown from patients are flu-like symptoms and injection-site reactions. Furthermore, elevated liver enzymes may be observed (Mendes & Sa, 2011; Kamm et al., 2014). A factor that has to be taken into account when treating patients with IFN-β1a is the development of neutralizing antibodies (NABs). IFN-β1a is considered to be less immunogenic than the other interferons (Rieckmann et al., 2008).
Glatiramer acetate (GA)

Glatiramer acetate (GA) is a synthetic polypeptide of four amino acids found in myelin basic protein (L-glutamic acid, L-lysine, L-alanine and L-tryosine). Although several mechanisms of action have been proposed, the biological effects of GA are not fully understood yet. It has however been proven, that GA affects the T and B cells and antigen presenting cells (Mendes & Sa, 2010; Buc, 2013).

GA belongs to the first lineage of drugs used to treat MS. The treatment is approved since 1997 in a daily 20mg subcutaneous dosage for patients with RRMS and CIS (Mendes & Sa, 2011; Kamm et al., 2014). Reduced relapse rates, inflammatory activities and lesion load measured by MRI can be seen after GA treatment (in responders) (Hemmer et al., 2006).

The complex mechanism of GA activity may be explained by different interdependent processes that result in the inhibition of pro-inflammatory activities. GA activated cells (glatiramer specific T-cells) migrate into the CNS and develop anti-inflammatory and neuroprotective activities as they produce neurotrophic factors (Buc, 2013; Finkelsztejn, 2014; Hemmer, Nessler et al., 2006; Mendes & Sa, 2011). These neurotrophic factors might also favor remyelination and axonal protection (Mendes & Sa, 2011). Furthermore, GA is believed to interfere with the activation of specific T-cells against myelin protein. Macrophages under GA influence produce less IL 1, TNF and IL12, the later one supporting the polarization of naïve T-cells into Th1 subsets (Buc, 2013; Finkelsztejn, 2014; Hemmer et al., 2006). GA promotes further anti-inflammatory activities by inducing a shift in glatiramer-reactive T-cells from Th1 to Th2 phenotype (Finkelsztejn, 2014) and supporting suppressive activities of Treg cells (Buc, 2013).

GA is considered to be generally safe. The most common side effects are injection site reactions. Some patients also reported post-injection systemic reaction of flushing, chest tightness, dyspnea, chest palpitations and anxiety (Mendes & Sa, 2011; Kamm et al., 2014).

Failure of basic immune-modulatory treatments

The assessment of the efficacy of immunotherapy is based on observations of the patients during the first year of treatment utilizing standard MS scales. Rieckmann et al. (2008) suggest to carry out clinical evaluations every three months in order to ensure an optimal tolerance of and adherence to treatment and furthermore establish a confident patient-physician relationship. The physician receives a continuous feedback on the clinical activity of the patients. It is important to take side-effects of injectable treatments and hidden symptoms,
such as depression or urinary tract infection, into account as they may mimic treatment failure (Rieckmann et al., 2008).

Rieckmann et al. (2008) sum up the criteria developed by US MS centers to define treatment failure: “US MS centers [...] included relapse rates of either one per year or unchanged from pretreatment rates, incomplete recovery from multiple attacks, evolution of polyregional neurologic involvement, recurrent brainstem or spinal cord lesions, and cumulative loss of neurologic function sufficient to disrupt daily activities [to determine treatment failure]" (p.182-183).

The first step taken if patients show suboptimal response to first-line disease-modifying therapy is to exclude other reasons such as hidden symptoms, to improve symptomatic treatment and to reduce side effects. If this doesn't lead to improvement patients treated with IFN-β should be treated with a higher dosage and frequency. Furthermore, in primary nonresponders the basic treatment may be switched to another modality. The different pathogenic mechanisms may operate, while others don’t. A study has shown that 3 years after switching from either GA to IFN – β or vice versa 56-81% of the patients were relapse-free due to a suboptimal response to the initial treatment (Rieckmann et al., 2008). For secondary nonresponders monthly intervals of high-dose corticosteroid pulses have been suggested as well as the combination of basic DMT. For patients who show no improvement escalating treatment should be considered (Rieckmann et al., 2008).

3.1.4 Escalating treatment

Escalating immunotherapy represent the second-line therapy for patients with MS. This therapeutic strategy is chosen for non-responders or patients whose ARR and symptoms worsen. Second-line agents with the best risk-benefit ratio are preferred and if needed drugs with increased power and/ or toxicity are adopted (Rieckmann et al., 2008).

Choosing the optimal escalating treatment strategy should be based on the patient’s age at onset and the degree of disease activity during basic therapy as well as a consideration of the different modes of drug action (Rieckmann et al., 2008).

Natalizumab, Fingolimod and Mitoxantrone are the drugs currently used as second-line agents in escalating immunotherapy.
**Mitoxantrone**

Mitoxantrone is an immunosuppressive cytotoxic drug used as a second-line treatment for SPMS, primary relapsing multiple sclerosis and worsening RRMS (Rieckmann et al., 2008; Castro-Borrero et al., 2012). Mitoxantrone was developed to treat malignancies. It has a major effect on B-cell function and reduces lymphocyte proliferation. By intercalating into DNA strands Mitoxantrone induces strand breakage. Mitoxantrone inhibits the DNA repair enzyme topoisomerase II and thereby delays cell-cycle progression of rapidly dividing cells (Rieckmann et al., 2008; Castro-Borrero et al., 2012).

Mitoxantrone was approved for treatment on basis of the study by Hartung & colleagues (Rieckmann et al., 2008). They showed that the treatment with Mitoxantrone led to a change from baseline EDSS at 24 months, a change from baseline in ambulation index in 24 months, a change in the number of treated relapses, a change at the time to first treated relapse and a change from baseline- standardized neurological status at 24 months (Rieckmann et al., 2008; Castro-Borrero et al., 2012).

Over the years, Mitoxantrone has been shown to be efficacious in reducing exacerbations and number of GAD+ lesions in MRI. Some studies also suggest effects on disease course up to 5 years after discontinuing therapy (Castro-Borrero et al., 2012).

The drug is given as an intravenous infusion. 12 mg/m² are given over a 30 minute period every 3 months for 2-3 years. The lifetime cumulative dosage consist of 140mg/m² (Castro-Borrero et al., 2012). Common side effects include hair loss, cardiotoxicity, leukemia, infertility, increased risk of infections, leucopenia, anemia, nausea, vomiting and thrombocytopenia (Castro-Borrero et al., 2012).

Although the efficacy of Mitoxantrone is undeniable it remains a second-line agent due to its risk of severe side effects. One major side effect is therapy related leukemia that occurs with an incidence of approximately 0.21-0.81%. Usage of Mitoxantrone can also lead to decreased left ventricular ejection fraction and congestive heart failure (rate of 12% and 0.4%) (Castro-Borrero et al., 2012; Kamm et al., 2014).

**Natalizumab**

Natalizumab is a humanized monoclonal antibody against α4-integrin that reduces immune-cell traffic across the BBB (Kamm et al., 2014; Finkelsztejn, 2014; Buc, 2013; Rieckmann et al., 2008; Castro-Borrero et al., 2012). α4-integrin is a subunit of the cell adhesion molecule “very late antigen 4” (VLA-4) that is expressed on surface of lymphocytes and monocytes and therefore on the membranes of T-cells. After Natalizumab intake it is not possible for activated
T-cells to transmigrate into the CNS anymore, because they cannot successfully bind to their endothelial receptors (Buc, 2013; Castro-Borrero et al., 2012). The number of functions of regulatory T-cells on the other hand are not effected by Natalizumab. The effects of Natalizumab are not restricted to T-cells as it has also been shown that it reduces the number of dendritic cells (Buc, 2013).

Natalizumab was approved by the FDA by 2004. Patients are treated with a 300mg dose intravenously every 28 days (Kamm et al., 2014; Castro-Borrero et al., 2012).

Natalizumab was tested for treatment of RRMS in two large phase III clinical trials (Rieckmann et al., 2008; Castro-Borrero et al., 2012). Natalizumab reduces the ARR by 68% and disease progression by 42% (Kamm et al., 2014; Rieckmann et al., 2008; Castro-Borrero et al., 2012). Active MRI lesions were reduced by 92% (Rieckmann et al., 2008; Castro-Borrero et al., 2012). Natalizumab was also tested in combination with INF-β 1a. Compared with patients continuing INF-β 1a monotherapy a combined therapy led to reduced risk of sustained disability progression. Furthermore, a combined therapy resulted in fewer new or enlarging T2 lesions and were more likely to remain relapse free (Rieckmann et al., 2008; Castro-Borrero et al., 2012).

The most significant potential adverse effects of Natalizumab treatment is the development of progressive multifocal leukoencephalopathy (PML). PML is a demyelinating disease caused by the John Cunningham (JC) virus, that is lethal in 20% of the patients. The risk of developing PML is estimated at 1 per 1000 patients (Kamm et al., 2014; Finkelsztejn, 2014; Buc, 2013; Rieckmann et al., 2008; Castro-Borrero et al., 2012). Survivors of PML suffer from neurological impairments ranging from severe (30%), over moderate (50%) to mild (15%). Only few survivors are free from any neurological impairments (Kamm et al., 2014). Due to the PML-cases Natalizumab was temporary withdrawn from the market but was reintroduced in 2006 (Finkelszteijn, 2014). Other infections, such as immune reconstitution inflammatory syndrome (IRIS), may occur must be taken into consideration when starting treatment with Natalizumab (Bruc, 2013; Rieckmann et al., 2008).

Natalizumab is an extremely effective therapy and is restricted to RRMS patients with high active disease activity despite basic therapy or in treatment-naïve patients (Kamm et al., 2014; Castro-Borrero, Graves, Frohman et al., 2012). Patients must be carefully selected and pretreatment brain MRI is required (Traboulsee et al., 2008).
Fingolimod

Fingolimod is an immunomodulatory and immunosuppressive spinosgine-1 phosphate (S1P) receptor modulator. Fingolimod binds to four of five S1P receptors on lymphocytes leading to the internalization and downregualtion of their expression. Through this sphingosineanalogue acting CD4+ and CD8+ Tcells and Bcells are unable to egress from the lymph nodes. This leads to the decrease of these cells in the periphery, their reduced recruitment to sites of inflammation and the reduced recirculation of autoaggressive lymphocytes to the CNS (Kamm et al., 2014; Finkelszteijn, 2014; Buc, 2013; Castro-Borrero et al., 2012). 3-5 hours after fingolimod application approximately 80% of lymphocytes undergo this reversible process (Buc, 2013).

The effects of Fingolimod on Treg cells are controversial. Some researchers claim that the drug supports the Treg mechanisms. Clinical experience may support the theory of the positive influence of Fingolimod on Treg cells. On the other site some reports show that Fingolimod decreases the activities of Treg cells (Buc, 2013).

In the EAE model Fingolimod application has been shown to have potential neuroprotective effects. This effect was caused by the interactions of S1P receptors on neutral cells (Castro-Borrero et al., 2012).

Fingolimod is an oral drug that has been approved as first- line therapy for RRMS in September 2010 by the FDA. In 2011 the approval of the EMA followed, but it was restricted to patients whose condition fails to respond to first-line therapy or only in cases of severe, rapidly developing cases of MS (Kamm et al., 2014; Castro-Borrero et al., 2012).

In pivotal trials the intake of 0.5mg and 1.25mg doses of Fingolimod was tested and compared. Both dosages reduced the ARR by 54% compared to placebo and 52% compared to INF- β 1a. Both dosages furthermore decreased the risk of disability progression by 17.7% (0.5mg) and 16.6% (1.25mg). 90% of patients treated with either one of the doses were free of enhancing lesions over the course of 2 years and approximately 50% were free of new or enlarging T2 lesions (Kamm et al., 2014; Finkelszteijn, 2014; Castro-Borrero et al., 2012). Because of slightly better results in those tests, 0.5mg of Fingolimod is now the recommended dosage.

The treatment with Fingolimod has shown some serious side effects. The risk of infections and cardiovascular effects, including bradycardia and artioventricular block, especially at the first dose was increased by Fingolimod intake. All the symptoms were more common with the higher 1.25mg dose treatment (Kamm et al., 2014; Finkelszteijn, 2014; Castro-Borrero et al., 2012). Therefore the EMA recommends a 0.5mg dose as treatment. Furthermore the EMA recommends an increased patient monitoring during the first dose of Fingolimod including
electrocardiogram monitoring before treatment and the continuously for the first 6 hours after the first dose is administered. Additionally measurement of blood pressure and heart rate every hour over the same time are recommendable (Castro-Borrero et al., 2012).

Emerging MS DMT

The last decennium has brought the development of new biological agents that can modulate the MS disease processes. Currently many trials to verify the modes of action, benefits and adverse reactions of these drugs can be witnessed. The most promising new agents are novel monoclonal antibodies (mAb), especially anti CD20, anti CD52 and anti CD25. Anti CD20 mAbs attenuate autoimmune processes by the destruction of B lymphocytes (Buc, 2013).

