Fatigue in Multiple Sclerosis

Background, Clinic, Diagnostic, Therapy

Iris-Katharina Penner
Editor

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Preface

Fatigue in the context of multiple sclerosis is one of the most relevant neuropsychiatric symptoms of the disease and is considered one of the most distressing ones from the patient's perspective. Fatigue often occurs abruptly without any external reason in everyday life and thus complicates a normal daily functioning. Often, patients' fatigue-associated behavior leads to stigmatization in the sense of "laziness attribution," "inability to work under pressure," or "simulating and exaggerating the symptoms." This lack of understanding in the social environment is increased by the fact that fatigue occurs independently of the degree of disability and thus also affects patients who do not appear to have any "obvious" disease symptoms. But especially the group of patients with a low degree of disability have been shown to feel fatigue forces them to reduce their workload or even to give up employment completely, consequently resulting in social isolation and depressive episodes.

This book is the first English edition following the recently published second German edition. It is dedicated to all those dealing with fatigue symptoms directly or indirectly in the context of multiple sclerosis. This includes various professional groups (e.g., doctors, psychologists, therapists, nurses a.o.) as well as the patients themselves and their relatives. The aim of the book is to present the latest scientific findings, from the basics to clinics and diagnostics to therapy, in order to increase our understanding of the whole spectrum of fatigue. To achieve this, renowned colleagues from the clinical and scientific communities have agreed to illuminate various aspects from their respective research and practice perspective. I would therefore like to take this opportunity to thank my esteemed colleagues for their support and enthusiasm in the endeavor to publish this English edition of the Fatigue book.

Bern, Switzerland
April 2022

Iris-Katharina Penner

Contents

Part I

Background

On the History of Fatigue

J. Kesselring

In the nineteenth century, labor, with its political and economic dimensions, represented a central interest in the sociological and medical literature. With its various forms of organization, its significance and productive potential toward the end of the century, attempts were made to solve the "worker question" with the help of science: Body movements and rhythms were subjected to detailed laboratory studies, exposed to new measuring techniques, and recorded photographically. This attempt to replace moral disputes with science is particularly visible in the discussion of fatigue by European physiologists after 1870. Although descriptions of this phenomenon can already be found in numerous literary accounts of *ennui, lassitude, languor,* and *Weltschmerz,* they did not find their way into the medical literature until the end of the nineteenth century (Lepenies 1985). In 1892, for example, Lagrange provides descriptions of lamentable French schoolchildren: "Muscles without energy only painfully support the body, the face is pale, the body without nerves, the posture as if under weight turned downward. All the external aspects of the child give the impression of a plant longing for air and sunlight. All the functions of the organism are doomed."

Fatigue thus became the most obvious sign of the external limitations of body and mind, the most reliable indicator of the need to preserve the forces and prevent their abuse. The paradigm shift consisted in the replacement of the earlier conception of laziness as a reason for resistance to work with fatigue.

Physiologists and discoverers such as *Etienne-Jules Marey* or *Angelo Mosso* (1891) from Turin, whose classic *La Fatica* in 1891 was enormously influential, attempted to describe for the body in work what *Helmholz, Lord Kelvin*, or *Clausius* had achieved for the universe: to establish dynamic laws of energy conservation and thus of fatigue through rigorous experiments and new measuring techniques.

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In the 1890s, there was an international avant-garde of fatigue experts, laboratory specialists, and social hygienists who used fatigue to create a new field of experience in which science and politics met. The body without fatigue became a nineteenth century utopia. Toward its end, fatigue and exhaustion were the constant threats and challenges to the idea of progress, the great fear of the age. *Nietzsche*, for example, equated fatigue with modernity: his time was characterized by disintegration and, accordingly, by uncertainty (Nietzsche 1938); *Balzac* planned to write a pathology of social life to show how people wasted their energies by overexerting themselves. Accordingly, doomsday fantasies were also in vogue in the fin de siècle.

Before 1860, there were hardly any medical or scientific studies on fatigue, but around the turn of the century afterward there were already hundreds of studies on muscle fatigue as well as "nervous exhaustion," "neurasthenia," etc., which were understood as "maladie de l'énergie." In 1875, *George Poore* (1875) published an article in the Lancet in which he distinguished between general and local, acute and chronic symptoms of fatigue. In France, *Carrieu* (1878) in his pioneering work "De la fatigue et de son influence pathogénique" in 1878, complained that the term fatigue did not appear in any of the major medical dictionaries of his time and that all attempts at definition remained purely subjective, offering the following definition: "Un trouble dans l'activité des éléments anatomiques, causé par un fonctionnement exagéré au point que la réparation y est momentanément impossible" ("A disturbance in the activity of anatomical elements, caused by exaggeration of functions until recovery is no longer possible").

Fatigue was seen as both a physical and a moral disorder, a sign of weakness and lack of will (see discussion in Rabinbach 1990). Reflecting a breakdown in physical and mental functioning, fatigue was increasingly seen as a "modern" disorder with overwhelming social and physical consequences.

The experiments of the chemist and physiologist *Wilhelm Weichardt* at the University of Erlangen in Germany "on fatigue substances" caused a great stir. He announced in 1904 that he had invented a vaccination against fatigue. He was convinced that accumulated fatigue substances accumulated in the body could lead to stupor and death. *Mosso* was also convinced in 1891 that by transferring blood from one fatigued and exhausted animal to another, the latter would also succumb to fatigue. Even in World War I, soldiers were experimented on with substances that were supposed to be directed against fatigue toxins. In time, however, all these experiments turned out to be artifacts. At least they led to other "nerve stimulants" such as tea, coffee, and cocaine being studied more closely. In the following years, there were many publications on physical and mental fatigue, new apparatuses were introduced that would allow these symptoms to be quantified more precisely. In 1901, the psychiatrist *Kraepelin introduced* a distinction between "fatigue" and "tiredness." Based on this, he also proposed very specific measures for timetabling in schools in order to prevent the collapse of the child's working capacity.

The term "neurasthenia," which had been introduced by the New York physician *Georg Miller Beard in* the 1860s and was intended to express "all forms and kinds of nervous exhaustion in the brain and spinal cord," later became particularly popular. He attributed the cause to "excess pressure in the higher nervous centers" and

feared that this pathology was particularly typical of Americans. He referred to neurasthenia as "the central Africa of medicine: an undiscovered territory into which few men dare enter" (Beard 1869). In the 1980s, "Beard's disease" neurasthenia was the most widely used fashionable diagnosis, sometimes referred to by other terms such as "névroïsm," "irritation spinale," or "neuropathie cérébrocardiaque" (see Rabinbach 1990). While in America, following *Beard,* neurasthenia was attributed to the culture shock of modernity, in France, under the influence of *Charcot* and his students, the view of an inherited degenerative disease ("La famille névropathique") held more sway. The most important textbook on neurasthenia in fin de siècle France was that of *Dr. Achilles-Adrien Proust,* father of the great novelist *Marcel Proust.* He was a director at the Ministry of Health in Paris for many years and wrote L'hygiène du neurasthénique with *Gilbert Ballet in* 1897. These authors also attributed neurasthenia primarily to the moral and intellectual pressures of modernity. They attributed the fact that this diagnosis occurred only very rarely among physically working people and was limited almost exclusively to the "cultivated class" to the fact that it was caused primarily by "brain work," whereby they did not attribute neurasthenia itself directly to intellectual work, but to the moral pressure that weighed on such activity.

Neurasthenia was not only a disease but was often seen as a great imitator of other diseases. *Proust* mentions that even his most intelligent patients could usually only describe their disorders in a disjointed and rambling manner, for which *Charcot* introduced the term "L'homme du petit papier," meaning that neurasthenics often appeared with slips of paper or manuscripts on which they had just endlessly recorded their complaints.

The book by the Swiss neurologist *Paul Dubois* 1909 "L'éducation de soi-même," published in 1909, became particularly popular, in which he propagated the "Socratic dialogue" as a therapeutic principle and anticipated the paradoxical intention as a form of therapy, which was later popularized by *Viktor E. Frankl.* He writes that "in the wake of *George Beard*'s (1881) work, a new nervous disease [found] its way to Europe and is beginning to spread like an epidemic. Neurasthenia is on everyone's lips; it is the new fashionable disease." Whole walls of books were subsequently filled with treatises on the causes, theories of neurasthenia, and recommendations for the treatment of this "disease of the will," which was often disguised as "abulia." Historically, four interpretive traditions of the term neurasthenia can be identified: (1) a vague symptom of "general nervousness," (2) the male counterpart to female hysteria, (3) a term for less severe depressive states, and (4) a label for chronic fatigue states (Shorter 1993).

In those days "everything could be explained by neurasthenia: Suicide, decadent art, dress, infidelity" (Wessely 1994). The evaluation of neurasthenia showed great cultural differences, so the diagnosis did not find recognition among the "Giants of Queens Square" such as *Gowers, Gordon Holmes, Ferrier, Buzzard*, or *Kinnier-Wilson (*Shorvon and Compston 2018*).*

It has been said that the diagnosis was made "for the comfort of the relatives and peace of mind of the patient" by avoiding the stigma of psychiatric illness and thus the need for hospitalization in a psychiatric institution.

Fatigue cannot be measured objectively, this soon became apparent at the beginning of the twentieth century despite intensive efforts: “The remarkable changes in the nerve cells which had been found and which became very fashionable and a source of pride for both patients and diagnosticians, could not be replicated on the whole and the concept of nerve cell exhaustion could not be maintained.” Criticism of the “mechanical symbolism” of descriptions of neurasthenia was increasingly voiced, and the decrepitude (futility) of purely anatomical concepts of disease was deplored. With regard to social concepts, the focus of interpretation changed from overwork to underwork, but soon poor housing conditions, inadequate dental hygiene, and ice cream licking were also blamed for widespread fatigue. It is interesting in historical retrospect to observe how views on the class dependence of neurasthenia shifted: As late as *Freud* and *Kraepelin*, it was “a disease of brilliant intellectuals, its victims being leaders and masters, captains of industry ... especially affecting many physician colleagues ... .” Those who spoke out in this regard as being affected by neurasthenia helped to legitimize neurasthenia as a disease. Like class membership, therapeutic recommendations varied from complete bed rest to more active muscle activity. Interestingly, etiology was associated with class: the more the cause was thought to be “organic,” the more the author insisted on a predominance of the disease in the upper social classes, a differentiation from hysteria as the archetypal disease of women, a preference for the male sex and the “civilized races”... (Wessely 1994). In order to distinguish themselves from hysteria, it was noted that neurasthenics “do everything to make themselves feel only better, and long with all their might for good health, if they only knew how to obtain it. Accordingly [the] neurasthenics, unlike the hysterics, would also always cooperate well with the physicians.” In the first half of the twentieth century, the concept of neurasthenia became increasingly less important because, on the one hand, a neuropathological basis was lacking, rest cures proved beneficial mainly for psychological reasons, and the distribution by social class shifted. As a result, almost every infectious agent from brucellosis to all sorts of viruses to rickettsiae was blamed for fatigue (see Wessely 1994, Table 1). Actual epidemics of fatigue have also been described, most strikingly one at Los Angeles County Hospital in 1934 and then at the Royal Free Hospital London in 1955, although in both cases only medical staff at these hospitals were affected, not their patients. Both episodes were associated with atypical poliomyelitis, which was never proven. Later interpretations then focused on “transmitted emotional stress” and “mass hysteria.”

In the second half of the twentieth century, myalgic encephalomyelitis was published as a new disease entity of fatigue (Acheson 1959), and this gave rise to the diagnosis of “chronic fatigue syndrome,” which is still widely used today. Later, symptom criteria for chronic fatigue syndrome were established (Fukuda et al. 1994), which include limitations of short-term memory or concentration, as well as sore throat, tender neck and axillary lymph nodes, muscle pain, pain of multiple joints without swelling or redness, headache of a new type, pattern or severity, no recovery from sleep, condition worsening for more than 24 hours after exertion. Despite an intensive search for etiological factors, no single agent has been found to

be responsible, so chronic fatigue syndrome is coded as R 53 in the new classification system of ICD-10 GM version 2008 and is conceived as a "neuroimmunological regulatory disorder." Occasionally, traumatic stress in early childhood is also causally associated (Heim et al. 2006).

The essential criteria for this classification and definition are persistent and agonizing feelings of exhaustion after low mental or persistent agonizing fatigue and weakness after low physical exertion, and the duration of the disorder must be at least 3 months (Schäfer 2000). Thus, chronic fatigue syndrome is currently the most significant neurasthenia variant, but arguably overlaps with fibromyalgia and multiple chemical sensitivity.

Neurasthenia lost its claim to organicity and thus legitimacy because Beard's explanatory concept could not be scientifically sustained and psychoanalytic views of the mental causation of neuroses became increasingly widespread. Therefore, other models of illness were formed with recourse to the symptom pool, which again corresponded to the changed time-typical collective conceptions of organic illness. Chronic fatigue and its variants arguably retain their role as socially legitimate disease models and will continue to be used as a terminological and diagnostic label as long as the organicity question cannot be decided.

Regardless of whether individual causes can ever be found for the feeling of fatigue that afflicts so many patients with multiple sclerosis, it remains a special challenge for any medical practice to find solutions to problems in the border area between neurology and psychiatry. Fatigue may indeed be a window through which brain functions can be studied more generally (DeLuca 2005).

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Definitions, Epidemiology, and Etiological Factors

P. Flachenecker

1 Definitions and Terminology

There is no generally and widely accepted definition of fatigue. Despite its increasing importance and awareness, it remains a poorly defined construct that is predominantly found in MS, but also in other diseases such as tumors, strokes, or chronic inflammatory processes. The term most likely refers to "abnormal fatigability," "abnormal exhaustion," or "increased exhaustibility." In any case, MS-related fatigue is quite different from the tiredness that healthy people report and that persons with MS themselves experienced before the onset of the disease: They complain of a lack of drive and energy that is exacerbated or persistent depending on mental and/or physical load and that may affect both, mental and physical performances. Often, fatigue is worsened by increased ambient or body temperature, whether due to heat, fever, or physical exertion ("Uhthoff phenomenon"). Not infrequently, both the quality of life and the ability to work and perform activities of daily living are impaired to such an extent that, particularly in a less adaptive working environment, early retirement is inevitable and those affected increasingly withdraw from social activities (Sterz et al. 2016).

In the literature, fatigue is variously defined as "a feeling arising from difficulty initiating or sustaining voluntary effort," "an overwhelming feeling of fatigue disproportionate to the activity performed," or "a feeling corresponding to a lack of motivation to provide resources and perform at a high level of effort to deal with the situation" (Manjaly et al. 2019). While these descriptions express well the heterogeneous nature of fatigue; they all share an emphasis on the subjective experience. The difficulty for clinicians and scientists is to objectify the description of complaints and to operationalize it for clinical-scientific studies.

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In addition to physical (motor) fatigue, which predominantly manifests itself in, for instance, a load-dependent restriction of walking ability (Sehle et al. 2014), cognitive (mental) fatigue may also often be present. Many people with MS report that, either in addition to physical fatigue or independently of it, they suffer from fatigue that occurs predominantly or exclusively during mental activities, such as the ability to concentrate, and increases in particular during monotonous activities. Moreover, in addition to the subjectively experienced fatigability described above, there may also be an objectifiable decrease in performance (mental or physical) during the course of activities (Flachenecker and Meissner 2014). In this regard, Kluger et al. distinguish "fatigue" as a term for a permanently present subjective perception of fatigue from "fatigability," i.e., an increasing exhaustion in the course of an exertion that can be objectively measured (Kluger et al. 2013). Similarly, Genova et al. distinguish a "state" component, which is temporary and can change depending on time and internal or external influencing factors, from a "trait" component, which is persistent and stable (Genova et al. 2013).

Thus, the current conceptual notion of fatigue includes two basic components: (1) the subjective feeling of fatigue, tiredness, and lack of energy ("empty battery") that affects physical and/or cognitive performance, and (2) the inability to sustain normally expected motor or mental performance over an extended period of time (Flachenecker and Kos et al. 2011) Support for this assumption is provided by a meta-analysis of all studies that examined the correlation between subjectively experienced fatigue and objectively measurable (motor) performance decline (Loy et al. 2017). Thereby, a positive correlation between fatigue and fatigability was detectable in almost 95% of the 19 included studies. However, the correlation was only moderately ($r = 0.31$), which means that although the two components are related, they are probably different constructs with possibly different underlying mechanisms (Loy et al. 2017).

Moreover, fatigue in the narrower sense ("primary fatigue syndrome") must be distinguished from a number of other conditions that can also be accompanied by increased tiredness due to sleep disorders, concomitant diseases, or the effects of medication; this so-called "secondary fatigue syndrome" (Kos et al. 2008) is dealt with in detail in the following chapter.

2 Prevalence and Significance of Fatigue

Up to 90% of people with MS suffer from fatigue to a more or less extent (Ayache and Chalah 2017). It may occur early in the course of the disease, even independently of severe physical limitations. In an initial evaluation of the German MS Registry, fatigue was documented in 65% of registered patients, making it the most common symptom, even more than spasticity, bladder dysfunction, or ataxic disorders, which are usually associated with MS. Especially in the early course of the disease, i.e., in patients with a disease duration of less than 2 years, fatigue occurred comparatively frequently, even more frequently than spasticity, ataxia, and bladder disorders. Only in patients with a long-lasting disease course (> 15 years), spasticity

Table 1 Frequency of MS symptoms according to the German MS Registry

	n	Frequency	DD < 2 years	DD > 15 years
Spasticity	7012	4142 (59.1 %)	68 (17.3 %)	1,796 (75.8 %)
Fatigue	6726	4245 (63.1 %)	167 (40.6 %)	1,461 (67.6 %)
Pain	6548	3399 (36.6 %)	100 (24.6 %)	902 (42.2 %)
Bladder dysfunction	6573	3723 (56.6 %)	79 (20.5 %)	1,619 (74.0 %)
Bowel dysfunction	6040	1260 (20.9 %)	18 (4.8 %)	613 (31.1 %)
Sexual dysfunction	4951	1073 (21.7 %)	28 (8.0 %)	409 (27.3 %)
Ataxia/Tremor	6384	2985 (46.8 %)	96 (24.4 %)	1,181 (56.5 %)
Cognitive dysfunction	6239	2244 (36.0 %)	76 (19.6 %)	823 (40.6 %)
Depression	6632	2411 (36.4 %)	96 (23.6 %)	806 (38.0 %)
Oculomotor disturbances	6542	1268 (19.4 %)	60 (14.6 %)	506 (24.3 %)
Dysarthrophonia	6189	901 (14.6 %)	18 (4.6 %)	410 (20.4 %)
Dysphagia	6183	485 (7.8 %)	5 (1.3 %)	256 (12.7 %)
Epileptic seizures	6215	188 (3.0 %)	6 (1.6 %)	75 (3.7 %)
Paroxysmal symptoms	5980	219 (3.7 %)	8 (2.1 %)	76 (3.9 %)

DD (disease duration) = time since onset of MS
The first line of the table gives the total number of patients recorded in the data set
The column "*n*" shows the number of patients for whom data on a particular symptom were available.
The numbers in the "Frequencies" column give the absolute number of patients with this particular symptom. The percentages refer to the total number of entries per symptom shown in column "*n*"
The columns "DD < 2 years" and "DD > 15 years" denote the numbers of recorded symptoms according to disease duration of patients. The percentages refer to those patients with a particular disease duration for whom data on this symptom were available (not shown)
According to Stuke et al. 2009

and bladder disorders dominate the clinical picture. However, even in this group of patients, fatigue was reported comparatively often (Table 1) (Stuke et al. 2009).

In a renewed evaluation of the German MS registry with now more than 18,000 documented patients, fatigue was still reported in 52% of the registered patients, and here too it was by far the most frequent symptom MS patients suffered from (Flachenecker et al. 2020). In the National MS Cohort, which includes patients with clinically isolated syndrome (CIS) or early relapsing-remitting course immediately after diagnosis and comprises 1124 patients, the prevalence of fatigue was 36.5%; a high proportion considering that only a few other symptoms were present at this earliest possible time point (von Bismarck et al. 2018). Another study reported a prevalence of 63% in newly diagnosed patients; in this context, the objective parameters mainly revealed an impairment of mental ("cognitive") performance, while in the subjective assessment, physical fatigue was more pronounced (Engel et al. 2004). Fatigue is thus one of the most common symptoms of MS and may be the first symptom of the disease, or the only symptom of a relapse (Flachenecker and Meissner 2008).

Fatigue is not only common but also important. It is not uncommon for it to be the predominant and most distressing symptom of MS altogether (Penner and Paul 2017). In our own study of more than 150 patients, 75% of people with MS

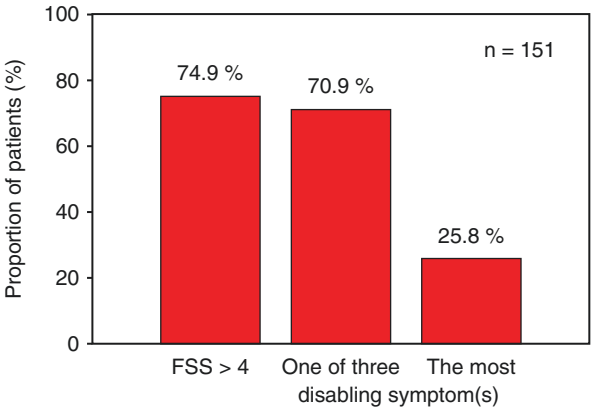

Fig. 1 Frequency of fatigue according to standardized questionnaires in a cohort of 151 consecutive MS patients entering the outpatient clinic of the University of Würzburg (Flachenecker et al. 2002). FSS = Fatigue Severity Scale

complained of fatigue, and a quarter reported that fatigue was the symptom that was the most affected troublesome (Fig. 1) (Flachenecker et al. 2002).

Furthermore, it also has a great impact on health economics: According to the current cost-of-illness study in Germany, the quality of life was reduced with increasing severity of fatigue, whereas resource consumption and the probability of premature retirement were increased (Kobelt et al. 2020). In particular, premature retirement from working life is not infrequently caused by fatigue if it is severe enough, with fatigue then representing the dominant symptom of the disease (Sterz et al. 2016).

3 Demographic and Clinical Factors

Fatigue is independent of gender and occurs thus equally in both, men and women (Colosimo et al. 1995; Ghajarzadeh et al. 2013). Although in some studies older age was correlated with the severity of fatigue, this relationship could not be confirmed in multivariate analyses (Flachenecker et al. 2008; Ghajarzadeh et al. 2013; Colosimo et al. 1995). The same is true for disease duration, which means that fatigue may be present early in the course of the disease, sometimes long before the onset of the first symptoms recognized to be due to MS (Flachenecker et al. 2008, 2002). In fact, many MS patients report having suffered from previously unexplained fatigue even before the first onset of physical symptoms. Often, fatigue may be increased during a relapse and may even be the only symptom of an MS exacerbation (Flachenecker and Meissner 2008). In the long term, however, there is no difference between patients with an active (2 relapses in the last 2 years and/or progression by at least 1 point on the EDSS) and stable course of the disease, so that disease activity does not appear to have any influence either (Fig. 2).

A connection between fatigue and the type of MS progression is widely discussed but has not yet been proven beyond doubt. Patients with a progressive course are said to suffer more from fatigue than those with a relapsing course (Kroencke et al. 2000), as also suggested by our own study (Fig. 2). However, this could neither

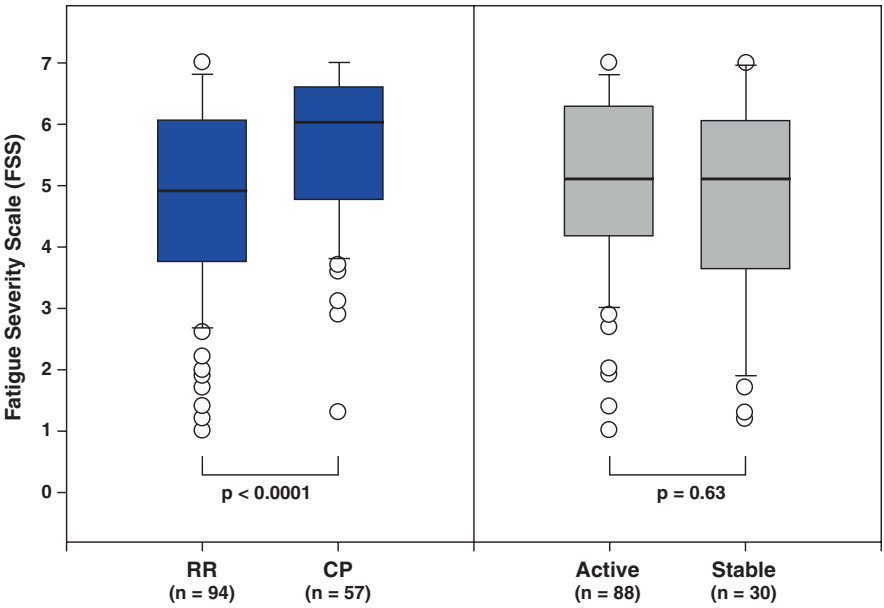

Fig. 2 Fatigue Severity Scale (FSS) of 151 unselected MS patients (Flachenecker et al. 2002) according to disease course (left, RR = relapsing-remitting MS, CP = chronic progressive MS) and disease activity (right, active = more than two relapses or progression of more than one point on the EDSS within the last 2 years, stable = neither relapse nor progression within the last 2 years)

be confirmed in the multivariate analysis (Flachenecker et al. 2002) nor in a large follow-up study with 580 MS patients with different disease courses: Here, the frequency and severity of fatigue were comparable in primary progressive, secondary progressive, and relapsing-remitting patients (Flachenecker et al. 2008).

The relationship between physical disability and fatigue is controversial. In particular, "fatigability" is thought to be due to a lesion of the pyramidal tract, preferably the spinal conduction pathways. At first glance, this hypothesis seems attractive. The load-dependent decrease in walking distance, which many affected persons suffer from and which is a typical symptom of the disease, is perceived by the patients as a sign of fatigue and might correspond most closely to the construct "fatigability." On the other hand, the mechanism of a load-dependent increase in muscle weakness is a typical feature of central paresis and certainly cannot explain all the phenomena of fatigue—especially that of cognitive fatigability. Although significant correlations between the subjectively experienced fatigue, measured on the "Fatigue Severity Scale" (FSS), and the "Expanded Disability Status Scale" (EDSS) or the functional system "pyramidal tract" of the EDSS were found in several studies—which is in line with the above mentioned hypothesis—these were no longer present in multivariate analyses (Bakshi et al. 2000; Flachenecker et al. 2002; Iriarte et al. 2000). In our own study, there was at best a weak and—even contrary to the hypothesis—negative correlation between fatigue (measured with the

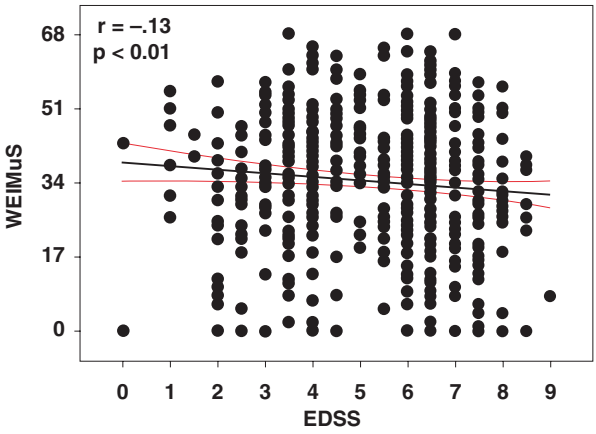

Fig. 3 WEIMuS ("Würzburger Erschöpfungsinventar bei MS") (Flachenecker et al. 2008) sum scores and physical disability (EDSS = Expanded Disability Status Scale) of 580 patients with MS

"Würzburg Fatigue Inventory in MS, WEIMuS") and the EDSS, which means that patients with more severe motor impairment had reported *less* fatigue (Fig. 3). Thus, these studies confirm the clinical experience that fatigue can also occur in physically less severely affected patients, even in patients without any physical impairment, and that the underlying mechanisms are not (exclusively) attributable to a pyramidal tract lesion.

Overall, it can be concluded from these findings that fatigue is largely independent of demographic and clinical factors and thus cannot be characterized by them.

4 Etiological Factors

In the literature, more than 30 different etiological factors are found that are supposed to have an association with the subjective experience of fatigue. These include, for example, an impairment of muscle function or neuromuscular transmission similar to myasthenia, slowed or interrupted excitation conduction in the case of diffuse demyelination or axonal damage, inflammatory processes, neuroendocrine and autonomic dysregulations, regional and global cerebral lesions, reduced glucose metabolism in the prefrontal cortex and many others (Langeskov-Christensen et al. 2017). There is a long lasting debate about whether fatigue may simply reflect depression. Several studies including our own have indeed found (moderate) correlations between fatigue and depression (Bakshi et al. 2000; Flachenecker and Kos 2011; Simpson Jr et al. 2016). However, these correlations were on the one hand dependent on the depression scales used (less pronounced with the Center for Epidemiologic Studies Depression Scale (CES-D) than with the Beck Depression Inventory (BDI), which is more strongly confounded by somatic complaints), and on the other hand no longer detectable in multivariate analysis (Flachenecker et al. 2008, 2002). Fatigue is therefore an independent symptom complex that must be distinguished from depression.

Interestingly, the phenomenon of fatigue is not limited to MS. In a number of other diseases such as tumors, inflammations, or secondary conditions after stroke and head injury, patients also suffer from a puzzling, pathologically increased fatigability, which is independent of the severity of the acute disease and can even impair performance after the disease has been overcome. Another important differential diagnosis is the "chronic fatigue syndrome" (CFS), which, however, is an independent clinical picture and, despite some similarities, has clear differences from MS-related fatigue (DeLuca et al. 1995; Flachenecker 2009).

Ultimately, despite the enormous impact on the individual patient, the causes of fatigue have not been conclusively clarified. In the following, I will particularly refer to our own studies on various etiological factors of MS-related fatigue and discuss them in the context of other studies. The underlying pathophysiological mechanisms are dealt with in the following chapter.

4.1 Personality Traits

Assuming that fatigue is a multidimensional syndrome with somatic, cognitive, and psychosocial aspects (Flachenecker 2017), the question arises whether certain personality traits do predispose to fatigue. There are only a few usable studies dealing with this topic, which found higher scores for neuroticism and reduced extroversion; however, these were strongly influenced by depression and were no longer significant after adjustment for this (Schreiber et al. 2015). In a larger, multicenter study of 102 MS patients, nearly half (n = 48) suffered from fatigue (as measured by the WEIMuS questionnaire). The coping strategies "depressive processing," "trivialization," and "wishful thinking" were more pronounced in these patients than in those MS patients without fatigue. Significant group differences were seen in the personality profile, especially in "life satisfaction," "inhibition," "excitability," "stress," "physical discomfort," "openness," and "emotionality." No differences were found between physical and cognitive fatigues. The authors interpret their findings in terms of a depressive personality structure with maladaptive disease processing, which should underline the psychological dimension of fatigue and its character as a "trait" variable (Schreiber et al. 2010). However, the extent to which the personality structure postulated here is influenced by psychological factors (simultaneously and independently present of fatigue) such as depressiveness or anxiety remains unclear, particularly as there are no reliable data on the premorbid personality profile (Schreiber et al. 2015). Despite these uncertainties, however, psychological factors appear to play a role in MS-related fatigue, and knowledge of these could provide a helpful therapeutic approach. A detailed illumination of the relationship between personality traits and fatigue follows in Chap. 7.

4.2 Autonomous Regulation

Autonomous dysfunction is common in MS and encompasses not only the well-known bladder disorders but also disorders of cardiovascular function; particularly orthostatic dysregulation is not uncommon and can be clinically relevant (Flachenecker et al. 1999; Sakakibara et al. 1997). Some of the characteristic symptoms of fatigue, such as drowsiness, weakness, and exhaustibility, are similar to those observed in autonomic dysfunction, especially in orthostatic intolerance or treatment with beta-receptor blockers. We found in a study of 60 MS patients that heart rate variation after standing up ("30/15 test") and the blood pressure increase during sustained handgrip were significantly decreased compared to a healthy control group (Flachenecker et al. 2003), a pattern of autonomic dysfunction already demonstrated in an earlier study with another patient and control group (Flachenecker et al. 1999). When looking at the MS group, both test results were only reduced in MS patients with fatigue, so that the autonomic dysfunction could be attributed exclusively to fatigue (Table 2).

Similarly, the individual test results of the heart rate variation after standing up and the blood pressure increase during handgrip were correlated with the scale scores of the FSS as well as of the MFIS ("Modified Fatigue Impact Scale"), and here in particular with the physical subscale (Fig. 4). This pattern of autonomic dysfunction, also found in orthostatic intolerance, corresponds to a lesion of sympathetic vasomotor, which means that the symptomatology of fatigue may be at least partly caused by a (subclinical) circulatory regulatory disorder.

However, although the association was statistically significant, it was only moderately pronounced, implying that autonomic dysfunction may only be partly responsible for fatigue. Our findings are supported by a study by Heesen and colleagues in which the increase in heart rate during a mentally demanding task was

Table 2 Cardiovascular reflex tests in MS patients with and without fatigue

	MS Patients	MS-F	MS-NF	Controls
	(n = 60)	(n = 27)	(n = 16)	(n = 36)
$HRV_{Valsalva}$	1.64	1.65	1.64	1.67
$HRV_{Breathing}$ [min^{-1}]	15.8	14.6	15.2	16.2
$HRV_{Standing}$	1.30 *	1.25 $^{**\,\S}$	1.44	1.38
$BP_{Standing}$ [mmHg]	−2	−2	−2	1
$BP_{Handgrip}$ [mmHg]	15 ^{t}	11 *	18	18

The numbers given represent the median values of the test results
MS-F: MS patients with fatigue (FSS ≥ 5,0), MS-NF: MS patients without fatigue (FSS < 4,0), $HRV_{Valsalva}$: Valsalva ratio, $HRV_{Breating}$: heart rate variability during forced breathing, $HRV_{Standing}$: heart rate variability during active change of posture, $BP_{Standing}$: blood pressure changes during active change of posture, $BP_{Handgrip}$: blood pressure change during sustained handgrip
** $p < 0.0001$, * $p < 0.05$, t = trend ($p = 0.06$), MS vs. Kontrollen, § $p < 0.025$, MS-F vs. MS-NF (Mann-Whitney rank sum test)
According to Flachenecker et al. (2003)

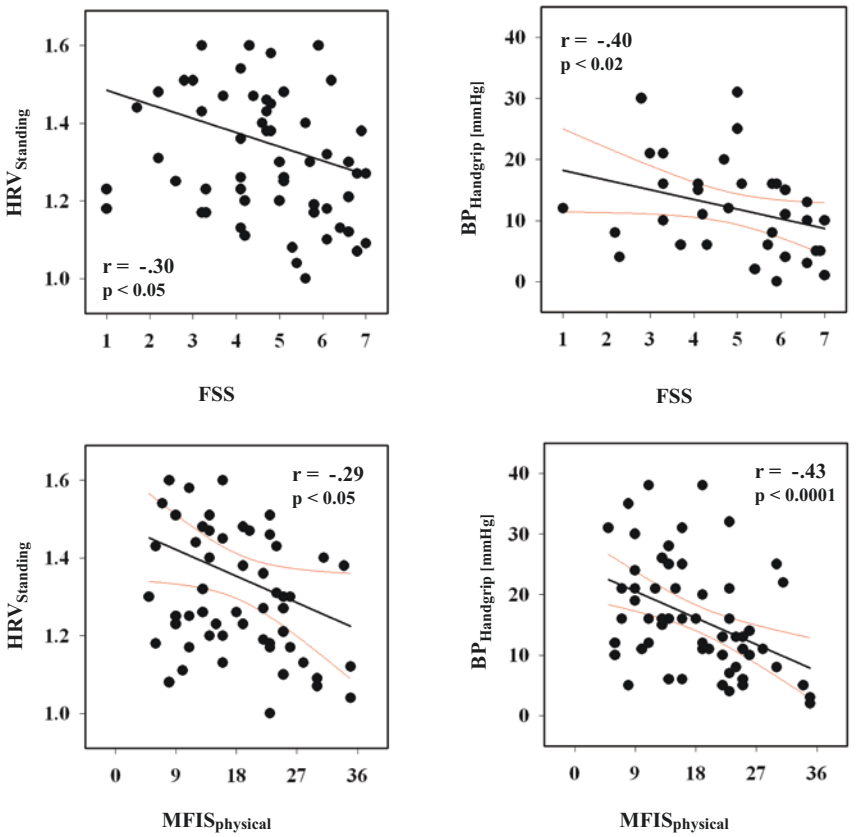

Fig. 4 Cardiovascular reflex tests of 60 patients with MS and severity of fatigue ($HRV_{Standing}$: heart rate variability during active change of posture, $BP_{Handgrip}$: blood pressure changes during sustained handgrip, FSS: Fatigue Severity Scale, $MFIS_{physical}$: Modified Fatigue Impact Scale, physical subscale)

attenuated in patients with fatigue (Heesen et al. 2005), and by a Brazilian study in which blood pressure increased less during sustained handgrip, similar to our findings, in fatigue patients compared to MS patients without fatigue (Lebre et al. 2007).

4.3 Endocrine Factors

It has long been known that there is an interaction between endocrine regulation and the immune system. In particular, the interactions between the sympathetic nervous system and the immune system have been well studied. Thus, in sympathectomized animals, immune responses such as T-cell-independent antibody response, T-cell

proliferation, and macrophage activation are markedly enhanced (Chelmicka-Schorr and Arnason 1994). An animal model of MS, experimental allergic encephalomyelitis (EAE), is more severe in sympathectomized animals (Chelmicka-Schorr et al. 1988). Conversely, EAE can be attenuated by treatment with the β2-adrenergic agonist salbutamol (Wiegmann et al. 1995). In patients with progressive MS, increased adrenergic receptors could be detected on lymphocytes, indicating sympathetic denervation (Karaszewski et al. 1991; Zoukos et al. 1994, 2003). This upregulation is specific to CD-8 suppressor cells (Karaszewski et al. 1993), which is of particular interest as these cells are thought to play a special role in the pathogenesis of MS. Treatment with the α-adrenergic agonist terbutaline normalized the elevated -receptors within 1 week and was accompanied by a moderate increase in suppressor function (Chelmicka-Schorr and Arnason 1994).

There are only a few studies on catecholamine levels in MS patients. However, existing findings suggest that serum norepinephrine is lower in progressive patients or in those with an active disease course than in patients with a stable disease course (Flachenecker et al. 2001). Surprisingly, no data on catecholamines in MS-associated fatigue can be found in the literature. This is remarkable because fatigue has also been described in families with the (rare) syndrome of norepinephrine transporter gene defect resulting in orthostatic intolerance and abnormally elevated norepinephrine levels (Shannon et al. 2000). Therefore, we determined serum levels of epinephrine and norepinephrine in 33 MS patients who had participated in a study on autonomic dysfunction in MS-associated fatigue (Flachenecker et al. 2003) while they were lying down and after 5 min of orthostatic stress. With regard to norepinephrine levels, no differences were found compared to healthy control subjects. However, serum levels of epinephrine were lower in the MS group than in control subjects both while lying down (15 vs. 27 ng/l, $p < 0.003$) and after 5 min of standing (23 vs. 45 ng/l, $p < 0.02$). Differentiating MS patients into those with (FSS $\geq$ 5, MS-F, n = 14) and without (FSS < 4, MS-NF, n = 9) fatigue, supine adrenaline levels tended to be higher in MS-F patients than in patients without fatigue, whereby these differences did not reach statistical significance (Fig. 5). However, correlation analyses using MFIS showed a statistically significant relationship for both the total scale ($r = 0.40$, $p < 0.025$) and the physical ($r = 0.37$, $p < 0.04$) and cognitive ($r = 0.39$, $p < 0.03$) subscales. The increase after 5 min of standing was negatively correlated with fatigue severity ($r = -0.34$, $p = 0.07$). This means that patients with severe fatigue had higher adrenaline levels when lying down, and that the expected increase after standing up was less pronounced than in patients with less or no fatigue.

In contrast to the paucity of data on catecholamines, the function of the hypothalamic–pituitary–adrenal (HPA) axis has received much more attention in the context of MS and fatigue. While it is relatively unequivocal that hyperreactivity of the HPA axis is associated with the progressive course of MS, the relationship to fatigue is much less clear. Heesen et al. (2002) found no correlation between fatigue and HPA axis reactivity in 40 MS patients, but preferentially included chronic progressive patients in whom hyperreactivity could already be assumed based on the type of disease course (Then Bergh et al. 1999). In addition, these

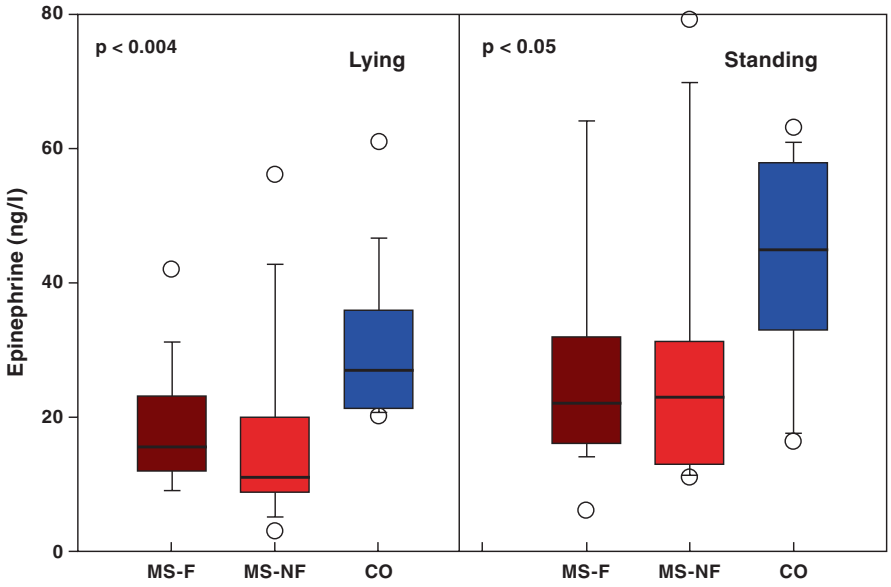

Fig. 5 Serum levels of epinephrine during lying (left) and after 5 min of standing (right) in 14 MS patients with fatigue (FSS ≥ 5, MS-F), 9 MS patients without fatigue (FSS < 4,0, MS-NF) and 12 healthy controls (CO)

patients received immunomodulatory or immunosuppressive medication, which could also influence the HPA axis via interaction with cytokines. Therefore, in the study by Gottschalk et al. only relapsing patients without any immunomodulatory or immunosuppressive therapy were included. In patients with fatigue (FSS ≥ 4.0), ACTH levels, but not cortisol levels, were significantly elevated after the combined dexamethasone-ACTH test compared to MS patients without fatigue pointing to a hyperreactive HPA axis in MS patients with fatigue (Gottschalk et al. 2005). In a systematic review, Pereira et al. evaluated 20 individual studies, each with between 24 and 173 MS patients (Pereira et al. 2018). Divergent results emerged here: While the majority of studies found elevated cortisol levels in MS patients and confirmed hyperreactivity of the HPA axis (9 out of 20 studies), cortisol levels were decreased in four studies and not different from the normal values of the participating laboratories in three other studies. When considering the association with MS symptoms such as depression or fatigue, an even more heterogeneous picture emerged: three studies reported a correlation between hyperreactive HPA axis and depression, while this was not detectable in three other studies. The four studies that investigated the relationship with fatigue found either low levels in the morning, higher levels, or no difference at all compared to control subjects (Pereira et al. 2018). Thus, the role of the HPA axis in fatigue remains unclear. The positive findings could possibly be explained by the fact that proinflammatory cytokines such as TNF-α, IL-1, and IL-6 could be responsible for both HPA axis dysregulation and fatigue in MS patients.

4.4 Proinflammatory Cytokines

The fact that patients with febrile infections complain of exhaustion and tiredness similar to MS-associated fatigue suggests that proinflammatory cytokines such as TNF-α, IL-6, or IFN-γ may also be responsible for the increased fatigability in MS. Indeed, data from in vitro and animal studies suggest that such a link exists (Patejdl et al. 2016). The results in clinical studies are less clear. In an older study by Bertolone et al., fatigue scores were improved in parallel with reductions in serum levels of IL-1, soluble IL-2 receptor, and IL-6 (Bertolone et al. 1993). On the other hand, serum levels of IL-2 and soluble IL-2 receptors were not increased in eight other patients with fatigue (Rudick and Barna 1990). Giovannoni et al. could not find any correlation between fatigue scores and inflammatory parameters such as urinary neopterin (a marker of IFN-γ-dependent macrophage activity), C-reactive protein, and soluble ICAM-1 (Giovannoni et al. 2001). In line with this, fatigue was not associated with signs of systemic inflammation (ESR and IFN-), but with the mRNA expression of TNF- in peripheral blood cells in our own study (Fig. 6).

For the anti-inflammatory cytokine IL-10, no difference was found between the two groups (Flachenecker 2017).

The selective increase of TNF-α according to the severity of fatigue is particularly interesting because TNF-α is not only increased in tumor-associated fatigue or other diseases with excessive daytime sleepiness, but because it can also trigger fatigue in animal experiments (Sheng et al. 1996). Thus, TNF-α seems to be responsible for the development of increased fatigability in MS. Confirmation of these findings was provided by Heesen and colleagues, who were able to demonstrate an increase in TNF-α (479 vs. 228 pg/ml) and IFN-γ (57.6 vs. 27.8 pg/ml) in 15 MS

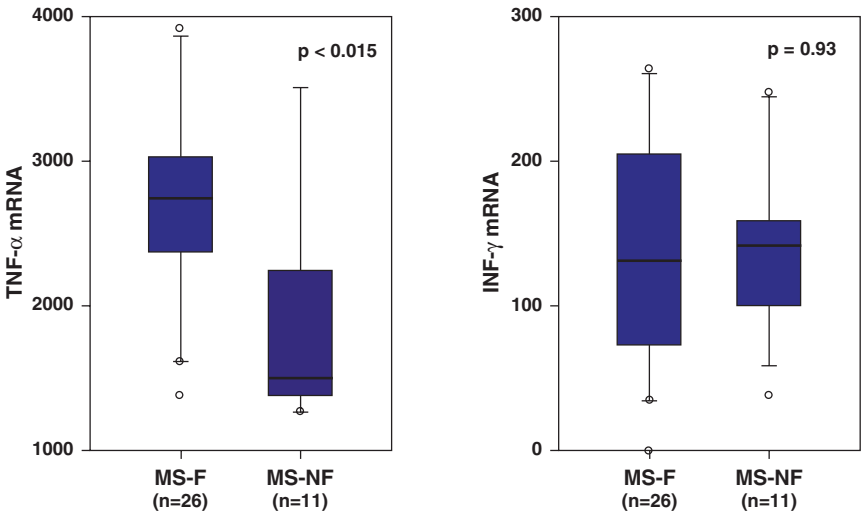

Fig. 6 Cytokine mRNA levels in peripheral lymphocytes in MS patients with (MS-F) and without (MS-NF) fatigue (Flachenecker et al. 2004)

patients with fatigue compared to 15 MS patients without fatigue (Heesen et al. 2006). As further evidence of the role of TNF-α in MS-associated fatigue, levels of TNF-α correlated significantly with daytime sleepiness as measured by the Epworth Sleepiness Scale ($r = 0.64$, $p = 0.001$).

These and other studies are summarized in a systematic review: Despite overall scarce data and heterogeneous results, here proinflammatory cytokines, especially Il-6, TNF-α, and IFN-γ appeared to show an association with fatigue, while no such association was present with T-cell populations such as $CD3^{+}CD4^{+}$lymphocytes or regulatory T cells and other inflammatory parameters such as CRP, ESR, or soluble ICAM-1 (Chalah and Ayache 2018).

4.5 Attention Deficit Disorder

The role of attentional impairment in the etiology of MS-related fatigue is comparatively well studied and undisputed. The relationship between fatigue and tonic alertness (measured with the Test Battery for Attention, TAP), but not with other cognitive tests, has been repeatedly demonstrated (Claros-Salinas et al. 2013; Meissner et al. 2009, 2007; Neumann et al. 2014; Pfitzner et al. 2014; Weinges-Evers et al. 2010). A detailed description of these studies can be found in Chap. 6. It is now well recognized that fatigue on the one hand is at least partly caused by an attention deficit disorder, but on the other hand can be clearly distinguished from a cognitive disorder.

4.6 Structural and Functional Brain Changes

A number of studies have attempted to establish a link between fatigue and a wide variety of cerebral abnormalities, both at the structural and functional levels. These are summarized in several reviews (Bertoli and Tecchio 2020; Hanken et al. 2015; Palotai and Guttmann 2020), which point to a heterogeneous and partly contradictory picture.

The majority of studies found no association with global MRI parameters, neither for brain volume measures (global, gray matter, cortex, white matter) nor for lesion load, whereas—when regional structures were considered—fatigue was more frequently associated with frontoparietal atrophy and particularly with changes in subcortical areas (Hanken et al. 2015). However, even here, inconsistent and sometimes contradictory results were found. Thus, fatigue cannot be explained by lesions or changes in specific brain regions, and although MRI is invaluable for the diagnosis and progression of MS, global measures such as brain atrophy and lesion volume are obviously too non-specific to identify causes and mechanisms of fatigue.

More promising than attempts to uncover the structural basis of fatigue seems to be the depiction of functional changes in brain function. A complex pattern of neuronal activity and functional connectivity is beginning to emerge that may underlie fatigue. On the one hand, differential activation in the sensorimotor network, and on

the other hand, communication of the primary motor and sensorimotor cortex, or interhemispheric communication, seem to be important (Bertoli and Tecchio 2020). In addition, the thalamus and the cortico-striato-thalamic network are probably also involved in the mechanisms underlying fatigue (Bertoli and Tecchio 2020; Capone et al. 2020).

A detailed discussion of imaging and fatigue can be found in Chap. 11.

4.7 Summary of the Considerations on the Etiological Factors

Given the multitude of etiological factors discussed above, MS-associated fatigue is not likely to be a single symptom, but a multifaceted syndrome that shares common features with depression and cognitive impairment but is certainly independent of them. Secondary causes of increased fatigue or daytime sleepiness, such as sleep disorders, side effects of medication, and concomitant diseases, must be distinguished from the primary fatigue syndrome and should be treated properly. Etiological factors that contribute to primary fatigue are altered network function in cortical and subcortical areas, certain personality traits, sympathetic dysfunction, endocrine factors, proinflammatory cytokines, and/or a disturbance in the intensity of attention. An overview of contributing factors is given in Fig. 7.

It is very likely that different mechanisms may be responsible in different patients, and several factors may be involved in some patients. This hypothesis may explain why only heterogeneous results were obtained in therapeutic trials for MS-associated fatigue, i.e., with modafinil (Neumann et al. 2014; Shannon et al. 2000). This underscores the need to identify the underlying etiological factors in a targeted manner in order to be able to develop treatment concepts tailored to the individual patient.

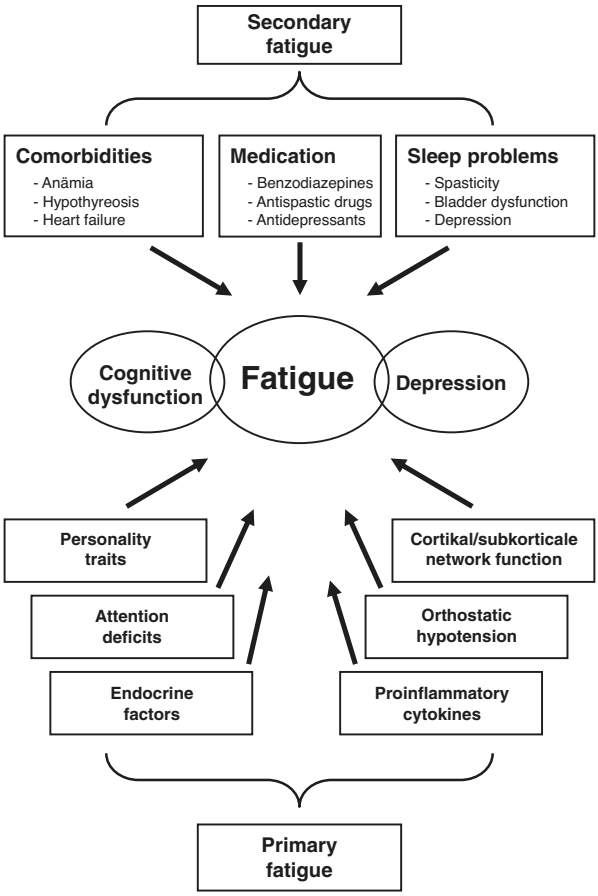

Fig. 7 Etiological factors of secondary (above) and primary (below) fatigue and its relationship to depression and cognitive dysfunction

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Pathophysiology and Differentiation from Other Symptoms and Diseasess

F. Paul

1 Introduction

Fatigue is considered the most common symptom, reported by up to 90% of people with multiple sclerosis, which can have a significant negative impact on quality of life, regardless of age, gender, disease duration, and extent of neurological impairment (Paul and Veauthier 2012; von Bismarck et al. 2018) and is also one of the main risk factors for reduced employment and early retirement. In addition, quite a few sufferers name fatigue as the most distressing symptom of MS. In contrast to the high prevalence and the considerable socio-medical relevance, the pathophysiology of fatigue in MS is at best only rudimentarily understood, which therefore makes causal therapeutic approaches difficult (Penner and Paul 2017). This is further complicated by the fact that fatigue is ultimately a subjectively experienced symptom that is difficult to objectify and quantify. Therefore, stricter definitional discrimination between fatigue as a subjective perception and objectively measurable performance in motor or cognitively demanding tasks ("load-dependent fatigability") (Kluger et al. 2013) has been proposed, especially since "fatigue" and "fatigability" are not necessarily closely associated. Recently, an even more differentiated taxonomy has been proposed and also used in a fatiguing motor paradigm in MS fatigue. According to Drebinger, Kluger, Wolff, Enoka et al. (Drebinger et al. 2020; Wolff et al. 2019; Enoka and Duchateau 2016) different constructs can be distinguished: "state fatigue" ("perception of exertion in situations of effort-demanding activities that is physiologically transient and recovers with rest") from "trait fatigue" ("pathological fatigue as frequent, prolonged, or constant disabling sensation of weariness and exhaustion over longer time frames, interfering with

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usual/desired activities") and from "performance fatigability" ("reduced capacity to maintain activity which can be observed as a decline in performance measures with effort-demanding activities"). To what extent these constructs will contribute to a more precise classification of patient-reported fatigue remains to be seen.

For a better understanding of fatigue and for a rational diagnostic approach to this symptom in the context of MS, it is useful to differentiate so-called "primary" from "secondary" or "comorbid" fatigue. "Primary" fatigue refers to the symptomatology presumably directly associated with the immunological, endocrinological, metabolic, neurophysiological, and imaging changes occurring in the context of MS, whereas "secondary" or comorbid fatigue may occur as a result of other conditions often associated with MS, such as depression or sleep disorders, but also internal medicine diseases such as anemia, thyroid dysfunction, or as side effect of immunotherapy or symptomatic pharmacotherapy in MS. This shows that a sharp syndromal and etiopathogenetic separation of primary and secondary fatigue is not always possible or that there are overlaps. The anamnestic and clinical differentiation of fatigue from daytime sleepiness or daytime fatigue can also be difficult, which can have a variety of causes. However, especially from a diagnostic point of view, the attempt at a classificatory approach is to be welcomed. In the following, the most important pathophysiological aspects of primary and secondary fatigue are discussed, whereby there are always cross-connections to subsequent chapters in this book.

2 Primary Fatigue

From imaging and neurophysiological studies we know that in the pathophysiology of MS-associated fatigue, in addition to immunological, autonomic, and neuroendocrine changes (already discussed in the previous chapter), the disruption of cortical-subcortical neuroanatomical and functional connections plays a crucial role, with a focus on cortico-striato-thalamo-cortical connections. In addition to directly lesion-associated damage to strategically important white matter fiber connections, increasing importance is also being ascribed to so-called "microstructural" damage, especially in "normal appearing white matter," which can be quantified using DTI ("diffusion tensor imaging"), for example, as well as damage to gray matter (Paul 2016; Kuchling and Paul 2020). Some of the imaging and neurophysiological findings are discussed in more detail below. However, it has to be emphasized that the results from imaging studies are often contradictory and usually only small sample sizes were examined cross-sectionally. In addition, causality cannot be inferred from statistical correlations.

2.1 Structural and Functional Imaging

Palotai and Guttmann recently presented the neuroanatomical correlates of MS-associated fatigue in a comprehensive review (Palotai and Guttmann 2020).

Numerous studies with predominantly double-digit case numbers have related lesional (T2 lesion volume and number, and localization) or volumetric (gray and white matter volume, total brain volume, cortical volumes, so-called "deep gray matter" (DGM) volumes) and microstructural (DTI, TBSS ["tract based spatial statistics"])MRI parameters to the subjective extent of MS-associated fatigue, with overall predominantly inconclusive results. While some papers showed clear correlations between fatigue severity and imaging parameters, others failed to demonstrate such associations. The discrepant results can be explained by differences in the field strengths and sequences of the MRI scanners used, in the methods used for lesion quantification and atrophy quantification, in the selection of patients, and in the questionnaires used for fatigue quantification.

However, there are now quite convincing structural and functional imaging findings that point to an association of damage to the thalamus and basal ganglia as well as certain cortical (especially frontal, temporal, and parietal) areas with MS-associated fatigue. According to this, fatigue is understood as a consequence of disturbed connectivity, e.g., between cortical areas and the DGM, whereby a so-called cortico-striato-thalamo-cortical loop is thought to play a special role. In addition to directly disturbed signal transduction through afferent fiber connections, a dysbalance of glutamatergic and dopaminergic transmitter systems is also postulated, which have a close connection with the striatum.

In a cross-sectional study of 44 patients with relapsing-remitting MS (59% female, mean EDSS 2.3, mean disease duration 125 months, mean FSS 3.94) and 20 healthy control subjects, Finke et al. investigated the association of fatigue with structural (DTI, volumetric analyses [VBM ("voxel based morphometry"), FSL ("FMRIB software library")], T2 lesions), and functional parameters ("resting state fMRI" with an examination of basal ganglia connectivity) as well as clinical data of disease severity and cognitive findings (PASAT ["Paced Auditory Serial Addition Test"], SDMT ["Symbol Digit Modalities Test"]) (Finke et al. 2015). Using VBM and FSL-FIRST, significant volume reductions in various gray matter regions could be detected in patients compared to healthy controls, including the prae- and postcentral gyrus and the supplementary motor area, as well as deeper DGM structures such as the caudate nucleus, putamen, pallidum, and thalamus. Microstructural changes in the white matter in terms of a reduction of fractional anisotropy in DTI imaging were accentuated in parts of the corpus callosum, optic radiation, and forceps major and minor. In addition, patients showed reduced functional connectivity between caudate nucleus, putamen, and pallidum on the one hand and numerous cortical areas on the other, including superior, medius, and inferior frontal gyrus, medial prefrontal cortex, orbitofrontal cortex, precentral gyrus, supplementary motor area, supramarginal gyrus, insular paracingulum, praecuneus, and parts of the parietal lobe.

The extent of fatigue, measured with the FSS, did not correlate with the cognitive tests PASAT and SDMT, but with the disease severity on the MSSS ("Multiple Sclerosis Severity Score"). Fatigue severity was also not associated with volumetric and microstructural imaging parameters of the gray and white matter including the basal ganglia, but was associated with alterations in functional connectivity of the

basal ganglia with the frontal and parietal cortex. Fatigue severity correlated inversely with functional connectivity of the right and left putamen with the dorsal and ventral medial prefrontal cortex, praecuneus, and posterior cingulate. Functional connectivity of the right and left pallidum with the dorsal and ventral medial prefrontal cortex and of the right pallidum with praecuneus and posterior cingulate was also inversely associated with fatigue severity. A different picture emerged for the right and left caudate nucleus: functional connectivity with more caudal portions of the medial prefrontal cortex including the anterior cingulate was negatively associated with fatigue severity. In contrast, fatigue severity was positively correlated with functional connectivity of the right and left caudate nucleus with motor cortex. These associations were not found in the healthy control group.

Thus, in summary, this work showed no association of fatigue severity with cognitive performance and volumetric structural imaging findings, but with functional connectivity of the basal ganglia with other brain regions. The basal ganglia are closely connected to the cortex via diverse structurally and functionally delineable control circuits that play an important role in numerous brain functions, including control of motor functions, learning, and memory, but also motivation and reward-driven behavior (Draganski et al. 2008; Graybiel 2005). It is known from various clinical pictures such as cerebral ischemia or postencephalitic or idiopathic Parkinson's syndromes that lesions of the basal ganglia can cause considerable fatigue. In MS, in addition to volume loss of these deep GM structures, reduced blood flow and metabolic changes of the basal ganglia have been described in association with fatigue (Roelcke et al. 1997; Téllez et al. 2007). In addition, so-called "task-based" functional MRI studies found increased activation of the basal ganglia during the performance of cognitively demanding tasks, which could be interpreted as a compensatory mechanism or increased efforts to maintain normal function (Genova et al. 2013; DeLuca et al. 2008).

Interestingly, a negative association of fatigue severity with functional connectivity with the medial prefrontal cortex was found for all three basal ganglia nuclei studied (putamen, pallidum, caudate nucleus), which is in agreement with an older work by Roelcke and colleagues who found decreased glucose metabolism in the basal ganglia and medial prefrontal cortex of MS patients with fatigue in an F-fluorodeoxyglucose positron emission tomography study (Roelcke et al. 1997). These findings may suggest an important pathomechanism of fatigue: The medial prefrontal cortex and basal ganglia are considered to be part of the reward system (Téllez et al. 2007; Elliott et al. 2000), and various authors postulated a dysbalance between effort and reward ("effort-reward imbalance") as a central feature of fatigue (Chaudhuri and Behan 2000; Dobryakova et al. 2013). It is possible that the diverse imaging findings of impaired functional and structural connectivity of control circuits between cortex and basal ganglia represent correlates of this imbalance. Consistent with this hypothesis were also the negative associations of functional connectivity of the caudate nucleus with the anterior cingulate, as the latter is also involved in motivational processes and cingulate lesions can lead to decreased effort and lethargy, which has been neurophysiologically linked to decreased dopaminergic transmission (Dobryakova et al. 2013). In contrast, the positive association of fatigue severity with functional connectivity between the caudate nucleus and motor

cortex observed by Finke et al. could be understood as a compensatory mechanism to maintain normal function with increased effort, but also as a maladaptive process.

Against the background of the above-mentioned findings on the relevance of the basal ganglia and here in particular the striatum for the pathophysiology of MS fatigue, Jaeger et al. in a follow-up study examined 77 patients with relapsing-remitting MS (38 of them with fatigue (FSS > =4), 39 without fatigue) and 41 healthy control subjects matched for age and sex using Resting State fMRI in addition to structural MRI (Jaeger et al. 2019). Subjects with a BDI 20 (indicating moderate to severe depression) were excluded. The aim was to investigate changes in functional connectivity of the striatum and dorsolateral prefrontal cortex (dlPFC). For a so-called seed-based connectivity analysis, three caudate and putaminal subregions of the striatum were selected in addition to the dlPFC on the basis of previous studies. EDSS and BDI scores correlated positively with fatigue severity on the FSS. Structural MRI revealed lower white matter volume and putaminal volume in MS patients compared to control subjects in volumetric analyses. Functional MRI studies revealed interesting differences between MS patients with fatigue and those without fatigue: patients with fatigue had reduced functional connectivity of the bilateral caudate nucleus and left superior ventral striatum with the motor and sensory cortex (supplementary motor area and prae- and postcentral gyrus). In addition, connectivity of the right caudate nucleus with the median frontal gyrus, parts of the parietal lobe, and the praecuneus was decreased in MS with fatigue compared with patients without fatigue, as was functional connectivity of the entire left caudate nucleus with the parietal lobe and the left superior ventral striatum with the parietal lobe and the median frontal gyrus. Compared to healthy controls, MS patients with fatigue showed reduced functional connectivity of the left ventral superior striatum with the inferior temporal gyrus. In contrast, MS patients without fatigue showed no differences from healthy controls in functional connectivity of the caudate nucleus and superior ventral striatum. Compared to healthy subjects, the overall group of MS patients showed decreased functional connectivity of the left dlPFC with the praecuneus, inferior parietal lobe, and posterior cingulate. Within the overall MS group, greater fatigue severity in terms of higher scores on the FSS was associated with lower functional connectivity between left caudate nucleus and bilateral superior ventral striatum and supplementary motor area and praecentral gyrus. Moreover, higher FSS values were associated with higher functional connectivity between right dlPFC and supramarginal gyrus, parietal operculum and praecentral and postcentral gyrus, and between left dlPFC and supramarginal gyrus. In contrast, no correlation was found between fatigue scores and functional connectivity in the control group. This work goes beyond previous work that had already shown the great importance of the basal ganglia for fatigue, as it performed more detailed analyses of the functional connectivity of basal ganglia subregions and was able to show a strong association, especially of the connectivity of the superior ventral striatum with MS fatigue. Interestingly—and here these findings fit well into the older literature on motivation, reward ("effort-reward imbalance") and motor functions and fatigue—the striatal subregion is connected to other brain areas that play a role in reward regulation, attention, and motor functions (Draganski et al. 2008). Accordingly, one could view the superior ventral striatum as a "connectional

hub" to which connections from different cortical areas converge, which could explain the overlap of different networks/functional systems ("effort-reward imbalance," sensorimotor function, attention, etc.) in MS fatigue (Dobryakova et al. 2015; Hanken et al. 2016; Weinges-Evers et al. 2010; Urbanek et al. 2010). The so-called "effort-reward imbalance," which had been postulated several times as a central feature of fatigue, might have a functional correlate in the reduced cortical-ventrostriatal connectivity described by Jaeger et al. This is supported by another fMRI study in MS patients by Dobryakova et al. who showed that activation of the fronto-striatal network by offering a reward ("monetary gain" in the "gambling task") led to improvement of fatigue with concomitant higher BOLD ("blood oxygen level dependent") activation in the ventral striatum (Dobryakova et al. 2018). Furthermore, Jaeger et al. found an association of fatigue severity with reduced connectivity between the caudate nucleus and ventral striatum on the one hand, and the intraparietal sulcus, frontal eye field, and dlPFC on the other, thus affecting central components of the fronto-parietal attention network. The assumption to be formulated from this of a lack of cortico-striatal integration of the fronto-parietal attentional network in MS fatigue is supported by an fMRI study in healthy subjects in whom the connectivity of the fronto-parietal attentional network was disrupted after a fatiguing fMRI task (Esposito et al. 2014). Another paper from our group on altered saccadic eye movements in MS patients with fatigue also points to an impairment of the fronto-parietal attentional network in fatigue (Finke et al. 2012).

The positive correlation between fatigue severity and functional connectivity between dlPFC and the parietal operculum and supramarginal gyrus detected in Jaeger et al. could—in light of the functional importance of these regions and their connections for processing motor and sensory information, representing perceived effort and reward, and maintaining and directing attention—be understood as a maladaptive process contributing to MS fatigue, e.g., by supporting an "effort-reward imbalance."

In summary, the abundance of mainly functional imaging studies from recent years speaks for disturbed functional connectivity, especially between the basal ganglia (especially striatum) and cortical regions with the consequence of affection of sensorimotor networks as well as attention and reward networks as a central pathophysiological correlate of MS fatigue (Penner and Paul 2017; Chaudhuri and Behan 2000). Consideration of therapeutic interventions and initial small studies suggest that noninvasive brain stimulation using tDCS ("transcranial direct current stimulation") or rTMS ("repetitive transcranial magnetic stimulation") could favorably influence the disturbed functional connectivity and thus achieve a clinical improvement in fatigue symptoms (Chalah et al. 2017; Gaede et al. 2017).

2.2 Neurophysiological Findings

A wealth of work over the last 20 years has looked at neurophysiological findings in MS and their association with fatigue, sometimes in combination with imaging studies. The most important findings from EEG (electroencephalography), MEG (magnetoencephalography), TMS (transcranial magnetic stimulation), ENG

(electroneurography), EMG (electromyography) studies, and less frequently used methods such as ANS ("autonomic nervous system") tests are briefly summarized here (Bertoli and Tecchio 2020; Capone et al. 2020; Mamoei et al. 2020).

2.2.1 Electroencephalography

Leocani et al. studied MS patients with minimal disability (EDSS <1.5) and with and without fatigue (measured with the FSS) by EEG and found, in contrast to healthy controls, a positive correlation of the FSS score with event-related desynchronization (ERD) over midline frontal structures during a movement paradigm and an inverse correlation with contralateral sensorimotor ERS. ERD ("event-related desynchronization") over midline frontal structures during a movement paradigm and an inverse correlation with contralateral sensorimotor ERS ("event-related synchronization") after the paradigm (Leocani et al. 2001). These findings have been interpreted as overactivation of frontal regions in MS patients with fatigue, possibly compensating for subcortical dysfunction. Another "graph theory" EEG study in only mildly affected patients (EDSS 2) with a wide range of fatigue scores on the MFIS determined the so-called "small world" index and implied the involvement of the sensory network of the dominant hemisphere in MS fatigue (Vecchio et al. 2017).

2.2.2 Transcranial Magnetic Stimulation

Different TMS protocols can be used to investigate different functionalities of the CNS (such as the corticospinal tract, cortico-cortical connections, and cortical excitability), yielding different measurement parameters. RMT ("resting motor threshold") putatively reflects corticospinal excitability and tract integrity. While some studies reported higher RMT in MS patients, other authors found no differences from control subjects (Mamoei et al. 2020). MEP ("motor evoked potential") latency maps signal transmission from the motor cortex to the lead electrode on the limb muscles. There are also inconsistent findings regarding this parameter; while some authors reported delayed MEP latencies, others could not detect any differences compared to healthy subjects. CMCT ("central motor conduction time") is the conduction time from the motor cortex to the spinal motor neuron and has been investigated in numerous studies in MS patients. Most studies have reported a prolonged CMCT compared to healthy controls, with no difference found between MS patients with and without fatigue in a paper by Morgante et al. (Morgante et al. 2011). MEP ("motor evoked potential") amplitude is considered a measure of corticospinal excitability. With few exceptions, most papers show reduced MEP amplitudes in MS patients compared to healthy controls (Mamoei et al. 2020). During fatiguing exercise, MEP amplitude generally increases in healthy individuals, then decreases. Findings in MS on this are variable. However, two papers showed decreased MEP facilitation in the pre-movement phase after motor exercise in MS patients with fatigue compared to MS patients without fatigue and healthy controls, which may indicate disruption of movement initiation networks as well as alterations in fronto-thalamic connections (Capone et al. 2020; Morgante et al. 2011; Russo et al. 2015). The CSP ("cortical silent period") maps intracortical inhibition

and manifests as an interruption of EMG activity following a suprathreshold TMS pulse (Mamoei et al. 2020); it is thought to be an expression of GABA-B-mediated inhibitory neurotransmission (Capone et al. 2020). CSP has been described in some studies as prolonged in MS, and in a paper by Chaves et al. longer CSP was associated with poorer cardiorespiratory fitness and greater fatigue (Chaves et al. 2019). Neurophysiological methods to examine the peripheral nervous system such as ENG and EMG have also been widely used in MS. Electroneurographic studies in MS have yielded inconsistent findings with sometimes normal findings, but sometimes prolonged distal motor latencies and reduced amplitudes and nerve conduction velocities in MS compared to healthy controls, without this being studied in the context of fatigue to date. In contrast, there are some EMG studies also on MS fatigue, which often showed altered or pathological findings compared to healthy controls, such as reduced volitional activation, or also a correlation between fatigue perception and the drop in maximal innervation during a sustained contraction (Steens et al. 2012). These changes in EMG parameters are considered a consequence of CNS alterations rather than a primary pathogenetic factor of MS fatigue (Capone et al. 2020). Other interesting procedures include the determination of so-called "high frequency oscillations" that overlay the cortical response of the median SEPs and, according to one study, suggest a possible role of the thalamus in the generation of MS fatigue (Capone et al. 2019). Numerous studies have used procedures to test autonomic nervous system functions such as testing of quantitative sudomotor axon reflex, examination of cardiovascular parameters such as heart rate variability during deep breathing and pupillometry. An involvement of the autonomic nervous system in MS, caused among others by demyelinating lesions in eloquent regions, and partly also an association with MS fatigue is well proven (for further details see the previous chapter).