Currently three different types of anti CD20 mAbs are used in MS treatment (rituximab, orelizumab and ofatimumab) and two have entered clinical trials (alemtuzumab and daclizumab). Anti CD20 monoclonal antibodies bind to B cells and destroy them by activation of the complement system of killer cells (Buc, 2013).

As those emerging DMT are not widely used, they will not be further discussed.

While drug based treatment is an effective treatment method for patients with MS, it has some considerable downsides. Side effects, too general targeting, a lack of drug treatment for side effects and the dependence on a number of different drugs are just a few of the negative sides of drug based treatment. A promising addition or in some situations even a promising alternative for drug based is exercise training. In many conditions, such as cardiac and pulmonary diseases and cancer, exercise training has established itself as an important treatment approach. In multiple sclerosis, exercise training still lacks the status of an effective treatment method, mostly because of prejudice against exercise in MS patients, lack of knowledge on the topic and the fear of provoking an attack. The following depiction of exercise therapy in patients with MS should provide a state of the art on effectiveness, fields of application, possible negative effects and guidelines on the topic.

4. Exercise training

4.1 Exercise and MS

Patients with MS have been shown to be less physically active compared to healthy individuals and the adoption of a sedentary lifestyle is common. Romberg et al. (2004) investigated the physical activity levels of 95 patients with mild to moderate MS over a four week period through
a self-report questionnaire. During the test period the majority of patients engaged in less than one hour of aerobic exercise or resistance training per week and spent between one and two hours walking. The study showed that patients with MS engaged in a low amount of physical exercise, which was performed at a moderate intensity (evidenced by breathlessness and some sweating). The study group was further able to show a correlation between disease severity and exercise capacity stating that the disability, measured by the EDSS, could predict the peak oxygen uptake (Romberg et al., 2004).

Barriers to exercise are MS related symptoms as well as a lack of confidence in ones own capabilities and abilities to manage the symptoms. Patients with MS often find themselves in a vicious cycle: because of their disability, they adopt a physically inactive and sedentary lifestyle, which leads to deconditioning and a worsening of symptoms. The worsening of symptoms further contributes to a physically inactive behaviour (figure 3) (Motl & Pilutti, 2012; Döring et al., 2012).

In MS as in other conditions with reduced mobility, a lack of physical activity can lead to a variety of complications and comorbidities. On the contrary physical activity and exercise has been shown to improve various aspects of the physiological profile of MS patients (figure 4) (Döring et al., 2012; Motl & Pilutti, 2012; Giesser, 2015).
4.2 Impact of body temperature on MS: thermoregulation, Uhthoff-phenomenon and exercise

The earliest medical reports of thermal sensitivity in patients with MS were documented by Charles Prosper Ollivier d’Angers, who observed that a hot bath induced numbness in the right leg and reduced feeling and dexterity in the hands of a patient with MS in 1824. The German ophthalmologist Wilhelm Uhthoff (1853 – 1927) however made the landmark observation regarding dysfunctional thermoregulation in patients with MS. Uhthoff described visual impairment and paresis occurring after a hot bath or after physical activity. As the body temperature of the patients was not measured it was assumed by Uhthoff that the physical activity itself caused the symptoms. This led to the long standing recommendations for patients with MS not to participate in physical activity (Davis et al., 2010; Döring et al., 2012; Frohman et al., 2013).

Frohman et al., (2013) define Uhthoff’s phenomenon as “disturbances in neurological functioning that are stereotyped, short in duration (less than 24h), reversible, and related to recurrent fluctuations in axonal conduction properties” (p.535). Factors that provoke Uhthoff’s phenomenon in patients with MS include fever, infection, taking a hot bath or shower, exposure to high ambient temperatures, perimenstrual temperature elevation, exercise and psychological stress. All of these are factors that potentially modify core body temperature (Frohman et al., 2013). Heat exposure can affect the patient’s daily life activities as well as the safety of individuals as it can impair both physical and cognitive functions (Davis et al., 2010).

The underlying mechanism of Uhthoff’s phenomenon relates to the influence of temperature on sodium channels. Derangement in sodium-channel mediated axonal depolarization as well as an unmasking of potassium channels leads to hyperpolarization and termination of actions potential (figure 5). Temperature escalation of as little as 0.2-0.5°C can lead to temperature – induced pore closure (Baker, 2002; Frohman et al., 2013).
While temperature increases reduce the depolarizing current decreases in temperature have the opposite effect. Through active body cooling depolarization is augmented. Pharmacologically 4 – aminopyridine (4-AP) can help prolong action potential duration by blocking potassium channels. Some formulations of this agent are FDA – approved for MS patients with walking difficulties (Baker, 2002; Frohman et al., 2013).

Deficits caused by increases in core body temperature dissolve by the removing of heat stressors and allowing of subsequent cooling. The positive effects of cooling even go as far as patients with MS feel as if the disease was “turned off” for at least a little while. Reduces in core body temperature gives patients the freedom to exercise or work again (Davis et al., 2010; Baker, 2002).

The impact of MS on the thermoregulatory system varies wildly and depends on lesion location and severity. About 60-80% of patients with MS are believed to suffer from worsening of clinical signs and neurological symptoms due to elevated core body temperature (Davis et al., 2010). Baker (2002) further describes that, “with any location and lesion load [...] the impact of the disease depends on the body temperature, worsening as activity is diminished in more and more demyelinated axons. In addition, thermoregulatory impact is worsened by lack of physical fitness and lowered blood volume” (p.1779).

For patient care, it is important to distinguish between Uhthoff’s phenomenon and a relapse. In most patients who are treated with DMD, exacerbations occur infrequently whereas the disturbances associated with the Uhthoff’s phenomenon generally occur more frequently (Frohman et al., 2013).

Generally spoken elevated core body temperature leads to a worsening of symptoms whereas cooling improves negative symptoms. Even little variations in temperature can have great impacts on patients with MS. The elevation of core body temperature can be caused by passive heat exposure, exercise or a combination of heat exposure and increases in metabolism. Even
so much of the MS research published has shown that patients with MS can exercise without exacerbations (Gallien et al., 2007).

4.3 EAE and exercise
The effects of exercise in the animal model of MS, EAE, have been investigated in a small number of studies using different exercise paradigms.

EAE induced rodents, most commonly mice and rats, were divided in exercising and control or sedentary groups. The interventions in the exercise group were either running or swimming regimes. Compared to the controls the exercising rodents in all studies showed a significant delay in onset and decreased severity of disease. One study (running-wheel intervention) also showed less neural damage and increased dendritic spine density than the sedentary rodents. The swimming intervention led to the observation, that exercising rodents showed increased brain-derived neurotrophic factor and decreased demyelination in the exercising group (Giesser, 2015).

One study with EAE induced rats compared an exercising group completing a swimming intervention (30 min/day for 14 consecutive days) with a sedentary group. The study showed that short-term memory of the rats was disturbed by the induction of MS. The swimming exercise however alleviated the MS-induced short-term memory impairment and suppressed the MS-induced increase in DNA fragmentation (Jin et al., 2014).

Most of the studies with exercising EAE induced rodents showed beneficial effects of exercise on disease course and are promising for exercise training in patients with MS, but the studies vary greatly and comparison is hardly possible. Therefore, further research is needed to draw conclusions from the findings in the studies (Giesser, 2015).

4.4 Exercise and immune function
Exercise and physical activity are known for their influence on the susceptibility to infectious diseases. Vigorous physical activity on one hand can lead to an increased susceptibility to infections. On the other hand, moderate exercise may contribute to their prevention (Döring et al., 2012; Gleeson, 2007; Petersen & Pedersen, 2005).

Physical strain has been shown to initially increase the peripheral lymphocyte count in healthy individuals. This temporary depressive effect on the immune function is similar to the responses induced by infection, sepsis or trauma. All of which show a substantial increase in the number of circulating leukocytes. Furthermore, increases in the plasma concentrations of various inflammatory cytokines, such as TNF-α, macrophage inflammatory protein 1 and IL-1b
lead to a greater susceptibility for infectious diseases (Döring et al., 2012; Gleeson, 2007; Petersen & Pedersen, 2005). Gleeson (2007) states that “immune function depression is most pronounced when the exercise is continuous, prolonged (> 1.5h), of moderate to high intensity (55-75% maximum O₂ uptake), and performed without food intake” (p.698). In athletes, it is known that the downregulation of the immune function after a strenuous training provides an “open window” for infections. During this time, the athletes are most susceptible for the contraction of infections (Gleeson, 2007).

Post-exercise however the lymphocyte count falls below the initial level. The increased plasma concentrations of anti-inflammatory cytokines IL-6, IL-10 and IL1-receptor antagonist (IL-1ra) and acute phase proteins lead to this decline. Additionally the concentration of several hormones that are known to have immunomodulatory effects are also increased. The observed lymphocyte reduction is short lasting, with a duration of 3-24 hours depending on the duration and intensity of the exercise (Döring et al., 2012; Gleeson, 2007; Petersen & Pedersen, 2005).

The first cytokine to be present in the circulation during exercise is IL-6. The level of this anti-inflammatory cytokine increases in an exponential fashion up to 100-fold, related to exercise intensity, duration, the mass of muscle recruited and ones endurance capacity according to Petersen and Pedersen (2005). Due to the higher levels of IL-6, the cytokines IL-1ra and IL-10, both anti-inflammatory in nature, increase post-exercise. The IL-6 levels can influence the TH1 and TH2 balance, as the elevation of the circulating IL-6, IL-10 and IL-1ra decreases the type 1 T-cells in the circulation. Furthermore, IL-6 directly stimulates type 2 T-cell production and supresses the production of TNF-α (Döring et al., 2012; Gleeson, 2007; Petersen & Pedersen, 2005). This shift from a TH1 – mediated pro-inflammatory to a TH2 – mediated anti-inflammatory milieu is beneficial and relevant for patients with MS.

Some immunomodulatory drugs like interferon – β and glatiramer acetate lead to similar mechanism which leads to the suggestion, that drug treatment and physical activity / exercise complement each other in terms of modulating the immune system.

The beneficial but short-lasting effects of exercise on the immune system promote regular and frequent training sessions for patients with MS (Döring et al., 2012). Training intensity and duration should be chosen carefully to prevent great susceptibility for infections.

4. 5 Exercise training
The understanding of exercise training varies greatly and it is therefore important to clarify how the term exercise training is used in the following. A definition of exercise training was adopted from Motl and Pilutti (2012) who defined exercise training as a "planned, structured and repetitive physical activity undertaken over a prolonged period to maintain or improve physical
fitness and functional capacity. This definition includes aerobic exercise training such as cycling or walking, progressive resistance exercise or weight training, and non-traditional exercise training” (p.2).

Exercise training in rehabilitation follows the main principles of trainings science with respect to disease-related limitations. Usually exercise training in rehabilitation consists of resistance training, aerobic training and a combined form of these two. Additionally, other forms of training, such as yoga, climbing and balance training are commonly carried out. The optimal form of training for patients is determined by the clinical picture, individual state and well being of the patient (Hofmann et al., 2004, p.353-355).

The effect of training is determined by the duration and characteristics of the exercise, the intensity of the execution, duration and characteristics of the rest period and the number of exercises. Each component is important for the effectivity of the training and the change of only one component can change the outcome (Platanov, 1999, p.12). In order for the organism to adapt to a training stimulus, the stimulus has to stress the system at a sufficient intensity and duration. An adaption after the training can only happen, if the stimulus was sufficient. In cardiac patients it has even been suggested, that a certain “threshold intensity” has to be reached to guarantee a successful adaptation (Smekal et al, 2004, p.4; Hofmann et al., 2004, p.156).

The disease itself and the bad metabolic condition and cardiorespiratory fitness level of the patients provide challenges for the prescription of exercise training. In prescribing exercise for patients, the functional goal of the subject and the current wellbeing have to be considered with full understanding of underlying causes of deficits (Hofmann et al., 2004, p.354-355).

**4.5.1 Resistance training**

There are various types of resistance training as, theoretically, any object can be used for the training. The source of resistance can therefore vary based on the needs of the individual and provide benefits for certain populations.

Aquatic exercises for example provide resistance through the buoyancy force of the water without putting individuals in a weight-bearing environment, which could be beneficial for patients with neuromuscular disabilities. For patients with MS, aquatic exercises would further be beneficial as heat exposure is reduced in the water (Ratamass, 2014, p.5-6).

Machine training provides added stability to its users and ensures a better sequence of motions for beginners. Individuals with balance and coordination problems benefit from this type of training. Training with free weights, medicine / stability balls and related balance equipment on the other hand ensures enhanced neuromuscular function (Ratamass, 2014, p.5-6).
Bodyweight exercises provide the most basic source of resistance. Nonetheless, these exercises can be used in a variety of ways with varying complexity and difficulty (Ratamass, 2014, p.5-6).

Advantageously the different resistance training types can provide training variability and can be easily adapted to meet the needs of any healthy or special population (Ratamass, 2014, p.5-6).