3 Secondary Fatigue

3.1 Sleep Disorders

In recent years, numerous papers have shown a strong association between fatigue and sleep disturbances (Veauthier et al. 2016a; Veauthier and Paul 2016; Veauthier and Paul 2014). In a study by Veauthier et al. 49 out of 66 consecutively recruited MS patients had detectable sleep disturbances in an outpatient polysomnography (PSG), mainly obstructive sleep apnea (OSA), insomnia, "periodic limb movement disorder" (PLMD), restless legs syndrome (RLS), and sleep interrupted by nocturia (Veauthier et al. 2011). In this study, 96% of MS patients with fatigue (defined as MFIS >45) suffered from polysomnographically confirmed sleep disturbance. Interestingly, higher fatigue scores on the FSS and MFIS were associated with the presence of sleep disturbance, but scores on the ESS ("Epworth Sleepiness Scale"), a screening instrument for daytime sleepiness, were not. An open follow-up of participants in this outpatient PSG study was able to show that consistent treatment of the respective sleep disorder led to a clinically significant decrease in fatigue (Veauthier et al. 2013). Several other papers were also able to show a high

association of fatigue with obstructive sleep apnea (Braley et al. 2014; Kaminska et al. 2012). Interestingly, in the work of Kaminska et al. there was an association between high fatigue scores (FSS > = 5) but not subjective and objective sleepiness with OSA and nocturnal arousals in MS patients (Kaminska et al. 2012). A very recent paper retrospectively studied 65 MS patients with and without OSA; patients with OSA were older, had higher BMI, and had higher apnea-hypopnea index (AHI). After adjustment for covariates, there was a significant association of AHI with pontine and mesencephalic lesions, but not medullary lesions on cMRI (Levit et al. 2020). Recent work suggests that OSA and other sleep disorders may also contribute to poorer cognitive performance in MS, and consistent treatment of OSAS may improve certain cognitive performance (McNicholas et al. 2020; Hughes et al. 2018).

The prevalence of RLS in MS is approximately four times higher than in the general population (prevalence rates in MS vary from just over 10% to approximately 65%) (Sevim et al. 2020) and imaging findings suggest greater cervical cord damage in MS patients with RLS. EDSS is also higher in MS patients with RLS than without, as are patients with a higher number of periodic leg movements during REM sleep (Veauthier et al. 2015a). As with OSAS, there appears to be an association of sleep quality with (subjective) cognitive performance in MS sufferers with RLS (Cederberg et al. 2020). It should be noted that renal function and ferritin levels should also be measured when assessing RLS.

It should not be overlooked that there is a high overlap of fatigue and depression in MS (Hasselmann et al. 2016), see also Chap. 8 "Fatigue and depression." In the general population, obstructive sleep apnea is associated with depression, and treatment of this sleep disorder using CPAP ("continuous positive airway pressure") may help improve depressive symptoms. In MS, it has been shown that sleep quality, measured with the PSQI ("Pittsburgh Sleep Quality Index"), is not only associated with fatigue, but also with depression, measured with the BDI (Veauthier et al. 2016b). Therefore, even in MS—although not yet well studied here—consistent treatment of concomitant sleep disorders could improve not only fatigue but also depressive symptomatology.

In summary, these findings show a high prevalence of sleep disorders in MS (especially OSAS, RLS/PLMD, and insomnia) and a strong association of abnormal sleep medical findings with the severity of fatigue. In addition, sleep disturbances lead to significantly impaired disease-related quality of life (Veauthier et al. 2015b). Every MS patient should be specifically asked not only about fatigue but also about sleep disturbances, and a significant proportion of those affected will require a sleep medicine diagnosis. With overall limited sleep laboratory capacity, a screening tool could help identify patients with a high pretest probability for a sleep medical condition. Veauthier et al. could show in a retrospective ROC analysis of MFIS and PSQI data from the above study that the MFIS with a cut-off of 34 points and PSQI with a cut-off of 5 points could predict the presence of a sleep disorder with a sensitivity of almost 90% (Veauthier and Paul 2012), which could help to pre-select patients who should definitely be further clarified by sleep medicine. In the future, "home-based" polysomnography (Veauthier et al. 2011) or "visual perceptive computing" technology could be an alternative to classical sleep laboratory diagnostics (Veauthier et al. 2019).

3.2 Other Causes

In any case, when fatigue or daytime sleepiness is reported, in addition to the diagnosis of sleep disorders, a comprehensive assessment of various medical conditions (anemia, thyroid disorders, renal dysfunction, iron deficiency, vitamin D deficiency, chronic infections, pulmonary dysfunction, etc.) as well as psychiatric problems (including depression) and a careful medication history should be performed (Veauthier et al. 2016a).

4 Summary and Outlook

Fatigue is an extremely common, so far underdiagnosed and often insufficiently treated symptom in MS. Recent imaging and neurophysiological findings indicate disease-related functional or structural disturbances of the connections between the DGM and cortical areas, which could lead to a so-called "effort-reward imbalance" or to alterations in attention networks. These findings provide interesting approaches for targeted noninvasive therapeutic neuromodulation, for example, by means of rTMS or tDCS. With regard to a diagnostic approach useful for the patient, a clarification of further causes of fatigue such as sleep disorders as well as internal and psychiatric diseases is required. Future research should, besides methodologically high-quality studies on noninvasive brain stimulation, address a hitherto little investigated aspect of MS, namely the influence of the loss of retinal ganglion cells (RGC) including so-called intrinsic photosensitive RGC, which can be measured very well by optical coherence tomography, on so-called homeostatic networks and the resulting effects on fatigue (Zimmermann et al. 2018; Oberwahrenbrock et al. 2018; Meltzer et al. 2017; Oertel et al. 2018). Other exciting recent developments include new imaging modalities (e.g., PET ("positron emission tomography") imaging of microglial activation) and serological markers of axonal damage (e.g., NfL ["neurofilament light"]), on which there is initial work in the context of MS fatigue (Singhal et al. 2020; Aktas et al. 2020; Saraste et al. 2021; Tavazzi et al. 2020) This could not only contribute to a broader understanding of the pathophysiology of MS fatigue but also open up further therapeutic options.

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Immunopathology and Pathogenesis

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1 Introduction

Fatigue is one of the most common and severe symptoms of multiple sclerosis (MS), a disease with "a thousand different faces." Several studies have found values of 85% or more for the prevalence of fatigue during the course of the disease (Fisk et al. 1994; Ford et al. 1998; Greim et al. 2007; Rommer et al. 2019). Fatigue can manifest at any stage of MS, as an initial symptom before diagnosis as well as in late chronic progressive stages. However, in contrast to many other symptoms of MS, such as paresis, cranial nerve deficits, or sensory disturbances, its occurrence is much more difficult to grasp and is only weakly related to the current course of the disease. Furthermore, the differentiation from other symptoms of MS is problematic, as many patients experience fatigue combined with affective and cognitive impairments (Fernández-Muñoz et al. 2015). All these points complicate investigations on the complex phenomenon of MS-fatigue and its etiopathogenesis. Recently, Hubbard and colleagues even fundamentally questioned the use of the term "MS-fatigue" (Hubbard et al. 2020).

From a nosological and pathophysiological point of view, a differentiated consideration of various manifestations and aspects of fatigue is relevant. When considering the clinical symptoms, the distinction between rest fatigue ("fatigue at rest") and load-dependent fatigue or pathological fatigability ("fatigability") is particularly important. In order to understand the underlying disease process, it is also essential to differentiate between **primary** and **secondary fatigues:**

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Primary fatigue is the component of the clinical syndrome that arises directly from changes in the central nervous system (CNS) and the systemic effects of mediators and neuroendocrine dysregulation.

Peripheral changes caused by the disease process in the CNS and the accompanying immunological reactions lead to **secondary fatigue.** These include, for example, changes in the metabolism of the musculature due to reduced activity or complications of chronic urinary tract infections.

The assessment of fatigue in the course of MS is associated with considerable difficulties, especially because symptoms in other functional systems often have a direct (e.g., motor function) or indirect (e.g., depression) effect on the clinical scores used to assess fatigue. This particularly affects specific sub-aspects such as "asthenia." An impression of the complexity of the attempt to systematically capture fatigue and its subtypes in MS from a clinical perspective is provided by Mills and Young and Pust et al. (Mills and Young 2008; Pust et al. 2019).

Due to the various dimensions of the symptom and its overlap with other aspects of the underlying disease, a systematic scientific presentation is challenging and virtually impossible to achieve through individual studies. This chapter will thus focus exclusively on the immunological and endocrine processes associated with primary fatigue and the general immunopathology of MS.

2 Immunopathology and Pathomorphological Changes in MS

Both the descriptive pathology of the MS-specific changes in the CNS and the mechanisms of the underlying immune response have been able to contribute new aspects to the understanding of the course of the disease in recent years and are briefly presented here in order to clarify terminology and to enable a classification of the symptom "fatigue" in the biological disease process. Figure 1 provides an extremely condensed overview of the factors that are relevant for primary fatigue in MS.

2.1 Demyelination

The occurrence of focal inflammatory demyelination in the central nervous system (CNS) is a pathomorphological hallmark of MS. For many decades, detailed study of the mechanisms leading to focal inflammation, demyelination, and ultimately gliotic remodeling have been the focus of efforts to understand the organic manifestations of the disease. Only by the end of the twentieth century, it has been recognized that MS pathology goes far beyond mere demyelination: on the one hand, it has become clear that, in addition to myelin and oligodendrocyte loss, damage and structural loss of axons and synapses occur to a much greater extent than had previously been assumed (Ferguson et al. 1997; Trapp et al. 1998; Mandolesi et al. 2015; Cardozo et al. 2019). On the other hand, systematic histological studies have shown

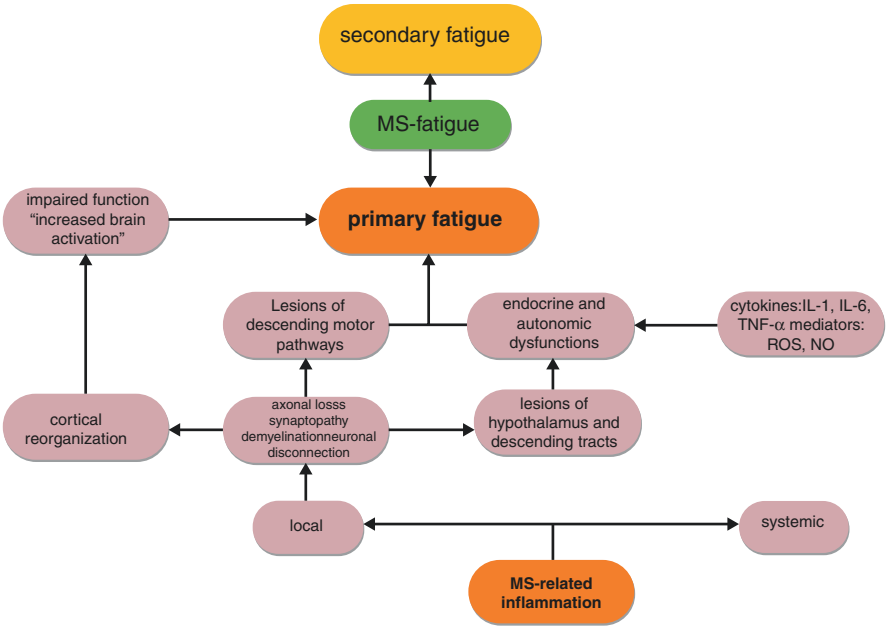

Fig. 1 Classification of MS-fatigue in general and factors underlying the immunopathogenesis of primary fatigue

that the disease is not confined to individual lesions, but that instead pathological changes also occur in apparently unaffected areas—the so-called "*normal appearing white matter*"—even in the absence of local inflammation (Seewann et al. 2009; Vrenken and Geurts 2007).

For several decades, the concept of the cellular immunopathology of MS was shaped by studies in the animal model of *experimental autoimmune encephalomyelitis* (EAE) (Mix et al. 2010). Extensive data from the EAE model led to the assumption that T lymphocytes in particular were essential drivers in the pathophysiology of MS inflammation. However, neuropathological studies on histological preparations of human MS lesions as well as the results of targeted therapy interventions with cell-specific monoclonal antibodies have meanwhile led to a shift in focus toward B lymphocytes, macrophages, and microglial cells and their interactions. With respect to demyelination, four different basic patterns of focal demyelination were defined in the 1990s in tissue samples from MS patients. These differ in terms of the presence of T cells, antibodies, and complement, or in the extent of de- and remyelination, and in the degree of oligodendrocyte damage (Lucchinetti et al. 2000). Lucchinetti et al. postulated that the active lesions of individual patients would show consistent patterns virtually throughout life, which would also explain differences in response to individual treatment strategies. Implicit in this was the hypothesis that MS is not a homogeneous disease at the biological level. Later studies by the groups involved in the development of this concept have provided further

evidence for their hypothesis (Metz et al. 2004; Jarius et al. 2017; Stork et al. 2018). On the other hand, other authors claimed that the observed differences in the histology of lesions largely depended on the temporal stage of the individual lesions and doubted the proposed uniformity of the individual lesion type (Barnett and Prineas 2004; Breij et al. 2008).

Partially decoupled from the debate on the possible heterogeneity of MS, the development of focal lesions and the damage processes occurring within them continues to be a subject of intensive research. Although it is still unclear what triggers MS in principle and whether activation of microglia or lymphocytes causes the local initiation of inflammatory lesions in the CNS, the involvement of both cell types in the early stages of inflammatory lesions is now considered certain. **Microglial cells** are present in large numbers in the CNS even under physiological conditions. They perform a variety of important immunological functions but are also relevant for the formation and maintenance of neuronal networks (Benarroch 2013). They have been detected in active central areas of fresh lesions as well as in the active marginal areas of older lesions. Once relevant tissue damage has occurred there, these microglial cells transform their phenotype and then act as macrophages to clear the plaque. Invasion of monocytes from the blood seems to play only a minor role (Henderson et al. 2009; Zrzavy et al. 2017). Of the numerous effects of microglia, their ability to generate oxidative stress through the production of reactive oxygen species should be emphasized here, since it can drive the pathological inflammatory process by enhancing local cellular damage (Lassmann and van Horssen 2016).

Besides microglia cells, both **B and T lymphocytes are considered to be essential for** MS pathogenesis **in** current models (Gharibi et al. 2020; van Langelaar et al. 2020). This is based on the finding that dysfunction at peripheral immune system self-tolerance checkpoints does not effectively eliminate B cells with autoimmunogenic antigen specificity, causing them to interact with specific T cell subsets later on (Kinnunen et al. 2013). As part of this interaction, B lymphocytes develop into special memory cells ("T-bet-positive B cells"), which in turn promote the development of aggressive, pathogenic T cell populations (Th17). Their ability to migrate into the CNS is particularly favored by the expression of specific surface molecules (CXCR3, CCR6, VLA-4) (van Langelaar et al. 2018; van Langelaar et al. 2019). There, T and B cells might jointly drive the production of proinflammatory cytokines and antibodies, promoting local cell injury and recruitment of additional immune cells (van Langelaar et al. 2020).

2.2 Gray Matter Lesions

Whereas early work on the pathology of the "sclérose en plaques" assumed that demyelination was virtually limited to white matter with special emphasis to the periventricular medullary bed ("Steiner's weather angle"), pronounced cortical demyelination in the cerebrum and cerebellum was demonstrated unequivocally by many groups over the last years (Kutzelnigg et al. 2005; Kutzelnigg et al. 2007; Filippi et al. 2007; Eshaghi et al. 2018; Kiljan et al. 2020).

However, cortical foci histopathologically often show a weaker inflammatory response than the classic "white matter lesions." Nevertheless, there is evidence that not only impairment of higher cognitive functions but also of walking ability is closely correlated with gray matter loss (Preziosa et al. 2017; Jakimovski et al. 2018; Rocca et al. 2019).

2.3 Axonal Lesions and Neurodegeneration

On the whole, there are far fewer data on the causes, course, and extent of axonal damage and neurodegeneration than on demyelination (Trapp et al. 1998; Arnold 1999; Pascual et al. 2007; Friese et al. 2014; Petrova et al. 2018). Nevertheless, the phenomenon itself has been known in the context of MS for over 100 years and was already described in the first systematic papers on the disease (Charcot 1868). It is now accepted that axons are lost to a considerable extent already in the early stages of the disease and that this loss has a major impact on the later clinical course of the disease (Kiljan et al. 2020; Rocca et al. 2019; Petrova et al. 2018).

Particularly in the context of chronic progressive courses, axonal degeneration is considered to be of crucial importance. The degrees of demyelination and axonal loss correlate with each other only to a limited extent (DeLuca et al. 2006). This partly explains the clinical observation that only a few circumscribed demyelinating foci may be detectable in individual patients who nevertheless may suffer from severe physical limitations. Various hypotheses exist regarding the mechanisms of axonal damage. Based on the consideration that loss of the myelin sheath leads to disruption of saltatory conduction of action potentials, compensatory overexpression of sodium channels with subsequent metabolic exhaustion, calcium entry and excitotoxicity has been suggested as a non-immunological cause of axonal demise (Smith 2007). Furthermore, experimental models show that even the smallest structural lesions of the axonal membrane may lead to direct calcium influx (Witte et al. 2019). Other mechanisms discussed include oxidative stress, mitochondrial dysfunction, dysfunctional RNA-binding proteins, and direct damage mediated by CD8-positive T lymphocytes (Skulina et al. 2004; Sobottka et al. 2009; Libner et al. 2020).

A conclusive concept on the pathogenesis of axonal damage derived from preparations of human MS lesions is not yet available. In addition to the above stated mechanisms of damage, the causes of impaired regeneration or remyelination have recently received more attention as possible therapeutic targets (Gruchot et al. 2019).

3 Inflammatory Mediators and Fatigue in MS

Fatigue symptoms that are clinically similar to those in MS commonly occur in the context of other systemic inflammatory or neoplastic diseases. These include such diverse diseases as tuberculosis, post-mononucleosis syndrome, coronaviral disease, and numerous neoplasms. Common to all the diseases mentioned are changes

at the level of cytokines, including TNF- α, IL-1, and IL-6 (Elenkov et al. 2005; Malekzadeh et al. 2015; Ceban et al. 2021). For the mentioned molecules, interactions with hypothalamic receptors and corresponding effects on autonomic functional systems have been known for a long time. In particular, alterations in the hypothalamic-pituitary–adrenal (HHNA) axis are also discussed in relation to fatigue in MS, but also in other autoimmune diseases. Among patients with multiple sclerosis, both enhancements and attenuations of the activity of this axis are found, which also seem to be relevant for the course of the disease: Patients with stronger activity of the HHNA are more prone to disease progression and neurodegeneration. Moreover, in an autopsy study, active MS lesions in the relevant hypothalamic nuclei were described as prognostically unfavorable (Then Bergh et al. 1999; Chaudhuri and Behan 2004; Huitinga et al. 2004; Melief et al. 2013; Anagnostouli et al. 2020; Kantorová et al. 2017).

Whether and to what extent changes in the concentrations of cytokines in MS during acute relapses correlate with the development and severity of fatigue symptoms is controversial (Chalah and Ayache 2018): While Giovannoni et al. (Giovannoni et al. 2001) were unable to establish a correlation between elevated cytokine levels and fatigue, studies by Flachenecker et al. (Flachenecker et al. 2004) and Heesen et al. (Heesen et al. 2002; Heesen et al. 2005) found positive correlations. In the study by Flachenecker et al. the correlation between a fatigue score and the basal concentrations of mRNA for IFN-γ, IL-10, and TNF-α was investigated, furthermore concentrations of peripheral catecholamines were measured. A correlation was found in this study only for TNF-α. In contrast, Heesen et al. investigated the release of the mentioned mediators under in vitro *conditions* from peripheral immune cells after stimulation with phytohemagglutinin. Cells obtained from MS patients with fatigue showed a significantly increased release of TNF-α and IFN-γ under these conditions compared to cells from MS patients without fatigue. TNF-α continued to correlate well with the occurrence of daytime fatigue in this study. In other studies, parallel analyses of multiple cytokines revealed an association between fatigue and serum IL-6 concentrations (Malekzadeh et al. 2015; Alvarenga-Filho et al. 2016). Taken together, these results support the hypothesis that immunological mediators are relevant in MS-fatigue. Further evidence comes from clinical side effects of immunomodulatory therapeutics such as α- and β-interferon preparations: many patients treated with these drugs report the occurrence of fatigue in close temporal association with their application (Zivadinov et al. 2003). In patients receiving glatiramer acetate, on the other hand, there is apparently no change in the associated biomarkers in the serum despite a subjective improvement in fatigue (Neuhaus et al. 2021).

However, it should be noted that both the studies mentioned here and the typical side effects of β-interferon preparations primarily produce "fatigue at rest," i.e., a state of exhaustion corresponding to the old concept of *asthenia* without previous exertion. The MS-specific exercise- and temperature-dependent fatigue and its correlations with the inflammatory parameters mentioned have not been assessed separately in any of the studies mentioned.

4 Pathological Patterns of Damage and Fatigue in MS

Indirect evidence for the special significance of distinct neuroanatomical structures and functional systems for the genesis of fatigue was provided by studies published in the 1990s (van der Werf et al. 1998; Bakshi et al. 1999), which were unable to establish a clear correlation between the pure number of lesions or the cumulative lesion load and the occurrence of fatigue. There was also no close correlation to MR morphological signs of blood–brain barrier disruption in the sense of contrast uptake of individual lesions with fatigue manifestation (Mainero et al. 1999). Numerous attempts to establish correlations with paraclinical parameters derived from conventional MRI imaging, for example, have proved unsuccessful despite intensive efforts (van der Werf et al. 1998; Bakshi et al. 1999; Codella et al. 2002). With the advancement of imaging techniques, the relevance of diffuse neurodegenerative changes in gray matter as well as in "normal appearing white matter" has become increasingly apparent in recent years (Eshaghi et al. 2018; Pellicano et al. 2010; Bisecco et al. 2016; Patejdl et al. 2016). The current state of imaging correlates of MS-fatigue is discussed in detail in Chap. 11 of this book.

Essentially, the following different hypotheses regarding the correlation between pathomorphological changes and MS-fatigue are currently being discussed:

Diffuse axonal degeneration and the functional cortical reorganization processes induced by it.

In the aforementioned study by Tedeshi et al. (Tedeschi et al. 2007) on 222 patients with relapsing-remitting MS without relevant physical disability, the level of a common fatigue score (FSS) was associated with:

- The patients' total lesion burden in T1 and T2 weighted MRI.
- The proportion of altered white matter.
- The degree of atrophy of gray and white matter.

However, only brain atrophy was an independent predictor of fatigue severity. Thus, axonal damage can indeed be assumed to be relevant in the pathogenesis of fatigue. Pathophysiologically, it is likely not the loss of axons or synapses that causes the association between brain atrophy and MS-fatigue. Rather, it might be a consequence of the cortical reorganization that occurs as a part of the complex adaptive processes that are induced by neurodegeneration (Pardini et al. 2010; Park and Friston 2013). In the course of this compensatory reorganization significantly larger cortical areas become involved in the accomplishment of even simple motor or cognitive tasks, leading to increased metabolic demands and regeneration needs, which could result in increased fatigue (Reddy et al. 2000; Rocca et al. 2016; Stefancin et al. 2019). Cumulative lesion load and internal compensatory mechanisms in particular lead to altered activity patterns of frontoparietal cortex areas which can be visualized by clinical electrophysiology and functional imaging and could provide a potential target for symptomatic treatment of fatigue (Zwarts et al. 2008; Cogliati Dezza et al. 2015; Capone et al. 2019).

Localized damage to the ascending pathways of the brainstem, in particular, the formatio reticularis, the nucleus coeruleus, and the so-called non-specific thalamic nuclei with subsequently reduced activation of the cerebral cortex.

To maintain wakefulness ("arousal") and to accomplish the whole spectrum of cognitive functions, the cerebral cortex relies on a complex projections system originating in subcortical nuclei and the brain stem, the so-called the "ascending reticular activating system" (ARAS) or, according to a newer concept, ERTAS ("extended reticulo-thalamic activating system") (Watt 2001; Jones 2003). Pronounced MS-fatigue syndromes may share considerable similarities with the clinical picture of damage to the aforementioned structures, particularly with regard to disturbances in alertness and attention (Dickinson 1997). Further evidence for an association between axonal damage in the ARAS and neuropsychological deficits in MS was also found in spectroscopic studies of the nucleus coeruleus (Gadea et al. 2004). However, in the aforementioned work no specific examination with a common fatigue score was performed, but only the parameter "attention-dysfunction" was examined. Later on, MR spectroscopic analyses were able to demonstrate an association between fatigue and reduced noradrenaline concentrations in the pontine tegmentum as a sign of functional impairment of the ARAS, at least in a small cohort of patients with relapsing-remitting MS (Zaini et al. 2016).

Lesions in motor pathway systems lead to rapid fatigability during physical activity.

Insufficient training of the musculature in MS patients and lesions in the descending motor pathways may underlie the rapid fatigue that is experienced by MS when performing motor tasks (Ng et al. 1997; Ng et al. 2004; Schwid et al. 1999; de Haan et al. 2000). Liepert et al. (Liepert et al. 2005) were able to show that not only alterations of the direct descending pathways, but also of intracortical inhibition and altered excitability of neurons of the motor cortex correlate with pathological fatigue. Furthermore, the activity of the putamen and thalamus is reduced during the performance of complex motor actions (Bermel et al. 2008). An overview of the neurophysiological changes in the context of motor deficits in MS is provided by Mamoei et al. (Mamoei et al. 2020) and in Chap. 5 of this volume.

5 Neuroendocrine Regulatory Disorders in MS

Changes in the hypothalamus and corresponding autonomic changes are discussed both as a consequence and as a possible cause of MS-associated disease activity. Findings on HHNA activity in MS are controversial, possibly due to differences in the patient populations studied (immunomodulatory treated vs. untreated) (Heesen et al. 2002; Gottschalk et al. 2005; Akcali et al. 2017). In contrast to fatigue in other syndromes, hyperreactivity of this axis is often, but not always, seen in MS. Studies on the relationship between the functional state of the HHNA axis and the presence of fatigue should be distinguished from work that focuses on a direct relationship between actual HHNA activity and fatigue. Kern et al. found an increased morning rise in cortisol in patients with disease progression in relapsing-remitting MS (Kern

et al. 2013). Another study among 223 MS patients found no clear association between the circadian rhythm of cortisol release and the severity of fatigue (Malekzadeh et al. 2019). An altered release of stress hormones as a cause of fatigue, whether for psychological reasons or through the effect of inflammatory mediators, is also discussed by other authors (Morris et al. 2002; Powell et al. 2015; Hildebrandt et al. 2020).

Markou et al. (Markou et al. 2005) report on a patient who developed MS after the removal of a cortisol-producing adrenal tumor. Although it is tempting to assume that lowered cortisol levels might promote the autoimmunological process in MS, this association has not yet been confirmed in systematic studies (Michelson et al. 1994; Harbuz 2002). On the contrary, higher basal cortisol levels seem to tend to be associated with a less favorable course, whereas low levels are associated with the occurrence of fatigue (Pereira et al. 2018).

6 Multidimensionality of Fatigue and Damage Processes in MS

There are complex relationships between the multidimensional symptom "fatigue" and immunological processes in MS. Following a suggestion of Iriarte et al. (Iriarte et al. 2000), fatigue may be dissected into the components "Asthenia," "pathological exhaustibility," and "Symptom exacerbation due to exertion." When considering these three manifestations of MS-fatigue, the following hypotheses can be made about the connection between organic pathological processes and its clinical correlates:

Asthenia would thus be an expression of central dysregulation at the level of the hypothalamic–pituitary–adrenocortical axis and in ascending activating pathways caused by increased concentrations of cytokines produced in the context of inflammation and/or by increased central sensitivity to them (Chalah and Ayache 2018; Gottschalk et al. 2005).

Pathological exhaustibility can be considered as a correlate of focal axonal and demyelinating lesions of motor pathways as well as cortical reorganization by diffuse axon loss. The latter adaptation processes at the cortical level, together with changes in the ascending activating pathways from the brainstem and thalamus, are also likely to be responsible for the pathological exhaustibility during cognitive and attentional tasks (Liepert et al. 2005). As a consequence of the lesion load acquired during the course of the disease, the activity of the activated brain regions can apparently be coordinated less efficiently (Chen et al. 2020).

According to current understanding, **symptom exacerbation during stress and temperature change**—the long-known Uhthoff phenomenon—is most likely a consequence of increased temperature sensitivity of the non-saltatory propagation of action potentials at completely or partially demyelinated central axons. Furthermore, increased stress on the pre-damaged pathways can also lead to significantly increased local energy requirements, oxidative stress, and subsequent release of tissue mediators, which in turn themselves cause systemic reactions (Guthrie and

Nelson 1995; Tataru et al. 2006). MS patients with a relapsing course also appear to have a fundamentally higher body temperature compared to healthy controls and patients with a chronic progressive course, which correlates with the presence of fatigue (Sumowski and Leavitt 2014).

A better understanding of the necessity of a differentiated consideration of the various fatigue components for a conclusive clarification of their causal and formal pathogenesis seems to be increasingly gaining ground. The goal of developing a general theory of the immunopathogenesis of "the" fatigue has not yet been reasonably realized in view of the heterogeneity of the symptom complex. However, a close association of fatigue symptoms with MS-related CNS-lesions has been demonstrated in a large number of studies over the last decades. From a clinical point of view, this is important insofar as it gives rise to the hope that improvements in immunomodulatory therapies may also have a positive influence on the development and progression of certain forms of fatigue.

7 Summary

Morphological and functional changes underlie the development of the highly prevalent and highly variable symptoms commonly referred to as MS-fatigue. According to the current state of knowledge, demyelinating lesions and accompanying disturbances of axonal integrity, locally circumscribed lesions and diffuse changes throughout the CNS with extensive involvement of cortical areas are essential elements of the underlying pathophysiology. Accurate differentiation between the various forms and aspects of fatigue continues to gain importance for its appropriate interpretation and targeted treatment. In particular, this applies to the clear differences in the morphological and functional causes of the MS-fatigue dimensions **asthenia** ("fatigue at rest"), **cognitive and motor exhaustibility (**"fatigability") and **symptom exacerbation** caused by stress **and** exogenous factors (e.g., temperature) ("Uhthoff phenomenon").

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Part II

Clinic

Motor Performance Fatigability in MS

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1 Introduction

Based on the definition and framework of Kluger et al. (2013) as well as Enoka and Duchateau (2016), a distinction should be made between trait and state fatigue (see also Chap. 3). This chapter focuses on activity-induced state fatigue, which can be described as a temporary decline in motor and/or cognitive performance (performance fatigability) and/or an increase in the perception of fatigue (perceived fatigability) in response to a motor or cognitive task. Thereby, motor performance fatigability is determined by the activation characteristics as well as contractile

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function of muscles (Enoka and Duchateau 2016) and cognitive performance fatigability by the integrity of the central nervous system (e.g., brain activity, metabolites, and neurotransmitters) (Tommasin et al. 2020; Behrens et al. 2018; Linnhoff et al. 2019). Perceived fatigability strongly depends on the psychophysiological state of the individual and is influenced among others by effort perception, motivation, and self-regulation (Enoka and Duchateau 2016; Venhorst et al. 2018). Importantly, performance fatigability and perceived fatigability are interdependent and should be investigated in conjunction (Behrens et al. 2021).

The quantification of motor performance fatigability and perceived fatigability is essential for improving therapy and quality of life as well as for the sociomedical assessment of working ability usually carried out for people with MS (pwMS) who have been admitted to rehabilitation by the pension insurance provider in Germany. For a comprehensive understanding of the fatigue phenomenon, it is important to combine clinical observations as well as the patient's subjective perceptions and objective measures. Because the ability to walk is of particular importance for activities of daily living and working ability, we focus primarily on the quantification of gait-related motor performance fatigability and perceived fatigability. In the following paragraphs, the fatigue taxonomy proposed by Enoka and Duchateau (2016) is applied, even if the cited studies have not strictly applied the terminology proposed here.

2 Clinician and Patient Perspective

Many patients are familiar with the feeling of exhaustion and altered movement patterns induced by sustained and/or intense motor tasks. They are aware that they can go a certain distance before walking becomes increasingly effortful and unsteady. When the patients are asked to state their maximum walking distance, they often answer that it depends on their daily status. Indeed, their gait performance strongly depends on how rested or exhausted patients are from tasks performed earlier that day. If a patient reports that he or she can only walk 500 m and needs rest afterward, the clinician should ask: "What happens after 500 m?" Or: "Why do you have to take a break after 500 m?" As a response, many patients describe that they start to drag one leg or cannot properly lift one foot as well as walk with increasing unsteadiness or even stumble. Although they are able to continue walking after a sufficient rest period, the distance covered is shorter than before. If the medical history and/or the clinical assessments indicate that this occurs frequently, this might be indicative of an increased motor performance fatigability.

Of course, many pwMS exhibit a deviating gait pattern compared to healthy controls (Cameron and Wagner 2011). Thus, one could argue that this impairment is already an explanation for the shortened walking distance. However, experienced clinicians have a rough idea of how far a patient with hemiparesis or hemispasticity is able to walk. If the short walking distance cannot be explained by the extent of the paresis, spasticity, or ataxia, an increased motor performance fatigability might be

present (Sehle et al. 2014). This assumption can be verified if the patient reports an increase in the perceived impairments or a worsening of the gait pattern when the maximum walking distance is reached or even develops gait abnormalities, which might not have been apparent before. Some patients also experience paresthesias with increasing exhaustion, which diminishes with appropriate rest. In general, motor performance fatigability becomes visible in the individual impairments caused by previous relapses or by progression of the disease.

Sometimes motor performance fatigability is also the first usually unrecognized sign of primary progressive MS, i.e., patients describe a feeling of physical weakness during unusual exertion like hiking. The next day, many patients have forgotten this sensation or justified it with the unaccustomed intensity of the physical activity. Something similar can also occur during long runs, i.e., patients develop an increasing foot drop, tend to stumble, or are partially unable to continue running.