**Health benefits**

Resistance training has numerous performance enhancing and health promoting benefits. Furthermore, resistance training reduces several risk factors for disease – or physical ailments. In many physiological conditions promoting catabolic breakdown of the muscle and connective tissues, resistance training presents the only natural method to offset these conditions. Additionally, through the improvement of functional capacity and performance of activities of daily living (ADL) resistance training improves the Quality of Life (QoL) of patients (Ratamass, 2014, p. 6; Delise et al., 2005, p.407).

<table>
<thead>
<tr>
<th>General health benefits</th>
<th>Potential benefit for patients with MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased muscle strength, power and endurance</td>
<td>Counteract muscle weakness, improve walking performance, improve QoL</td>
</tr>
<tr>
<td>Increased lean body mass and basal metabolic rate and reduced body fat</td>
<td>reduce complications and secondary diseases, improve overall fitness and wellbeing, improve QoL</td>
</tr>
<tr>
<td>Increased left ventricular and septal wall thickness</td>
<td></td>
</tr>
<tr>
<td>Decreased cardiovascular demands to activity</td>
<td></td>
</tr>
<tr>
<td>Improved blood lipid profiles, increased HDLs, decreased LDLs and triglycerides</td>
<td></td>
</tr>
<tr>
<td>Improved glucose tolerance and insulin sensitivity</td>
<td></td>
</tr>
<tr>
<td>Decreased risk of sarcopenia</td>
<td></td>
</tr>
<tr>
<td>Increased bone mineral density, bone mass and reduced the risk of osteoporosis</td>
<td></td>
</tr>
<tr>
<td>Increased tendon and ligament strength, metabolism, thickness and weight</td>
<td></td>
</tr>
<tr>
<td>Improved flexibility</td>
<td></td>
</tr>
<tr>
<td>Increased cardiorespiratory fitness</td>
<td></td>
</tr>
<tr>
<td>Prevention and management of low back pain</td>
<td>Improve QoL</td>
</tr>
<tr>
<td>Maintained long-term independence and functional capacity, Improvement of ADL</td>
<td></td>
</tr>
<tr>
<td>Increased balance, coordination and functional ability</td>
<td>Improve walking performance, improve self-confidence, reduce risk of injuries</td>
</tr>
<tr>
<td>Reduced risk of falling</td>
<td></td>
</tr>
<tr>
<td>Improved psychological well-being</td>
<td>Improve psychological well-being</td>
</tr>
</tbody>
</table>

**Resistance training design**

In order to achieve the above mentioned benefits from resistance training the exercise regimen must be of sufficient frequency, intensity and duration in order to challenge the physiological components of the muscles (Frontera et al., 2006, p.28). According to a description provided by Ratamass (2014) “the critical component of resistance training is the design of the program.
A resistance training program involves the interaction between several variables, including muscle actions utilized, exercise selection and sequence of performance, intensity, volume, rest intervals, lifting velocity, and frequency all aimed at targeting specific goals and adaptations" (p.7). Further, the manipulation of these variables is important to minimize potential boredom and increase adherence, reduce training plateaus and allow the individual gradual progression (Ratamass, 2014, p.7).

Resistance training intensities are divided in low (≤ 60% 1RM), moderate (60-85% 1RM) and high (85-100% 1RM). The effects of resistance training depend on the training intensity, which varies in different populations. In untrained individuals for example, low intensities of 45-50% of 1RM can already increase muscular strength with the largest effect shown at 60% of 1RM (Ratamass, 2014, p.13).

Training intensity is dependent on loading and repetitions, showing an inverse relationship between the amount of weight lifted and the number of repetitions completed (table 4). Light (≤ 60% 1RM) to moderate (60-85% 1RM) loading elicits high repetition numbers (12-20 reps.). These training modes promote strength and hypertrophy in untrained individuals and special populations, but most prominent increases muscular endurance. Moderate (60-85% 1RM) to heavy (85-100% 1RM) loading elicits moderate repetition numbers (6-12 reps.), resulting in increased strength, hypertrophy and muscular endurance. Heavy loads (85-100% 1RM) require low repetition numbers (1-6 reps.) and most specific target the increase of maximal strength (Ratamass, 2014, p.13-14).

<table>
<thead>
<tr>
<th>Repetitions</th>
<th>Load</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximal strength training</td>
<td>1-5 reps</td>
</tr>
<tr>
<td>Hypertrophy</td>
<td>6-20 reps</td>
</tr>
<tr>
<td>Muscular endurance</td>
<td>≥ 20 reps</td>
</tr>
</tbody>
</table>

RM= repetition maximum; reps.= repetitions

The American College of Sports medicine recommends resistance training twice a week with one set of 8-12 repetitions (60-70% 1RM) for healthy adults and 10-15 repetitions (30-50% 1RM) for older and frail individuals (ACSM, 2013).
As research on exercise training in patients with MS increased throughout the last years, many studies on resistance training have been published. Those included in the thesis are summed up in table 5 and assigned to a training method.

Table 5: Resistance Training

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Intervention</th>
<th>Endpoints</th>
<th>Participants</th>
<th>EDSS</th>
<th>Intervention</th>
<th>Main Results</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guillen et al. (2005)</td>
<td>8 week progressive resistance training; 2x/week supervised</td>
<td>Kinematic gait parameters; isometric strength; stepping; fatigue; disability</td>
<td>8 (1.7 y.; 46 ± 11.5 y.; RRMS; GA</td>
<td>2.5-5.5</td>
<td>5 exercises</td>
<td>Improvements in kinematic gait parameters; decreased fatigue; decreased EDSS; improved walking</td>
<td>Hypertrophy</td>
</tr>
<tr>
<td>White et al. (2004)</td>
<td>8 week progressive resistance training; 2x/week</td>
<td>Lower extremity strength; ambulatory function; fatigue</td>
<td>8 (1.7 y.; 46 ± 12 y.; INFβ 1a; INFβ 1b; GA</td>
<td>3.7±0.8</td>
<td>Warm up: 1 set, 5 rep. at 40% IRM; Session: 1 set, 10-15 reps. at 60-70% IRM</td>
<td>Increases in lower extremity strength; decreased fatigue; decreased EDSS; Improved walking</td>
<td>Hypertrophy</td>
</tr>
<tr>
<td>Souza-Teixeira et al. (2008)</td>
<td>8 week progressive resistance training; 2x/week</td>
<td>Muscle function; muscle mass; functionality</td>
<td>13 (4.9 y.; 43 (35-51) y.</td>
<td>3.4 ± 1.7</td>
<td>Warm up: 7 min bicycle, stretching, 5 reps with light weight; Session: 3 sets, 10-15 reps. at 40-70% MVC; 3 min. rest</td>
<td>Significant improvements in isometric strength, muscular endurance, maximal power, muscular hypertrophy and functionality</td>
<td>Hypertrophy/Muscular endurance</td>
</tr>
<tr>
<td>DeBolt et al. (2004)</td>
<td>8 week home based resistance training; 3x/week</td>
<td>Balance, power, mobility</td>
<td>37 (8.29 y.; 51,1 ± 7,1 y.; 50,3 ± 8,5 y.</td>
<td>1.0-6.0</td>
<td>Body weight + Vest exercises 2-3 sets of 8-12 reps.</td>
<td>Significant improvements in leg extensor power; no changes in mobility or balance</td>
<td>Hypertrophy</td>
</tr>
<tr>
<td>Perez (2007)</td>
<td>6 week callisthenic or bodyweight resistance training; 3x/week</td>
<td>Strength, mobility, balance, walking</td>
<td>36 (14.22 y.; 44.4 ± 9.5 y.</td>
<td>1-6 (~1.5)</td>
<td>Warm up: balance + coordination exercises; Session: 2 sets of callisthenic exercises + medicine ball exercises</td>
<td>Significant improvements in strength and walking; no improvements in balance</td>
<td>-</td>
</tr>
<tr>
<td>Finland et al. (2010) A</td>
<td>Standard rehabilitation + maximal strength training (e.); 3 weeks - 15 sessions</td>
<td>Isometric strength; evoked responses</td>
<td>14 (8.8 y.; e.: 53 ± 4 y. c.: 54 ± 2 y.</td>
<td>e.: 4.6±0.4 c.: 3.5±0.5</td>
<td>4 sets of 4 reps. At 85-90% of IRM; 1-2 min rest</td>
<td>MVC increased in e. group; increased effector motor outflow from spinal motor neurons to lower limb muscles</td>
<td>Maximal strength training</td>
</tr>
<tr>
<td>Dodd et al. (2011)</td>
<td>10 week progressive resistance training; 2x/week</td>
<td>Muscle performance, QoL, fatigue</td>
<td>e.: 36 (10.26 y.; 47,7 y. c.: 35 (9.26 y.; 50,4 y.</td>
<td>-</td>
<td>2 sets of 10-12 reps. At 60-80% 1RM; 6 exercises</td>
<td>Short term fatigue reduction, increase in muscle endurance, muscle strength and quality of life</td>
<td>Hypertrophy/Muscular endurance</td>
</tr>
<tr>
<td>Finland et al. (2010)</td>
<td>3 week lower leg resistance training; 15 sessions</td>
<td>Neural drive</td>
<td>e.: 7 (4.3 y.; 53 ± 4 y. c.: 7 (4.3 y.; 54 ± 2 y.</td>
<td>e.: 4.6±0.4 c.: 3.5±0.5</td>
<td>4 sets of 4 reps. at 85-90% of IRM; 1-2 min rest</td>
<td>Increased effector motor output</td>
<td>Maximal strength training</td>
</tr>
<tr>
<td>Medina-Perez, et. al. (2014)</td>
<td>12 week resistance training for knee extensor muscles</td>
<td>Knee extension MVIC, muscle power, muscle endurance</td>
<td>42 (19.23 y.; e.: 49,6 ± 11 y. c.: 12 46,2 ± 7,5 y.</td>
<td>e.: 4.5±2.1 c.: 4.1±0.5</td>
<td>Warm up: cycling + 1 set of 5 rep (light load) Session: 3 sets of 8-12 reps. At 35-70% of MVIC</td>
<td>Increased MVIC and muscle power; no effects on muscle endurance. After 12 weeks of detraining MVIC returned to pre-training values, but muscle power was still greater than pre training</td>
<td>Hypertrophy/Muscular endurance</td>
</tr>
</tbody>
</table>

P1RM= predicted 1 repetition maximum; reps.= repetitions; IRM= Individual 1 repetition maximum; MVC= Maximum voluntary isometric contraction; y. = years, e= exercisers, c= controls, gr.= group
From the nine studies included in this thesis, two performed resistance training at the intensity of maximal strength, three at the intensity of hypertrophy, three used a mixed hypertrophy and muscular endurance approach and one study could not be assigned to any training intensity (bodyweight exercises without further description of training method). Most of the trials focused on the lower body muscle groups. Targeting lower body muscle groups in patients with MS may be favoured due to the often seen deficits in those muscle groups, which may lead to an insufficient walking performance. Kjolhede et al. (2012) conducted a review on resistance training in patients with multiple sclerosis showing similar results. The intensity of the sixteen included studies ranged from 60%-90% of 1RM and 8-15 repetitions, which mostly represents hypertrophy training.

4.5.2 Aerobic training
Aerobic training methods can be subdivided into continuous method (consistent intensity), interval method (high intensities with rest periods in-between) or fartleking runs (changes between higher and lower intensity). For a long time the interval method and fartleking runs have been deemed inappropriate for patients, but in many conditions, such as heart insufficiency, they have been shown to be effective. Most commonly aerobic exercises in rehabilitation include walking, running, cycling, arm cycling and swimming (Hofman et al., 2004, p.355).

The difficulty in designing an aerobic exercise regime for patients lies in the determination of appropriate training stimuli, which is believed to regulate gained physiological benefits.

Although neither in healthy individuals nor in special populations standardized lower limits of prescribeable aerobic training have been established yet, some guide values can be given. Hofmann and Tschakert (2011) described that “the intensity should be above a minimal level required to induce a training effect which was shown to be at 40-49% of heart rate reserve (HRR) or 64-70% of HFmax or even lower at 30% oxygen uptake reserve (VO2R) in unfit subjects” (p. 4). The use of percentages of the maximum heart rate (HRmax) and the maximal oxygen uptake (VO2max) as standard variables to prescribe exercise is widespread. However, this traditional concept has been criticized for leading to differing levels of metabolic stress among patients and risks of too demanding intensities for patients with an inverted heart rate response. Many authors have therefore suggested to apply a threshold concept to consider the demand of exercise (Hofmann et al., 2001; Hofmann & Tschakert, 2011).

The upper limit of prescriptible aerobic training intensity should be chosen individually, as those limitations are crucial for safety and control of exercise related risks. In the general population
higher training intensities have been related to significant greater improvements than moderate to low intensity training sessions with the same volume of exercise or similar energy expenditure. However, for special populations approaching the limits of tolerance is potentially dangerous and requires more precise and sophisticated diagnostics and exercise intensity prescriptions (Hofmann & Tschakert, 2011).