In this context, it should be mentioned that, in the case of a former optic neuritis, visual acuity might worsen during heat exposure (Uhthoff phenomenon) or during exercise. Patients often report that the vision becomes more strenuous with increasing exhaustion and that the image in one eye becomes blurred, fades, or flickers. Moreover, an increasing nystagmus or oculomotor dysfunction (in the presence of an old lesion in the brainstem) can also provoke acute visual disturbances during intense physical exercise (e.g., on an ergometer) (Gütler et al. 2019). Oculomotor dysfunction often comes along with double vision and nystagmus with impaired vision. Most of the time, however, it is not possible to clearly distinguish such a condition from cognitive performance fatigability, for example, in the context of screen-based work. The patients are usually unaware of this phenomenon and it is often not correctly identified from the medical history. For confirmation, visual acuity has to be tested after the respective activity. Moreover, a differentiation from the Uhthoff phenomenon, i.e., a worsening of neurological function due to an increase in body temperature, is crucial, which can be observed after bathing in hot water. Here, a deterioration of visual function cannot be explained by exhaustion.

3 Gait-Related Motor Performance Fatigability

In MS, weakness of the hip flexor and knee flexor/extensor as well as the foot drop are common limitations (Filli et al. 2018; Ramari et al. 2018; Güner et al. 2015). Especially, the increasing foot drop with exhaustion is visually and auditorily easy to identify by a loud clap while placing the foot on the ground at the beginning of the stance phase. In addition, an increase in spasticity, gait unsteadiness, or lateral swaying of the upper body (see Box 1) is often observed. So far, there is no gold standard to categorize gait-related motor performance fatigability in clinical practice, although this is very important for the assessment. Therefore, early on, we engaged in the quantification of gait-related motor performance fatigability in pwMS (Sehle et al. 2011).

Box 1
Common clinical manifestations of gait-related motor performance fatigability:
Increasing foot drop/dorsiflexion weakness/plantarflexion spasticity (stumbling)
Increase in hip flexor weakness (dragging of one leg)
Increase in knee extensor weakness (hyperextension of the knee)
Decrease in gait stability (unsteadiness)
Increase in gait variability (larger step width variations)
Increase in lateral compensatory swaying of the upper body
Increase in paresthesias or pain

To date, there are two systematic reviews summarizing studies on the quantification of motor performance fatigability in pwMS (van Geel et al. 2020; Severijns et al. 2017). There are several methods to assess motor performance fatigability of single muscles or muscle groups using isometric or concentric contractions. However, no gold standard exists for whole-body movements such as walking in pwMS. In this regard, most methods are based on linear approaches analyzing spatiotemporal gait parameters, or indices derived from these, recorded over a certain test duration (often 6-min walk test/6MWT). Furthermore, there are a few studies that have used nonlinear dynamic approaches for gait analysis to quantify gait-related motor performance fatigability. Both are outlined in more detail below.

3.1 Linear Approaches for Gait Analysis

The acute change in the gait pattern during sustained walking can be quantified by calculating spatiotemporal gait parameters such as gait velocity, stride length, stride width, cadence, minimum foot/toe clearance, and their variability over time. Common measurement devices are photoelectric systems, pressure-sensitive walkways, marker-based/markerless motion capturing systems, and inertial measurement units. Escuerdo-Uribe et al. (2019), for example, demonstrated that gait velocity, cadence as well as step length decreased and the respective variability increased in moderately to severely affected pwMS from prior to after the 6MWT. Moreover, Socie et al. (2014) have shown that primarily step length variability and step time variability increased over the 6MWT in pwMS who required assistance while walking. However, several studies investigating mildly affected pwMS have reported that the duration and/or intensity of the 6MWT might be not sufficient to provoke changes in gait parameters over time (Broscheid et al. 2022a, b; Burschka et al. 2012a). Therefore, it is important to adapt the duration and/or intensity of the walking test protocol to the level of disability (Expanded Disability

Status Scale/EDSS) to induce gait-related motor performance fatigability. In the following, two common indices to assess gait-related motor performance fatigability based on spatiotemporal gait parameters are presented.

3.1.1 Distance Walked Index

The Distance Walked Index (DWI), introduced by Leone et al. (2016), is calculated on the basis of the distance walked in the first compared to the last minute of the 6MWT. If the walked distance is reduced by more than 15%, gait-related motor performance fatigability can be assumed. This threshold was later revised to a reduction of 10% (van Geel et al. 2020). The former multicenter study considered not only disease severity (EDSS) but also the MS phenotype. At the first glance, the DWI seems reasonable. However, in some patients, there may be observable gait pattern changes but the walking velocity and therefore the distance walked can be kept constant during the 6MWT. For instance, in an unpublished pilot study, the observable changes in gait performance of 27 pwMS were classified into four categories (no, mild, moderate, and severe visible motor performance fatigability) by experienced health professionals (Peters 2020). The observations were compared with the DWI. Based on the subjective assessment of the physiotherapists, seven exhibited mild, seven moderate, and six severe motor performance fatigability toward the end of the 6MWT. However, the DWI was below the threshold of −10% in only six patients. Three of them had severe, one moderate, one mild, and one no gait pattern changes by visual assessment. Accordingly, observable gait pattern changes that were not reflected in a reduction in velocity were present in 15 pwMS. In contrast, gait velocity was reduced in one patient with no visible changes in gait. This preliminary finding strengthens the view that, on the one hand, the duration and/or intensity of the 6MWT were not sufficient to provoke gait-related motor performance fatigability in mildly to moderately affected pwMS. On the other hand, the walking distance/gait velocity alone seems not to be an adequate parameter to quantify gait-related motor performance fatigability.

Another aspect that should be considered is that the first minute of the 6MWT can only be used as a reference baseline to a limited extent. For example, it was shown that gait variability was higher (Broscheid et al. 2022a, b) and gait stability was lower (Broscheid et al. 2022) in the first minute due to transition effects, which might have an influence on gait velocity. Furthermore, Aldughmi et al. (2017) have demonstrated a clear decrease in gait velocity in the first minute and only a very discrete decrease in the subsequent 5 min in 52 pwMS during the 6MWT. Moreover, Burschka et al. (2012b) have shown that the gait velocity of mildly affected pwMS and healthy controls exhibited a u-shape and only in moderately affected pwMS a significant decrease over the course of the 6MWT was observable. Accordingly, it might be a better approach to consider the second minute of the 6MWT as the baseline reference for the calculation of the DWI. To detect gait-related motor performance fatigability in less affected pwMS, it might be necessary to perform longer and/or more intensive walking test protocols.

3.1.2 Deceleration Index

The deceleration index (DI), established by Phan-Ba et al. (2012), relates the walking velocity during the last 100 m of the 500-m walk test to the walking velocity during the 25-foot walk test with a dynamic start. This ratio between the final velocity during the 500-m walk test and the fastest possible walking velocity was significantly lower only in pwMS with an EDSS score of 4–6, a pyramidal or cerebellar function system score of 3 (EDSS) or a maximum reported walking distance of ≤ 4.000 m. Piérard et al. (2015) defined a DI cutoff value of 0.8 for gait-related motor performance fatigability. Furthermore, they demonstrated that pwMS with a DI ≤ 0.8 showed different indicators of gait-related motor performance fatigability depending on the degree of disability. People with MS with an EDSS ≤ 3 predominantly showed variations in step width, which can be interpreted as poorer dynamic balance, while pwMS with an EDSS > 3 exhibited a reduction in walking velocity over the 500-m walk test.

3.2 Nonlinear Approaches for Gait Analysis

The conventional linear gait analysis methods described above are established and well studied but have the disadvantage that individual gait characteristics are derived from single gait cycles or gait velocity and the dynamics of continuous movement as well as its fluctuation are neglected. However, nonlinear approaches take these aspects into account and two of them are described subsequently in more detail.

3.2.1 Local Dynamic Stability

The most common nonlinear dynamic approach for gait analysis is the determination of local dynamic stability (LDS) that provides information about gait stability (Dingwell and Cusumano 2000). This approach requires recording of 3D acceleration data during walking to determine the LDS via the largest Lyapunov exponent (λ). The λ is a measure of chaos in a dynamic system. If two trajectories are analyzed, λ describes to what extent they diverge from each other over time. The greater the divergence, the more unstable the system (Rosenstein and Collins 1993). However, the methodological procedure for determining the LDS is controversially discussed in the literature. There are different approaches for the placement of the inertial measurement units (feet or trunk), the type of walking test (treadmill, overground, outdoor, or indoor), and the calculation of λ, which have to be adapted depending on the objective (Hamacher et al. 2015). Arpan et al. (2020) demonstrated that pwMS did not differ from healthy controls in LDS during the first 3 min of the 6MWT. Thereafter, approximately 60% of the pwMS showed an increasingly unstable gait till the end of the 6MWT. The authors interpreted this decrease in gait stability as a sign of gait-related motor performance fatigability.

3.2.2 Fatigue Index Kliniken Schmieder

A nonlinear dynamic system such as walking can be described by an attractor, i.e., a stable state to which the system tends. Based on this idea, Vieten et al.

(2013) developed the attractor method, which is the basis for the Fatigue Index Kliniken Schmieder (FKS) (Sehle et al. 2014). The FKS requires pwMS to walk on a treadmill for 60 min or until exhaustion (Borg Scale: 17). During treadmill walking, 3D acceleration and gyroscope data of the feet are recorded with inertial measurement units at the beginning and at the end of the test for 1 min. For each minute, a limit-cycle attractor is calculated, which represents a kind of average or individual ideal gait pattern of all gait cycles (trajectories). The difference between the two limit-cycle attractors and their variability is the basis for the calculation of the FKS. Only if this individually very stable gait pattern (Broscheid et al. 2018) and the variability of the trajectories change from beginning to end of the walking test, this is interpreted as motor performance fatigability (threshold value: FKS $\geq$ 4) (Sehle et al. 2014). However, the FKS has not yet been used for the clinical assessments of gait-related motor performance fatigability in pwMS because its execution is time consuming (up to 1 h) and not sufficiently user-friendly for clinicians.

4 Motor Performance Fatigability and Perceived Fatigability

Most studies examined either the correlations of trait fatigue with motor performance fatigability (Loy et al. 2017) or were inaccurate in their wording (exertion and not exhaustion) when asking for perceived performance fatigability prior and after a motor task (change in subjective perception of fatigue/exhaustion induced by motor activity) (Drebinger et al. 2020). There are very few studies that have investigated motor performance fatigability and perceived fatigability in conjunction. For instance, Karpatkin et al. (2015) assessed exhaustion/perceived fatigability after a continuous and intermittent 6MWT in mildly to moderately affected pwMS. They have found that pwMS covered less distance and had higher exercise-induced perceived fatigability during the continuous 6MWT. These results indicate that quantification of perceived fatigability in the context of sustained motor activity is sensitive to exercise-duration variations in pwMS. Another study by Andreopoulou et al. (2021) investigated gait-related performance fatigability over 20 min on a treadmill in pwMS and healthy controls. Even though the authors reported perceived fatigability in response to the walking task only descriptively, no differences between the groups regarding the mean values were observed.

One of the most important factors regarding perceived fatigability is the perceived effort, which appears to be elevated in pwMS during submaximal motor tasks (such as walking) (Thickbroom et al. 2006). Due to the fact that exercise-induced effort perception contributes to exercise behavior, performance reduction, and termination of sustained motor activity (Venhorst et al. 2018; Staiano et al. 2018), it could be an important contributor to motor performance fatigability in pwMS. Overall, exercise-induced perceived fatigability as well as its determining factors are not well studied in pwMS.

5 Interactions between Sustained Cognitive or Motor Activity and Performance Fatigability

Behrens et al. (2018) have shown that performing a cognitive sustained task had a negative effect on gait performance during dual-task walking (increase in the coefficient of variation of gait velocity, stride length, and stance time) in healthy older individuals. To the best of our knowledge, there are no comparable studies with either single-task or dual-task walking in pwMS. In pwMS, the results of the study by Claros-Salinas et al. (2013) indicated that strenuous physical exercise on a treadmill resulted in poorer cognitive performance (increase in reaction time in an alertness task). These data reveal that an overlap of motor and cognitive functions exists that is modulated by the psychophysiological changes associated with state fatigue.

Accordingly, sustained motor or cognitive activity can have a negative impact on cognitive or motor performance, respectively. First approaches to investigate the underlying mechanisms have already been made (Arm et al. 2019; Müller and Apps 2019; Chen et al. 2020) (for further information see Chap. 11 "Imaging and Fatigue").

6 Motor Performance Fatigability and Trait Fatigue

Loy et al. (2017) published a systematic review with a meta-analysis on the association between motor performance fatigability and trait fatigue. The included studies showed inconsistent results regarding this association, presumably in part due to the greatly differing testing methods/protocols. Drebinger et al. (2020), for example, revealed no correlation between gait performance changes induced by a 6MWT and trait fatigue (Fatigue Scale of Motor and Cognitive Function/FSMC questionnaire) in pwMS (Drebinger et al. 2020). Likewise, Sharma et al. (1995) could not find a correlation between motor performance fatigability of the tibialis anterior muscle and trait fatigue (Krupp fatigue severity scale questionnaire/10-cm visual analogue fatigue scale). Furthermore, the Fatigue Index (based on the force-time integral) of the knee extensor and flexor muscles assessed during 30 s maximal isometric contractions also did not correlate with trait fatigue (FSS questionnaire) (Surakka et al. 2004a). In contrast, some studies focusing on the upper extremities revealed correlations between motor performance fatigability and trait fatigue (Loy et al. 2017). However, in this regard it should be considered that MS affects the upper and lower extremities differently (Schwid et al. 1999), while the lower extremities are more relevant for mobility and therefore daily living. In conclusion, there is no clear correlation between motor performance fatigability in the lower extremities and trait fatigue. Therefore, both seem to be distinct concepts and should be considered separately.

7 Motor Performance Fatigability and Trait Self-Control

Self-control refers to the mental processes people use to control thoughts, feelings, and behaviors that conflict with important goals (Baumeister et al. 2007). Self-control is particularly relevant when people have to exert or sustain effort. It is argued that the sense of effort, that accompanies the exertion of self-control, functions as a signal for accumulating control costs (Wolff and Martarelli 2020). A large body of evidence shows that individuals with high self-control are better at accomplishing effortful tasks (de Ridder et al. 2012). In turn, it is possible that individuals with high levels of self-control experience demanding tasks and actions as less costly. The relevance of self-control is particularly evident in sport, where the ability to sustain great levels of exertion is of crucial relevance.

Based on these considerations, we investigated the role of self-control in the management of trait and state fatigue (Wolff et al. 2019). We asked 51 pwMS to squeeze a force transducer with one hand at 10% of their maximal force until exhaustion. At the same time, changes in prefrontal cortex (PFC) oxygenation were continuously recorded using functional near-infrared spectroscopy. The PFC has been associated with the application of self-control and increased oxygenation was measured as a proxy for increased activity in this area. Furthermore, perceived motor and cognitive fatigability were assessed at regular time intervals. Beforehand, the patients had to complete a trait fatigue questionnaire (Penner et al. 2009) and the German version of the Brief Self-Control Scale (Bertrams and Dickhäuser 2009) as a measure of trait self-control. As expected, self-reported perceived motor fatigability increased steadily and substantially throughout the handgrip task. Importantly, perceived cognitive fatigability and PFC oxygenation also increased. Remarkably, in a stepwise regression, only the trait self-control scale, but not the trait fatigue scale, was a significant predictor of how steep the increase in PFC activity and perceived cognitive fatigability would be. This finding suggests that trait self-control plays an important role during physically exhausting tasks in pwMS. More specifically, it seems that at the perceptual and neuronal level, pwMS with high trait self-control might be more efficient in dealing with rising physical exhaustion. In turn, they might cope better with motor performance fatigability than pwMS who display low trait self-control.

This interpretation is consistent with evidence from sports science suggesting that the use of self-control strategies is also associated with a blunted increase in PFC activity (Wolff et al. 2018). Thus, it is a plausible assumption that the use of self-control strategies (Gollwitzer 2014) or the use of self-control training (Friese et al. 2017) might help pwMS to better cope with the limitations caused by state and trait fatigue. This highlights the relevance of psychological processes and constructs for understanding and potentially altering phenomena that are deemed primarily organic.

8 Pharmacological and Non-pharmacological Treatment of Motor Performance Fatigability

Miller and Soundy (2017) conducted a systematic search of reviews and summarized pharmacological and non-pharmacological treatments (physical exercise and education) of trait and state fatigue in pwMS. There are only a few studies that reported the effect of these interventions on motor performance fatigability as primary outcome. With regard to the pharmacological treatment, very little is known and no recommendations were given. The effect of non-pharmacological treatments was investigated by more studies, but only a few focused on motor performance fatigability. For example, Surakka et al. (2004b) examined the impact of aerobic training together with strength exercises performed over 26 weeks on motor performance fatigability of the knee flexor and extensor muscles in mildly to moderately affected pwMS (47 intervention/48 control group). They analyzed the force decline, represented by a Fatigue Index (Surakka et al. 2004a), during a 30-s maximal isometric contraction before the intervention, after 3 weeks and after 6 months. Additionally, the Ambulatory Fatigue Index was utilized, which is based on the gait velocity decline from the first to the last 50 m lap during a 500-m walk test (Schwid et al. 1999). Motor performance fatigability (Fatigue Index) of the knee flexors and extensors was reduced by the intervention in female but not in male pwMS from week 3–26. In another study, Dettmers et al. (2009) investigated whether low-intensity endurance training performed for 3 weeks (three times a week for 45 min) has an influence on the maximal walking distance on a treadmill in mildly to moderately affected pwMS (15 intervention/15 control group). Compared to the control group, who only received a balance as well as coordination training and stretching, the maximal walking distance increased significantly. Salem et al. (2011) also reported that a 5-week aquatic exercise program (twice a week for 60 min) improved walking velocity (10-m walk test), static balance (Berg-Balance Scale), functional mobility (Timed Up and Go test), and grip strength in pwMS ($N = 10$).

Overall, the studies on the treatment of motor performance fatigability are difficult to compare due to the different interventional approaches as well as heterogeneity of the included pwMS (disability level/sex) and measurement methods. In addition, it should be considered to include a sufficient number of males and to adapt the intervention because of the physiological differences as well as different disease progression compared to female pwMS. For more information on non-pharmacological treatments for state and trait fatigue, please see Chap. 16.

9 Summary

– Gait-related performance fatigability can be quantified in pwMS using linear (spatiotemporal gait parameters, their variability and derived indices: DWI/DI) and nonlinear approaches (largest Lyapunov exponent/FKS) for gait analysis. However, it is important (1) to monitor not only one parameter (e.g., gait velocity)

for quantifying gait-related motor performance fatigability, (2) to adapt the test protocol in duration and/or intensity to the degree of disability, and (3) to pay more attention to sex differences.
- The interactions between motor performance fatigability and perceived fatigability as well as their associations with trait fatigue measures are partly insufficiently investigated and conflicting due to different test protocols.
- Sustained (motor or cognitive) activity can have a negative impact on motor or cognitive performance.
- To the best of our knowledge, there are no studies on pharmacological treatments for motor performance fatigability in pwMS. However, non-pharmacological treatments such as physical activity may be beneficial. To date, motor performance fatigability is rarely assessed in the clinical context and it is highly recommended to improve therapeutic approaches. Additionally, it is important to inform patients that motor performance fatigability is reversible, i.e., that no damage to the nervous system can result from exertion and exhaustion. This is of particular importance because patients might experience their activity-induced exhaustion as a punishment for pushing themselves too much and might avoid physical activity in the future. This may lead to a vicious circle of avoidance behavior, deconditioning, and increasing motor performance fatigability. Therefore, physical training is definitely recommended.

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Cognitive Fatigue

Iris-Katharina Penner, P. Flachenecker, and H. Meißner

1 Introduction

Contrary to earlier assumptions that MS fatigue is a unidimensional construct that can be captured by scales quantifying severity (e.g., Krupp et al. 1989; Schwartz et al. 1993), there is at least agreement at the symptom level that fatigue may manifest physically and/or cognitively. Chalder et al. (1993) were among the first to attempt to map this distinctiveness in a fatigue scale that captures both components. Most commonly, patients can be observed complaining of both physical and cognitive fatigue, albeit to varying degrees. The previous chapter dealt exclusively with motor fatigue and fatigability. The following chapter will focus on the cognitive manifestation of the symptom.

2 Definition of Cognitive Fatigue

As already explained in Chap. 2, a comprehensive and uniform definition of fatigue proves to be difficult, since, similar to pain, it is a phenomenon subjectively perceived by the individual, which largely eludes direct observation and thus objective recording and quantification. Detailed knowledge of the nature and manifestation is therefore based exclusively on reports from affected patients. In the case of cognitive fatigue, these patients complain of a lack of mental energy, which prevents them from carrying out their usual activities of daily life and, in particular, severely

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restricts them in their professional life. The more mentally demanding the occupation, the more stressful the negative impact on working life is experienced by those affected.

As with motor fatigue, the symptoms of cognitive fatigue vary according to the time of day, with a marked worsening in the afternoon and during evening hours (Comi et al. 2001; Krupp et al. 1988) and can also be triggered or intensified by stress and heat (Comi et al. 2001). Cognitive fatigue can be distinguished from normal mental daytime fatigue by the fact that it occurs unexpectedly and without any direct external correlate (such as hours of PC work or other mental activities requiring concentration and stamina) with severity and intensity that acutely prevents patients from performing their usual tasks. Cognitive fatigue is one of the leading symptoms of so-called central fatigue. Central fatigue is understood as the inability to initiate and/or maintain attentional performance ("mental fatigue") and physical activities ("physical fatigue") that require a high degree of self-motivation (Chaudhuri and Behan 2000).

While motor fatigue has been repeatedly examined by numerous imaging studies (e.g., Filippi et al. 2002; Roelcke et al. 1997), the understanding of the cognitive fatigue component can still be described as limited in comparison. This may be mainly due to the difficulty of distinguishing cognitive fatigue from a purely cognitive problem in the sense of impaired cognitive performance and to attach it to an external criterion. In the past, there were two different conceptualizations. In the first, cognitive fatigue was understood as a decrease in performance over a longer period of time, for example, in the course of a working day. However, there is little clinical evidence for this type of definition, as it has not been possible to map it reliably and objectively (DeLuca 2005). The second defined cognitive fatigue as a decline in performance during acute yet "sustained mental effort" (Schwid et al. 2003). This latter conceptualization is what we now refer to as "cognitive fatigability." In contrast to cognitive fatigue, which is purely a matter of self-perception and self-assessment on the part of the patient, cognitive fatigability describes the measurable and thus objectifiable decline in the patient's mental performance (Kluger et al. 2013).

3 Neuroanatomical Correlates of Cognitive Fatigue

As mentioned earlier, *central* fatigue is characterized by a loss of function in physical and/or mental tasks that require self-motivation and internal stimulation, in the absence of cognitive deficits or motor weakness. Chaudhuri and Behan (2000) postulated that dysfunction in the basal ganglia area was responsible for the occurrence of *central* fatigue. The authors based their assumption on the results of DeLong and Georgopoulos (1981), who were the first to describe two functionally distinct processing loops that connect the basal ganglia with the neocortex. One of them is of a purely motor nature ("motor loop"), whereas the other is of a complex, associative nature ("complex or association loop"). The latter loop receives input from the

cortical association areas via the caudate nucleus, and the basal ganglia in turn project to the prefrontal cortex. A non-motor processing route between the basal ganglia, thalamus, and frontal cortex, in addition to the projection to the motor cortex, was confirmed in subsequent studies (e.g., Alexander and Crutcher 1990).

Stahl (1988) went one step further in his work and proposed to divide the basal ganglia into a neurological (motor), a psychological (cognition), and a psychiatric (emotion) part. In his model, the putamen is considered to play a crucial role in extrapyramidal motor disorders, while the connection from the caudate nucleus to the dorsolateral prefrontal cortex, as well as the ventral striatopallidal system, and here, in particular, the nucleus accumbens, are more associated with cognitive and behavioral syndromes. The connection between the caudate nucleus and the dorsolateral prefrontal cortex (= psychological part of the basal ganglia) has been shown to be a major switch point in Parkinson's disease (PD, Fuster 1989), in which the occurrence of *central* fatigue is common. A direct link between basal ganglia integrity and motivational, self-initiated processes receives clinical evidence from patients with akinesia (Denny-Brown 1962), which can be considered the most severe form of an unmotivational state. *Central* fatigue can be attributed, according to the foregoing, at least in part to a disturbed motivational component, the essential origin of which appears to lie in the dysfunction of the basal ganglia.

In relation to fatigue in MS patients, hypometabolism in the basal ganglia and frontal cortex was already discussed in the older PET literature as possible causal factor of fatigue (Roelcke et al. 1997). The results of subsequent imaging studies supported the hypothesis of a strong involvement of the basal ganglia, thalamus, and prefrontal cortex in the context of MS fatigue. The hypothesis that fatigue results from changes in distinct areas of the CNS was also functionally corroborated by the results of an fMRI study (Filippi et al. 2002). MS patients with severe physical fatigue symptoms showed a decrease in activation in regions including the thalamus involved in the planning and execution of motor actions during a simple motor task. A limitation of this study is that only physical fatigue was considered.

A paper by DeLuca et al. (2008) aimed to map the functional neuroanatomical correlates of *cognitive* fatigue. Starting from the idea that cognitive fatigue is defined as the inability to sustain a mental effort over a longer period of time, 15 MS patients and 15 healthy controls were studied while performing a modified version of the Symbol Digit Modalities Test (mSDMT [Rypma et al. 2006]) using fMRI. Contrary to imaging findings for motor fatigue, where both metabolically and functionally a decrease in activation was found in brain regions discussed as critical for fatigue (mainly frontal cortex, basal ganglia, thalamus), DeLuca et al. reported an increase in activation in these critical regions for cognitive fatigue. The authors related their results to those found in imaging studies of cognition in MS and argued that the additional recruitment of brain areas to perform a cognitive task reported in these studies (e.g., Mainero et al. 2004; Penner et al. 2003) does not represent compensatory or plasticity processes, but rather cognitive fatigue. This argumentation seems questionable against the background of the numerous existing imaging results on motor fatigue and cognition in MS and is furthermore refuted by the results of

another fMRI study on motor and cognitive fatigue in MS (Lange et al. 2006). Rather, it appears that the operationalization of cognitive fatigue must be critically questioned once again. A study by Bailey et al. (Bailey et al. 2007), who focused on MS patients in an advanced stage of progressive MS, found little evidence for objective signs of cognitive fatigue (defined as a decline in working memory over time). Subjective measures of fatigue, using a simple rating scale to the question, "How fatigued do you feel right now?" (response continuum from 0 = not at all to 8 = extremely) was collected multiple times during performance of the working memory task showed an increase over testing for both patients and healthy controls, which was more pronounced for patients in the higher working memory load condition. Nevertheless, correlation analyses between subjective fatigue statements and the cognitive measures (conceptualized as a measure of cognitive fatigue) did not yield significant results in the patient cohort either. This result illustrates that a decline in cognitive performance over time is not necessarily due to cognitive fatigue and that other factors, such as motivation and affect, should be taken into account.

However, the importance of the basal ganglia and prefrontal cortex in the context of MS fatigue was reconfirmed in a recently published study (Jaeger et al. 2019). In this MRI study, MS fatigue was shown to be characterized by impaired connectivity of the striatum with the sensorimotor, attentional, and reward networks. The superior ventral striatum was here thought to play a key role in MS fatigue.

4 Cognitive Fatigue and Cognition

The concept of cognitive fatigue as a loss of mental performance over time was reconsidered by results that reported no or only very weak relationships between the extent of subjective fatigue and cognitive performance (e.g., Bailey et al. 2007; Paul et al. 1998). Krupp and Elkins (2000) investigated the relationship between the objectifiable cognitive performance of MS patients over a test period of 4 h and the subjectively experienced fatigue by the patients. Again, no demonstrable relationship was found between the two variables. Findings from our own work (Penner et al. 2009) also suggest only a weak relationship between objective cognitive performance and cognitive fatigue. In this extensive validation study of a new fatigue questionnaire (FSMC—Fatigue Scale for Motor and Cognitive Functions), which was carried out multicentrally on a collective of 309 MS patients, only a weak relationship (in view of the low correlation coefficients) between cognitive fatigue and two neuropsychological tests, which primarily assess information processing speed, attention-concentration ability and working memory (SDMT, PASAT), could be demonstrated. All other neuropsychological instruments for visual-spatial and verbal short- and long-term memory as well as for word fluency (executive functions) showed no significant correlation with cognitive fatigue.

5 The Role of Attention in the Diagnosis of Fatigue

In addition to the subjective assessment of fatigue with the help of questionnaires and a detailed anamnesis, the examination of attention has become more and more established in fatigue diagnostics in recent years. Attentional functions are understood as basic functions involved in almost any intellectual or practical demand. They are relatively independent of control strategies that can be used to compensate for fatigue and thus represent an objective parameter for the assessment of fatigue. Attention is not a unidimensional phenomenon but is categorized according to intensity and selectivity aspects (Van Zomeren and Brouwer 1994), which in turn can be assigned to different components and functional networks (Fig. 1). The aspect of attentional intensity can be understood as a state of general alertness and cognitive activation. This comprises the domains of alertness (tonic, phasic), sustained attention, and vigilance, which represent basic processes of short- and longer-term attentional activation or the maintenance of an activation. The dimension of attentional selectivity, on the other hand, is subdivided into the components of selective or focused attention, the spatial orientation of attention, mental flexibility, and the ability to divide attention.

Based on this classification, the *neuropsychological* examination of the intensity of attention for the objectification of cognitive fatigue is of particular importance (Fig. 1).

In a first systematic study with 57 MS patients, a correlation between subjectively experienced fatigue, measured with the WEIMuS questionnaire, and the intensity of attention could be demonstrated (Meissner et al. 2007). For this

Dimension	Domain	Functional Network
Intensity	Alertness: intrinsic, tonal, phasic Sustained attention Vigilance	Brain stem portion of formatio reticularis, in particular noradrenergic core areas, dorsolateral prefrontal and inferior parietal cortex oft the right hermisphere, intralaminary and reticular thalamic nuclei, anterior part of the cingulate gyrus
Selctivity	Selective oder focused attention	Dorsolateral and inferior frontal cortex, in particular of the left hemisphere (inhibition ?), fronto-thalamic connections to the nucleus reticularis of the thalamus, anterior cingulum
	Visual-spatial selective attention, mental flexibility	Inferior parietal cortex clear right (disengage), superior colliculi (shift), posterior-lateral thalamus, especially pulvinar (engage)
	Divided attention	Prefrontal cortex (bilateral), anterior sections of the cingulum

Fig. 1 Adapted from Sturm (2000): Attention dimensions and domains and functional networks

purpose, tonic alertness (test duration of about three minutes) was first tested, followed by a 15-minute measurement of sustained attention and a renewed test of tonic alertness. After this first repetition, an examination of attentional selectivity took place. The final test was another measurement of tonic alertness. Already the first examination of alertness showed a highly significant correlation of mean reaction times with WEIMuS scale scores ($r = 0.46$, $p < 0.0001$), especially with the cognitive fatigue subscale. After correction for depression, the correlation coefficient increased to 0.51 (Meissner et al. 2007). The repetitive measure depicted a further increase in reaction latencies with concurrent poorer performance on the sustained attention subtest. In contrast, there was no correlation with selective attention. Thus, at least in the patients who mainly complain of mental fatigue, there seems to be a simultaneous disturbance in the intensity of attention, but not in its selectivity aspects. This also explains the divergent results of earlier studies reported in the literature, which document a lack of correlation with various cognitive function tests. On the one hand, in these studies fatigue was predominantly assessed by the Fatigue Severity Scale (FSS), which focuses exclusively on physical aspects of fatigue, while on the other hand neuropsychological tests were used that mapped cognitive aspects such as memory or focused attention. These cognitive functions are therefore obviously unsuitable to make an objective contribution to the diagnosis of fatigue.

The results of other research groups support the reported findings on alertness. For example, Weinges-Evers et al. (Weinges-Evers et al. 2010) were able to show in 110 MS patients that the group suffering from fatigue (51.4%, defined as FSS ≥ 4.0) had significantly higher reaction times in tonic alertness than the group of patients without fatigue, while no differences between the two groups were detectable for other neuropsychological test results (visual scanning or executive control). However, this study unfortunately also used the FSS, which does not allow measurement of cognitive fatigue. Also, in a study by Claros-Salinas et al. tonic alertness proved to be the most sensitive test for detecting fatigue (Claros-Salinas et al. 2013). Consistent with what has been reported so far, in another study, reaction times in the alertness subtest were significantly increased in MS patients with fatigue compared to healthy controls and continued to increase after cognitive load, while in contrast they even slightly decreased in healthy controls (Neumann et al. 2014). Further evidence comes from a controlled, randomized study on the effects of intensive ergometer training (with and without an altitude chamber): Again, only attention intensity, measured with the "Alertness" subtest of the Test Battery for Attention (TAP), correlated significantly with WEIMuS scale scores. After the two-week training, there was a decrease in subjective fatigue, which was associated with improved reaction times on the attention test. Fatigue and attentional parameters were also significantly correlated at this second measurement point (Fig. 2). Along the lines of the studies presented so far, fatigue values and other tests of cognitive performance ("executive control") did not show a significant correlation at any of the measurement points (Pfitzner et al. 2013).

Most patients complain of an increase in fatigue over the course of the day, which is why a single measurement is often insufficient, especially for questions relating

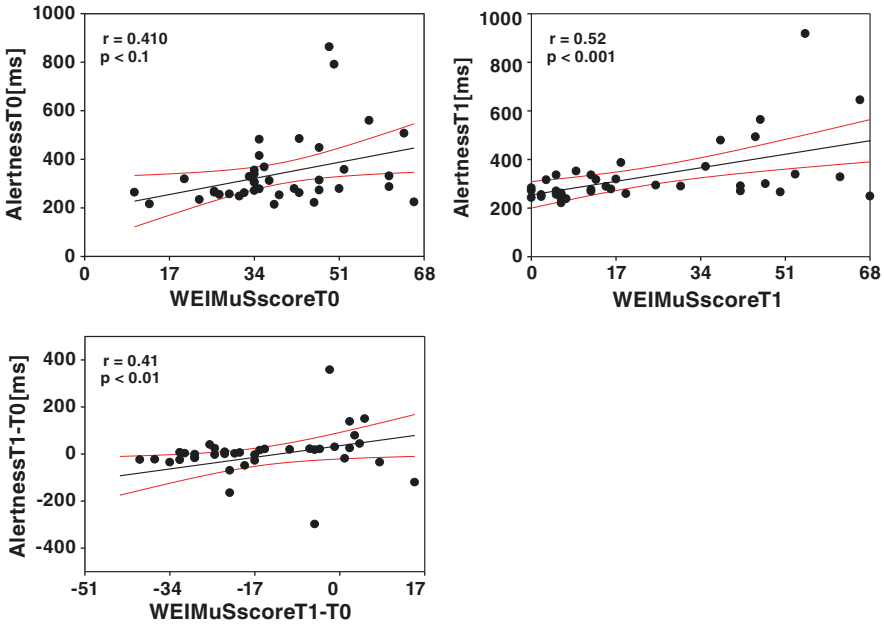

Fig. 2 Correlation between subjectively experienced fatigue (WEIMuS Score) and reaction times in the subtest "alertness" of the test battery for attention testing (TAP) before (T0) and after (T1) a two-week ergometer training. The graph below shows the reaction times of each patient against the differences in the WEIMuS scale values plotted (Pfitzner et al. 2013)

to occupational performance. In this respect, the work of Claros-Salinas et al. is worth mentioning, in which the circadian attentional performance of 76 rehabilitation patients with various neurological diseases (of which MS patients formed the etiologically largest group with 37 participants) was investigated and compared with the findings of 76 employed, brain healthy control subjects (Claros-Salinas et al. 2010, 2012). For this purpose, different subtests of the attentional test battery (Alertness, Go/Nogo, divided attention) were administered over 2 days at three defined measurement time points. In the control group, the mean reaction times in the "Alertness" subtest remained stable over the six measurements and even showed an increase in performance in the sense of a reduction in the mean reaction times in the other subtests. In the patient group, however, the mean reaction times were significantly longer. In addition, over the course of the day, the mean reaction times increased in the sense of circadian deterioration, especially in the "Alertness" subtest. In case of inconspicuous findings in the morning and subjectively reported fatigue, a new test should therefore be performed in the afternoon.