The threshold concept describes exercise intensity through the rise of blood lactate concentration and heart rate, as well as ventilator changes. The concept is best described with two turning points, the ventilatory thresholds or lactate turn points. As exercise intensity increases, 3 phases of energy supply and two intersection points can be defined. Although highly debated over the years the thresholds are most commonly named “aerobic threshold” and “anaerobic threshold” (Binder et al., 2008).

The first phase of the threshold concept is characterized by a linear increase in oxygen consumption (VO\(_2\)), CO\(_2\) output and ventilation (VE). Although blood lactate is produced it does not lead to a significant increase in blood lactate concentration, as the muscle cell is able to aerobically metabolise it. Lactate production and elimination is balanced in the working muscle (Lactate steady state), with the blood lactate values remaining at resting level (Tschakert & Hofmann, 2013).

During the second phase of energy supply the lactate production rate is higher than the metabolizing capacities in the muscle cell. Blood lactate concentrations increase, as lactate is shifted to other organs that are able to metabolize it. During phase 2 metabolically balance conditions can be observed on a systematic level. In order to scope with the incoming lactate the oxidative capacity of the whole system is sufficiently high (Tschakert & Hofmann, 2013).

Is the workload further increased (above LTP2) the muscular lactate production rate exceeds the systemic lactate elimination rate. Phase three is therefore characterized by an exponential increase in blood lactate concentration. Further, nonlinear increases in VCO\(_2\) and more pronounced VE are observed. Hyperventilation cannot compensate the risen H\(^+\) and a drop in P\(_{ET}\)CO\(_2\) can be seen (Tschakert & Hofmann, 2013; Binder et al., 2008).
To provide a detailed differentiation between the three phases data from three different trials (Hofmann et al., 2001; Hofmann et al., 2001b; Kleinrath, 2011) are compared. The adaptations of the values received from cycling tests have been adapted for running and cycling by Kleinrath (2011).

Additionally to heart rate, lactate, oxygen uptake and power values ratings of perceived exertion (RPE) at the thresholds are provided. Irving et al. (2006) described RPE as “[…] a useful tool for prescribing exercise intensity based on its relationship with physiological indicators of exercise stress, including La, HR, oxygen uptake (VO2) and minute ventilation (VE) (p.1348). The most common RPE used are the BORG scale and the OMNI scale. Results from the BORG-RPE can be used to predict and produce blood lactate responses to exercise. The BORG-RPE can be used for a variety of populations, as it does not appear to be impacted by gender, training state or exercise modality. The OMNI-scale has established itself as an alternative to the BORG-RPE, as it provides not only verbal descriptors of exertion, but also pictorial (Irving et al., 2006).

To this point several studies have pointed out that the RPE at the lactate threshold is quite constant. The perceived exercise intensity at the lactate threshold was described as “somewhat hard” corresponding to a BORG scale rating of 13-14 (Demello et al., 1987).

Through the results obtained from various trials on the RPE at the lactate thresholds, the BORG and OMNI values shown in table 6 have been calculated (Demello et al., 1987; Robertson, 2004; Scherr et al., 2013; Irving et al., 2006).
Table 6: Calculated phases of energy supply (modified after Stübinger, 2014)

<table>
<thead>
<tr>
<th>Type</th>
<th>%HRmax</th>
<th>%VO₂max</th>
<th>%Pmax</th>
<th>La [mmol]</th>
<th>BORG</th>
<th>OMNI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LTP1</td>
<td>LTP2</td>
<td>LTP1</td>
<td>LTP2</td>
<td>LTP1</td>
<td>LTP2</td>
</tr>
<tr>
<td>Cycling</td>
<td>68.5%</td>
<td>85.6%</td>
<td>51.7%</td>
<td>75.5%</td>
<td>41%</td>
<td>72%</td>
</tr>
<tr>
<td>Running</td>
<td>76.8%</td>
<td>92.7%</td>
<td>66.1%</td>
<td>87.2%</td>
<td>53.3%</td>
<td>79.4%</td>
</tr>
<tr>
<td>Arm cycling</td>
<td>63.5%</td>
<td>79.3%</td>
<td>43.2%</td>
<td>63.6%</td>
<td>40.3%</td>
<td>70.5%</td>
</tr>
</tbody>
</table>

HR= heart rate; VO₂max= maximum oxygen uptake; Pmax= ; La= lactate, LTP1= aerobic threshold, LTP2= anaerobic threshold

In the following aerobic exercise with an intensity below LTP1 will be referred to as either phase I exercise or light exercise. Intensities ranging from LTP1 to LTP2 will be referred to as either phase II exercise or moderate exercise. Finally, intensities above the LTP2 will be referred to as strenuous exercise or phase III exercise.

The included studies investigating aerobic exercise training in patients with multiple sclerosis are displayed in table 7. The training interventions were assigned to one of the three phases of energy supply.

Of the studies included in this thesis, nine exclusively examined the effects of aerobic training (reviews not included). Eight studies used a continuous method of aerobic training and one an interval method. From the continuous aerobic training trials two operated in phase I, one in phase II and four used a mixed phase I and II protocol. The trial using interval training was carried out in all three phases of energy supply.

When analysing the effects of aerobic training on MS related processes and symptoms a critical approach to the results from studies using phase I aerobic training should be chosen, as those training intensities do not reach a required “threshold intensity” (see above).
4.5.3 Combined Training

The trials using combined training regimes were assigned to a phase of aerobic training and a type of resistance training (table 7).

Three combined trials have been reviewed for this thesis, but only two could be assigned to a training modality. Hansen et al. (2015) conducted a study with phase II (moderate) aerobic training and hypertrophy resistance training mode. Hornich (2015) examined the adaptations from four week combined rehabilitation with special attention to blood lactate levels. The aerobic training sessions were of light intensity and the resistance training intensity was in the region of muscular endurance. The study conducted by Romberg et al. (2004) could not be...
assigned due to a lack of information on the aerobic training and a change from machine resistance training to Theraband exercises, without a description on the intensity of the training.

Table 8: Combined training

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Intervention</th>
<th>Endpoints</th>
<th>Participants</th>
<th>EDSS</th>
<th>Intervention</th>
<th>Main results</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Romberg et al. (2004)</td>
<td>6 month combined strength and aerobic training</td>
<td>Walking speed, lower extremity strength, upper extremity endurance, dexterity, static balance</td>
<td>e.: 47 (17♂/30♀) 43.8 ± 6.3 y. c.: 48 (17♂/31♀) 43.9 ± 7.1 y.</td>
<td>e.: 2 (1-5.5) c.: 2.5 (1-5.5)</td>
<td>Week 1-3: circuit resistance training; 10 exercises, 2 sets of 10.15 reps. Week 4-26: home based Theraband exercise program; 10 exercises, 10-15 reps., aquatic training or other aerobic exercise</td>
<td>Walking speed improved significantly, muscular strength and endurance improved; EDSS did not change</td>
<td>-</td>
</tr>
<tr>
<td>Hansen et al. (2015)</td>
<td>6 month combined endurance (treadmill) and resistance training</td>
<td>HR changes, exercise tolerance</td>
<td>e.: 14 (4♂/10♀) 46± 10 y. c.: 9 (4♂/5♀) 50 ± 7 y.</td>
<td>e.: 3.2±1.5 c.: 3.1±1.4</td>
<td>Aerobic: from 1x6min up to 3x10 min. at 12-14 BORG Resistance: 1x10 – 4x15 reps. at 12-14 BORG</td>
<td>Long-term exercise does not improve HR changes; improvements in exercise tolerance</td>
<td>II/Hypertrophy</td>
</tr>
<tr>
<td>Hornich (2015)</td>
<td>4 week combined aerobic (cycling, treadmill walking &amp; Lokomat) and resistance training</td>
<td>Changes in blood lactate</td>
<td>E: 35 45.8±9.7 y.</td>
<td>3.8 ± 2.0</td>
<td>Aerobic training: 20 min below LTP1; 3 min cool down Resistance training:</td>
<td>Ulmuscular endurance</td>
<td></td>
</tr>
</tbody>
</table>

Reps= repetition; EDSS= Expanded Disability Scale; e= exercisers; c= controls; y= years; Hr= heart rate

Although research data on exercise training in patients with MS has increased significantly throughout the last years, it still shows methodological problems. Small sample sizes, lack of an appropriate control group, unblended design, failure of differentiation between various courses and stages of disease, heterogeneous groups of patients and different interventions are challenging for researchers. The comparability of studies is further limited by non-standardized training regimes and hardly sufficiently described interventions. Exercises vary in their duration and frequency as well as intensity. The effects of interventions are mostly reported over a short period of time and are almost exclusively been studied in patients with mild to moderate MS (EDSS less than 7) (Döring et al., 2012). All of those problems should be kept in mind when analysing the trials on their effects on patients with multiple sclerosis.

4.6 Effects on MS pathogenesis (Inflammation/ neurodegeneration)

4.6.1 Cytokine response
Interleukin – 6 (IL-6), tumor necrosis factor (TNF- α) and interferon – y (INF-γ) are strongly linked to the process of demyelination and axonal damage in patients with MS and it is therefore relevant to investigate the impact of exercise on these cytokines. The effect of
exercise on the immunological responses through cytokine production in healthy individuals has been shown to be beneficial. In patients with MS the effect of exercise on inflammatory modulators remains rather elusive.

Heesen and colleagues (2003) as well as Castellano, Patel and White (2008) showed that endocrine and proinflammatory immune responses were influenced by exercise but the responses were not significantly altered in patients with MS. Furthermore, the cytokine response to a single bout of exercise in trained patients with MS is similar to that of healthy individuals (Castellano et al., 2008).

In strenuous and eccentric exercise, Heesen and colleagues (2003) reported cytokine findings to be most consistent, showing an induction of proinflammatory (TNF-a, IL1) as well as inflammation-responding (IL6) and anti-inflammatory cytokine (IL10). They further noticed a shift in cytokine patterns towards TH1 cytokine post-exercise (Heesen et al, 2003).

IL-6

IL-6 may be involved in lesion formation in the CNS. Abnormally high IL-6 concentrations in the periphery may result in excess inflammation that can exacerbate disease activity in patients with MS. Elevated IL-6 levels may further disrupt the clearance of microbial pathogens and participate in T-cell activation. Additionally, IL-6 levels may be involved in skeletal muscle controlled metabolic regulation. Exercise and physical activity have the ability to change resting levels of IL-6 and therefore influence metabolic changes in subjects (Castellano et al., 2008).

Castellano and colleagues (2008) examined the cytokine response to 30min phase I aerobic training in patients with MS. They observed similar IL-6 responses to exercise in patients and healthy control: post-exercise IL-6 increased significantly and stayed elevated for 2h. Baseline levels were measured again 3h after exercise. IL-6 responses were not significantly different in the two groups, but the response seems blunted in patients with MS. Resting levels of IL-6 decreased across weeks of training in this study. Previous studies did not see any changes in IL-6 resting levels. The different outcomes could be explained by the fact that IL-6 levels need longer training programs to show changes in resting levels or that IL-6 maintains at higher levels in patients with MS to counteract other inflammatory cytokine activity (Castellano et al, 2008).

TNF-α and INF-γ

TNF-α has been shown to have a dual role in autoimmune diseases such as MS. On one hand TNF-α has been linked to inflammatory demyelination in MS. On the other hand TNF-α “may
be neuroprotective through the enhancement of oligodendrocyte proliferation and stimulation of remyelination” (Castellano et al., 2008, p. 1701). Furthermore, elevated TNF-α concentrations in the blood could correlate with the degree of blood-brain-barrier dysfunction, but it may also lead to favourable decreases in relapses while on interferon – β treatment (Castellano, Patel & White, 2008).

Castellano et al. (2008) found different TNF-α responses to phase I aerobic training and resistance training. Following 8 week of aerobic training the resting concentrations of TNF-α increased, whereas the resting levels decreased after 8 weeks of resistance training.

INF-γ seems to be following similar dynamics as TNF-α, as the concentrations of both cytokines showed similar responses to exercise (Castellano et al., 2008; Heesen et al., 2008).

Post exercise Castellano and colleagues (2008) reported decreases in INF-γ and TNF-α concentrations in both patients with MS and healthy controls. Heesen and colleagues (2003) on the contrary found increased INF-γ and TNF-α concentrations post exercise. The study group suggested that the moderate correlation between IFN-γ production and disease duration “might indicate that in later disease stages MS patients may produce stronger IFN-γ response to exercise” (Heesen et al., 2008, p. 479).

TNF-α and IL-10 seems to follow the opposite dynamics to IL-6 following a single bout of exercise, as both were not significantly induced during exercise in any group (Heesen et al., 2003; Castellano et al., 2008). Heesen and colleagues (2003) additionally found out that MS patients without training showed weaker cytokine responses to exercise and baseline levels for IL-10 and IFN-γ were lower than in healthy controls. These differences may be explained by the fact that cytokine production is genetically determined and varies strongly even in healthy individuals (Heesen et al, 2003), or by the different training methods used in the trials.

Before the initiation of exercise, MS subjects show similar cytokine responses compared with healthy controls. Current literature suggests that individuals with MS respond to physical stress similarly to matched healthy controls. However, cytokine response seems to depend on the degree of disability, with benign MS showing a fairly balanced cytokine and neuroendocrine network and higher disability levels showing stronger immune dysregulation (Castellano et al., 2008).

The training status of the patients might also influence the cytokine induction: patients without training showed a weaker response to exercise, indicating a immunomodulatory effect of exercise training (Heesen et al., 2003). Heesen and colleagues (2003) further note that “in healthy individuals, exercise has a J-curve effect on the susceptibility to infections with moderate exercise [between the aerobic and anaerobic threshold] being beneficial and
exhaustive exercise [above the anaerobic threshold] increasing the risk of infections. Maybe the same is true in disease as MS with respect to the autoimmune disease activity. Moderate exercise [between the aerobic and anaerobic threshold] may therefore increase tolerance while strenuous exercise might enhance inflammation” (p.480).

Overall, cytokine response in patients with MS seems to follow the same patterns as those in healthy individuals. Whether exercise has beneficial effects on the immune system of patients with MS however is still elusive and further research is needed to provide solid data.

4.6.2 Nerve growth factor and brain derived neurotrophic factor

Physical activity can promote brain health and function. Research suggests that exercise increases neuronal survival and resistance to brain insult. These beneficial effects might be triggered by neurotrophic factors, as neurotrophic factors might mediate the effects of physical activity and are involved in neuroprotection, neuroplasticity and the maintenance of neuronal health. Studies in animals and research on aged humans confirmed these findings (Motl & Pilutti, 2012; Heesen et al., 2008; Gold et al., 2003). Neurotrophic factors might exert its effects via immunomodulation and therefore positively influence inflammation and demyelination. Supporting this assumption are the elevated nerve growth factor (NGF) serum levels in several inflammatory and autoimmune diseases. Nonetheless, elevated levels of NGF should be interpreted with caution, as their effects could either be neuroprotective or detrimental and is depended on the receptors (Gold et al., 2003).

Some literature showed elevated baseline serum concentrations of NGF in MS lesions and CSF compared to healthy controls. Literature on basal brain derived neurotrophic factor (BDNF) levels is inconsistent. One study showed that unstimulated BDNF levels did not differ between patients with MS and healthy controls but were significantly elevated in patients with an ongoing relapse (Gold et al., 2003).

Transiently acute stress enlarges serum levels of NGF in animals and humans, the effect of acute physical stress on neurotrophic serum levels however is yet unknown (Motl & Pilutti, 2012; Gold et al., 2003; Heesen et al., 2008). Only a few studies have examined the effects of exercise training on BDNF and NGF in patients with MS. Two studies of 8-week aerobic exercise training in patients with MS at 60% VO₂max showed no change in resting BDNF serum levels (Motl & Pilutti, 2012). One study comparing aquatic versus land exercise training reported increases in BDNF levels following aquatic exercise (Giesser, 2015).

Gold and colleagues (2003) showed that acute moderate exercise can induce increased BDNF serum concentrations as well as NGF levels. This confirms previous findings that showed increased NGF levels following acute stress. Findings of transient NGF induction by acute
exercise is promising for patients with MS suffering from neurodegeneration and cognitive decline: through BDNF induction moderate exercise might help promote neural recovery and plasticity. The long term effects of moderate exercise training on neurotrophic factors remains elusive (Gold et al., 2003).

Aerobic training in phase I of energy supply might have a positive influence on the brain in patients with MS through the induction of neurotrophic factors. A few studies as well as animal research and research on elderly people further suggest such beneficial effects. However, additional research is needed to clarify the exact processes. It would further be interesting to investigate the effects of aerobic training above the aerobic threshold.

4.6.3 Effects on Body structure (axonal damage/ loss and neuronal loss)

To date there is little data on the effect of physical activity on brain structure parameters, but there is some evidence that regular physical activity counteracts the structural degeneration of brain tissue in patients with RRMS. Furthermore, regular exercise could have a neuroprotective impact (Döring et al., 2012).

In patients with multiple sclerosis both gray and white matter atrophy is prominent from early stages of the disease onwards, leading to physical and cognitive deficits, including walking impairments, lesser information processing speed and learning and memory deficits. However, a difference between physically active and inactive patients can be seen. Patients with a higher level of cardiorespiratory fitness have a comparatively larger local volume of gray matter than lesser active patients. Moreover, a greater recruitment of cortical regions in fitter patients has been detected and improvements in walking and cognitive function might be directly linked to the effects of cardiorespiratory fitness on deep gray matter structures. (Döring et al., 2012; Motl et al. 2015; Leavitt et al., 2013).

In elderly people, cardiorespiratory fitness has already been associated with hippocampal volume. A trial of aerobic exercise training (50-60% heart rate reserve = phase I) in 120 older adults reported increases in hippocampal volume by 2% in the exercising group compared to controls (Erickson et al., 2011). Similar results can be seen in patients with Schizophrenia. Aerobic exercise training (1.5 – 2mmol lactate = phase I/II) led to an increase in hippocampal volume and improvements in short-term memory (Pajonk et al., 2010). Cardiorespiratory fitness may also be associated with other deep gray matter structures in the brain such as the thalamus and basal ganglia. This has been shown in older adults but the association was weak (Leavitt et al, 2013).
Based on such promising findings from studies approaching cardiorespiratory fitness, aerobic exercise and brain structures in elderly people, preadolescent children and patients with Schizophrenia a few studies on cardiorespiratory fitness and brain structure parameters in patients with MS have been conducted.

Leavitt and colleagues (2013) examined whether light to moderate (phase I/II) aerobic exercise affects hippocampal volume and influences memory in patients with multiple sclerosis. Over a period of 3 months 30 minutes of stationary cycling was performed 3 times a week by one patient suffering from memory-impairment. Compared to a non-exercising memory-impaired control aerobic exercise led to an increase in hippocampal volume, memory and hippocampal resting-state functional connectivity. Changes in overall gray matter, non-hippocampal deep gray matter structures and non-memory cognitive function did not alter significantly (Leavitt et al., 2013).

Although the trial provides important new insights on the effects of aerobic exercise on gray matter structures and memory in patients with multiple sclerosis, its findings are greatly limited due to the testing of only two patients.

Motl and colleagues (2015) reported an association between cardiorespiratory fitness and volumes of the basal ganglia and hippocampus but not the thalamus in patients with MS. They showed that patients with higher levels of cardiorespiratory fitness had larger volumes of caudate putamen, pallidum and hippocampus. These findings could have a substantial impact on the life of patients with MS, as volumes of the caudate, putamen, pallidum and hippocampus have been associated with cognitive and motor outcomes in MS. Motl and colleagues (2015) highlighted the importance of their findings as it suggests, “MS related loss in volume of the basal ganglia and hippocampus may be remediated through regular exercise participation” (p.665). The study group promotes the design and delivery of aerobic exercise interventions for changing deep gray matter structures within the brain (Motl et al., 2015).

Prakash and colleagues (2010) found a positive association between cardiorespiratory fitness (defined by VO$_{2\text{peak}}$) and regional gray matter volumes. 21 patients with relapsing-remitting MS and 15 in age and education matching controls were enrolled in the study and underwent an assessment of aerobic fitness (exhaustion cycling test to assess VO$_{2\text{peak}}$). The study group showed that higher levels of fitness were associated with greater gray matter volume in the midline cortical structures. Furthermore, they showed that increased levels of fitness can be associated with higher fractional anisotropy in the left thalamic radiation and right anterior corona radiata. Importantly gray matter atrophy was linked with worsening of motor and cognitive outcomes, whereas preserved gray matter volume and white matter tract integrity
were linked to better performances on measures of processing speed (Prakash et al., 2010; Motl et al., 2015).

Cardiorespiratory fitness, defined by maximal oxygen uptake, and light to moderate (phase I & II) aerobic training might influence the deep gray matter structures and therefore the cognitive and motor functions in patients with multiple sclerosis. This hypothesis was corroborated by the studies targeting the topic so far. Still the data is not yet sufficient to prove beyond doubt the impact of light to moderate (phase I & II) aerobic exercise on brain structure in patients with multiple sclerosis.

All of the studies have significant limitations. They lack a proper sample size and are almost incomparable due to different interventions, protocols and measuring tools. The aerobic regimes used in the trials are insufficiently described and differ in intensity and duration. Further, the extent of disability in the subject groups is not given.

However, studies support the assumption that light to moderate aerobic exercise has beneficial effects on the deep gray matter structures of patients with MS and even memory impairments. The findings also strongly correlate to those of other studies targeting brain structure changes due to aerobic exercise in phase I to II of energy supply and cardiorespiratory fitness (defined by VO\textsubscript{2peak}) in older people and patients with Schizophrenia. Further research is clearly required to confirm the beneficial effects of cardiorespiratory fitness on brain structures and to promote aerobic exercise as treatment regime in patients with MS. Additionally, the optimal aerobic exercise intensity should be investigated.

### 4.7 Body function

#### 4.7.1. Depression

Depression affects many patients suffering from MS and requires effective treatment methods. Unfortunately, the American academy of neurology reported insufficient evidence for the efficacy of antidepressant medications or therapies for the management of depression in MS.

Exercise training is known to reduce depressive symptoms in the general population suffering from depression. Studies on the effects of exercise training in patients with MS have been equivocal. Reviews noted heterogeneous results of trials using aerobic and resistance training of various intensities and durations with several reporting a beneficial effects and others failing to note improvement (Giesser, 2015; Motl & Sandroff, 2015; Motl & Pilutti, 2012).

Such inconsistencies may be explained by the fact that most studies do not have depression as primary outcome. Further, MS patients without depressive symptoms have been included
in the trials sophisticating the outcomes (Giesser, 2015; Motl & Sandroff, 2015; Motl & Pilutti, 2012). Another important factor leading to heterogeneous study results are the often insufficient described training methods, making studies hard to compare.

A questionnaire on fatigue, depression and quality of life in exercising and non-exercising patients with MS assessed the self-perceived depression levels of the participants. 121 patients, 52 exercisers completing at least two 30 minute sessions per week and 69 non exercisers, were included in the study. In order to assess depression the Beck’s Depression Inventory (BDI) was used. Through twenty-one items the patients were asked how they felt over the past week. Every question is scored and higher scores equal more severe depression. The questionnaire showed significant lower BDI scores in the Exercisers, indicating a positive correlation between exercise and beneficial effects on depression (Stroud & Minahan, 2009).

### 4.7.2 Fatigue

Experienced by up to 90% of patients with MS fatigue is a major factor of limitation in daily living as well as physical activity.

The problematic coping mechanism of some patients are described by Döring et al. 2012) as follows: "[...]some MS patients end up in a vicious circle: out of a wish to reduce fatigue they decrease physical activity which over time reduces endurance, muscle strength, and quality of life and may enhance fatigue, which then thus in turn further limits physical activity and social life" (p.9.). Generally, spoken improved fatigue is beneficial for both the physical and psychological status of the patients (Smith et al., 2009).

So far, studies on the influence of exercise on fatigue in patients with MS have yielded heterogeneous results, as some demonstrated positive results, whereas others demonstrated no effects. The comparison of the study results is often difficult due to different fatigue scales used to measure the fatigue, mixed fatigued and non-fatigued subject groups and fatigue not being the primarily study outcome. Further, the design of the training intervention differs greatly between the trials. Using different levels of intensity, duration and frequency and additionally lacking sufficient description of the used regimes, comparability is almost impossible (Döring, Pfueller, Paul and Dörr, 2012; Andreason, Stenager & Dalgas, 2011).

A questionnaire on fatigue, depression and quality of life in exercising and non-exercising patients with MS assessed the self-perceived fatigue levels of the participants. 121 patients, 52 exercisers completing at least two 30 minute sessions per week and 69 non exercisers, were included in the study. To assess fatigue levels the Modified Fatigue Impact Scale (MFIS) was used, which provides information on the physical, cognitive and psychosocial status. Higher scores indicate a greater impact of fatigue on the individual. In the Exercisers, the
overall MFIS scores were significantly lower than in the Non-Exercising group (Stroud & Minahan, 2009).

Andreason et al. (2011) compared the effects of different types of resistance training in healthy individuals and patients with MS. Four studies, two using hypertrophy training and two using a mixed hypertrophy and muscular endurance training, were compared by the group. They noted that the central motor activation is improved in healthy individuals compared to patients with MS and that resistance training has been shown to enhance the efferent motor drive in patients with MS (Andreason et al., 2011).

In aerobic exercise trials, fatigue is often a secondary outcome. Rampello and colleagues (2007), van den Berg and colleagues (2006) and Newman and colleagues (2007) all examined the effects of light to moderate aerobic training on walking parameters but had a look at fatigue levels as well. Only Rampello and colleagues (2007) reported improved fatigue levels after exercise. It should be noted, that Rampello et al. (2007) were the only group using phase II aerobic training, whereas both of the other groups used a mixed phase I and phase II training protocol.