In line with the findings on alertness presented so far, a review of numerous studies reports that an association with fatigue was only present for those neuropsychological tests that assessed aspects of attention intensity (alertness or vigilance) (Hanken et al. 2015). It is now well established that fatigue is at least partly caused

by a specific attention impairment, but that it can also be clearly distinguished from performance in other cognitive domains.

The neuropsychological examination of attention intensity thus provides a sensitive and time-efficient way of objectively detecting cognitive fatigue symptoms. This represents a considerable improvement over a purely subjective survey by means of a questionnaire, particularly in the case of socio-medical questions such as the assessment of occupational performance. The discrepancy between the partially inconsistent results in the literature is probably due to sampling and methodological effects, among other things. For example, in previous studies fatigue was predominantly assessed by the FSS, which measures only physical fatigue. However, this is not adequately represented by testing attentional performance. On the other hand, mainly neuropsychological tests were used, which examined different cognitive aspects such as memory or visuospatial performance. These cognitive functions were also not correlated with fatigue in the studies cited above and are obviously unsuitable for making an objective contribution to fatigue diagnostics.

6 Summary

The comments on cognitive fatigue illustrate how difficult it is to define and objectively record the cognitive dimension in addition to the motor component. Based on the above-mentioned study results, it can be assumed that a dysregulation in the processing loop between the basal ganglia, thalamus, and prefrontal cortex plays a decisive role in the development and maintenance. In this context, however, motivational as well as emotional factors also seem to play a significant role. Attention tasks such as "alertness" seem to be the most suitable for operationalization. In combination with behavioral observation, comprehensive neuropsychological profiling in general and attentional performance profiling, in particular, can be used to approximate the objectification of cognitive fatigue.

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Personality Factors and Motivation

M. Filser and Iris-Katharina Penner

1 Introduction

As discussed in detail in other chapters, the causes of MS-associated fatigue are poorly understood. The etiology is thought to be multifactorial, with pathophysiological mechanisms such as demyelination and axonal damage in predilection sites such as the basal ganglia, thalamus, and prefrontal cortex appearing to play a major role. However, these factors alone cannot fully explain the spectrum of fatigue symptomatology. Various additional influencing variables such as depression, sleep disorders, personality factors, and motivational aspects also contribute significantly to fatigue (for the complexity of possible influencing factors, see Penner and Paul [2017]). In this chapter, personality factors as well as motivational aspects will be discussed in more detail. The question arises as to whether there are specific personality patterns or motivational aspects that promote or even intensify the development and maintenance of fatigue in MS.

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2 Personality and MS

Personality is a construct within psychology that is defined differently depending on the theoretical background. Across the different approaches, personality can be described as a unique, relatively stable, behavioral characteristic of humans that persists over time.

As early as 1877, Charcot described changes in the personality and affect of MS patients (Charcot 1877). With regard to affect, various research studies have linked affective disturbance patterns such as depression and anxiety with multiple sclerosis (Fromont et al. 2013; Marrie et al. 2015). In addition, behavioral changes in terms of pseudobulbar affect disorder (PBA), also called pathological laughter/crying, have been observed (Haussleiter et al. 2009). Also, a form of pathological euphoria, defined as excessive optimism regarding disease-related impairments and their regression, has been described in the literature in patients with MS (pwMS) (Duncan et al. 2016). Furthermore, agitation (40%), irritability (35–42%), apathy (20–31%), and disinhibition (13%) are among those behavioral changes most commonly observed in pwMS (Diaz-Olavarrieta et al. 1999; Figved et al. 2005). Very different methods were used to record these symptoms, so there is little reliable information on how often these phenomena are actually observed clinically in pwMS. Therefore, the so-called "MS personality," a term found mainly in older publications, has been abandoned, not least because of the risk of stigmatizing patients.

3 Personality Trait Assessment Instruments

In international multiple sclerosis research, the questionnaire for the assessment of a narcissistic tendency in the personality (Narcissistic Personality Inventory, NPI) by Raskin and Terry (Raskin and Terry 1988) is predominantly used. The questionnaire is based on the DSM-III criteria for diagnosing Narcissistic Personality Disorder. When comparing patients with lupus erythematosus and multiple sclerosis, pwMS showed significantly higher scores in the areas of apathy, agitation, and irritability (Figved et al. 2005).

Furthermore, numerous older but also more recent studies have described increased neuroticism scores in pwMS (Johnson et al. 1996; Taillefer et al. 2003). In these two studies, similarly increased levels of neuroticism were found in pwMS and patients with chronic fatigue syndrome (CFS). Johnson and colleagues suggested that this might indicate an unfavorably changing personality due to the chronic disease, since neuroticism is interpreted as a stable personality trait and as such should not be affected by changing life circumstances.

In addition, Costa and McCrae's (1992) multidimensional NEO Five-Factor Inventory (NEO-FFI), based on the Big Five model, is a widely used instrument to assess trait expressions. Five dimensions of personality are postulated: Neuroticism, Extraversion, Openness to Experience, Agreeableness, and Conscientiousness.

These have been elaborated as essential personality traits using a factor analytic procedure and are now used as determinants of personality both in practice and in research in personality psychology. Benedict et al. (2001) investigated essential personality changes in pwMS by having patients and their relatives complete a personality questionnaire assessing themselves and others. They were able to show that the patients had lower scores in extraversion, agreeableness, and conscientiousness as well as increased scores in neuroticism compared to healthy individuals. In addition, they were rated as less empathic by their relatives and friends than they were self-reported. Consequently, there was a significant discrepancy in self- and peer-assessment. The authors concluded that pwMS showed little self-awareness of their partly maladaptive behavior.

In a recent study by Roy et al. (2018), pwMS were examined longitudinally over a period of 5 years. In addition to various cognitive parameters, personality dimensions were also assessed. PwMS showed a significant deterioration in the areas of extraversion and conscientiousness compared to healthy control subjects over time.

While the epidemiology of altered personality traits is still unclear, there is evidence that they can occur even before the definitive diagnosis of multiple sclerosis in the sense of a prodromal phase (Disanto et al. 2018). In these cases, a long-term and stable change in personality can be assumed (Roy et al. 2018, 2016).

There are few studies to date that have examined a direct relationship between personality traits and fatigue in MS. Merkelbach et al. (2003) were able to find a significant relationship between fatigue, increased neuroticism, and decreased extraversion. The study by Penner et al. (2007) also came to the same conclusion. However, when controlling for depression as a covariate, the previously mentioned relations between fatigue and personality factors no longer occurred, and only a relation to motivation was found. A multicenter study by Schreiber et al. (2010) examined the influence of aspects of personality, coping, and depression on fatigue symptoms in patients with early relapsing-remitting MS. PwMS and fatigue symptoms showed a reduced willingness to perform, less self-confidence, and were less extroverted than patients without symptoms of fatigue. In addition, these patients were more reserved and showed increased irritability, aggressiveness, and more pronounced neuroticism. Furthermore, the studied pwMS with fatigue showed a depressive personality structure associated with maladaptive disease processing compared to the patients without fatigue symptoms.

The studies indicate that fatigue in pwMS, particularly in the early stages of the disease, appears to be associated with vulnerable personality traits. However, it remains unclear what proportion of this is due to depressive symptoms and dysfunctional strategies for coping with the disease (Schreiber et al. 2015). In addition, there are usually no premorbid personality measurements of the patients, so that the question of whether the personality patterns were only developed in the course of the disease or whether they were already present before the initial event of multiple sclerosis remains unanswered (Merkelbach et al. 2003; Schreiber et al. 2015). Therefore, other aspects of the relationship between personality traits and MS-fatigue must be considered.

4 Motivation

In addition to personality, aspects of motivation are also discussed in the literature as a possible influencing factor on fatigue in pwMS (Penner et al. 2007). The concept of action control (Kuhl 1994) refers to the ability to shield and maintain an intention, once formed, against competing action tendencies in order to achieve the planned goal. It is interpreted as a central aspect of motivation. A distinction is made between situation orientation and action orientation, where in the latter the individual focuses attention on both the present situation and alternative actions. In situation orientation, on the other hand, the inability to complete the decision-making process is considered essential. In the study by Penner and colleagues (Penner et al. 2007), a tendency toward situation orientation emerged in MS patients with fatigue. According to this, individuals with MS tend to have more difficulty initiating and performing new actions. The question arises as to why this is so and how this relates to fatigue. A paper by Pardini et al. (2013) explored the extent to which cognitive appraisal of reward plays a role here. Reward-related cognition was measured using scales of behavioral inhibition and activation (Carver and White 1994). It was found that MS patients with fatigue showed lower scores on the activation scale than patients without fatigue. The negative correlation found was evident for both physical ($r = -0.42$) and cognitive fatigue ($r = -0.62$) and was highly significant for both dimensions. Accordingly, responsiveness to the perception of reward, which is related to one's own actions and behavior, is reduced in MS patients with fatigue. Thus, this study showed a clear relationship between motivational aspects and fatigue. Changing the perspective of patients so that they recognize a meaning and thus a reward in their behavior thus represents a future therapeutic approach in the treatment of fatigue. In the study by Pardini and colleagues, pharmacotherapeutic action was taken by testing escitalopram against bupropion. It showed superiority of bupropion in the patients with significantly decreased activation levels, which the authors attribute to the focused dopaminergic/noradrenergic mechanism of action. Unfortunately, there is a lack of follow-up studies on larger samples to substantiate the specific efficacy of bupropion.

5 Behavioral Aspects: Coping and Disease Management

As already shown in the work by Schreiber et al. (2010), in addition to the aforementioned influencing factors of personality and motivation, aspects such as coping with illness and the perception of one's own illness in relation to fatigue should also be taken into account.

In general, the confrontation with a chronic disease with an uncertain course and outcome presents those affected with an extremely stressful situation that must be mastered. Coping strategies are required at the emotional, cognitive, and somatic levels. Emotional coping strategies are preferentially used in situations that are beyond the individual's control (e.g., health-related situations), whereas problem-oriented cognitive coping mechanisms are used in situations that are within the individual's control (Aikens et al. 1997; Folkman and Lazarus 1980). Both coping strategies seem to be required in pwMS, whereby a focus on emotional coping can be observed at the beginning, which is subsequently accompanied by a more cognitive-focused style.

In a study by Schwartz et al. (1996), environmental mastery was described as another factor influencing fatigue. This is understood as the ability of individuals to shape their environment to meet their own needs. In individuals with severe fatigue, this ability was significantly less pronounced compared to individuals with less severe fatigue symptoms.

Jopson and Moss-Morris (2003) made an important contribution to illness representations of pwMS. In their study, a strong "disease identity" was found to be a significant predictor of both forms of fatigue. Disease identity is the tendency of a person to attribute any symptoms to the disease of MS, which can lead to misattributions. Thus, a healthy confrontation with the disease and its symptoms, as well as an appropriate adaptation to and acceptance of them, may not succeed. This result was replicated in a follow-up study (Skerrett and Moss-Morris 2006). In the same study, additional factors were identified that can lead to or maintain fatigue. Those patients who catastrophized potential consequences of their symptoms or interpreted their symptoms as physical harm were more likely to suffer from fatigue. Increased fatigue levels were also observed in patients who were ashamed of their illness. In addition, two responses to experiencing symptoms were found to be unfavorable: avoidance of activity and "all-or-nothing" behavior, in which patients become overactive when symptoms subside and, as a result, require extended periods of recovery again. Based on the findings on illness perception and patients' illness representations and interpretations just discussed, van Kessel and Moss-Morris (2006) developed a cognitive-behavioral model (Fig. 1). In this model, biological factors, cognition, emotion, and behavior are related as mutually influencing and maintaining elements.

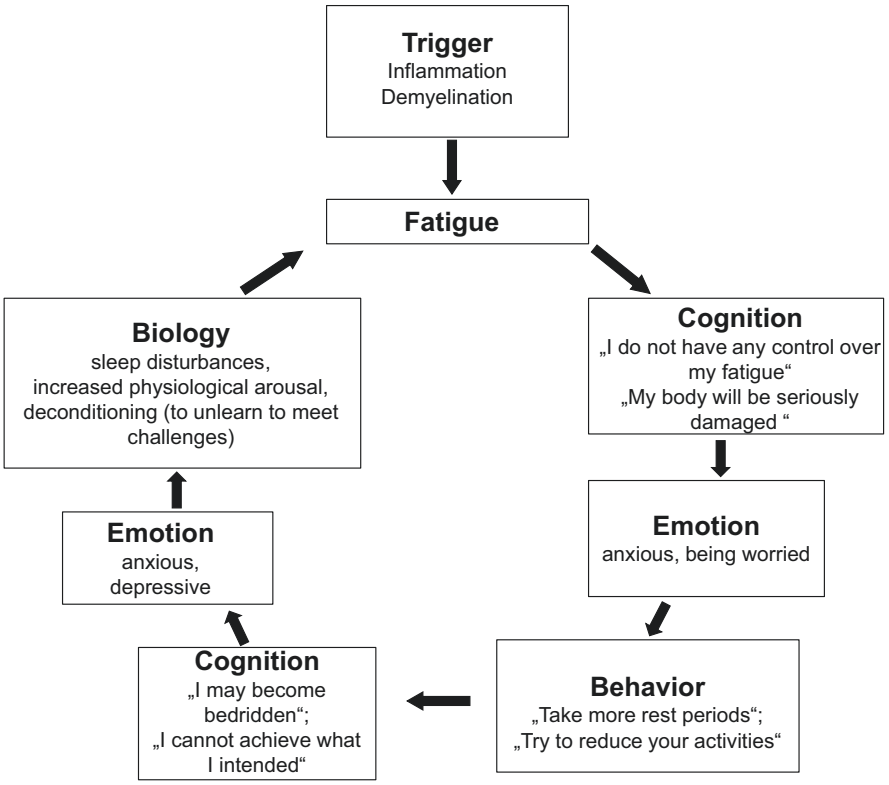

Fig. 1 Cognitive-behavioral model of MS-fatigue (according to van Kessel and Moss-Morris 2006)

6 Conclusion

Personality factors, aspects of motivation, coping and the patient's reaction to symptoms (e.g., lack of acceptance, catastrophizing, and pathologizing), in addition to pathophysiological factors, seem to explain part of the development and maintenance of fatigue symptoms. MS patients with fatigue show increased scores in the neuroticism domain and exhibit decreased extraversion. In addition, it can be assumed that pwMS and fatigue symptoms have a tendency toward positional action control. The way how patients deal with their fatigue and their MS disease overall shows significant effects on fatigue symptomatology.

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Fatigue and Depression

S. M. Gold

1 Introduction

Many chronic diseases are associated with a significantly increased risk of depression (Gold et al. 2020). In particular, patients with cardiometabolic and neurological diseases have a point prevalence of major depressive disorder (MDD) of 25–35%. Thus, the risk of being diagnosed with MDD is three to four times higher in these groups than in the general population, where the point prevalence of MDD is estimated around 5–7% in most industrialized countries (Otte et al. 2016).

Depression is also one of the most common symptoms of MS (Marrie 2017). In a recent meta-analysis, the prevalence of depression in MS—depending on sample characteristics and survey method—was around 25% (Boeschoten et al. 2017). Here, an average of 21% of patients met the diagnostic criteria for MDD and up to 35% of patients had clinically relevant depressive symptoms, even if these did not fully meet the MDD criteria.

Depression in MS is associated with a substantial psychosocial burden and correlates with cognitive impairment, lower treatment adherence, and increased suicidality (see review in Feinstein et al. 2014). The latter point, in particular, is of great clinical importance, as several studies, including large register-based studies from Scandinavia, have demonstrated an approximately twofold increased risk of suicide in patients with MS compared to the general population (Erlangsen et al. 2020).

In addition to the importance of the psychosocial burden associated with depression, there is also a link between depressive symptoms and disease progression in

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MS, which further exacerbates clinical impact. For example, in a Canadian study, MS patients with depression (but not bipolar disorder) were found to have higher disability scores (EDSS) after 10 years than MS patients without affective disorders (McKay et al. 2018). In a registry-based study in Sweden of two large cohorts of MS patients, the presence of depression was found to predict shorter time to disability milestones (EDSS 3.0 and EDSS 6.0, respectively), indicating faster disease progression in depressed MS patients (Binzer et al. 2019).

Despite its immediate clinical importance, depression in MS is often not adequately treated. For example, a study from the USA shows that up to two-thirds of MS patients with depressive symptoms requiring treatment in neurological clinics or outpatient departments did not receive adequate psychiatric or psychotherapeutic treatment (Mohr et al. 2006). This may be explained in large part by substantial underdiagnosis of depression in this patient group. The reasons why depressive disorders are often not recognized and therefore not treated in the context of MS are multifactorial. However, one major factor can be the difficulty in differentiating between symptoms of depression and affective, cognitive, and vegetative symptoms of MS.

2 Symptom Overlap Between Fatigue and Depression

MDD is diagnosed according to current diagnostic manuals ("Diagnostic and Statistical Manual of Mental Disorders, 5th Edition," DSM-5; or "International Classification of Diseases and Related Health Problems, 10th revision," ICD-10). According to these, the diagnostic criteria for MDD include fatigue as well as concentration difficulties or memory impairments. As these symptoms may also occur in MS or resemble MS symptoms, the diagnosis of depressive disorders may be complicated. The literature thus often refers to a possible "confounding" of depression scores in patients with MS. The assumption behind this is that MS symptoms such as fatigue or cognitive disturbances could lead to increased scores in depression questionnaires or ratings, which would therefore only partially indicate "real" depression. Indeed, moderate to high correlations exist between scores on depression and fatigue questionnaires in MS. Given the overlap in symptoms, this is not surprising. The question, therefore, arises whether fatigue symptoms could also (or possibly even better) be explained by MS or whether they should be "added" to the symptoms of depression. Ultimately, the difference between the two interpretations lies mainly in the interpretation of these symptoms and their possible causes. The following sections will therefore discuss to what extent the overlap of MS symptoms such as fatigue and symptoms of depression must be taken into account from a diagnostic, pathophysiological, and therapeutic point of view and what a clinical-pragmatic approach to this problem might look like.

3 Depression and Fatigue in MS from a Diagnostic Perspective

Because of the symptomatic overlap between depression and fatigue outlined above, the diagnosis of affective disorders such as MDD can be significantly more difficult in patients with comorbid physical illnesses such as MS. In diagnostic manuals such as the DSM5, symptoms that can be clearly attributed to a physical illness should not be considered in the count of relevant symptoms (5 of 9 according to DSM5) for MDD. Therefore, for example, the separation of MDD symptoms from MS-associated fatigue, decreased appetite, anhedonia, psychomotor changes, and sleep problems can be difficult.

Both the DMS5 and the ICD10 allow the diagnosis of depression with organic causes (DSM5: Depressive Disorder due to Another Medical Disorder; ICD10: Organic mood [affective] disorder). However, this diagnosis is based on a clear attribution regarding the cause of the symptomatology, which is difficult to make in individual cases. Therefore, the two disorders (MDD and MS) are typically coded separately in clinical practice. With regard to depression, guidelines generally state that organic diseases do not usually trigger depressed mood, feelings of worthlessness or suicidality per se, and such symptoms should therefore be considered as guiding further diagnosis of possible depression (Minden et al. 2014). In case of doubt, it is recommended to conduct a structured interview (e.g., S.C.I.D. or M.I.N.I.) by a trained rater.

In clinical practice, a screening instrument can also be used first. Here, there is a simple 2-question algorithm for assessing the core symptoms of depressive mood and anhedonia ("Whooley Questions"), which indicate the presence of MDD with a sensitivity of 99% and a specificity of 87% in the case of an affirmative answer to both questions (Mohr et al. 2007).

Validated depression questionnaires such as the Beck Depression Inventory (BDI), the Patient Health Questionnaire 9 (PHQ-9) or the Center for Epidemiological Studies Depression (CES-D) scale can also be used to quantify depression severity in patients with MS (Patten et al. 2015). These and similar scales have also been validated in German for use with MS patients (Fischer et al. 2015a).

Various studies in the past have suggested that MS symptoms such as fatigue or cognitive impairment may lead to an "inflation" of depression scores, and it has therefore been proposed to adjust the corresponding cut-off values (Fragoso et al. 2014) or even to omit somatic items (Aikens et al. 1999) for use in MS. Accordingly, abbreviated versions of existing questionnaires (without somatic/vegetative items) such as the BDI-FS (the 8-item BDI-Fast Screen) or questionnaires such as the Hospital Anxiety and Depression Scale—Depression (HADS-D) have been developed specifically for use in chronic physical illnesses, which have also been validated for MS.

However, more recent studies have shown that a strong predominance of "somatic/vegetative" symptoms in total scores of depression questionnaires in MS is mainly due to a selection bias (Hasselmann et al. 2016), as in general these symptoms are more prevalent in mild depression and many of the comparative studies include a group of patients with "idiopathic MDD" (i.e., without underlying physical illness) compared with a mixed sample of MS patients that included both depressed and non-depressed individuals. Hasselmann et al. demonstrated that the relative proportion of somatic/vegetative symptoms on the depression score was similar when MS patients and patients with MDD were matched for age, sex, and depression severity. Furthermore, this study showed that symptom clusters across all aspects of depression were not different between the two groups.

Taken together, therefore, the literature suggests that commonly used depression questionnaires are valid and reliable in MS and can be used without major adjustments to cut-off scores. However, it is always recommended that a thorough psychiatric examination by an experienced clinician, ideally using a structured interview, should follow any suspicion of the presence of MDD. Since the diagnostic criteria of MDD require the presence of the main symptoms of anhedonia and/or depressed mood, focussing attention on these can minimize the risk of misdiagnosis due to fatigue or cognitive disorders.

4 Depression and Fatigue in MS from a Research Perspective: Pathophysiology

To date, there are comparatively few studies that have addressed differential pathobiological correlates of fatigue and depression in the context of MS. In general, a variety of overlapping mechanisms are discussed as pathobiological correlates of depression and fatigue in MS (including inflammation, regional structural and functional brain changes, dysregulated stress systems, see Feinstein et al. 2014 vs. Penner and Paul 2017). Unfortunately, there are few studies to date that have directly compared biological substrates of affective vs. somatic/vegetative symptoms of MS. Some smaller studies concluded that inflammatory markers are more strongly related to autonomic aspects and fatigue (Gold et al. 2011), whereas affective or cognitive symptoms show more of an association with neuroendocrine-limbic correlates (Gold et al. 2010, 2011, 2014). However, replications in larger longitudinal, ideally interventional studies are lacking here in order to gain a clearer insight into possible pathobiological mechanisms.

5 Depression and Fatigue in MS from a Therapeutic Perspective

A putative differential or converging pathobiology of fatigue and depression is certainly scientifically interesting and could possibly be helpful for the development of more specific interventions in the future. However, there are already indications that certain behavioral interventions such as exercise or cognitive behavioral therapy (CBT) can have a positive effect on both depression and fatigue.

Interestingly, an app based on cognitive behavioral therapy, which was primarily aimed at the management of depressive symptoms, showed significant improvements in depressive symptoms as well as in aspects of fatigue (Fischer et al. 2015b). In contrast, a very similarly designed app for self-management of fatigue in MS was only able to alleviate fatigue symptoms, but not depressive symptoms (Pöttgen et al. 2018). These findings make it clear that fatigue is a component of a depressive syndrome and is therefore also addressed in CBT approaches to a depression therapy, while many MS patients with fatigue do not have depression and the corresponding therapy programs therefore may not help to alleviate fatigue.

6 Summary

Depression is a common comorbidity of MS and represents a diagnostic and therapeutic challenge due to symptomatic overlap with various MS symptoms. As a pragmatic approach, diagnostic examinations should be based primarily on the presence of leading affective symptoms (depressed mood, anhedonia) and possible signs of suicidality. Any suspicion of suicidality should be thoroughly investigated, if necessary with a psychiatric consultation. In general, it can be said that diagnostic instruments (ratings by the clinician, structured interviews, or patient-based questionnaires) for the assessment of depression in general are also valid and reliable in MS patients. It is recommended to consider the relevant literature for the potential adjustment of corresponding threshold values.

Although individual studies suggest a differential pathophysiology of fatigue and affective/cognitive symptoms of MS-associated depression, replicable findings in larger samples, longitudinal studies or ideally in the context of randomized controlled intervention studies, are still lacking.

There are some evidence-based behavioral treatment options for both fatigue and depression in MS. However, individual availability is highly dependent on the individual context of care. Sufficiently powered RCTs of pharmacological therapies for MS-associated depression are unfortunately still lacking, so that current guidelines do not come to any clear recommendations here (Minden et al. 2014).

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Sleep and Wake Disturbances

U. Kallweit, A. Chan, and C. L. A. Bassetti

Sleep and/or wake disturbances exist in most neurological, especially neuroimmunological diseases. However, the complex interactions between the immune system, the nervous system and sleep-wake regulation are only recently becoming understood.

Narcolepsy can be cited as a model for this, where there is a significant decrease of so-called hypocretin-producing neurons, most probably through an autoimmune, most likely T-cell-mediated mechanism (Latorre et al. 2018). Hypocretin plays a central role in sleep-wake regulation and maintenance of stable, prolonged wakefulness. The reduction of hypocretin-producing cells results in hypocretin deficiency. This is then responsible for the symptoms of narcolepsy, including the repeated, sudden falling asleep during the day (Bassetti et al. 2019).

In multiple sclerosis (MS), autoimmune cellularly and humorally mediated pathomechanisms are prevalent and can be therapeutically targeted at least during certain disease stages. Mechanisms that lead to disturbances of sleep and wakefulness in MS however are unclear and presumably multifaceted. A connection between chronic inflammation and the occurrence of fatigue is being discussed (Patejdl et al. 2016).

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1 Epidemiology

In multiple sclerosis (MS), various sleep and wake disturbances exist. Depending on the diagnostic criteria and survey instrument, these affect between 25% and 95% of MS patients (Braley and Boudreau 2016; Veauthier 2015).

Insomnia and fatigue are particularly common, but restless legs syndrome, sleep-disordered breathing, and excessive daytime sleepiness are also often found. Table 1 provides an overview of frequently occurring sleep and wake disorders in MS.

1.1 Sleep Diagnostics

Sleep-wake diagnostics includes a detailed medical history on sleep and wakefulness in particular, the use of various questionnaires (see Table 2), and instrument-based sleep diagnostics: respiratory polygraphy, video-polysomnography, multiple sleep latency test (MSLT), multiple wakefulness test (MWT), actigraphy, and other vigilance tests. To exclude other medical causes for the sleep disorders, a laboratory test (vitamin B_{12}, folic acid, thyroid, iron metabolism, etc.) must also be performed. In few patients, a lumbar puncture for the measurement of CSF hypocretin levels is necessary.

Table 1 Key-results from meta-analysis and systematic reviews on sleep and wake disturbances in MS

Sleep/Wake Disturbance	Results
Insomnia	• Prevalence 25–55%. • Strong association with depression and pain.
Restless legs syndrome	• Prevalence: 5–19%; female > male. • Can be comorbid or symptomatic.
Periodic leg movements in sleep (PLMS)	• Prevalence 36%.
Sleep-disordered breathing	• Prevalence 21–58%. • Associated with excessive daytime sleepiness, fatigue, cognitive deficits, depression, cardiovascular disorders, stroke. • PAP therapy can improve fatigue.
Fatigue	• Association with several sleep disorders, e.g., sleep-disordered breathing, insomnia, RLS.
Narcolepsy	• Rarely co-existing or symptomatic.
REM sleep behavior disorder (RBD)	• Prevalence not known.
Nocturia	• Prevalence 21–49%. • Often symptomatic (i.e., spinal lesions).

Table 2 Frequently used questionnaires in sleep and wake disorders

Questionnaire	Sleep/Wake Disturbance
Epworth sleepiness scale (ESS)	Excessive daytime sleepiness
Swiss narcolepsy scale (SNS)	Narcolepsy vs. EDS of other origin
Insomnia severity index (ISI)	Insomnia
Pittsburgh sleep quality index (PSQI)	Quality of sleep
Berlin-questionnaire (BF)	Sleep-disordered breathing
International restless legs syndrome study group (IRLSSG) questionnaire	Severity of restless legs syndrome

2 Sleep-Wake Disorders

2.1 Insomnia

Insomnia is defined as having problems falling asleep and/or staying asleep as long as desired, for a period of at least one month. This disturbance is accompanied by an impairment of daytime well-being or reduced performance during the day. Insomnia is one of the most common disorders worldwide.

In MS, insomnia is present in 25–54% of those affected (Braley and Boudreau 2016, Caminero and Bartolomé 2011, Veauthier 2015). Insomnia occurs with increasing duration of MS and the presence of fatigue (Sadeghi Bahmani et al. 2018, Kotterba et al. 2018). The causes are manifold and include primary insomnias, especially psychophysiological insomnia, and secondary insomnia due to other sleep disorders (e.g., restless legs syndrome/periodic leg movements; sleep-disordered breathing), or symptoms that occur in the context of MS, such as pain, nocturia/incontinence (in the context of neurogenic bladder dysfunction), spasticity, or obesity. Insomnia is also very common in depression.

In addition, side effects of MS-specific therapies can also cause or deteriorate insomnia symptoms, such as the flu-like side effects by betaferon preparations or flush/gastrointestinal side effects of dimethyl fumarate. However, these side effects often last only a short time and often occur only at the beginning of therapy.

Insomnia is associated with physical and functional impairment and depression, also in MS. Sleep-disordered MS patients subjectively reported greater cognitive impairment (Hare et al. 2017, van Geest et al. 2017) than those sleeping well. The neuropsychological finding of higher arousal levels typically present in insomnia has also been documented in MS patients (Schellaert et al. 2018). An MRI study showed that thalamic functional connectivity was reduced in sleep-disordered MS patients (van Geest et al. 2017).

For the treatment of insomnia, the existence of sleep-affecting comorbidities or other MS symptoms has to be considered (see Table 3). This sleep disorder or other symptom should then be treated first (e.g., sleep apnea or pain). If drug treatment is

Table 3 Comorbidities of insomnia—Treatment recommendations

Insomnia und Comorbidity	Pregabalin/ Gabapentin	Sleep-promoting antidepressive drug	Baclofen	Opioids[a]
RLS	X			(X)
Pain	X	X		X
Spasticity	(X)		X	
Depression		X		

X = Strong recommendation; (X) = Weak recommendation
a Sleep apnea has to be excluded before treatment initiation

needed for insomnia, a medicine should be selected that acts on the different disorders (e.g., a sleep-promoting antidepressant for depression and insomnia).

The further treatment algorithm follows the general principles of insomnia therapy: information on sleep hygiene, psychoeducation on sleep disorders, relaxation exercises, treatment of existing neurological, medical or psychiatric sleep disorders, of other MS symptoms, and implementation of cognitive behavioral therapy for insomnia (CBT-I). Some studies have also demonstrated positive effects of CBT-I in MS patients (Clancy et al. 2015). One study described a positive effect of melatonin in MS insomnia on sleep quality (Adamczyk-Sowa et al. 2014). In the short term (< 4 weeks), benzodiazepine agonists may be used.

2.2 Restless Legs Syndrome

Restless legs syndrome (RLS) is a 24-hours movement disorder. In RLS, a dysregulation of the CNS iron/dopamine metabolism is found. Genetic causes as well as a large number of other factors, such as vitamin B12 deficiency or renal insufficiency contribute to the occurrence of RLS. Also, several medications, e.g., antidepressants, can have a triggering or exacerbating effect (Trenkwalder and Paulus 2010).

RLS is characterized by an unpleasant feeling in the legs during inactivity/rest, which is associated with an urge to move. Movement then leads to a (brief) relief of the discomfort. The complaints have a circadian distribution and mainly occur in the evening and at night (Trenkwalder and Paulus 2010). RLS diagnosis is made clinically. Differentiation from MS-related spasticity or paresthesias and dysesthesias can sometimes be difficult. The aspect of RLS symptoms only occurring at rest—in contrast to paresthesias—can be helpful for a better differentiation. RLS is classified into an intermittent and a chronic form. Approximately 80% of RLS patients also experience periodic leg movements during sleep.

Restless legs syndrome is often accompanied by problems falling asleep and sometimes also staying asleep. Daytime symptoms include fatigue, but also rarely excessive daytime sleepiness (Kallweit et al. 2009).

In multiple sclerosis, RLS is found in up to 19% of those affected. Hence the disease is more frequent than in the general population, where it occurs in approx. 3–8%. The frequency varies according to the type of progression and is more

common in the secondary chronic progressive type (Manconi et al. 2007, Sieminski et al. 2015). Female gender, older age, and higher EDSS are also further risk factors for the occurrence of RLS in MS. RLS may occur symptomatically, especially in spinal cord lesions in the context of MS (Manconi et al. 2007). Also, an interaction between (chronic) inflammation and the iron/dopamine system seems possible (Sieminski et al. 2015, Vela 2018).

First step of the management of RLS is the evaluation of potential causal therapies, e.g., a vitamin deficiency can be corrected. Further, behavioral measures such as moderate physical activity in the evening, having cold showers of the legs before going to bed, or avoidance of RLS-enhancing foods (e.g., wine) or stimulants in the evening are recommended. Another part of the management includes the achievement of high-normal iron storage levels. A ferritin value of >75 ng/ml or a transferrin saturation value >40% should be aimed for (Allen et al. 2018). Pharmacotherapy is necessary for some RLS sufferers, especially for those having a chronic form. L-dopa or a dopamine agonist can be used as "on demand" therapy, in particular, but also regularly. The permanent administration of L-dopa often leads to a so-called RLS augmentation (temporal shift of the symptoms into the afternoon and/or extension of the symptoms to other parts of the body, especially arms). Other therapeutic options include the use of pregabalin/ gabapentin (off-label) or an opiate (Trenkwalder et al. 2015). The majority of antidepressants can exacerbate or trigger RLS. The few exceptions are, e.g., trazodone, bupropion, tianeptine, or maybe agomelatine. The influence of disease-modifying MS therapies on RLS is still unclear.

2.3 Sleep-Disordered Breathing

This group of diseases include obstructive and central sleep apnea and nocturnal hypoventilation. The most common form of sleep-disordered breathing (SDB) is obstructive sleep apnea (OSA). In OSA, the pharyngeal muscles collapse, causing partial or complete obstruction of the upper airways. The occurrence of so-called central apneas can have various causes, such as heart failure, stenosis of the brain-supplying arteries, or different CNS lesions, especially in the brain stem. In central sleep apnea, the respiratory impulse is intermittently absent. Alveolar hypoventilation often occurs in obesity or in diseases associated with respiratory insufficiency. Sleep apnea, OSA in particular, is often accompanied by difficulties staying asleep through the night. Affected people do not feel refreshed in the morning, and are tired or sleepy during the day. In the morning, a dry mouth and a diffuse head "pressure" or headache are often described. Cognitive impairment or depressive mood are also mentioned. As several of the abovementioned symptoms can also occur in MS, a possible OSA diagnosis is often overlooked or only considered with great delay (Brass et al. 2010).

In MS, obstructive sleep apnea is found in 20–30% (Veauthier et al., 2015; Braley et al., 2014). The incidence of central respiratory disorders is not precisely known. Obesity and neuromuscular weakness may exacerbate the occurrence of sleep-disordered breathing.

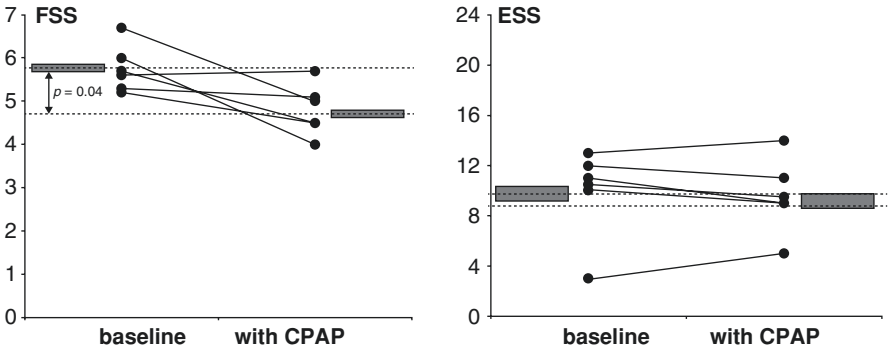

Fig. 1 Change of FSS and ESS scores before and under PAP therapy in MS patients, suffering also from obstructive sleep apnea (modified from Kallweit et al. 2013)

The standard treatment for obstructive sleep apnea is positive airway pressure (PAP). In mild cases, other measures (avoidance of the supine position during sleep, mandibular advancement splint, etc.) can be helpful and considered for treatment. Recently, hypoglossal nerve stimulation has also been used. In the case of central apneas, more complex ventilation therapies can sometimes be used. MS patients sometimes require assistance with the fitting of the respiratory mask due to their physical deficits. If PAP therapy is performed regularly, an improvement in night sleep and daytime well-being can be achieved. Kallweit et al. (2013) were able to show in MS patients with PAP therapy that this leads to an improvement in sleep quality and fatigue (see Fig. 1).

2.4 Excessive Daytime Sleepiness and Fatigue

Daytime sleepiness needs to be distinguished from fatigue. Excessive daytime sleepiness (EDS) includes the inability to stay awake, sleep attacks, microsleep episodes, and increased tendency to fall asleep. Prolonged sleep duration of more than ten out of 24 hours is called hypersomnia. Excessive daytime sleepiness and hypersomnia are grouped under the term hypersomnolence (Lammers et al. 2020). EDS and fatigue can also be result of other diseases. These include sleep deprivation, shift work, circadian disorders, or other sleep disorders such as obstructive sleep apnea.

A differentiation of daytime symptoms can be made on the basis of the medical history and questionnaires. In the anamnesis, indications such as “suddenly falling asleep against one’s will” or “need for lying down to sleep” may indicate daytime sleepiness, whereas “need to rest” or “am exhausted and powerless” may indicate fatigue. In addition to fatigue questionnaires, questionnaires focusing on EDS can be used. The Epworth Sleepiness Scale (ESS) questionnaire is the most frequently

used questionnaire for this purpose (see also Table 2). For further objectification of a tendency to fall asleep, the multiple sleep latency test and/or various vigilance tests can be performed in the sleep laboratory. Excessive daytime sleepiness is the main symptom of narcolepsy. Only in rare cases, narcolepsy and MS are comorbid (Kallweit et al. 2018). While fatigue in MS is well studied, there is little data on excessive daytime sleepiness in MS. Up to 38% of MS patients suffer from excessive daytime sleepiness (Chen et al. 2014). In a retrospective study, Braga et al. (2016) found a correlation between fatigue, excessive daytime sleepiness, depression, and EDSS score.

Treatment of excessive daytime sleepiness, also in MS, involves various behavioral measures. Most important is the implementation of short daytime sleep periods (Popp et al. 2017) and a regular sleep-wake rhythm. Also, regular physical exercise and a low-carbohydrate diet are probably helpful. Pharmacological therapies mainly include wake-promoting drugs such as modafinil or methylphenidate. There are also new wake-promoting drugs available such as pitolisant and solriamfetol. All drugs are not approved for the treatment in MS.

3 Nocturia

Nocturnal urination is present in up to 50% of people with MS. Often there is symptomatic neurogenic bladder dysfunction. Various patterns of dysfunction can lead to incontinence or urinary retention. Autonomic nervous system disorders can also lead to nocturia. In particular, urinary incontinence and an imperative urge to urinate lead to interruptions of sleep: insomnia. This can be aggravated by other MS symptoms such as spasticity or even pain. Neuro-urological diagnosis including micturition protocols is necessary to explain and treat the specific disorder (Peyronnet et al. 2019).

Treatment includes an appropriate fluid intake in the evening, self-catheterization, insertion of a (permanent) catheter and medication, depending on the type of dysfunction (e.g., antimuscarinics for detrusor muscle overactivity). The sporadic use of desmopressin (ADH analog) at night is also possible.

3.1 Other Sleep and Wake Disturbances

Other sleep disorders that may be present in MS include parasomnias, such as sleepwalking or REM sleep behavior disorder. There are no studies on the frequency in MS. Spasticity or pain also has a negative influence on night sleep.

There are only few data on the influence of disease-modifying MS therapies on sleep or wake disturbances. In a few studies, an improvement of the abovementioned symptoms could also be demonstrated for individual MS drugs (Kotterba et al. 2018, Penner et al. 2015).

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Part III

Diagnostics

Clinical Assessment Tools for Fatigue

Iris-Katharina Penner

1 Introduction

Fatigue in multiple sclerosis (MS) is an elusive, but in the majority of patients dominant and prominent symptom that can have a serious impact on quality of life and ability to work. Often, those affected are forced to reduce their workload or even give up their employment completely. Often, this results in social withdrawal and depressive episodes. A reliable, early diagnosis is therefore of particular relevance not only for the affected individual, but also for the treating physician, as the latter is faced with the challenge of assessing the severity of fatigue or the patient's impairment due to fatigue and providing the affected person with the best possible intervention. Due to the subjectivity of fatigue, which is probably most comparable to pain, MS fatigue defies clear objectification, which is further complicated by the fact that there is still too little clarity about the underlying pathophysiological basis. As a result, we as clinicians are faced with the challenge of reliably recording a symptom in clinical routine, which we can only approach to a large extent through the experiences and reports of those affected. The following chapter is devoted to the methodological approaches to fatigue assessment.

2 Neurological Interview

In the clinical-diagnostic interview, a *rough estimate of what the* patient reports in terms of severity of fatigue and influence on everyday life may be possible for the attending physician. However, experience even in 2021 shows that in the overall

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context of the neurological consultation, the significance of fatigue still plays a subordinate role and it is often underestimated. Thus, a reliable, detailed diagnosis of fatigue by means of a simple conversation can hardly be realized.

The patient–doctor conversation is of particular importance in the context of fatigue in that the treating physician obtains a picture from the ongoing consultations as to whether a patient reports fatigue as a new symptom or whether it is an aggravation of an already existing symptomatology. Furthermore, the treating physician can make a statement as to whether fatigue manifests as an accompanying symptom in the context of a new relapse or whether the fatigue symptoms accompany the progression of the MS disease. When fatigue occurs for the first time, the treating physician will first try to diagnostically exclude possible other causing factors (including anemia, sleep disorders, thyroid dysfunction, renal insufficiency, psychiatric symptoms) before proceeding to a qualitative and quantitative characterization of MS fatigue.

3 Fatigue Diaries

Diaries are a helpful tool for precisely mapping the course of a symptom over the course of a day (Greenhalgh et al. 2004). The use of a diary is particularly advisable when a symptom shows large fluctuations over time. In MS fatigue, we distinguish trait fatigue from state fatigue, which can be caused by various external conditions (e.g., stress, heat) and can exacerbate trait fatigue. The fatigue symptoms are therefore not constant in frequency and extent. In this respect, a diary is a suitable recording instrument when it is a question of documenting a diurnal course (onset and duration, frequency and variability in expression) or generally the course over several months. Furthermore, it is possible to obtain information about triggers and the presence of covarying factors by means of a diary recording. However, a diary that includes accompanying factors, emotional and personal remarks of the patient in addition to the main symptomatology requires a certain degree of structure and flexible handling, so that clinically and scientifically valuable conclusions can be drawn from the collected data in retrospect. In this context, the use of electronic diaries via tablet would be interesting in the future, in which, for example, the essential accompanying factors could be defined in advance in order to detect interacting and causal relationships over time.

4 Fatigue Questionnaires

In general, it is a difficult undertaking to validly record a symptom whose pathophysiology and genesis cannot be grasped by means of a questionnaire. Although a questionnaire is able to depict the existence, the severity and the frequency of occurrence, the subjective perception of the patient with regard to the ability of introspection, self-knowledge and honesty in answering questions represents a problem that should not be underestimated. Seen together, these last three points can strongly

influence the quality of the results in the sense of a deliberate or unintentional falsification (Bortz and Döring 1995). This is particularly important to bear in mind with regard to assessments. From a methodological point of view, a good fatigue scale is characterized by the fact that it a) depicts what those affected experience on a daily basis, b) contains clearly and precisely formulated items, c) has a high level of specificity and sensitivity, d) is able to differentiate between motor and cognitive fatigue and e) is as short as possible so as not to induce exhaustion through its own length and complexity. These intended properties ultimately need to be confirmed in an extensive validation process.

The number of fatigue questionnaires developed for MS is considerable. Fourteen different fatigue questionnaires were developed between 1989 and 2019 (see Table 1), eleven of which were developed within 10 years. There is hardly any other symptomatology that can boast such a flood of survey instruments and which still gives rise to constant discussion as to the best way of recording fatigue. Accordingly,

Table 1 Overview of the most important fatigue assessment instruments

Fatigue scales	Year of publication
FSS (Fatigue Severity Scale[a])	1989
FAI (Fatigue Assessment Instrument[b])	1993
FRS (Fatigue Rating Scale[c])	1993
FIS (Fatigue Impact Scale[d])	1994
MFI (Multidimensional Fatigue Inventory[e])	1995
MAF (Multidimensional Assessment of Fatigue[f])	1996
CIS (Checklist of individual Strength[g])	1996
FAMS (Functional Assessment of Multiple Sclerosis[h])	1996
MFIS (Modified Fatigue Impact Scale[i])	1998
FDS (Fatigue Descriptive Scale[j])	1999
WEIMuS (Würzburger Erschöpfungsinventar bei MS[k])	2006
FSMC (Fatigue Scale for Motor and Cognitive Functions[l])	2005
FSIQ-RMS (Fatigue Symptoms and Impact Questionnaire-Relapsing Multiple Sclerosis[m])	2019

[a] Krupp et al. (1989)
[b] Schwartz et al. (1993)
[c] Chalder et al. (1993)
[d] Fisk et al. (1994)
[e] Smets et al. (1995)
[f] Schwartz et al. (1996)
[g] Vercoulen et al. (1996)
[h] Cella et al. (1996)
[i] Multiple Sclerosis Council for Clinical Practice Guidelines (1998)
[j] Iriarte et al. (1999)
[k] Flachenecker et al. (2006)
[l] Penner et al. (2009)
[m] Hudgens et al. (2019)

as already mentioned elsewhere, there is still an ongoing debate on whether fatigue is a one-dimensional or rather a multidimensional phenomenon, which consequently in the past resulted in different conceptions of questionnaires. Last but not least, the abundance of existing survey instruments also reflects a general disagreement about which aspects exactly a valid fatigue scale should capture. When designing a scale for such a complex symptom as fatigue, it is difficult to integrate all points of view in order to present an instrument that is adequate in length and complexity. Because of this problem, it seems essential to focus on the two main aspects (motor/cognitive) and to measure them methodically and reliably by means of a comparable number of items. However, most of the scales developed show deficiencies precisely in the aspects of content focus and methodological implementation. For example, in very few cases was there a process of item generation, nor was validation carried out in a manner appropriate to the statistical criteria. It is therefore all the more surprising that some of the questionnaires nevertheless achieved great popularity and are still used today in multicenter studies as a measurement instrument for fatigue (e.g., the Fatigue Severity Scale (FSS) by Krupp et al. (1989), the Fatigue Impact Scale (FIS) by Fisk et al. (1994), the Fatigue Assessment Instrument (FAI) by Schwartz et al. (1993), or the Modified Fatigue Impact Scale (MFIS) by the MS Council (Multiple Sclerosis Council for Clinical Practice Guidelines 1998)).

A self-conducted, unpublished comparison of the three most common scales on a collective of 18 MS patients and 18 healthy control subjects was able to show how inaccurate the instruments are in the clear assignment of the severity of fatigue. Table 2 provides information on the classification of MS patients with high or low fatigue values depending on existing cut-off values or median splits in cases where no cut-off values were available. It turned out that the classification of the patients depended on the respective instrument, which resulted in the same patient being classified at the same time as a person with high or low fatigue expression (example marked in bold). Such a variance is not tolerable, especially against the background of assessments, since the instrument selected in each case obviously determines the degree of severity, but not the actual experience on the part of the patient.

The instruments listed in Table 2 therefore hardly meet the requirement for *reliable* recording. A further problem lies in the lack of limit values in some cases. For example, there is no statistically determined cut-off value for the FAI. The same applies to the subscales of the MFIS.

A look at Table 3 makes it clear that the specificity of the three scales is not given in part. Since all scales represent clinical instruments intended to differentiate a pathological form of fatigue from normal daytime sleepiness, a healthy collective should be classified as unimpaired. However, it can be seen from Table 3 that for the FAI and the MFIS cognitive scale, approximately half of the control subjects were classified as having pathological fatigue symptoms as well. As with the patient population, it is also clear that it depends on the procedure used whether a person is considered conspicuous or not (indicated in bold).

In summary, it can be stated that a reliable assessment of fatigue with the instruments developed until 1999 is questionable. New methods have therefore recently been developed with the aim of meeting the requirements of objectivity, reliability,

Table 2 Comparison of fatigue severity while using different fatigue questionnaires on a sample of 18 MS patients

	FSS values	FSS cut-off (4.6)	FAI values	Median FAI (19.33)	MFIS total	Median MFIS total cut-off (38)	MFIS Cog.	Median MFIS Cog. (13)
Patients	4.09	Low	19.26	Low	36	Low	15	High
N = 18	5.64	High	18.64	Low	34	Low	12	Low
	5.64	High	23.14	High	57	High	28	High
	3.12	Low	17.78	Low	23	Low	9	Low
	2.73	Low	17.90	Low	9	Low	5	Low
	1.64	**Low**	20.47	**High**	36	**Low**	28	**High**
	4.73	High	16.57	Low	21	Low	7	Low
	5.73	High	19.40	High	52	High	21	High
	1.54	Low	12.21	Low	26	Low	11	Low
	2.81	Low	16.81	Low	19	Low	6	Low
	7.00	High	21.49	High	38	High	13	High
	6.45	High	25.61	High	38	High	11	Low
	2.27	Low	20.26	High	7	Low	6	Low
	5.54	High	21.37	High	38	High	17	High
	4.81	High	16.50	Low	34	Low	15	High
	2.54	Low	15.88	Low	29	Low	13	High
	5.55	High	20.88	High	41	High	28	High
	3.81	Low	20.47	High	32	Low	15	High

FSS Fatigue Severity Scale, *FAI* Fatigue Assessment Instrument, *MFIS* Modified Fatigue Impact Scale, *Cog.* Cognitive Subscale

validity, sensitivity (number of true positive results in patients), and specificity (number of negative results in healthy individuals). However, meeting the last two requirements of sensitivity and specificity is quite a difficult task in the absence of a gold standard.

The first instrument, the Würzburg Exhaustion Inventory in MS (WEIMuS [Flachenecker et al. 2006]), is based on the items of the FSS (Krupp et al. 1989) and the MFIS (Multiple Sclerosis Council for Clinical Practice Guidelines 1998). Those items with high discriminatory power, with high loading on one of the two factors (cognitive vs. physical) and moderate difficulty were selected. The WEIMuS consists of 17 items and refers to the experienced fatigue symptomatology during the past 14 days. It was validated in a collective of 67 MS patients and 68 patients with surgically or conservatively treated cervical or lumbar disc herniations. The WEIMuS has high internal consistency (Cronbach's between 0.94 and 0.95, corrected item-total correlation between 0.50 and 0.80) and good convergent validity and moderate discriminant validity to depression.

The second instrument, the Fatigue Scale for Motor and Cognitive Functions (FSMC [Penner et al. 2009]), was developed with the aim of differentiating between the two essential aspects of fatigue (cognitive and motor) and to allow reliable assessment in clinical routine by grading the severity (mild, moderate, severe).

Table 3 Comparison of fatigue severity while using different fatigue questionnaires on a sample of 18 healthy controls

	FSS values	FSS cut-off (4.6)	FAI values	Median FAI (16.47)	MFIS total	Median MFIS total cut-off (38)	MFIS Cog.	Median MFIS Cog. (7.5)
Controls	2.91	Low	15.14	Low	15	Low	13	High
N = 18	4.18	Low	18.52	High	30	Low	17	High
	2.73	Low	20.39	High	3	Low	3	Low
	3.36	Low	19.16	High	19	Low	12	High
	3.18	Low	16.84	High	7	Low	3	Low
	1.73	Low	17.73	High	21	Low	12	High
	1.82	Low	14.49	Low	4	Low	0	Low
	2.00	Low	15.33	Low	10	Low	2	Low
	3.09	**Low**	21.25	**High**	22	**Low**	13	**High**
	1.27	Low	12.61	Low	7	Low	6	Low
	1.36	Low	16.03	Low	0	Low	0	Low
	2.27	Low	18.44	High	16	Low	14	High
	2.36	Low	16.52	High	9	Low	7	Low
	2.00	Low	15.50	Low	6	Low	5	Low
	2.91	Low	16.41	Low	16	Low	12	High
	1.27	Low	14.77	Low	9	Low	8	High
	6.55	High	21.55	High	66	High	30	High
	1.27	Low	13.57	Low	0	Low	0	Low

FSS Fatigue Severity Scale, *FAI* Fatigue Assessment Instrument, *MFIS* Modified Fatigue Impact Scale, *Cog.* Cognitive Subscale

First, items with a cognitive or motor focus were compiled from existing scales, mostly reformulated and newly generated on the basis of interviews with treating neurologists, nursing staff, and MS patients. In a next step, these items were subjected to a plausibility check with regard to the focus on cognitive and motor elements of fatigue. Weak items were eliminated and new items were generated again based on the information provided by the assessing persons. These were then assessed again for their quality by students and MS patients in a second evaluation process. Afterwards, the final compilation of the items took place. The final version of the FSMC consists of 20 items, ten of which represent the cognitive and ten the motor aspects of fatigue. In contrast to the WEIMuS and other fatigue instruments, the FSMC does not ask about the fatigue experienced during the last 14 days, but about the symptoms in *general*. Thus, the FSMC maps trait fatigue rather than state fatigue. Since this instrument is used as a diagnostic tool in clinical routine, it is essential not only to illuminate a short period of time in which fatigue symptoms can be caused or aggravated, for example, by very special accompanying circumstances ("state fatigue"), but also to enable the treating neurologist to decide whether a patient generally exhibits fatigue symptoms or not. The answers are collected by means of a five-point Likert scale with values from 1 to 5.

The final instrument was subjected to an extensive validation process involving a total of 354 MS patients and 151 healthy controls from German-speaking

Switzerland and Germany. In relation to the patient group, both subscales showed a high internal consistency (Cronbach's between 0.91 and 0.93, corrected item-total correlation between 0.50 and 0.83). In contrast to the WEIMuS, various external criteria were included in the validation: the two currently most popular fatigue assessment procedures (FSS and MFIS), depression, various MS-specific measures of cognitive performance, physical functioning, quality of life, motivation, and personality. The individual test procedures can be found in Table 4**.**

The intercorrelation between motor and cognitive subscales of the FSMC was $r = 0.710^{**}$. From this result it can be deduced that cognitive and motor fatigue are not independent of each other, but that additional, separating aspects between both components seem to exist, through which a 1.0 correlation is not given.

As already critically mentioned, the determination of sensitivity and specificity in the conventional sense is complicated by the lack of a gold standard in fatigue. Nevertheless, in order to make a determination, the two subscales of the FSMC were included as predictor variables for the group variable (MS patient/control person) in a logistic regression. Based on the resulting classification table, the percentage of individuals correctly diagnosed as having MS ("sensitivity") and the percentage correctly diagnosed as non-MS ("specificity") could be determined. Because MS fatigue is by definition a clinical symptom that does *not* occur in healthy individuals, the terms "sensitivity" and "specificity" in this context reflect the ability of the subscales to relate fatigue symptomatology to the existing MS diagnosis. The analysis showed a sensitivity of 88.7 and a specificity of 83.0 for our

Table 4 Overview of the validation procedure

Dimensions	Tests	Time
Fatigue	FSMC	5 min
	MFIS	5 min
	FSS	5 min
Depression	BDI	5 min
Cognition	BRB-N	30 min
	MSNQ	5 min
	FST	5 min
Physical functioning	MSFC (without PASAT)	10 min
Quality of life	SF-36	10 min
	FAMS	10 min
Motivation	HAKEMP-90	10 min
Personality	NEO-FFI	10 min
	Total:	Approx. 110 min

FSMC Fatigue Scale for Motor and Cognitive functions, *MFIS* Modified Fatigue Impact Scale, *FSS* Fatigue Severity Scale, *BDI* Beck Depression Inventory, *BRB-N* Brief Repeatable Battery of Neuropsychological Tests, *MSNQ* Multiple Sclerosis Neuropsychological Questionnaire, *FST* Faces Symbol Test, *MSFC* Multiple Sclerosis Functional Composite, *PASAT* Paced Auditory Serial Addition Test, *SF-36* Short Form 36 Health Survey, *FAMS* Functional Assessment of Multiple Sclerosis, *HAKEMP-90* Fragebogen zur Erfassung von Handlungskontrolle nach Erfolg, Misserfolg und prospektiv, *NEO-FFI* NEO-Five-Factor-Inventory

newly developed total scale (FSMC). For the two subscales, the sensitivity values ranged from 86.4 to 89.0, and the specificity values ranged from 66.7 to 86.4. This result suggests that the FSMC can be used to reliably detect MS patients as being pathologically fatigued (fatigue patients in the context of MS disease) and to classify healthy individuals as not having the disease and in consequence no fatigue. A comparison of the FSMC with the FSS and MFIS in this context showed that although the FSS and MFIS performed only marginally worse than the FSMC in the area of sensitivity, there were significantly lower values in the area of specificity. The exact data can be found in Table 5.

For use in clinical routine, the FSMC is of particular benefit in that, for the first time, fatigue can also be graded from mild to moderate to severe. The cut-off values were determined by one standard deviation from the mean values of the healthy control group. Thus, using the new scale, patients can receive a finely graded diagnosis for the overall extent and the affected sub-areas (cognitive/motor). The evaluation scheme with the determined cut-off values is shown in Table 6.

Another interesting result of the validation study was that fatigue, and especially the cognitive aspect, is less associated with cognitive performance than with the personality traits neuroticism and extraversion as well as with motivational factors. This means that a cognitively impaired patient is not necessarily the one with pathological fatigue and vice versa. The relationship between MS fatigue and personality variables and motivation is discussed in detail elsewhere in this book.

The FSMC has now been translated into more than 75 languages and is used clinically in numerous studies as well as in neurological practices and university institutions. In addition to the assessment of trait fatigue, the instrument is also suitable for the characterization of symptoms in other primary diseases such as lupus erythematosus, rheumatoid arthritis, stroke (Hubacher et al. 2012), and others. A comprehensive systematic review explicitly recommends the use of the FSMC in MS as a multidimensional instrument due to its good methodological properties

Table 5 Comparison of sensitivity and specificity between the three fatigue instruments (FSMC, MFIS, and FSS) applied in the validation study

Scales	Sensitivity	Specificity	ROC-area	Alpha
FSMC_TOT	88.7	83.0	0.93	
FSMC_COG	86.4	66.7	0.88	0.93
FSMC_MOT	89.0	86.4	0.94	0.91
MFIS_TOT	87.1	71.4	0.89	
MFIS_KOG	83.8	59.2	0.82	0.95
MFIS_MOT	88.0	77.6	0.91	0.94
FSS_TOT	86.7	69.4	0.89	0.94

FSMC_TOT FSMC total scale, *FSMC_COG* FSMC cognitive subscale, *FSMC_MOT* FSMC motor subscale, *MFIS_ TOT* MFIS total scale, *MFIS_COG* MFIS cognitive subscale, *MFIS_MOT* MFIS motor subscale, FSS_TOT = FSS total scale

Table 6 Overview of the statistically determined cut-off values for the total FSMC and its subscales

FSMC total	≥43	Mild
	≥53	Moderate
	≥63	Severe
FSMC cognitive	≥22	Mild
	≥28	Moderate
	≥34	Severe
FSMC motor	≥22	Mild
	≥27	Moderate
	≥32	Severe

(Elbers et al. 2012). Like for most multidimensional fatigue scales, there is a question about the accuracy of the assumed factor structure. While different fatigue dimensions clinically exist (cognitive, motor, and possibly other dimensions), scales that have been explicitly studied for this purpose (MFIS, CFA, FSMC) can confirm these in an exploratory but not in a confirmatory factor analysis (Pust et al. 2019). Thus, the difficulty of depicting the real clinical presentation of symptoms by means of a questionnaire becomes apparent once again.

The most recent instrument to assess fatigue symptoms in patients with relapsing MS is the Fatigue Symptoms and Impacts Questionnaire-Relapsing MS (FSIQ-RMS [Hudgens et al. 2019]). This instrument was developed in accordance with FDA requirements for industry-conducted clinical trials when it comes to the use of PROs ("patient reported outcomes") and, finally, the ability to include results of PROs in the drug label, if applicable (Food and Drug Administration 2014, 2015). The FSIQ-RMS consists of two subscales, one of which is symptom-related and the other impact-related. The symptom scale uses seven items to capture symptoms related to fatigue that have occurred in the past 24 hours. An 11-item scale measures the severity of fatigue symptoms. The Impact scale includes 13 items and asks about the impact of fatigue symptoms on physical and cognitive domains as well as coping mechanisms in a seven-day time window. Although this scale meets FDA development criteria, there are several significant problems associated with it that should be noted: (1) The development of the scale was commissioned by a pharmaceutical company, resulting in the restriction to relapsing-remitting MS (use of the scale in the OPTIMUM trial for ponesimod). Since fatigue occurs independently of the course of MS, a scale that was only developed and tested for the relapsing course is questionable. Here, the instrument should be tested on all MS courses in the future. (2) The results generated with this scale on fatigue cannot be compared with any other study that also investigated the efficacy of a drug on fatigue. (3) There is a lack of a validation study in which the commonly used FSS, MFIS, and FSMC have been cross-tested to provide information about the psychometric properties in comparison. (4) The FSIQ-RMS is unsuitable for mapping trait fatigue due to its short temporal reference points (24 h and 7 days). Thus, the use of the FSIQ-RMS in the clinical setting is not expected to be timely due to the aforementioned restrictions. Meaningful data will have to be presented in the following years.

5 Neurophysiological Possibilities of Detection

In addition to the self-evaluation methods already described, on the side of objective methods for the assessment of fatigue, neurophysiological procedures should be mentioned, which, however, are still used for purely scientific purposes, but not in clinical routine.

From a neurophysiological point of view, motor fatigue can be defined as a reduction in voluntary muscle strength that comes into play at the moment when a movement is to be executed (Gandevia et al. 1995). Merton (1954) already distinguished between central and peripheral components of motor fatigue. Here, the central component was related to the inability to maintain the central motor impulse to the motoneuron, whereas the peripheral component referred to changes either in the muscle itself or else at the neuromuscular junctions. As mentioned in several places in this book, the pathophysiology of fatigue is still unclear. Nevertheless, in view of the characteristics of the underlying primary disease, it is favored to assume that MS fatigue is more likely to be caused by central abnormalities and that peripheral changes play a more subordinate role.

A transcranial magnetic stimulation (TMS) study by Liepert et al. (2005) examined MS patients with and without fatigue and a healthy control population before and after performing a fatiguing handgrip exercise. In the MS patients with fatigue, the authors found a significantly shorter exercise period and lower handgrip strength. Furthermore, before and after performing the motor exercise, the patients with fatigue showed reduced intracortical inhibition, which the authors attributed to disinhibition in the area of the primary motor cortex. Cortical disinhibition would thus be considered a neurophysiological surrogate marker of fatigue syndrome in MS patients. The severity of fatigue, determined via FSS (Krupp et al. 1989), also correlated significantly with the duration required for the motor threshold (= minimum stimulus threshold to generate a small muscle action potential in the relaxed muscle in at least 50% of cases) to return to normal after motor movement. This was discussed by the authors as an indication that membrane excitability is impaired in patients with fatigue. According to this result, motor fatigue would be considered a phenomenon caused due to changes in membrane properties, specifically in the ability of the membrane to return to a normal excitability level after a fatiguing motor exercise. As early as 1999, the triple stimulation technique (TST [Magistris et al. 1999]) was tested as a possible method to provide an indication of the functional capacity of corticospinal fibers. An application in MS patients with fatigue showed a *smaller* decrease in central motor conduction in MS patients compared to healthy controls during a fatiguing motor hand exercise, contrary to the established working hypothesis (Scheidegger et al. 2012). The authors justified the finding by the fact that the study did not include patients with obvious motor problems and also questioned whether an experimental setting focusing on a small hand muscle can generally represent motor fatigue as experienced by affected patients on a daily basis.

In addition to TMS, studies using electroencephalographic (EEG) methods have also been conducted on MS patients with fatigue. The study results of Leocani et al. (2001) showed for MS patients with fatigue a temporally and spatially abnormal

event-related desynchronization in sensorimotor areas during the execution of movement as well as an abnormal, late synchronization after the termination of movement. These results support the hypothesis of impaired intracortical inhibition put forward by Liepert et al. (2005).

Neurophysiological methods undoubtedly represent an interesting and valuable approach to further research into fatigue, as they offer a methodologically *objective* approach, unlike the methods already mentioned. Regarding objective possibilities for the assessment of cognitive fatigue, please refer to Chap. 6 on cognitive fatigue. Here, it is described in detail how attention-based measurement instruments can enable objective measurement of cognitive fatigue.

6 Summary

A reliable assessment of fatigue should take into account that it is a multi-layered, multidimensional symptom. From patient reports it can be concluded that there are two main aspects of fatigue on the experience side, one of which is physical, the other cognitive in nature. Since knowledge about the intercorrelation and the pathophysiological structure of the two components is still poor, a separate recording of the two symptom dimensions is important. Moreover, fatigue occurs more frequently with factors relevant to MS, such as depression, cognitive impairment, and sleep disturbances, but also other predisposing factors that should be considered in a reliable assessment (Penner 2006; Penner and Calabrese 2007; Penner and Paul 2017; Veauthier et al. 2011). This is all the more relevant as the measurement of fatigue can only be carried out in a limited way using objective parameters. Self-assessment tools such as questionnaires require the patient to be capable of self-assessment and introspection. However, since pure questioning within the routine clinical neurological examination is not a suitable procedure to reliably assess and quantify fatigue, standardized self-assessment instruments still represent our clinical gold standard. They are able to provide information about the severity and focus (dimension) of fatigue to the patient and his relatives as well as to the treating physician (Penner and Schläger 2006) and also allow changes in the course of the disease to be identified.

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Neuroimaging and Fatigue

Daniela Pinter and Christian Enzinger

1 Macrostructural Imaging Correlates of Primary Fatigue

1.1 Relevance of Inflammatory White Matter Lesions

MS-related focal inflammatory white matter changes can be visualized on MRI of the brain on T2-weighted sequences by hyperintense areas and are accordingly referred to as T2 lesions. In addition, hypointense areas on T1-weighted sequences (so-called chronic "black holes") can indicate more pronounced focal tissue damage up to irreversible white matter tissue loss, whereas contrast enhancement of lesions on T1 weighted sequences reveals acute MS foci in the stage of blood-brain barrier disruption (Fig. 1).

Although the majority of recent studies have failed to demonstrate an association between extent or volume of T1 or T2 lesions (Arm et al. 2019; Biberacher et al. 2017; Novo et al. 2018), previous studies have reported an association between higher white matter lesion volume and more pronounced fatigue (Calabrese et al. 2010; Mowry et al. 2009; Papadopoulou et al. 2013; Sepulcre et al. 2009; Tedeschi et al. 2007). However, a recent paper also concluded that global T2 lesion volume was increased in people with MS and prolonged fatigue, whereas patients with only a single episode of fatigue did not differ in global lesion volume. Consequently, the authors emphasized that the time course and evolution of fatigue should be better considered in future studies, as the pathophysiological mechanisms of persistent fatigue (due to irreversible white or gray matter damage) are likely to differ from those of fluctuating fatigue (e.g., due to inflammatory cytokines or hormonal changes) (Palotai et al. 2020).

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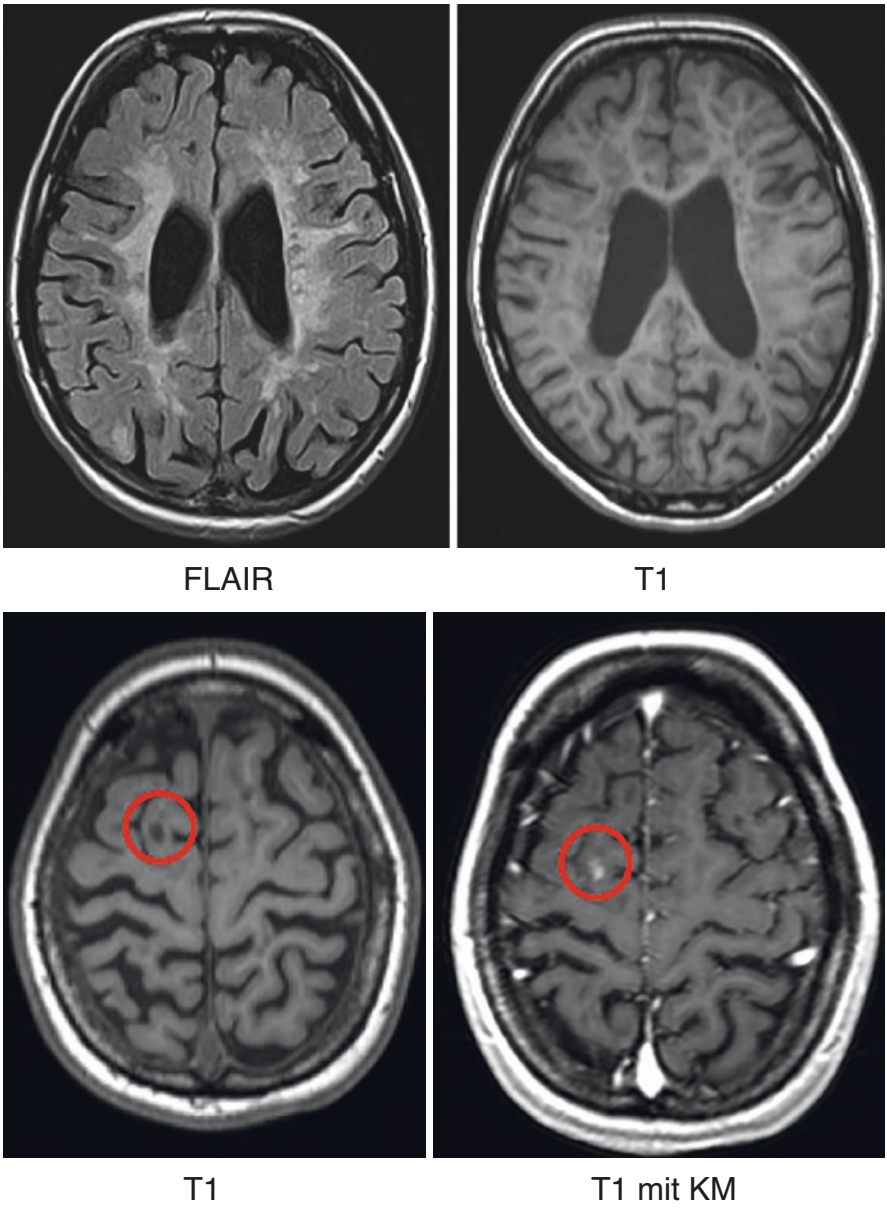

Fig. 1 The upper panel shows extensive, confluent, hyperintense and primarily periventricular localized white matter lesions after several years of MS (upper left, T2-FLAIR), some of these lesions are also visible on native T1-weighted images (upper right) by "dark" (hypointense) lesions ("black holes") representing focal tissue damage. Note: age-related strong expansion of inner and moderate expansion of the outer ventricles representing cerebral atrophy. The lower panel shows native and contrast-enhanced T1-weighted images ("mit KM"), presenting an active lesion (so-called "wet black hole" due to formation of edema). This represents active disease

Moreover, beyond these temporal dynamics, specific lesion localizations in the frontal (Morgante et al. 2011) and parieto-temporal white matter seem to be particularly associated with the occurrence of fatigue (Sepulcre et al. 2009; Altermatt et al. 2018; Palotai et al. 2019; Rocca et al. 2014). This suggests impairment or damage to pathways strategically relevant to the occurrence of fatigue, which play an essential role in cognitive processes such as task initiation, motivation, attention, and maintenance (Sepulcre et al. 2009).