Learmouth and colleagues (2014) conducted a study using phase I and II aerobic training interventions with fatigue-levels as a main result. 15 minutes of light to moderate aerobic cycling had no short-term effect on fatigue levels, but did not worsen the patients status either (Learmouth et al., 2014).

In a 2011 review on the effects of exercise on MS related fatigue Andreason et al., (2011) noted that research still lacks a comparison of the effects of different exercise modalities and therefore making it difficult to draw conclusion on the optimal type of exercise. Because of the consistently positive effects of resistance training it is speculated to be favourable over endurance training, but this speculations lack evidence (p. 1050). Döring et al., (2012) have made another training recommendation, suggesting performing training sessions in the morning, as fatigue often increases over the day (p. 9).

Smith et al. (2009) explored the influence of exercise on fatigue perception. As positive influences of exercise on fatigue, they defined “perceived physical improvements in strength, stamina, balance, as well as better sleep quality and positive feelings, including achievement, confidence and relaxation” (p.691). Negative influences on the other hand consisted of “perceived physical deterioration such as unsteady gait and reduced balance; and negative feelings of failure, anxiety and loss of safety.” (p.691).
A helpful component in exercise related fatigue management seems to be the social component involved either by supervised training, group exercise or through contact to other participants. The social interaction can have an influence on the perception of fatigue and may provide the psychological support to increase training motivation (Döring et al., 2012; Andreason et al., 2011).

Furthermore, exercise training has the ability to reduce secondary diseases and therefore bring relieve to patients suffering from fatigue.

Physiologically, the beneficial effects of exercise on MS related fatigue could be explained by a training-induced up-regulation of neuroendocrine growth factor production and anti-inflammatory cytokines (Andreason et al., 2011; Stroud & Minahan, 2009).

Although the exact influence of exercise on the fatigue levels of patients could not be clarified so far, no study has demonstrated a worsening due to exercise and most studies suggest beneficial results from exercise. Previous concerns that exercise potentially worsens fatigue in MS by taxing energy levels and reserves or due to increased core body temperature have been shown to be unjustified. All modalities of training seem to have the potential to reduce fatigue in patients with MS. Still it is currently not possible to provide training recommendations on optimal intensity, duration or frequency (Giesser, 2015; Motl & Pilutti, 2012; Andreason et al., 2011).

4.7.3 Cognition
Cognitive impairments include reduced information processing speed, attentional deficits and episodic memory deficits and are associated with unemployment, loss of employment, reduced social functioning and loss of driving abilities in patients with MS (Motl & Sandroff, 2015).

Beneficial effects of exercise on cognitive functions have been shown in several patient populations, including Alzheimer’s disease, elderly people, persons with schizophrenia as well as children and adolescents. Animal studies have also reported positive effects of exercise (Motl & Sandroff, 2015; Giesser, 2015).

Furthermore, positive correlations between physical fitness and cognitive function have been shown (Motl & Pilutti, 2012; Giesser, 2015). Giesser (2015) noted “improved physical fitness has been reported to correlate with improved cognitive function in persons with MS and that cardiorespiratory fitness in persons with MS predicts neuronal plasticity and increased gray matter volume, better white matter integrity and improved performance on test of information process speed” (p.126).
However, literature on the effects of exercise on cognition in persons with MS rarely exists. One literature review researching the effects of exercise training on cognition in patients with MS and one review in adults with neurological diseases including MS reported inconsistent evidence (Motl & Sandrof, 2015). On the contrary one trial using aerobic exercise intervention showed improvements in several neuropsychological domains compared to controls (Giesser, 2015), whereas two trials showed no effects (Motl & Pilutti, 2012).

Overall, the research on exercise training and cognition in MS lack distinct results. Methodological limitations further restrict comparability and does not permit conclusions. Limitations include studies not continuing the exercise programs long enough for effectiveness in changing cognition, poor compliance with the exercise program and prescription and insufficient supervision or monitoring (Motl & Sandroff, 2015).

Motl and Pilutti (2012) further criticise the nature of the exercise training stimulus (low intensity, infrequent, unsupervised delivery) used in some trials. Contrary to stimuli used in the gerontology field, where consistent evidence for improvement was reported, the stimuli in MS studies was to limply (Motl & Pilutti, 2012).

Positive associations between physical activity, fitness and cognition as well as promising results from gerontology studies promoted interest in the continued investigation of exercise training and cognition in patients with MS. The conduction of further well-designed studies on exercise training and cognition in patients with MS might provide a better understanding of the effects of exercise training on cognitive abilities.

4.7.4 Cardiovascular
Autonomic dysregulation is often present in patients with multiple sclerosis and manifests itself by abnormal sweating, urinary dysfunction, orthostatic dysregulation, gastrointestinal symptoms and cardiovascular dysfunction.

In patients with multiple sclerosis, a disturbed cardiac autonomic control can be observed during exercise: the heart rate response to graded exercise is generally linear with respect to work rate, but it is blunted compared to healthy controls. The heart rate increase during the first 20 seconds of exercise is smaller in patients with multiple sclerosis, which indicates the withdrawal of the tonic vagal activity after initiation of exercise. Furthermore, a correlation between a smaller heart rate increase during the first 20 seconds of exercise and walking capacity in patients with multiple sclerosis can be seen. The disturbed cardiac autonomic control in patients with multiple sclerosis might be linked with impaired exercise tolerance.
Many patients experience fatigue before reaching their age-predicted peak heart rate (White & Dressendorfer, 2004; Hansen et al., 2015).

Cardiovascular dysfunction can further lead to an attenuated rise in blood pressure during exercise, which could lead to insufficient perfusion of the brain, muscles and might result in the development of exertional symptoms (White & Dressendorfer, 2004).

In healthy subjects and animal studies long-term exercise interventions have been shown to improve cardiac autonomic control (pre-dominance of parasympathetic component, lower resting heart-rate, lower exercise heart-rate, faster heart-rate recovery after exercise). If exercise obtains the same effect in patients with multiple sclerosis is yet unknown (Hansen et al., 2015).

Hansen and colleagues (2015) examined whether long-term exercise interventions improve heart-rate changes during exercise and if it correlates with improvements in exercise tolerance. Fourteen subjects underwent six months of combined endurance-resistance training. The training resulted in no improvements in heart rate changes during exercise but significant improvements in exercise tolerance. Resting heart rate, 20- and 60-second exercise-onset heart rate increased and heart-rate recovery after exercise was not affected by the training.

Hornich (2015) provided evidence, that four week of light aerobic training resulted in an economization of cardiac activity in the cycling intervention group indicating that an effective stimulus is needed to trigger physiological changes.

The lack of improvement in cardiac autonomic control in patients with multiple sclerosis might be explained by a disturbed vagal nerve activity due to brainstem lesions or lesions in the central command brain structures. Hansen and colleagues (2015) further explain that a lack of improvement may be caused by an insufficient impact on the physiology from the intervention. This hypothesis is supported by a study conducted by Hornich (2015), who was able to show, that a certain level of intensity is need to provoke an adaptation after exercise. However, significant effects were observed for changes in blood lactate content and BORG ratings (Hansen et al., 2015).

The study group was able to confirm previous finding regarding interferon therapy and heart rate variability. Hansen and colleagues (2015) observed that “interferon therapy was significantly related to a greater increase in HR during the first 60 seconds of exercise, during follow-up and a lack of a decrease in exercise blood lactate content. These data might indicate that interferon therapy accelerates tachycardia during the first minute of exercise and inhibits improvements in exercise tolerance” (p.230). Exercise toleration could therefore be directly related to interferon therapy (Hansen et al., 2015).
In an earlier study Feltham and colleagues (2013) explored the cardiorespiratory and perceptual response and adaption to exercise at maximal and sub-maximal levels of physical exercise (p.766). The participants (n=21) underwent a twelve week continuous (n=12) or interval (n=9) cycling routine. During the first week all of the participants showed an abrupt or non-linear heart rate response to sub-maximal exercise. At the end of the intervention the cardiovascular response to sub-maximal exercise was gradual or linear and therefore analogous to the heart rate response reported in people with no neurological disorder. Feltham and colleagues (2013) concluded that the abrupt or non-linear heart rate response seen at baseline may be caused by deconditioning. Some autonomic dysfunctions could therefore be improved by physical activity (Feltham et al, 2013).

4.7.5 Aerobic power/cardiopulmonary fitness/ VO$_2$

In patients with MS respiratory problems and reduced cardiorespiratory fitness are common. This can be seen in many neurological disorders and might be associated with a chronic increase in arterial carbon dioxide tension. Physical inactivity is another factor that might contribute to the emergence of respiratory problems, as immobility can lead to reduced lung volume. Both factors might have an influence on the cardiorespiratory fitness in patients with MS, but so far there is inconsistence evidence for associations between either factor and the disability (Motl & Goldman, 2011; Klefbeck & Nedjad, 2003).

For a long time respiratory problems were believed to only occur in terminal stages of MS. Respiratory muscle weakness was considered to emerge in advanced stages of MS and little attention was given to early stages. Only in recent years the presence of cardiorespiratory dysfunction in the early course of the disease and in ambulatory patients has been described, but studies are limited. Bosnak-Guclu and colleagues (2012) described an early onset of respiratory muscle weakness, especially expiratory muscle weakness, which is often not recognized until later stages of the disease. They recommend routine measurements of respiratory muscle strength in patients with MS for the early detection of weakness. Respiratory muscle training and aerobic exercise training should be started early to prevent the occurrence of respiratory complications and to improve functional exercise capacity. Impairments in pulmonary function in patients with MS can have fatal consequences: the vital capacity decreases drastically when there is a 50% or greater loss of respiratory muscle strength (Bosnak-Guclu et al., 2012).

Some studies have examined associations between respiratory parameters and exercise training in patients with MS. For example, Hansen and colleagues (2013) examined the VO$_2$ kinetics during exercise in patients with multiple sclerosis. They observed significantly slower VO$_2$ during the onset of sub-maximal endurance exercise compared with healthy individuals.
They assumed that the lowered skeletal muscle oxidative capacity in patients with MS was responsible for the findings. Feltham and colleagues (2013) observed cardiorespiratory adaptations to exercise in patients with MS and suggested that skeletal muscle oxidative capacity, variable by heart rate and stroke volume adapt after exercise (Feltham et al., 2013).

Klefbeck and Nedjad (2003) examined whether 10 weeks of supervised inspiratory muscle training in patients with MS would affect their respiratory muscle strength, respiratory capacity and overall well-being and further investigated one-month follow up effects. During the training period the participants completed specific inspiratory threshold loading training twice every other day by 3 sets of 10 loaded inspirations. Maximal inspiratory pressure (Pmax) and maximal expiratory pressure (PEmax) improved significantly in the training group after the training period and one month follow-up, but respiratory parameters such as FEV, FVC; VC, PEF and FEV% were not affected. Whether effects in respiratory parameters could have been achieved by altering the training load and intensity remains elusive (Klefbeck & Nedjad, 2003).

Motl and Goldman (2011) published two studies examining the association between physical activity and cardio-respiratory fitness and the associations between physical activity, neurological disability and cardiorespiratory fitness in patients with RRMS. Both studies indicated that physical inactivity and neurological disability are independently associated with reduced levels of cardiorespiratory fitness in persons with MS.

One other study investigating correlations between physical activity and cardiorespiratory fitness reported contrary findings: no significant association between physical activity and VO₂peak consumption could be seen. Differences in study designs may be responsible for the positive and null-result outcomes in the studies (Motl & Goldman, 2011).

Inconsistent associations have also been seen between cardiorespiratory fitness and neurological disability in patients with MS. A growing body of research suggests a correlation between neurological disability and reduced cardiorespiratory fitness in patients with MS. Motl and Goldman (2011) further suggest that this association is independent of physical activity behaviour.

These study results underline the importance of promoting physical activity behaviour in patients with MS in order to obtain cardiorespiratory fitness and to ensure independence

4.7.6 Spasticity and Paresis

The lack of drug based treatment for paresis and insufficient results from antispastic drugs left physical and occupational therapy techniques as the most promising treatment options.
Only a small number of controlled studies on exercise training as a treatment for MS related spasticity and paresis exist, but these showed positive effects in reducing the conditions. Furthermore, muscle strength has been shown to significantly improve as well as walking speed, stepping endurance, stair climbing and timed up and go test results (Giesser, 2015; Döring et al., 2012).

One study examined the effects of four week locomotor training in two patients with multiple sclerosis suffering from paresis (Hornich, 2015). After four week of training, the patients were able to maintain the $p_{max}$, slightly economize their cardiac ability and significantly improve their quality of life. The study further showed that stress resistance slightly improved after four weeks of training (Hornsich, 2015).

Some authors provided recommendations for exercise training targeting spasticity- and paresis- related conditions. Aquatic exercises are favourable as the gravity impact is reduced and even patients with severe paresis of the lower extremities are able to perform standing and moving exercises. For patients with difficulties in standing and immobilized patients supporting measures are needed. Standing frames can be helpful in training torso, limb and respiratory muscles. Passive range of motion exercise proximal to the paralyzed region and locomotor training are other effective training methods (Giesser, 2015; Döring et al., 2012). It is further mentioned to carry out exercises regularly and with sufficient intensity. Affected muscle groups should additionally be lightly stretched for approximately 20-60 seconds prior to and after exercise (Döring et al., 2012).

With respect to the few and partially inconsistent data available so far, the evidence suggests a positive influence of exercise training on MS-related spasticity and paresis (Giesser, 2015; Döring et al., 2012).

4.7.7 Gait parameters/ Walking performance

Many trials have examined the effect of exercise training on walking outcomes in patients with MS. The main outcomes of modulation in these trials are walking speed and endurance.

Walking velocities are most commonly tested using the timed 25-foot walk or 10m walk test. Endurance tests include the 25 minute walking test.

Walking distance is commonly assessed through 2 or 6 minutes walking tests, where the distance patients are able to walk in the given time is measured.

Furthermore gait parameters are tested using the “timed up and go” test and to test functional capacity stair climb tests, chair stand tests and kinematic gait analysis.
The effects of resistance training on walking parameters in patients with multiple sclerosis are not consistent. One review examined the effects of resistance training on walking performance in patients with multiple sclerosis. Test results of 2 or 6 minute walking tests, timed 25 foot walk, 10m walk test and “timed up and go” test were mixed with some studies reporting beneficial outcomes and no change. The authors concluded that resistance training may have beneficial effects on strength and functional tasks, but there is few to no evidence for improvements in timed or distance based walking tests (Kjolhede et al., 2012).

Taking a look at three recent trials similar findings could be seen.

Gutierrez and colleagues (2005) observed significant improvements in walking performance of patients after 8 weeks of progressive resistance training. The subjects spent lesser stride time in the stance and double-support phases and increased the percentage of stride time in the swing phase, step length, stride length and foot angle. Overall the gait changed from lesser conservative to more conservative walking and came close to normative values (Gutierrez et al., 2005).

Dodd and colleagues (2011) on the other hand could not notice significant increases in the walking distance or maximal walking speed after a 10-week progressive resistance trial compared with the control group. The authors noted, that there may have been too few subjects to detect significant changes (Dodd et al., 2011).

Aerobic training seems to have more profound effects on gait parameters and walking ability in patients with MS.

Wonneberger and Schmidt (2015) reported significant improvements in gait parameters after a 12 month individualized aerobic endurance training. The patient’s treadmill - walking performance was video recorded and step cadence, step length and ground contact were analysed. After the endurance exercise - program significant increases in ground contact time, step and step length were detected as well as a significant decrease in step cadence (Wonneberger & Schmidt, 2015).

Newman and colleagues (2007) observed beneficial effects of a four-week light to moderate aerobic treadmill-training regime on walking effort and gait parameters. Walking effort was measured by oxygen consumption during treadmill walking of comfortable speed and gait parameters by the “gait-rite”, 10m time and 2-minute distance. The study group observed “a reduction in resting metabolism, increase in walking endurance, a more normal tempo-spatial gait pattern, increased self-selected walking speed and a decrease in walking effort” after four weeks of aerobic treadmill-training of light to moderate intensity (Newman et al., 2007, p.116).
Rampello and colleagues (2007) reported significantly improved walking distances and speed during self-paced walk, maximum work rate, peak oxygen uptake and oxygen pulse in subjects with multiple sclerosis after an 8 week aerobic training regime of moderate intensity (phase II of energy supply). They further noted, that patients who were most disabled tended to benefit more from this kind of aerobic training than lesser-disabled ones (Rampello et al., 2007).

In combined trials results suggest beneficial effects of exercise on the walking abilities of patients with MS. Romberg and colleagues (2004) reported significant improvements in the 7.62 MWT and 500 MWT in the exercise group with 22% of the patients improving their abilities over 20% after a 6 month exercise program. In a more recent trial Sangelaji and colleagues (2014) confirmed beneficial effects of combined exercise regimes with patients improving their 6MWT time. For the sake of completeness, it has to be added that walking performance was not the main result in this study.

Motl and Sandroff (2015) hypothesized that the beneficial effects from exercise training occur through effects on either the CNS and/or peripheral physiological functions. Their research revealed a consistent benefit of exercise training on walking parameters in patients with MS. They further noted that a larger effect with supervised training was achieved and a limited evidence for a long term maintenance effect (Motl & Sandroff, 2015). Two years earlier Motl and Pilutti (2012) published a review examining the effect of exercise training on ambulatory outcomes in patients with MS. Analysing more than 25 experimental trials they concluded that “walking speed is shown to improve following combined or isolated aerobic or resistance training, as well as after calisthenics, stability or aquatic training. Improvements in walking endurance are primarily seen following aerobic training, but resistance training or combined aerobic and resistance training exercise have also shown benefits on this outcome. Interestingly, walking speed and endurance have both been shown to improve following robot-assisted treadmill training in people with MS who have gait impairment, which may reflect an effect of the task-specific nature of this training modality” (p. 7).

Overall, there are collectively beneficial effects have been reported, whether walking abilities were a primary or secondary outcome. It can be said, that exercise training is a safe and beneficial method to improve gait parameters.

4.7.8 Sensory and balance
Next to walking balance is another domain of mobility that takes a toll on patients with MS. Balance skills and the patient's perceptions of their own balance are compromised. The effects of MS on the balance of patients is often seen in increased sway during quiet stance and is
related with falls and fall-related injuries (Döring et al., 2012; Kjolhede et al., 2012, Motl & Sandroff, 2015).

Only a handful of studies have chosen balance variables as primary outcome parameter. More commonly, balance is a secondary outcome parameter in studies examining the walking abilities and effect of exercise on gait parameters in patients with MS. One systematic review and meta-analysis of RCTs showed small but statistically significant effect of the exercise training modalities on balance in patients with mild or moderate MS (Motl & Sandroff, 2015). Kjolhede and colleagues (2012) reviewed the effects of resistance training on balance and concluded that preliminary findings might suggest improvements in balance of MS patients following resistance training.

One recent review showed small but beneficial effects of exercise training on balance in MS. The positive influence of exercise on balance might be explained by a rise in confidence due to exercise related progress. Further walking abilities could be improved post-exercise. Physiological the improvements might be explained by microstructural changes in brain regions associated with postural control and balance (Motl & Sandroff, 2015).

Exercise training can be challenging for patients with limited balance skills. The sitting position of cycling training and walking insecurities can be adventurous for patients. Post-exercise exhaustion can further lead to insecurities in walking and a negative self-perception of the patients balance skills. This might explain a negative association of the patient’s perception of training effects.

It should be mentioned that Motl and Sandroff (2015) criticised the methodological quality of many studies, mostly because of their small sample sizes and their validity.

4.7.9 Muscle strength/ muscle endurance/ intramuscular
Many patients with MS suffer from impaired strength and muscle function. Most of the time lower extremities are more affected, which leads to decreased ambulatory capacities of the patients. Several studies have demonstrated beneficial effects of exercise training, including resistance training, aerobic training, combined aerobic and resistance training, aquatic training and robot assisted gait training. Although the subject populations and protocols vary, the studies have consistently reported improvements in muscle strength after training (Medina-Perez et al., 2014; Motl & Pilutti, 2012; Giesser, 2015).

A review of progressive resistance training included 12 studies, with different training modalities ranging from free weights to resistance bands and weight machines. Increases in muscle strength of the trained muscles were reported in all of the studies that mainly have
focused on the lower extremities. Maximal voluntary contractions of the knee extensors, knee flexors and plantar flexor muscles were increased by 7-21%. Dynamic strength (1RM) was increased by 20-50% (Kjolhede, Vissing & Dalgas, 2012).

Trials underline these findings. All studies reported improvements in muscle strength following resistance training (Fimland et al., 2010; Dodd, Taylor, Shields, Prasad et al., 2011; Gutierrez et al., 2005; DeBolt & McCubbin, 2004; Perez, 2007; Medina-Perez et al., 2014; White, McCoy et al., 2004). Fimland and colleagues (2010) reported a mean increase of 20% in maximum voluntary contraction after three weeks of maximal strength training, which is a very similar outcome to that of healthy individuals after likely training loads. This result emphasises the potential for improvements in strength through resistance training for patients with multiple sclerosis (Fimland et al., 2010).

Strength was tested through maximal voluntary contraction and one repetition maximum. Some authors also measured muscle endurance, but the results were not as distinct. In the reviewed trials for example, one study reported increases in muscle endurance by 39.7% (Dodd et al., 2011), whereas another study reported no significant increases (Medina-Perez et al., 2014).

Medina-Perez and colleagues (2014) investigated the effects of detraining in patients with multiple sclerosis, a subject not many researchers have turned to so far. Detraining in healthy individuals is characterised by a loss of training adaptations and muscle performance and is determined by a detraining period, the subject’s age and physical fitness, and the frequency, intensity and duration of the training protocol. Detraining in patients with MS is not well analysed so far, although detraining affects training-induced adaptations.

In the study, 12 weeks of detraining followed 12 weeks of resistance training. After the training period, the maximum voluntary isometric contraction and muscle power increased, but the muscle endurance was not altered. After 12 weeks of detraining, the MVIC and torque reduced, but the exercise group still scored higher than the control group. The detraining period did not affect the average power, which remained significant higher than the pre-training scores (Medina-Perez et al., 2014).

In aerobic and combined trials muscular strength often represents a secondary outcome. However, many of these have reported improvements in muscle strength following training (Giesser, 2015).

There is strong evidence that resistance-training interventions increase muscle strength in patients with multiple sclerosis. These improvements however are restricted to the muscle
groups targeted during training, which is not unique in patients with multiple sclerosis. The effect of resistance training on muscular endurance is not as distinct and further research is needed. One study has shown that detraining reduces MVIC and torque, but not muscle endurance. Research has so far focused mostly on lower muscle groups and statements about upper body strength cannot be made.

4.8. Quality of Life (QoL)

The Quality of Life is influenced by a lot of factors and greatly depends on the patient. Physical activity and exercise can be beneficial for the Quality of Life (QoL) as many negative impacts on the patient can be reduced.

A questionnaire on fatigue, depression and quality of life in exercising and non-exercising patients with MS assessed the self-perceived fatigue levels of the participants. 121 patients, 52 exercisers completing at least two 30 minute sessions per week and 69 non exercisers, were included in the study. To assess the Quality of Life of the patients the Health Status Questionnaire Short Form 36 (SF 36) was used, which provides scores for eight dimensions: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health. The final outcome constitutes of a physical component summary score and a mental summary score. The higher the score is the higher is the QoL. Exercisers scored significantly higher on all scales of the SF36 compared to Non-Exercisers (Stroud & Minahan, 2009).

RCTs could not provide consistent findings. Some trials indicated improved QoL after resistance and aerobic training, whereas others could not report statistically significant findings.

One study including 35 patients with mild to moderate MS showed that four weeks of combined training led to a significant increase in both mental and physical quality of life, regardless of EDSS and disease course. Patients with an EDSS of 3 ± 1 reportedly had the highest quality of life. However, patients with an EDSS of 5 and above yield the biggest improvements after 4 weeks of combined training (Hornich, 2015).

One meta-analysis surveyed the effect of exercise training on QoL in patients with MS, reported significant improvements in QoL post-exercise, with aerobic, resistance, and combined protocols (Giesser, 2015; Motl & Pilutti, 2012).

A 2013 longitudinal study reported significant improvements in both physical and mental health aspects of quality of life after a combined training program compared to controls. Two earlier
studies showed similar outcomes, but one longitudinal study reported no effectiveness of exercise training on the quality of life in patients with MS (Sangelaji et al, 2013).

Methodological problems seem to be a major problem in order to obtain comparable results and lead to inconsistency in the literature. Small sample sizes often result in low statistical power per study. Furthermore, the use of different measure tools can cause differences in the analysis. Still, the literature provides small but consistent evidence that exercise improved the QoL in the patients (Motl & Pilutti, 2012; Motl & Sandroff, 2015; Giesser, 2015).

Participation in regular physical activity appears to have a positive influence on the patients perceived QoL. These positive effects might be mediated through changes in the body function or activities, for example a patients improved ability to perform physical tasks. Moreover, the patient’s perception of the impact the disability has on their physical functioning can improve (Motl & Sandroff, 2015; Stroud & Minahan, 2009; Motl & Pilutti, 2012; Sangelaji et al, 2013). Smith et al., (2009) additionally introduce the concept of self-efficacy, which describes the level of perceived control. Self-efficacy strongly influences adherence or avoidance of positive health behaviours and perceived level of quality of life according to the authors (Smith et al., 2009).

5. Exercise recommendations (so far published guidelines for persons with MS)

Despite the heterogeneity of the disease and the methods of trial of exercise as a therapeutic modality, a few authors designed guidelines for exercise that should be prescribed for patients with MS.

Dalgas and colleagues (2008), Latimer-Cheung and colleagues (2013) as well as White and Dressendorfer (2004) framed exercise recommendations for patients with MS that include resistance training, aerobic training and combined training.