1.2 Changes in Global and Regional Brain Volume

Some studies also showed an association between reduced global brain volume and the presence of fatigue (Biberacher et al. 2017; Mowry et al. 2009; Tedeschi et al. 2007). Interestingly, one study suggested an association between the presence of cognitive fatigue and a stronger decrease in brain volume over the subsequent 17 months (Sander et al. 2016). Whether fatigue is indeed a risk marker for disease progression should be investigated in further studies.

Importantly, regional analyses of cortical and subcortical gray matter suggest an association between neurodegeneration of striatal-thalamic-frontal regions and the presence of fatigue (Calabrese et al. 2010; Andreasen et al. 2010; Damasceno et al. 2016).

Both globally reduced cortex volume or thickness (Biberacher et al. 2017; Nourbakhsh et al. 2016; Nunnari et al. 2015; Nygaard et al. 2015) and specific reductions in frontal, insular (Sepulcre et al. 2009; Gonzalez Campo et al. 2019; Riccitelli et al. 2011), and parietal cortical volume (Hanken et al. 2016; Pellicano et al. 2010) have been related to the presence and severity of fatigue. Specifically, individuals with reduced cortical thickness of the primary motor cortex showed more severe motor fatigue, and there also tended to be a relationship between cognitive fatigue and cortical thickness in frontal and parietal regions responsible for attentional processes (Andreasen et al. 2019).

Also, decreased thalamic (Nourbakhsh et al. 2016; Bernitsas et al. 2017; Capone et al. 2019) and basal ganglia volumes (Damasceno et al. 2016; Bernitsas et al. 2017; Yarraguntla et al. 2018) have been frequently described in patients with fatigue. In addition, atrophy of the corpus callosum has been associated with more pronounced fatigue (Yaldizli et al. 2014; Yaldizli et al. 2011).

2 Microstructural Imaging Correlates of Primary Fatigue

Diffusion tensor imaging (DTI) allows the visualization and examination of nerve fiber connections of the brain in vivo. White matter integrity (“intactness”) using fractional anisotropy (FA) or the course of larger nerve fiber bundles using tractography can be assessed with this technique.

Reduced integrity of frontal nerve fiber connections (e.g., in the forceps minor) (Bisecco et al. 2016; Gobbi et al. 2014a; Pardini et al. 2010), in the cingulum

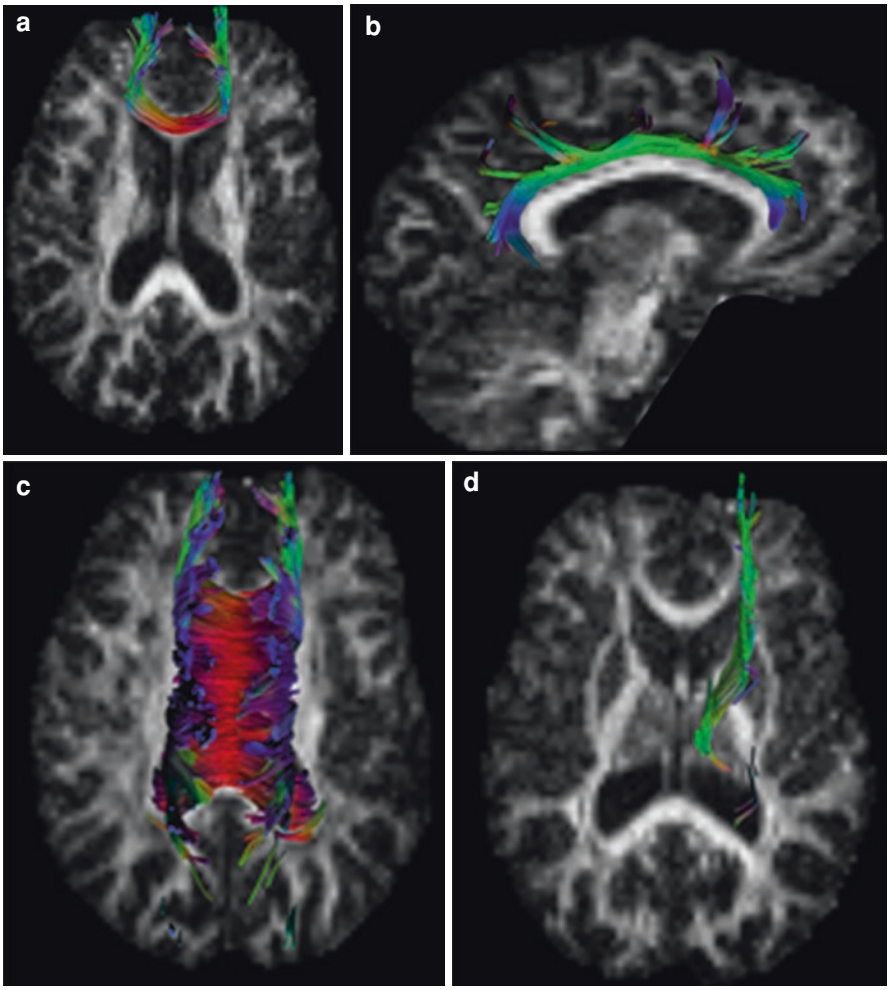

Fig. 2 Relevant fiber tracts of fatigue. Reduced white matter integrity of these fiber tracts are associated with more severe fatigue: (**a**) Forceps minor, (**b**) Cingulum, (**c**) Corpus callosum (red), and (**d**) anterior thalamic radiation (green). Created by DSI Studio

(Bisecco et al. 2016; Pardini et al. 2015), in the corpus callosum (Sander et al. 2016; Bisecco et al. 2016), and in fronto-temporal connections, (e.g., in the fasciculus uncinatus) (Gobbi et al. 2014a), has been associated with more pronounced fatigue (Fig. 2).

Also, reduced integrity of subcortical connections, particularly towards the basal ganglia (especially to the caudate nucleus and the putamen (Palotai et al. 2019; Pardini et al. 2015)) and within the anterior thalamic radiation (Rocca et al. 2014; Bisecco et al. 2016; Gobbi et al. 2014a; Bester et al. 2013), as well as microstructural changes in the thalamus, basal ganglia, and frontal lobe (Wilting et al. 2016)

have been described. Furthermore, in MS patients with fatigue, reduced integrity has been observed in the following structures: in the forceps major, the inferior fronto-occipital fascicle (Rocca et al. 2014), anterior capsula interna (Genova et al. 2013), and in nerve fiber connections from the hypothalamus to the brainstem (Hanken et al. 2015).

Interestingly, in contrast to the literature cited in the previous paragraph suggesting regionally selective processes, some DTI studies yielded findings suggesting that extensive white matter microstructural changes are related to the onset of fatigue independently from lesion burden and gray matter atrophy (Novo et al. 2018; Palotai et al. 2019).

Currently, it can be assumed that the continuous accumulation of focal lesions, independently or in concert with diffuse MS-related tissue damage, leads to an impairment of the cortical-subcortical brain connections, resulting in disturbances of the anatomical and functional connectivity. In particular, damage in cortico-striato-thalamo-cortical nerve fiber bundles ("cortico-striato-thalamo-cortical [CSTC] loop") seems relevant for fatigue. In addition to the presented structural correlates of fatigue, potentially underlying changes in brain function are increasingly being investigated (Bertoli and Tecchio 2020).

3 Functional Imaging Correlates of Primary Fatigue

Functional magnetic resonance imaging (fMRI) of the brain can identify changes in cerebral tissue blood flow caused by the increased energy demand of active neurons and thus indirectly allows imaging of brain activity (e.g., which brain regions are active during a task) and functional connectivity (FC) (e.g., which brain regions work together and therefore exhibit synchronous changes in blood flow).

In one of the first functional imaging studies of fatigue in MS using positron emission tomography (PET), reduced glucose metabolism was found in the prefrontal cortex (especially in the lateral and medial prefrontal cortex and in pre- and supplementary motor areas) and in the basal ganglia (especially in the putamen and caudate nucleus) as well as an increased metabolism in the vermis cerebelli and the anterior cingulate in patients with MS and fatigue (Roelcke et al. 1997). Based on the findings of this study, it was hypothesized that changes in cortico-subcortical (mainly thalamus, basal ganglia) activation are associated with fatigue. These findings were corroborated by subsequent fMRI and further positron emission tomography (PET) studies (Derache et al. 2013; Filippi et al. 2002).

The studies cited below frequently report increased brain activation or activation of additional brain areas in patients with MS and fatigue compared to patients with MS without fatigue or healthy controls during the performance of motor or cognitive tasks. When performing motor tasks, increased activations in the thalamus (Rocca et al. 2007), basal ganglia (Rocca et al. 2007; Specogna et al. 2012), frontal lobe (Rocca et al. 2007; Specogna et al. 2012; Pardini et al. 2013; Rocca et al. 2016), precuneus (Rocca et al. 2009), and cerebellum (Pardini et al. 2013; Rocca et al. 2009) were associated with fatigue.

In addition to these "overactivations," two of the aforementioned studies were able to observe parallel reduced brain activation in partially adjacent regions, e.g., in the frontal lobe, middle temporal lobe, postcentral gyrus, and basal ganglia (Rocca et al. 2016; Rocca et al. 2009), which were related to the severity of fatigue. Similarly, complex altered activation patterns (i.e., activity increases/decreases in the cingulate, frontal lobe, primary sensory cortex, or insula) have been reported in patients with fatigue after manual or mental effort during the performance of motor tasks (Tartaglia et al. 2008; White et al. 2009).

Regarding cognitive task performance, increased activity in the thalamus (DeLuca et al. 2008), basal ganglia (DeLuca et al. 2008), frontal lobe (DeLuca et al. 2008; Huolman et al. 2011; Spiteri et al. 2017), parietal lobe (DeLuca et al. 2008; Engström et al. 2013), and substantia nigra (Engström et al. 2013) have been observed in MS patients with fatigue. One study also reported parallel reduced activity in the thalamus, basal ganglia, and frontal lobe (Engström et al. 2013).

It should be noted though that most of these studies defined fatigue as a trait. In studies that used the definition of transient fatigue, i.e., a state, increased brain activation in MS patients was also reported during a cognitive task in the frontal lobe, caudate nucleus, and cerebellum (Genova et al. 2013).

Comparability of these findings is difficult due to the different applied tasks (motor vs. cognitive; simple vs. complex), small and frequently heterogeneous samples, and variability in operationalization (use of different questionnaires), prompting the increasing use of resting-state functional MRI examinations expecting identification of possible changes in functional connectivity (FC).

Recent studies emphasize that reciprocal FC of the thalamus and basal ganglia and subcortical FC to the cortex are particularly relevant for the occurrence of fatigue (Capone et al. 2019; Chaudhuri and Behan 2000).

Patients with fatigue showed greater FC between the thalamus and the precentral gyrus, reduced FC between the thalamus and the parietal operculum and superior frontal gyrus, and reduced FC between the insula and posterior cingulate (Stefancin et al. 2019). In the presence of fatigue, patients showed higher FC between the thalamus and insula and reduced FC between the dorsolateral prefrontal cortex (DLPFC) and posterior cingulate compared to healthy controls (Lin et al. 2019). In agreement, increased FC of the superior frontal gyrus with cortical regions (frontal, temporal, occipital) and reduced FC to the thalamus have been reported in cognitive fatigue (Pravatà et al. 2016).

Examining FC of the thalamus (Hidalgo de la Cruz et al. 2017), the authors found specific changes in connectivity to the precuneus and cerebellum (cognitive fatigue), the sensorimotor network (SMN; motor fatigue), and the insula (psychosocial fatigue).

Greater expression of fatigue correlated with reduced FC of the striatum with the SMN and increased FC of the DLPFC to the inferior parietal gyrus and sensorimotor cortex (Jaeger et al. 2019). Consistent with these findings, more severe fatigue has been reported to correlate with stronger FC between the caudate nucleus and DLPFC (Wu et al. 2016). Greater fatigue severity correlated with reduced FC of the

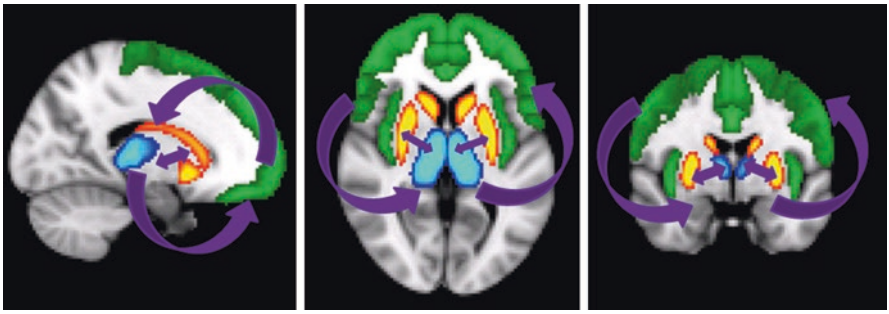

Fig. 3 Schematic overview of brain areas associated with structural or functional connectivity changes related to fatigue. Created using FSL View. Thalamus: blue. Striatum: yellow-red. Cortex (frontal, parietal, insular): green. $x = -18$, $y = -2$, $z = 4$

basal ganglia with the frontal and parietal cortex and increased FC between the caudate nucleus and motor cortex (Finke et al. 2015).

Patients with fatigue showed higher FC in the posterior cingulate and reduced FC in the anterior cingulate when investigating a so-called "resting network" ("default mode network" [DMN]). When focusing on the SMN, increased functional connectivity was observed in primary and supplementary motor areas (Cruz-Gómez et al. 2013), with changes in the DMN being more strongly associated with the occurrence of fatigue (Bisecco et al. 2018).

In general, FC, and thus the cooperation of brain areas responsible for maintaining and accomplishing sensorimotor function, motor planning, motivation, attention and executive function, as well as the resting network, appears to be disrupted in the context of MS in fatigue (Fig. 3).

Even though the presented functional MRI findings are partly in agreement with the macro- and microstructural findings and provide further possible MRI markers of fatigue, the exemplary and diverse results presented above show how complex the underlying mechanisms of fatigue are likely to be.

4 Functional Imaging Correlates of Fatigability

In contrast to subjectively perceived fatigue, the objectively measurable decline in performance due to fatigue ("fatigability") is increasingly being investigated by means of imaging. Although there is a positive correlation between fatigability and fatigue (Loy et al. 2017), distinct underlying mechanisms are suspected (Kluger et al. 2013).

Changes in brain activation associated with fatigue and fatigability in MS patients were specifically investigated. The findings revealed reduced activation in the insula, frontal and parietal lobes, basal ganglia and amygdala with higher cognitive fatigability, and increased activation in the anterior cingulate with increased fatigue (Spiteri et al. 2017). In contrast, increased activation in the caudate nucleus was found to be associated with higher cognitive fatigability (Berard et al. 2019).

5 Secondary Fatigue and Imaging Findings

Secondary fatigue describes the occurrence of severe fatigue that is not directly caused by MS, such as insomnia (Foschi et al. 2019), infections, chronic pain, medications, physical overexertion, and/or affective problems (especially depression). Even though fatigue and depression are distinct symptoms, both can overlap and lead to listlessness, exhaustion, and tiredness. It should be noted that the construct of secondary fatigue encompasses multifactorial etiologies and consequently correlations and specifically causalities can only be explored to a limited extent.

In this context, individual studies reported that regional cortical atrophy (Gobbi et al. 2014b) and cerebellar atrophy (Lazzarotto et al. 2020) in MS are related to both depression and fatigue. Another study demonstrated an association between reduced cortical thickness in the inferior parietal lobe and depression-independent fatigue, but cortical thickness provided little variance explanation for fatigue and depression, and the authors consequently emphasized the importance of subcortical mechanisms to study distinct brain markers (Hanken et al. 2016).

Regarding associated changes in white matter, damage to fronto-striatal and temporo-insular tracts appears to be crucial regarding the occurrence of persistent fatigue and independent of the presence of depression (Palotai et al. 2019). Reduced white matter integrity in frontal (forceps minor) and fronto-temporal (fasciculus uncinatus) fiber tracts has also been observed in fatigue, independent from depression (Gobbi et al. 2014a). Overlapping and distinct FC changes in the DMN were found for depression and fatigue (Høgestøl et al. 2019).

The identification of distinct and overlapping underlying brain mechanisms of depression and fatigue is only possible using a clear operationalization and comprehensive assessment of both impairments.

6 Summary and Outlook

Recent neuroimaging findings suggest that both macro- and microstructural as well as functional changes in specific brain regions (mainly frontal, parietal, temporal, and subcortical) and specific structural and functional connections (mainly cortico-striato-thalamo-cortical) are related to the occurrence of primary fatigue in people with MS (Arm et al. 2019; Palotai and Guttmann 2019) (Fig. 3).

Due to the diversity of fatigue assessment and the variety of operationalizations of this subjectively perceived impairment (Penner & Paul 2017), the identification of objective MRI markers of fatigue cohorts will continue to vary in the future. Furthermore, while the range of different analytical approaches (e.g., structural and functional, activation and connectivity, local changes vs. network analysis) allows for a more comprehensive investigation of underlying mechanisms, it also complicates the verification of "simple" markers, which are unlikely in this context. Currently, both structural and functional changes in the cortico-striato-thalamo-cortical network appear to be associated with fatigue. Consequently, multicenter

and longitudinal studies with sufficient sample size are needed to assess objective MRI parameters and their specificity independently of other possible influencing factors (e.g., age, physical and cognitive impairment, depression).

To date, imaging techniques cannot contribute to the individual clinical diagnosis of fatigue, because imaging of individual patients with fatigue often does not yield obvious MRI correlates, and imaging markers of fatigue do not necessarily imply causality. However, MRI markers do provide important relevant information for developing and optimizing possible more targeted treatment approaches.

Exploring the underlying cerebral mechanisms of the complex concept of fatigue and associated constructs such as "fatigability" and secondary fatigue will continue to lead to interesting research findings in the future.

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Electrophysiology and Fatigue

J. Liepert

1 Introduction

This chapter is devoted to the following topics:

1. Electrophysiological methods and results for the investigation of motor fatigue in healthy subjects. This always includes measurements before and after a muscular effort causing fatigue.
2. Electrophysiological methods and results for the study of motor fatigue in patients with multiple sclerosis (MS), distinguishing between MS patients with fatigue symptoms and those without fatigue signs. Here, work investigating a principal change in excitability in MS patients with fatigue can be distinguished from work performing measurements before and after an exhaustive task.
3. Electrophysiological methods and results to investigate different methods (pharmacological approaches and external brain stimulation) to influence fatigue symptoms in MS patients.

1.1 Fatigue and Exhaustibility

In recent years, more and more attempts have been made to differentiate the term "fatigue": A distinction is made between the subjective perception of "fatigue," which can be recorded by questionnaires, and exhaustibility ("fatigability" in English), which can be measured by various methods (Kluger et al. 2013). The question arises as to what can be captured by electrophysiological measurement

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methods: Fatigue as one's own perception, one's own experience or fatigability as abnormal exhaustibility and thus (concrete) motor phenomenon. And thus the question arises, how close is the relationship between fatigue and fatigability? According to Steens et al. (2012), there is a correlation between the two parameters.

1.2 Heterogeneity of Studies on Exhaustibility

A variety of study designs exists. The common feature is that a motor exhaustive task is performed. Some studies require continuous isometric contraction, others repetitive movements, and others complex sequences such as playing soccer. The use of force varies and may include a maximal continuous contraction or submaximal contractions or relatively weak contractions. This leads to very different time courses until exhaustion is reached. The electrophysiological measurements are performed either before and after the task or, especially in the case of repetitive tasks, repeatedly during the increasing exhaustion. Moreover, in some of the studies the TMS recordings are made on the relaxed muscle, in other studies during preinnervation of the target muscle. This variety of conditions together with a large number of electrophysiological parameters leads to limited comparability of the studies and makes meta-analysis difficult. Fatigue appears to be evoked in the same way by prolonged low force contractions as by shorter duration higher force contractions (Søgaard et al. 2006). However, Severijns et al. (2017) concluded that no gold standard for capturing fatigability exists to date.

Since it can be assumed that the development of fatigue is a dynamic process in which compensatory mechanisms play a relevant role, especially in the initial phase, the time at which the electrophysiological evaluation takes place is of decisive importance and can probably explain part of the sometimes discrepant results.

1.3 Peripheral and Central Fatigue

Motor fatigue can be divided into a central and a peripheral type. The central parts include secondary motor brain areas, primary motor cortex, the corticospinal tract, spinal anterior horn cells, and peripheral nerves. Peripheral factors include the muscle and neuromuscular synapse. Electrophysiological techniques can be used to more precisely delineate the area in which fatigue is occurring: If, in the context of an exhaustive motor task, strength decreases and a brief increase in strength is possible by electrical stimulation of the peripheral nerve supplying the target muscle, then the origin of fatigue must be proximal to the neuromuscular synapse and muscle. If a transcranial magnetic stimulus can achieve a transient increase in force, then the cause of fatigue does not lie in a dysfunction of the motor cortex or the corticospinal tract, but in brain areas that (should) activate the motor cortex.

However, previous research shows that fatigue-associated changes can occur at different levels. Mills (1982) described a fatigue-associated reduction in amplitude of the MSAP and a change in spectral analysis of the EMG with a prolonged

relaxation time, indicative of impaired neuromuscular transmission and impaired muscle metabolism. Other authors found MEP amplitude reductions but not changes in MSAP or F-waves (Kotan et al. 2015). This discrepancy likely comes from varying degrees of muscular fatigue. The firing rate of spinal motoneurons decreases in the exhausted state (Grimby et al. 1981), but this appears to be muscle-specific (Macefield et al. 2000).

1.4 Electrophysiological Methods for the Investigation of Fatigue

1. **Quantification of EMG activity** by registration of the EMG frequency spectrum.
2. **Peripheral electrical nerve stimulation:** This procedure tests the neuromuscular synapse, the responsiveness of the muscle, and the conductivity of the peripheral nerve. The amplitude of the compound action potential (CAP) is evaluated.
3. **Amplitude of the motor evoked potential (MEP)** generated by transcranial magnetic stimulation (TMS) over the primary motor cortex. In exhaustive tasks, it is necessary to also determine the compound action potential and to display the amplitude as a quotient (MEP amplitude/CAP amplitude), since an exhaustion-induced decrease in the amplitude of the CAP (Mills 1982) also has effects on the MEP amplitude (Kalmar and Cafarelli 2004).
4. **Central motor conduction time** as an indication of the conductivity of central motor nerve pathways.
5. **Cortical silent period (CSP):** The CSP that can be derived during voluntary pre-innervation of the target muscle, which appears as a passive innervation silence after a TMS impulse, is most likely mediated by GABA-B activity. A longer CSP indicates a stronger inhibition of predominantly cortical neurons.
6. **Short intracortical inhibition (SICI):** Transcranial magnetic double stimuli with a subthreshold first and suprathreshold second impulse and an interval of 1–5 ms can detect the cortical inhibition most likely mediated by GABA A. SICI is one type of cortical inhibition.
7. **Intracortical facilitation (ICF):** Transcranial magnetic double stimuli with a subthreshold first and suprathreshold second impulse and an interval of 10–15 ms can detect the cortical facilitation most likely mediated by glutamate.
8. **Long interval intracortical inhibition (LICI):** Two suprathreshold transcranial magnetic impulses, 100 ms apart, test the long-latency cortical inhibition most likely mediated by GABA B. The LICI is a cortical inhibition of the cranial motor system. However, using electrical stimulation at the cervicomedullary junction, McNeil et al. (2009) demonstrated that LICI is also influenced by spinal mechanisms.
9. **Evoked potentials:** Mainly visual evoked potentials (visual stimulation by viewing a screen with an alternating checkerboard pattern, VEP) and somato-

sensory evoked potentials (electrical stimulation of a peripheral nerve and recording over the somatosensory cortex, SSEP) are used.

10. **High frequency oscillations (HFO)** are waves with frequencies around 600 Hz that are superimposed on the potential of the median nerve SSEP. The early part of these waves is attributed to neuronal activity in the thalamus, the late part is based more on cortical neuronal activity.
11. **Event-related synchronization (ERS) and event-related desynchronization (ERD)** as changes in the amplitude of the EEG-derivable alpha activity. These changes are triggered, for example, by a movement.
12. **Event-related potentials (ERP),** which arise as responses of the brain to different stimuli. Auditory stimuli are most commonly used in the so-called oddball paradigm. Two sounds are presented at different frequencies, and the brain responds in particular to the infrequently presented (unfamiliar) sound.

2 Electrophysiological Findings in Healthy Subjects

2.1 Corticospinal Excitability

Corticospinal excitability, measured by the amplitudes of motor evoked potentials, shows a biphasic course when measured repeatedly *during* an exhaustive task. Initially, there is an increase in corticospinal excitability, and as exhaustion and force reduction increase, excitability decreases below baseline levels. Two phases can also be delineated *after completion of* an exhaustive motor task: First, there is a "post-exercise facilitation" with higher MEP amplitudes lasting for 30–60 seconds, followed by a much longer phase of "post-exercise depression" lasting up to 30 minutes with MEP amplitude reduction (Samii et al. 1996; Liepert 2009).

2.2 Intracortical Excitability

Exhaustive activity of the interosseus dorsalis I muscle showed that the SICI initially increased, then decreased with increasing force reduction. This change was specific to the muscle involved in the exhaustive task (Benwell et al. 2006). Other authors (e.g., Maruyama et al. 2006; Williams et al. 2014; Hunter et al. 2016; Latella et al. 2020) also found SICI reduction which reflects intracortical disinhibition. Hunter et al. (2016) examined the time course following completion of the exhaustive task (elbow flexions) and found that SICI reductions were still detectable 2 min after task completion, but then recovered within a further 5 min. ICF was only reduced within the first 2 min after task completion. Latella et al. (2020) indicated that Group III/IV muscle afferents were not involved in the changes in SICI. Sharples et al. (2016) not only examined corticospinal excitability, SICI, and ICF after a fatigue-inducing index finger abduction task, but also attempted to reverse fatigue-induced effects by 5 Hz-rTMS over the supplementary motor area. The authors

found a fatigue-induced reduction in corticospinal excitability, a (compensatory?) increase in ICF and decrease in SICI, and a partial normalization of these effects by rTMS administration.

SICI changes do not only affect the motor cortex involved in the exhaustive task. Takahashi et al. (2009) found a reduction of SICI also in the ipsilateral motor cortex and related this to a modulation of interhemispheric inhibition by fatigue. Bäumer et al. (2002) described a reduction in ICF in ipsilateral motor cortex for several minutes in homologous non-exhausted muscle. A transient reduction in MEP amplitude was also described (Humphry et al. 2004). In contrast, other studies (McKay et al. 1995; Samii et al. 1997) found no excitability changes for the homologous unexercised muscle.

The largely consistent SICI reduction found in the primary motor cortex, which is predominantly considered compensatory, may have a negative aspect, as Bächinger et al. (2019) postulate that disinhibition ("surround disinhibition") leads to more untargeted activation of muscles and thus may promote fatigue.

2.3 Cortical Silent Period

Aboodarda et al. (2019) examine fatigue-induced changes in other TMS parameters and found a prolongation of the cortical silent period immediately after an exhaustive elbow flexion task, but the change showed regression after 15 seconds. An exhaustive quadriceps muscle task also showed a prolongation of the cortical silent period, which recovered within 2 min, whereas maximal force did not fully recover over 6 min (Gruet et al. 2014). Temesi et al. (2019) also found a prolongation of the cortical silent period after both exhaustive elbow flexions and knee extensions for the respective target muscle. Goodall et al. (2018) described a prolongation of the CSP but no change in the SICI in the when recording from the M. quadriceps after exhaustive repetitive contraction of the knee extensors and concluded that fatigue affected GABA-B receptors but not GABA-A receptors.

However, a lengthening of the cortical silent period was not found by all research groups. O'Leary et al. (2018) found a *shortening of the* cortical silent period during an exhaustive ergometer task, which was interpreted as an expression of reduced inhibition.

Williams et al. (2014) demonstrated in a very complex experimental setup with transcranial magnetic and electrical stimulations at the cervicomedullary junction that there is decreased excitability of the alpha-motoneuron pool with increasing fatigue (elbow flexions). The prolongation of the CSP was interpreted as a predominantly spinal phenomenon. Stimulations of the motor cortex showed higher MEP amplitudes and decreased SICI reflecting increased excitability in the primary motor cortex. The fatigue-induced decrease in strength was attributed to both reduced spinal excitability and insufficient activation of the motor cortex by (frontal?) networks.

2.4 Potential Influencing Factors

There are no sex differences for fatigue-associated changes in corticospinal and spinal excitability (Yacyshyn and McNeil 2020). There were also no differences between unilateral and bilateral exhaustive knee extension in excitability studies (Koral et al. 2020).

In contrast, a decrease in spinal excitability of varying magnitude was described when comparing elbow flexions and knee extensions. The reduction in excitability was more pronounced for the upper extremity (Temesi et al. 2019). However, another research group demonstrated that a decrease in spinal excitability also exists in motoneurons representing the femoral nerve (Finn et al. 2018).

The intensity of the TMS stimulus may have an influence on the outcome: Bachasson et al. (2016) showed that MEP increases or MEP reductions were elicited depending on the stimulus intensity. The authors therefore suggested that more than a single TMS stimulus intensity should be applied. Similarly, Temesi et al. (2014) demonstrated through studies of endurance runners that changes in MEP amplitudes were detectable with one TMS stimulus intensity and changes in the duration of CSP were detectable with another stimulus intensity.

Age had an influence on the expression of supraspinal fatigue: old subjects (72 years on average) showed smaller increases in MEP amplitudes and a smaller increase in CSP than young subjects (20 years on average) (Yoon et al. 2012).

The motor task may play a relevant role, as writing (especially block letters) resulted in a greater increase in ICF than when isometric finger abductions were performed (Cinelli et al. 2019). Examination of semi-professional football players before and after a 90-minute game showed detectable reductions in strength as late as 48 hours later, but no change in SICI (Brownstein et al. 2017).

3 Electrophysiological Findings in MS Patients

3.1 Corticospinal Excitability

The first TMS study in MS patients with fatigue showed that during an exhaustive task, despite decreasing strength, the TMS parameters (MEP amplitudes and latency) remained the same, so that the muscular weakness was not due to a conduction disturbance of corticospinal pathways (Sheean et al. 1997). In fact, it has been reported that in MS patients, during submaximal fatigue-inducing tasks for both the upper and lower extremities, there was a greater increase in MEP amplitude than in healthy controls as a reflection of a greater increase in excitability of the corticospinal system (Thickbroom et al. 2006, 2008). Post-exercise facilitation was also more pronounced during non-exhaustive motor tasks than in healthy subjects (Nielsen and Nørgaard 2002). However, other authors found no difference in post-exercise facilitation between MS patients with and without fatigue and healthy individuals (Perretti et al. 2004). Liepert et al. (2005) described similarly pronounced MEP amplitude reductions in MS patients with and without fatigue and healthy

individuals after a highly exhaustive task, so that no additional effect due to fatigue complaints was apparent. However, recovery, measured as the time to normalization of the initially elevated motor threshold, correlated with the fatigue severity scale score (Liepert 2009). Other authors also found a MEP amplitude reduction in MS patients after an exhaustive task, which was less pronounced under interferon treatment (White and Petajan 2004).

3.2 Intracortical Excitability

There are heterogeneous results on these parameters: Liepert et al. (2005) described a decreased SICI in MS patients with fatigue already before the exhaustive task and considered this as a compensatory mechanism. Morgante et al. (2011) found comparable SICI and ICF values in MS patients with and without fatigue and in healthy controls, whereas Chalah et al. (2019) published a SICI reduction in MS patients without fatigue, but no changes in other TMS parameters such as ICF. Conte et al. (2009) showed that SICI changes depend on MS disease, among other factors: Patients with a secondary progressive course, compared with patients with a relapsing course, had a SICI reduction; the magnitude of SICI reduction was higher with a higher EDSS score.

3.3 Cortical Silent Period (CSP)

Chaves et al. (2019) found a correlation between prolongation of CSP and the extent of subjectively perceived fatigue.

3.4 Event-Related Potentials

In a study of MS patients with fatigue examined in the relaxed and exhausted states, it was found that exhaustion was accompanied by prolonged reaction times, whereas event-related potentials had shorter latencies and higher amplitudes. The excitability of the corticospinal system remained unchanged. The authors postulated that fatigue must involve neural processes between stimulus evaluation and activation of the motor cortex (Sandroni et al. 1992).

3.5 "Event-Related Desynchronization"

Leocani et al. (2008) found a correlation between the severity of fatigue, as measured by the fatigue severity scale, and the extent of ERD during exercise, and a negative correlation with ERS after exercise, and interpreted these results as indicating (compensatory?) overactivity of frontal networks. The same research group previously showed that MS patients with fatigue had weaker ERS after thumb extension movements (Leocani et al. 2001).

3.6 High Frequency Oscillations

Capone et al. (2019) examined changes in high-frequency oscillations overlying the median SSEP, which can be divided into early (most likely thalamic-related) and late (most likely originating in somatosensory cortex) components. MS patients with fatigue showed a reduction in the early component after an exhaustive task, suggesting impairment of thalamic but not cortical networks.

3.7 Fronto-Thalamic Networks

An Italian research group (Morgante et al. 2011; Russo et al. 2017) postulated that fatigue is caused by impairment of fronto-thalamic networks, as MS patients with fatigue exhibited reduced motor excitability just prior to movement initiation and this lack of facilitation prior to movement correlated with subjective fatigue severity. Also, Mordillo-Mateos et al. (2019) postulated, based on the fact that MS patients with fatigue exhibited similar levels of fatigue as healthy controls but, unlike healthy individuals, did not show significant MEP amplitude reduction, that the feeling of fatigue in patients does not originate from the primary motor cortex but from brain regions that influence the motor cortex. This fits with a study that examines the influence of attention on the induction of plasticity (Conte et al. 2016). In three groups of subjects (healthy, MS patients without fatigue and with fatigue), repetitive TMS (5 Hz) was used to try to increase the excitability of the motor cortex. MS patients showed no rTMS-induced increase in excitability. When rTMS was performed again during an attention-demanding task, an increase in excitability occurred in patients without fatigue but not in MS patients with fatigue. The authors concluded that fatigue has a negative influence on attention-associated cerebral networks.

4 Effects of Therapeutic Approaches on Electrophysiological and Clinical Parameters in MS Patients

4.1 Pharmacological Therapeutic Approaches

In one RCT, fampridine (20 mg/day) or placebo was administered for 8 weeks to 40 MS patients (mean EDSS: 6.0) with upper extremity(s) impairment. The primary outcome parameter was defined as the Nine-Hole Peg Test at 4 weeks, and secondary parameters included visual evoked potentials, somatosensory evoked potentials, and motor evoked potentials, as well as determinations of motor thresholds and transcranial magnetic double stimuli. Fampridine had no influence on any of the parameters recorded (Marion et al. 2020).