Table 9: Exercise recommendations

<table>
<thead>
<tr>
<th></th>
<th>Aerobic training</th>
<th>Resistance training</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalgas et al. (2008)</td>
<td>10-40 min.; 2-3 x/week; 50-70% VO2peak, 60-80% HRmax</td>
<td>2-3x/week, 4-8 whole body exercises; 1-3 sets of 10-15 repetitions, 2-4 min. rest</td>
</tr>
<tr>
<td>Latimer-Cheung et al. (2013)</td>
<td>30 min. 2x/week</td>
<td>2x/week; larger muscle group exercises, 2 sets of 10-15 repetitions, 1-2 min rest</td>
</tr>
<tr>
<td>White et al. (2004)</td>
<td>20-30 min; 2-3x/week; 50-70% VO2peak; 65-75% HRpeak, 11-14 RPE</td>
<td>2-3x/week; 1-3 sets of 8-15 repetitions for each major muscle group</td>
</tr>
</tbody>
</table>

VO2max: highest volume for oxygen uptake; HRmax: highest value for heart rate; RPE: rating of perceived exertion
White and Dressendorfer (2004) pointed out the importance for patients with MS to consult with physician in order to have an exercise programme designed especially for the needs of the patient. Nonetheless, the group framed exercise recommendations for aerobic, strength, combined, aquatic and flexibility training. For cardiorespiratory exercise, White and Dressendorfer (2004) recommend 2-3 sessions per week of moderate intensity. The group defined moderate exercise as ratings of 11-14 on the BORG scale, 65-75% of maximum heart rate and 50-70% of maximum VO$_2$. As training modalities stationary cycling with legs or arms, swimming, aquatic exercise and treadmill or elliptical trainer are suggested, with treadmill and elliptical trainer restricted to high functioning MS patients (White & Dressendorfer, 2004).

Recommendations for resistance training include exercises targeting the whole body. Strength sessions should be held 2-3 times per week consisting of 1-3 sets of 8-15 repetitions for each major muscle group. Resistance can be increased by 2-5% if 15 repetitions are correctly performed (White & Dressendorfer, 2004).

If combined, aerobic and resistance training should be alternate on separate days of the week. Between the session a rest period of 24-48 hours is recommended (White & Dressendorfer, 2004).

Dalgas and colleagues (2008) have designed guidelines based on a systematic review of the published papers discussing exercise and MS at that time. Their guidelines approach resistance, endurance and combined training.

The recommendations on resistance training are based on general resistance training recommendations and the information taken from literature dealing with resistance training in MS. The authors emphasize the importance of supervised resistance training for patients with MS until the patient feels comfortable performing the given tasks. It is considered superior by the authors to perform supervised resistance training and to use training machines. Dalgas and colleagues (2008) recommend resistance training 2-3 times per week consisting of a whole-body programme containing 4-8 exercises. Patients should perform 8-15 repetitions for a start, which should be progressively increased to intensities around 8-10 repetitions. The number of sets should at first range from 1-3 and later increase to 3-4 sets. Between each set a rest period from 2-4 minutes has been recommended (Dalgas et al., 2008). For Dalgas and colleagues (2008) bicycle ergometry, arm-leg ergometry, arm ergometry, aquatic exercise and treadmill walking are suitable endurance modalities for patients with MS. Their recommendations include 2-3 endurance sessions per week with an initial training intensity of 50–70% of VO$_2$-max corresponding to 60–80% of maximum heart rate. A session should last for 10-40 minutes. The study group suggested that during the first 2-6 months the training volume should be increased by longer training durations or by adding an additional
training day. Higher training intensities of up to 90% VO$_{2\text{peak}}$ should only be applied if the higher intensity is well tolerated by the patient (Dalgas et al., 2008).

For combined training, the proportion of resistance and endurance training should be equal and performed on alternate days. The weekly maximum at the start should be two days of resistance training and two days of endurance training. Furthermore, a rest period of 24-48 hours should separate the two bouts of resistance and endurance training (Dalgas et al., 2008).

Dalgas et al. (2008) pointed out that patients should consult experts before starting a new exercise programme. The new training programme has to be designed on an individual basis that considers one's capabilities and impairments as well as environmental conditions.

Latimer-Cheung and colleagues (2013) have released guidelines regarding physical activity and exercise for adults with minimal to moderate disability and either relapsing-remitting or progressive forms of MS. The guidelines have been published in cooperation with the MS society of Canada and can be accessed over their website via a patient-informative folder (N.N., 2012, Canadian physical activity guidelines).

The guidelines consist of recommendations for aerobic and resistance training, as well as general information regarding physical activity. Latimer-Cheung and colleagues (2013) recommended 30 minutes of moderate intensity aerobic training twice a week. Moderate intensity is classified as “a 5 or 6 on a scale out of 10, and [it] causes your heart rate to go up” (p. 1834). Recommendations for resistance training include strength-training exercises for the major muscle groups twice a week. The group suggests to work up to 2 sets of 10-15 repetitions, with a rest period of 1-2 minutes between each set and exercise. The resistance should be heavy enough to barely, but safely, finish one set. According to the guidelines aerobic and resistance exercises can be performed on the same day, but the patients should include a rest day between strength training days (Latimer-Cheung et al., 2013).

The practical information included in the patient information consists of activity examples, tips to avoid overheating and on fatigue (N.N. MS get fit toolkit).

The so far published guidelines provide patients with easy understandable, practical information and hazard warnings, but they fail to go into detail. Only vague information on the type of exercises and their correct carrying out are given. The guidelines further lack appropriate support for the patients and caretakers in the adaption of exercise for the individual needs of patients.

The above presented guidelines and recommendations are a step in the right direction, aiming to provide patients as well as caretakers with information on physical activity and exercising. Still there are many limitations to the guidelines that have to be considered. Primarily, the
individual needs, such as level of disability, cognitive status, fatigue, heat sensitivity and subject-specific impairments, of the patients must be taken into account. Further, it would be more appropriate to provide guidelines using the threshold concept to ensure well tolerable training intensities for all patients (problematic described in chapter 4.5). It appears to be an almost impossible task to provide guidelines aiming at the majority of patients with MS.

The above presented guidelines all lack information on the tolerability of the training modalities for specific EDSS. Dalgas and colleagues (2008) stated that their recommendations aim for patients with an EDSS of 7 or less, but specific information is not provided.

Resistance training programs do not include exercise-descriptions or any information on training conduction. Especially the recommendations presented by Latimer-Cheung and colleagues (2013) are in need of such information, as they aim to be practical guidelines for patients.

6. Conclusion and outlook

Multiple Sclerosis is a chronic inflammatory disease with a rather elusive etiology. Through the damage of CNS structures, the disease can affect many different body functions. It is well known that physical inactivity and deconditioning result in a worsening of symptoms and disease progress, whereas physical activity lead to beneficial effects on processes of MS.

Exercise training represents an approach for safely managing many of the consequences of MS. Motl and Sandroff (2015) recently summed up the current opinion of exercise training as “[…] the single most effective non-pharmacological approach for managing symptoms of MS and its functional consequences” (p.2). They further argue that exercise training is overall safe for patients with MS, with minimal, exercise-related adverse or serious adverse events reported in trials. Moreover, exercise training resulted in a reduced relapse rate and might exert a disease-modifying effect (Motl & Sandroff, 2015). Exercise training further provides the possibility to target specific symptoms.

Reviewing recent literature, these observations can be confirmed. Studies showed beneficial outcomes or null-results and listed almost no dropouts during the trials.

Many studies showed that physical activity and exercise in patients with MS triggers positive feeling in the exercisers. These include feelings of achievement, confidence and relaxation. Exercise training in patients with MS has the ability to show the exercisers what they are capable of and make progress visible. Additionally patients get more aware of their body and their abilities.
The so far published literature suggests small but consistent beneficial effects of exercise training on fatigue and cognition (table 4). Furthermore, there are proven beneficial physical components involved. Current literature suggests that strength, walking abilities, aerobic capacity and balance are positively influenced by exercise training (table 9).

**Table 10: Outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Effect of exercise training</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multiple sclerosis pathogenesis</strong></td>
<td></td>
</tr>
<tr>
<td>Inflammation</td>
<td>~</td>
</tr>
<tr>
<td>Neurodegeneration</td>
<td>~</td>
</tr>
<tr>
<td><strong>Body structures</strong></td>
<td></td>
</tr>
<tr>
<td>Axonal and neuronal loss</td>
<td>~</td>
</tr>
<tr>
<td><strong>Body functions</strong></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>+</td>
</tr>
<tr>
<td>Depression</td>
<td>~</td>
</tr>
<tr>
<td>Cognition</td>
<td>~</td>
</tr>
<tr>
<td>Aerobic capacity</td>
<td>++</td>
</tr>
<tr>
<td>Muscular strength</td>
<td>++</td>
</tr>
<tr>
<td>Gait</td>
<td>++</td>
</tr>
<tr>
<td>Balance</td>
<td>+</td>
</tr>
<tr>
<td>Quality of life</td>
<td>+</td>
</tr>
<tr>
<td>Activities of daily living</td>
<td>+</td>
</tr>
</tbody>
</table>

+ limited but supporting evidence for beneficial effects; ++ consistent supportive evidence for beneficial effects, ~ no consistent evidence for beneficial or negative effects; - probably negative effects

Nonetheless, negative influences of exercise on the patients have to be taken into account. Negative feelings triggered by exercise include perceived physical deterioration, feeling of failure, anxiety and loss of safety. Exercise training might lead to side effects or relapses, but these events have rarely been reported.

Although the growing number of trials is a step in the right direction, some aspects still need to be improved. There is a need for comparable studies that overcome the methodological problems trial have so far faced. Methodological problems include mixed target groups, small study groups and different EDSS in patients. Most trials include patients with an EDSS score less than seven. Further limitations of the trials are the relatively short time of the studies, that don not provide information on the long-time effects. The comparability of the studies is further limited by the inconsistent set of measures and different training protocols used. In addition, there is a need for more detailed descriptions of the exercise regimes in the trials. It will also be important to investigate the influences of different training stimuli. Study results often only reflect one specific training situation and other circumstances may influence the whole outcome.
Exercise recommendations should be clarified and more detailed. The available guidelines do not provide users with a sufficient amount of information on the design of training sessions. Most of the information, especially for aerobic exercise, is broad and most of the time spans more than one phase of energy supply.

Based on the so far published literature some general recommendations can be made.

Exercise training should be supervised for some patients, especially for patients with higher disability levels and those suffering from fatigue and depression. This not only allows the physicist to survey the training sessions and progress, but also gives the patients a feeling of security. It would also include a social aspect, which seems to be beneficial for patients suffering from fatigue and depression.

It is important to be aware of the day-to-day well-being of the patients. Patients with MS are often sensitive to weather changes and heat, which may alter their ability to participate in physical activity drastically. Exercise training should be started early in the morning for some patients, as some symptoms are not as severe at the beginning of the day and patients are commonly not fatigued early in the day.

For caretakers, training therapists and physicians one of the biggest problems in conduction the right training regime for their patients is to find the right training stimulus. The exercises should not overtax them, but it should still be challenging enough to receive effects.

Summed up, training therapists, caretakers and physicians should provide the following for patients with MS:

- Promotion of a healthy, physically active lifestyle
- Guidance in finding the right exercise
- Finding the right training stimulus
- Clear and detailed exercise recommendations should be given
- Creation of a safe exercise environment
- Support throughout the training

After examining the effects of exercise on patients with MS, it can be said that exercise training should become a core part of multiple sclerosis therapy.
7. References


76. N.N. ( ) MS get fit toolkit. http://mssociety.ca/physicalactivity/MS_GetFit_toolkit_ENG.pdf


8. Figures

Figure 1: MS courses (Douglas et al., 2006, p.86) .................................................................23
Figure 2: Expanded Disability Score (EDSS) (http://www.msatrium.com/evolutions-in-care/goals-of-therapy 29.04.2015) ..................................................................................28
Figure 3: Cycle of deconditioning and worsening of symptoms (adapted from Motl et al., 2013, p. 2) ..........................................................................................................................43
Figure 4: Influence of physical activity on MS (Motl & Pilutti, 2012, p. 3) .........................44
Figure 5: Effect of temperature on sodium channels (Frohman et al., 2013, p. 539) .............45
Figure 6: 3 phases of energy supply (Tschakert & Hofmann, 2013, p. 603) .......................54

9. Tables

Table 1: McDonald criteria for MS diagnosis (McDonald et al., 2010) ..............................26
Table 2: Current DMD in MS care (Kamm et al., 2014, p. 137) ........................................34
Table 3: Health benefits (Ratamass, 2014, p.8; Frontera, 2006, p.31-32; Delisa, 2005, p.407-408) .................................................................................................................................49
Table 4: Resistance Training types .........................................................................................50
Table 5: Resistance Training ..................................................................................................51
Table 6: Calculated phases of energy supply (modified after Stübinge, 2014) ..................55
Table 7: Aerobic Training ........................................................................................................56
Table 8: Combined training .....................................................................................................57
Table 9: Exercise recommendations .......................................................................................77
Table 10: Outcomes ...............................................................................................................81