An open-label study of eight MS patients with fatigue examined MEP latencies and amplitudes (derived from the adductor pollicis muscle) before and after 3 weeks of treatment with 3,4 diamino-pyridine. Six of eight patients reported improvement

in fatigue, but electrophysiological parameters remained unchanged, so the effects of 3,4 diamino-pyridine do not appear to occur at the corticospinal tract (Sheean et al. 1998).

Twenty-one patients with MS and fatigue underwent 8 weeks of placebo-controlled treatment with modafinil. In the modafinil group, there was an increase in intracortical excitability (measured by double stimulus TMS) and a reduction in fatigue. Motor thresholds and cortical silent periods, however, remained unchanged (Lange et al. 2009).

In ten MS patients with fatigue (FSS values between 3.8 and 7) and ten healthy subjects, CSP was determined before and after an exhaustive finger-tapping task. The patients had a shortened CSP (= lower inhibition) before the motor task, but after fatigue there was no longer any difference to the healthy subjects, as the CSP lengthened in patients but shortened in healthy subjects in the post-measurement. Subsequently, MS patients were treated with amantadine for 3 months and then again subjected to the exhaustive finger-tapping task. At the baseline time point, CSP tended to be longer after amantadine use, more in line with values in healthy individuals. CSP changes correlated with changes on the Fatigue Severity Scale (FSS) (Santarnecchi et al. 2015).

In summary, no consistent pattern can be identified with regard to drug-associated changes in electrophysiological parameters. However, different substances were tested, thus, it is possible that the reported changes are substance-specific and that results cannot be generalized for all studies.

4.2 External Brain Stimulation

4.2.1 Transcranial Direct Current Stimulation (tDCS)

Several studies have used anodal tDCS to reduce fatigue symptoms. An Italian study group using custom-made electrodes placed over the primary somatosensitive cortex reported significantly greater fatigue reduction with verum stimulation compared to placebo stimulation (Tecchio et al. 2015; Cancelli et al. 2018). A recent meta-analysis that included eleven tDCS studies concluded that tDCS can be effective against fatigue and that the relatively best evidence exists for a stimulation intensity of 1.5 mA and electrode placement over the primary somatosensitive cortex (Liu et al. 2019). Capone et al. (2020) also compiled the studies published up to early 2020 and described the left dorsolateral prefrontal cortex as another stimulation site, with three positive studies contrasting with two others with negative results. In summary, the data situation is still too limited and heterogeneous to recommend the treatment of fatigue with tDCS.

In healthy individuals, a recent study using anodal tDCS found no effect on fatigue perception or corticospinal excitability (Wrightson et al. 2020).

4.2.2 Repetitive Transcranial Magnetic Stimulation (rTMS) and Intermittent Theta Burst Stimulation (iTBS)

The evidence base is still relatively weak; three studies used different stimulation sites (motor cortex, left prefrontal cortex), different coils, and different stimulation

methods (rTMS or iTBS). Therefore, it is not yet possible to decide whether or which approach is promising (Capone et al. 2020).

In conclusion, it would be desirable for an effective intervention if more was known about the pathophysiology and the brain areas involved in fatigue development, so that more hypothesis-driven stimulation could then be undertaken.

5 Summary

The majority of electrophysiological findings during motor exhaustion tasks in healthy subjects indicate that fatigue arises at different levels. In the alpha-motoneuron pool at the spinal level, increased inhibition occurs, which is (partly) responsible for a reduction in corticospinal excitability. In the primary motor cortex, on the other hand, a disinhibition occurs, presumably as a compensatory activity. The activating influence that secondary motor areas should have on the primary motor cortex becomes weaker, which reduces voluntary force development.

MS patients with fatigue also show evidence that the activating influence of the thalamus and secondary, mainly frontal cortex areas on the primary motor cortex weakens during an exhaustive task, leading to a decrease in strength and a reduction in corticospinal excitability (Leocani et al. 2008; Capone et al. 2020). Corticospinal tract function does not appear to be altered in fatigue. Little is known about the influence of spinal motoneuron cells. Peripheral fatigue does not appear to play a significant role.

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Expert Opinion and Medicolegal Assessment

B. Widder

1 Basics of Expert Opinions

In his function as an expert witness, the physician unexpectedly finds himself in a role that is foreign to him due to his usual diagnostic-therapeutic tasks. Whereas in the context of usual medical care the physician concerned assumes that a patient who complains of disorders really has such disorders, the medical expert must critically question this and try to work out the actual extent of health disorders as reliably as possible. In doing so, the medical expert is obligated to objectivity and neutrality, and may represent neither the interests of the insurance involved nor the interests of the claimant of insurance benefits being assessed (Marx and Gaidzik 2019). Whoever cannot accept this different task should reject submitting medicolegal expert opinions.

Socio-medical assessments in the context of rehabilitation measures and medical certificates, e.g., on incapacity for work, are by definition also expert statements. Intentional or grossly negligent false statements may therefore have legal consequences for the issuing doctor in the same way as this applies to expert opinions.

In all areas of law, it should be noted that the claimant of benefits—e.g., for a pension grant or recognition of a severe disability—always has the burden of proof for the existence of the underlying functional disorders. An MS-related fatigability (see Chaps. 5 and 6) and the associated functional disorders must not only be "most likely" to be present or "plausible," but must be provable beyond reasonable doubt in so-called "full proof." If such a proof cannot be achieved, it is usually to the disadvantage of the claimant; an "in dubio pro aegroto" is not provided for in the legal context.

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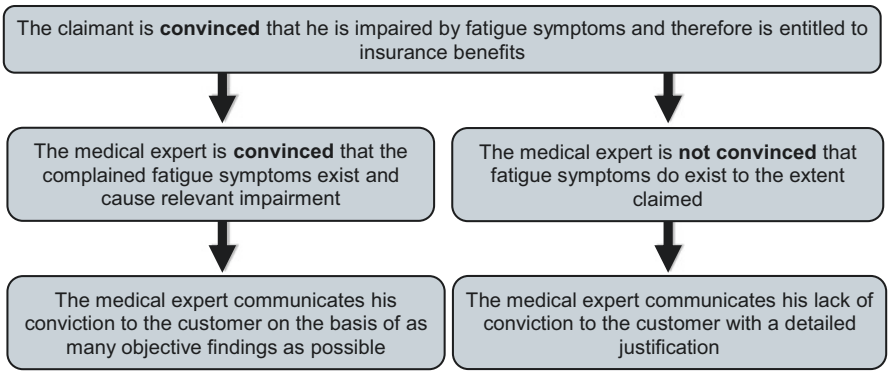

Fig. 1 Options to provide expert opinions

Accordingly, the objectification of MS-fatigability is of decisive importance. It is then the task of the medical expert to convey his conviction gained—or not gained—on the basis of his own examination to the usually non-medical customer of the expert opinion in a comprehensible manner (Fig. 1). Only if he or she succeeds in doing so convincingly, the customer usually will follow the expert's recommendation.

2 Objectification of Fatigability

2.1 Fundamental Aspects

The leading symptoms of multiple sclerosis-related fatigue with exhaustion, abnormal tiredness, and lack of energy are, by definition, primarily subjectively perceived disorders of well-being that correlate only to a limited extent with the "real" impairment due to fatigability (see Chaps. 5 and 6) (Mills and Young 2011; Loy et al. 2017). If one searches for ways to objectify fatigue symptoms, considerable problems arise:

- The extent of fatigability correlates only to a limited extent with the lesion burden seen on MRI.
- Fatigue symptoms may be to a considerable extent subject to motivational aspects (Penner et al. 2007).
- There is a strong overlap with depressive disorders (Greim et al. 2007), the assessment of which may require specific psychiatric competence.
- In expert opinions, it is always necessary to distinguish pathological fatigability from "normal" daytime sleepiness, which, by definition, has no occupationally restrictive character and no degree of disability.

The problem of objectifying subjective complaints is not limited to fatigue symptoms in multiple sclerosis. Comparable situations can also be found in the

assessment of mental disorders such as depression or somatoform disorders, as well as in chronic pain syndromes, if the demonstrable physical findings do not explain the extent of the complained symptoms. For the assessment of mental disorders and pain syndromes, guidelines have been developed by various scientific societies, which can be used by analogy for the assessment of fatigue symptoms (Widder 2017a; AWMF-Leitlinie 051/029 2019).

2.2 Value of Questionnaires

Questionnaires and self-assessment scales (e.g., "Fatigue Severity Scale" [FSS], "Fatigue Scale for Motor Function and Cognition" [FSMC], "Modified Fatigue Impact Scale" [MFIS], "Würzburg Fatigue Inventory in MS" [WEIMuS]), including profiles and scores calculated from them (Beckerman et al. 2020), are useful as screening instruments and for clinical monitoring (Sander et al. 2017). However, they give only an expression of the subjective self-assessment of the person concerned. For obvious reasons, however, such questionnaires do not necessarily represent the true extent of impairment in the expert opinion situation, where the claimant wants his fatigability recognized with the consequence of material compensation. This does not exclude their use, and their use is sometimes even expressly demanded in expert opinions. The physician working in rehabilitation or as a medical expert must, however, be aware of the limitations of such questionnaires and scales and must not make them the (sole) yardstick of his assessment.

2.3 Objectification of Cognitive Fatigability

The literature contains numerous studies on the objectification of cognitive fatigability using various neuropsychological tests. However, due to the limited correlation between cognitive impairment and the presence of cognitive fatigability (Morrow et al. 2009), neuropsychological performance tests such as the PASAT (see Chap. 6) or the SDMT (see Chap. 6) appear to be of only limited suitability for this purpose. Taking into account that the closest correlation exists with sustained attention and vigilance (Hanken et al. 2015), an approach via the following procedures can be recommended:

- **Testing sustained attention** with elaborated alertness tests, but also with simpler tests such as the Trail Making Test [TMT], where the complained decline in performance can be recorded by repeating the tests several times. Since such tests are subject to a possible intentional bias, the results should be additionally verified by specific symptom validity tests (see below).
- **Vigilance testing by** EEG examination preferably at the end of the investigation similar to the "Maintenance of Wakefulness Test" [MWT] commonly used in sleep medicine (Doghramji et al. 1997).

Moreover, the "stress test" of an expert exploration and examination lasting several hours should not be underestimated, as it provides the examiner with essential information regarding sustained attention and responsiveness.

2.4 Objectification of Motor Fatigability

A large number of tests to assess motor fatigability is described in the literature, all of which compare initial motor abilities with those after a more or less long exercise test, or determine after which time period motor deficits appear (Severijns et al. 2017; Van Geel et al. 2019) (see Chap. 5).

2.4.1 Upper Extremities

The hand force test using a spring dynamometer or balloon vigorimeter can be used here, for which extensive standard values are available depending on age and gender (Fig. 2). Repetitive or continuous contractions over a certain period of time or until fatigue appears can be used. After ten repetitive contractions, Greim et al. (2007) described an average decrease in hand strength of less than 5% in healthy

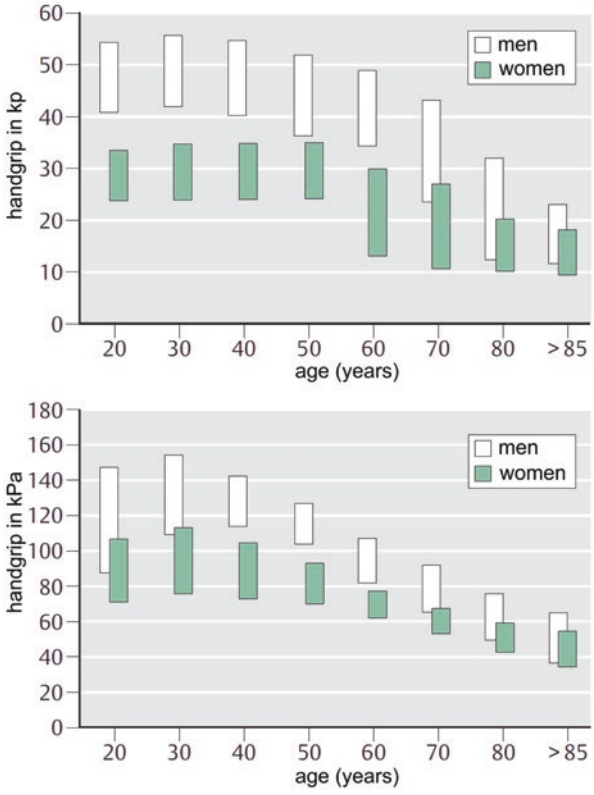

Fig. 2 Published reference values for handgrip testing depending on age and gender (after Widder 2018)

individuals as a reference, albeit with wide variability. Meldrum et al. (2007) found an average decrease of 15% (maximum approx. 25–35%) in healthy subjects after 16 contractions—remarkably strength reduction was more pronounced in younger than in older subjects. The latter started with lower values but maintained them better.

2.4.2 Lower Extremities

Predominantly, examinations of walking ability and gait pattern are used here. The walking times mentioned in the various studies usually vary between two (Gijbels et al. 2012) and 12 min (Burschka et al. 2012). Occasionally, studies with a knee dynamometer can also be found (Surakka et al. 2004), but this can hardly be used in the usual expert situation. The problem with such walking tests is the merely subjective assessment, which requires specific experience in the assessment of motor fatigue. Objectification, however, seems possible by means of video recording and kinematic analysis using ultrasound sensors (Sehle et al. 2011; Sehle et al. 2014) (see Chap. 5), but this as well may be beyond the possibilities of outpatient assessments.

3 Symptom Validity Assessment

3.1 Basics

In recent years, the term "symptom validation" has become established in connection with the objectification of complained functional disorders in expert opinions; the term "consistency assessment" is also used synonymously. Such a symptom validation can be carried out in two ways in the case of complained cognitive and/or motor fatigue symptoms:

- By **direct objectification** on the basis of a suitable longitudinal observation, e.g., in the context of an inpatient rehabilitation stay in a clinic whose staff has experience with the clinical picture of fatigability, and/or on the basis of the results of specific clinical tests that cannot be manipulated in the context of external motivation. As shown above, however, this is hardly feasible in the context of a single outpatient assessment.
- By **indirect objectification** in the sense of so-called "circumstantial evidence," if the entire spectrum of all available findings and observations produces a coherent impression that allows the expert to come to the conviction that the subjectively complained impairments actually exist in the complained extent and can thus be "transferred" into existing functional disorders (see Fig. 1). The more such positive signs can be detected, the more certain it is that the legally required "full proof" can be provided. A compilation of the most important negative signs can be found in the two AWMF guidelines already mentioned which can also be used in the objectification of fatigability.

3.2 Fatigue-Related Symptom Validity Assessment

The following specific findings appear to be relevant to the abovementioned "circumstantial evidence."

3.2.1 Medical History

The uniformity of complained fatigue symptoms in the anamnesis supports an actually existing symptomatology:

- Uniform, paroxysmal occurrence after similar effort and time.
- Uniform phenomenology of the symptomatology.
- Uniform course of the symptoms.

Supplementary criteria can be a diurnal link and/or a temperature dependence (Uhthoff phenomenon). In addition, the following questions help to distinguish between real and motivationally induced complaints:

- Are the complaints recognizably used to enforce one's own wishes for relief and attention towards third parties ("secondary gain of illness")?
- Do fatigue symptoms occur mainly during unpleasant activities, while pleasant activities (e.g., hobbies and leisure activities) are still performed to a considerable extent?
- Is there evidence of a relevant social and/or family withdrawal that supports the illness value of the complained fatigue symptoms?

3.2.2 Cognitive Fatigability

Together with specific neuropsychological symptom validity tests (Merten 2014) several findings of the abovementioned attention and vigilance tests can support or question complaints of cognitive fatigability:

- Does the picture correspond to the expected course when attention tests are repeated several times—even after a recovery phase?
- Do symptoms of cognitive fatigability appear at the end of the "stress test" of a several hours lasting expert assessment, and, if applicable, also in an EEG monitoring under resting conditions?
- Do neuropsychological symptom validity tests—if applicable, also with repetition—show conclusive results?

3.2.3 Motor Fatigability

According to Chap. 5, motor exhaustibility is particularly noticeable at the individual multiple sclerosis "weak spots" that have been damaged by previous relapses or by progression of multiple sclerosis, often concerning a weakness of the hip flexors and/or foot lifting. Accordingly, the following two questions need to be clarified:

- Correlates the demonstrated symptoms during an exercise test with the clinically apparent—possibly very minor—symptoms at rest (reflex status, spasticity) as well as with the documented "weak spots" in the available medical records?
- Is the claimed motor fatigability a reproducible phenomenon with a comparable course?

3.2.4 Clinical Symptom Validation

In addition, it is important to assess the extent to which the other reported sensorimotor deficits of the diseases "fit together" and correspond to pathophysiology. Important "markers" here are, for example, pointing tests and the Romberg standing test (Widder 2017b).

4 Assessing Occupational Capacity

In all forms of statutory and private insurance, the assessment of occupational capacity is usually carried out in four steps:

1. Which **health problems according to ICD-classification exist** "beyond reasonable doubt"?
2. Which qualitative performance limitations (so-called **"negative performance"**) can be proven depending on the specifications of the individual insurance conditions (general labor market or concrete occupational activity)?
3. What residual capacity (so-called **"positive performance"**) still exists and how is this to be assessed in terms of its quantitative extent?
4. How have the performance limitations developed and what **prognosis** is to be made for this—including therapeutic options, if applicable?

4.1 Quantification of Fatigability According to ICF

In each case, the functional impairments (fatigability) caused by fatigue symptoms should be worked out in detail and comprehensibly. The International Classification of Functioning, Disability and Health (ICF), which is authoritative in this regard, does contain a so-called "core set" for multiple sclerosis, but the specific symptoms of fatigability are not included in it. As an "auxiliary construct" in the assessment of occupational capacity, however, the banal fact can serve that affected persons who are impaired by fatigue symptoms during work also show limitations in daily living due to these symptoms. According to ICF, two areas of life must be comprehensively explored in this case:

- Limitations in the activities of daily living (ADL).
- Restrictions on participation in family and social life.

The most important criteria are summarized in the "Mini-ICF APP Social Functioning Scale" (Molodynski et al. 2013).

5 Assessing Driving Ability

5.1 Basics

A risk situation in driving a car usually is to be assumed if

- it is to be expected of a driver that the requirements for driving a motor vehicle, which include a stable performance level and also the mastering of stressful situations, can no longer be mastered due to an **impairment of the physical/mental capacity**, and/or,
- a driver is likely to suffer, within a foreseeable period of time, a **sudden loss of physical/mental faculties** (e.g., epileptic seizures, vertigo attack, syncope), and/or,
- there is no guarantee that the driver will behave in accordance with the rules and **in a safe manner** due to **behavioral disorders** or **lack of insightfulness** or **personality disorders.**

5.2 Driving with Fatigue Symptoms

Although an increased risk of accidents has been described in multiple sclerosis patients (Lings 2002; Schultheis et al. 2002), only isolated data are found on driving ability in the case of fatigue symptoms, which do not appear to be very useful for practical evaluation (Chipchase et al. 2003). It is also known that psychological tests have only limited significance. In case of doubt, a practical driving test or a test in a driving simulator is therefore recommended (Kotterba et al. 2003; Küst and Dettmers 2002). However, the following three approaches appear practicable for a rough assessment.

5.2.1 Orientation towards Self-Perception

Stein and Dettmers (2003) proposed an orientation towards self-perception and insightfulness of the person concerned and thus appeal above all to the personal responsibility of the driver. For medical briefing, this appears to be a viable approach.

5.2.2 Orientation towards Occupational Capacity

For the medical expert who has to assess the driving ability, the problem arises that he or she is only involved when abnormalities in driving are already documented, so that the self-assessment mentioned above has only little probative value. At least as a screening instrument for driving ability, the anamnesis of an **actually** still existing occupational capacity can serve here. If occupational performance is no longer given due to fatigue-related performance restrictions at the workplace, where as a rule short breaks are always possible, it must also be assumed that the driving ability, which requires a continuous ability to concentrate, is hardly given**.** In addition, according to country-specific guidelines, there are increased requirements for driving trucks and busses.

5.2.3 Orientation to Daytime Sleepiness

According to a recent meta-analysis, there is only a modest association between fatigue symptoms and increased daytime sleepiness in multiple sclerosis (Popp et al. 2017). Nevertheless, this may be an important, if not the main problem for driving. Since scores above 10 on the Epworth Sleepiness Scale (ESS) indicate significantly increased daytime sleepiness with increased risk, it can also be used as a screening tool in multiple sclerosis (Powell et al. 2002).

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Part IV

Therapy

Disease Modifying Immunotherapies and Fatigue

Iris-Katharina Penner and H. Schreiber

With a high prevalence of up to 90% (Ayache and Chalah 2017), fatigue is one of the most frequent accompanying symptoms of MS, being (and) associated with considerable negative effects on (the) quality of life and the ability to work of the affected patients (Flachenecker et al. 2017; Kobelt et al. 2017). As has (become clear) been outlined in (from) the preceding chapters on pathophysiology, etiology, and immunopathology, the origin of primary fatigue is still not fully understood. What all scientists agree on is that it is a multifactorial process in which individual predispositions play a role that should not be underestimated (Penner and Paul 2017). The lack of knowledge about the exact causalities has certainly played a decisive role in the fact that no targeted symptomatic therapy has been developed so far (see especially the following chapter). Thus, there is no approved drug therapy for MS-associated fatigue. Hence, the question whether there are direct or indirect positive or negative effects of MS immunotherapies on fatigue becomes more important. Positive secondary effects of MS therapeutics on fatigue would be very helpful in clinical practice from both the practitioner's and the patient's point of view, whereas negative effects, especially in fatigue-prone patients, should be avoided whenever possible. In answering this question, one is largely dependent (there is a strong reliance) on open follow-up studies and registry data. Fatigue has also been defined as a secondary outcome variable in some randomized controlled trials. However, to our knowledge, there is currently no study in which fatigue has

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been defined and tested as a primary outcome variable in a controlled design. The following statements and comments provide an overview of current data on the relation of disease-modifying therapies (DMTs) and fatigue.

1 Immunotherapies for Mild/Moderate Forms of MS

1.1 Interferons

Randomized clinical studies to clarify the question of whether beta-interferons have a primary effect on fatigue in the treatment of MS do not exist to date. However, it is considered undisputed that fatigue while using interferons is a known side effect, which was initially described as "asthenia" (Jacobs et al. 1996) and later subsumed under the term "flu-like symptoms." These usually occur 3–6 h after the injection and subside within 24 h thereafter (Walther and Hohlfeld 1999). The cause is assumed to be a temporary upregulation of proinflammatory cytokines and mediators such as interleukin-6 (IL-6), IFN-γ, and prostaglandin (Arnason and Reder 1994; Brod et al. 1996; Dayal et al. 1995). Nevertheless, fatigue is a rather frequently occurring enduring side effect of IFN therapy in MS, which might overlap with a subtle depressive state with vital deficit, not unfrequently observed at the same time. A non-blinded study investigating the side effect profile of interferon beta-1b showed that fatigue was one of the symptoms significantly associated with IFN therapy (Neilley et al. 1996). In addition, a regression analysis showed that fatigue and the interaction between fatigue and depression were factors that significantly contributed to discontinuation of therapy. Based on these results, it was explicitly pointed out that the side effects fatigue and depression should be seriously considered, as they have a decisive influence on the drop-out rate. A review published by Filippini et al. (2003) confirms the increased rate (occurrence) of fatigue in connection with interferon treatment. And at least a transient occurrence of the symptom fatigue was documented in five of the seven papers studied.

The **PRISMS study**, a large randomized, placebo-controlled, double-blind trial, compared interferon (IFN-)beta-1a (in two doses) against placebo in 267 patients with relapsing-remitting MS (RRMS) over 2 years. Fatigue was investigated as a therapy-associated secondary outcome parameter. After 3 months, there was no significant difference between interferon and placebo (Ebers et al. 1998). Thus, no direct evidence of any significant association between fatigue and IFN-1a could be found in this study.

An **Italian study** investigated the effect of interferon therapy on quality of life (MSQoL-54), fatigue (FSS), and depression (BDI) in 41 treated versus 77 untreated MS patients. After 2 years, both groups showed a worsening of fatigue and quality of life, but unlike some aspects of quality of life, this did not significantly discriminate between groups. Thus, no negative group-specific interferon effect could be demonstrated here either (Simone et al. 2006).

The **COGIMUS study** was a perennial, multicenter, open-label observational study that enrolled RRMS patients on first-time treatment with interferon beta-1a s.

c. at the two approved doses (22 g, 44 g) or placebo and evaluated the interferon effect on quality of life, depression, and fatigue. After 3 years, no significant change in fatigue, as measured by the Fatigue Impact Scale (FIS) by Fisk et al. (1994), was observed in the 331 IFN patients evaluated at either dose (treatment groups) compared to baseline. However, the severity of fatigue was very low in (across) the total patient cohort at all time points, raising the question of possible selection bias (Patti et al. 2011). In a subsequent five-year analysis, no fatigue results were reported, so that no conclusions can be drawn about the long-term effects of IFN-1a on fatigue beyond 3 years (Patti et al. 2013).

A **Canadian study** focused on a prospective clinical follow-up period under various interferons. Fifty RRMS patients were adjusted to different interferons after an observation period of 3 months. After 6 months of subsequent treatment, the 40 patients remaining in the study showed a trend towards reduced fatigue, although after 12 months follow-up this effect was evident only with one of the three IFN preparations (IFN-1a s.c.) (Melanson et al. 2010). Due to the small treatment groups, these data serve only as an orientation.

Specific study data on the occurrence of fatigue during pegylated interferon (IFN-peg) therapy have not been published to date.

1.2 Glatiramer Acetate

The study by Metz and colleagues is a seminal study since it compared the effect of three interferons (which were subsumed into one interferon group for the evaluation) versus glatiramer acetate on fatigue sensation (experience) in MS patients (Metz et al. 2004) (Fig. 1). The Fatigue Impact Scale (FIS) by Fisk et al. (1994) was used as a measure for fatigue. Fatigue was assessed at baseline and again after 6 months as part of a cohort study in 218 de novo MS patients (61% on glatiramer acetate [GLAT], 39% on interferon beta). At baseline, fatigue scores were comparable in both groups. After 6 months of treatment, improved fatigue was evident in 24.8% of GLAT patients but only in 12.9% of IFN-treated patients, indicating a significant advantage in favor of the GLAT group. The improvement was demonstrated for both dimensions, cognitive and physical fatigue. In contrast, worsening of fatigue in both treatment groups occurred in only about 8% of patients. However, due to the lack of randomization, the two treatment groups were not fully comparable. Specifically, IFN patients had a higher EDSS score, were older and had more secondary chronic progressive MS. The often postulated superiority of GLAT with respect of a more positive effect on fatigue compared to interferons, however, could not be substantiated in this study due to the lack of randomization. Nevertheless, individual clinical experience and case reports suggest this. They report on significantly reduced fatigue experience after switching from IFN to GLAT in individual fatigued MS patients.

Another study investigated the extent to which glatiramer acetate affects fatigue and work capacity in de novo treated MS patients (Kern et al. 2007; Ziemssen et al. 2008). Two hundred ninety-one hitherto untreated patients with relapsing-remitting

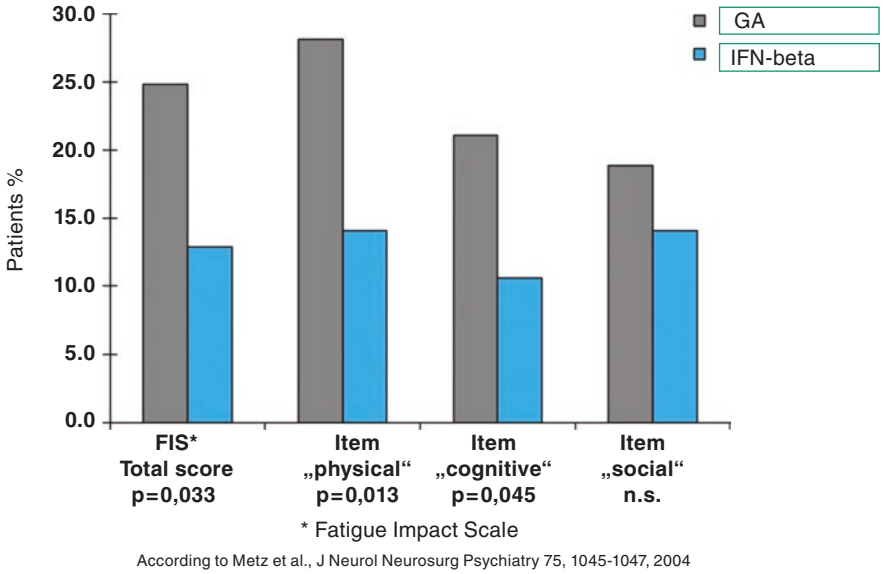

Fig. 1 Comparison of the influence of interferon-beta and glatiramer acetate on the different fatigue dimensions after 6 months of therapy. *FIS* Fatigue Impact Scale (according to Metz et al. 2004)

MS were included in the study and followed for 12 months. A comparison between baseline and one-year data showed a significant reduction in subjectively experienced physical, cognitive and psychosocial fatigue, as assessed by the Modified Fatigue Impact Scale (MFIS). In addition, the number of patients without days off work doubled already in the first 3 months after the start of therapy. The extent to which the reduction of fatigue had a decisive direct influence on this remains however open. In summary, it can be concluded from these two studies that glatiramer acetate appears to have a favorable effect on the patients' perception of fatigue.

The **FOCUS study** (Jongen et al. 2007) also investigated the long-term effect of glatiramer acetate on fatigue in MS patients with relapsing forms of the disease. One hundred ninety-seven patients were observed in a prospective, international, multicenter, open-label phase IV study at intervals of 6 months over a period of 1 year. A group of therapy-naïve patients was compared with a group of patients that had already been treated with immunomodulators. After 12 months of treatment with glatiramer acetate, a significant reduction in fatigue symptoms in all three dimensions of the FIS was demonstrated for the total group of patients compared to baseline. However, this significant effect was only seen in therapy-naïve, but not in pretreated patients, and it was stable at 12 months follow-up. Thus, the favorable effect of glatiramer acetate on MS fatigue reported by the Metz group (Metz et al. 2004) could not only be confirmed, but also verified as an enduring effect over 12 months.

However, another study by Putzki et al. (2008), in which 320 patients from a wide variety of treatment groups (no therapy [41%], immunosuppressive therapy [15.3%], immunomodulatory therapy [35%], other therapy [8.8%]) were compared regarding the prevalence and severity of fatigue, did not show any superiority of glatiramer acetate in terms of a lower incidence of fatigue compared with the interferons and also immunosuppressive treatments. However, as this was a cross-sectional study, the question concerning the development of fatigue across time cannot be answered.

1.3 Dimethyl Fumarate

Fatigue was not recorded as a specific endpoint in the two pivotal phase III studies **(DEFINE and CONFIRM**) with dimethyl fumarate (DMF). Fatigue was, however, documented in the spectrum of side effects and has proved to be, with an incidence of 10%, at placebo level (9%). There were also no relevant differences to the glatiramer acetate (GLAT) arm of the CONFIRM study (9%). Likewise, fatigue did not appear among the most common adverse events leading to discontinuation of therapy with DMF (Fox et al. 2012; Gold et al. 2012). The extension study of DEFINE and CONFIRM **(ENDORSE)** also documented a long-standing low incidence of fatigue (9–2%) across 6 years of observation. Although no data are available on the degree of fatigue, it is evident that fatigue was not a relevant reason for discontinuation in the further course of therapy with DMF (Gold et al. 2016).

Further study data derived from DEFINE and CONFIRM underline the favorable side effect profile of DMF regarding fatigue. A post-hoc analysis of these two studies, which focused on 678 newly diagnosed relapsing-remitting MS patients (RRMS) who were considered being particularly susceptible to fatigue, confirmed a low incidence of fatigue at 9% (Gold et al. 2015). When health-related quality of life (HRQoL) as assessed by SF-36 (Short Form Health Questionnaire) and EQ5D-VAS (European Quality of Life 5 Dimensions) was considered, HRQoL remained stable or even improved over time relative to baseline with DMF, whereas it worsened in placebo-treated patients. The difference between DMF- and placebo-treated patients turned out to be even significant for most subdomains of quality of life, which was especially true for the subdomain "vitality," which is closely related to fatigue (Kita et al. 2014).

This favorable data may have contributed to the fact that no controlled studies, neither placebo-controlled nor direct comparisons to other MS immunotherapies, have been available to date examining fatigue as a primary target parameter. However, a look at "real-world" data essentially confirms the favorable profile of DMF as reflected by the pivotal and extension studies. Thus, in a study of 55 RRMS patients in which fatigue and depression were systematically assessed with a self-reported instrument (Symptom MScreen), no significant difference was found before and after DMF therapy initiation (Pandey et al. 2017). Also, the first interim

analysis of 3000-patients from the **ESTEEM** global observational study tracking the long-term safety and efficacy of DMF across 5 years of daily treatment, reported that the level of self-rated fatigue, as measured by the modified 5-item Fatigue Impact Scale (MFIS-5), remained stable at low levels compared with baseline across the 24-month observation period (Giles et al. 2018). Another open-label phase IV study of 925 RRMS patients, which focused on patient-reported outcomes (PROs) as well as clinical parameters, DMF demonstrated significant improvement in fatigue (MFIS-5), work productivity, and HRQoL after 12 months compared to baseline (Berger et al. 2019).

Thus, the pivotal studies and real-world data unanimously confirm the clinical impression that DMF therapy in MS is not associated with an increased risk of fatigue.

1.4 Teriflunomide

The effects of teriflunomide on MS-associated fatigue are fairly well studied. There are four randomized controlled trials in which fatigue was defined as a secondary endpoint. Three of the studies investigated teriflunomide versus placebo, one study focused on a comparison in efficacy between teriflunomide and one interferon.

In the **TEMSO study,** 1088 RRMS patients were randomized 1:1:1 to 7 mg or 14 mg teriflunomide or placebo, respectively, and followed for 2 years (108 weeks). Fatigue was assessed using the Fatigue Impact Scale (FIS). All patient groups reported discretely higher FIS scores in the course of the study compared to baseline. There were, however, no significant group differences (O'Connor et al. 2011).

A very similar design was pursued by the **TOWER study**, which also involved double-blind, randomized assignment to the three treatment groups (7 mg or 14 mg teriflunomide or placebo). However, the observation period was only one year (48 weeks). Despite a positive effect again on the classic clinical and MRI endpoints, as in TEMSO, TOWER showed a slight increase in fatigue in all treatment groups, although without statistical relevance (Confavreux et al. 2014). However, compared to the placebo group, a significantly smaller increase in the FIS score was demonstrated for the patients treated with teriflunomide.

A similar picture can be drawn from the **TOPIC study**, which investigated the effect of teriflunomide in patients after a *first clinical episode* (clinical isolated syndrome/CIS) (Miller et al. 2014). In this study, patients were again randomly assigned to the three known treatment groups (teriflunomide 7 mg or 14 mg or placebo) in a double-blind manner. The observation period was 2 years (108 weeks). Again, both treatment groups and placebo developed comparably with respect to fatigue, in terms of a slight decrease in the FIS value in each group.

Overall, no significant direct influence of teriflunomide on fatigue during the course of treatment could be detected. Moreover, the studies indicate that fatigue is not a relevant side effect of teriflunomide.

In a non-blinded comparative study of teriflunomide versus interferon beta-1a **(TENERE study),** a moderate increase in fatigue was seen in mostly de novo

patients across an average period of 15 months, with this effect tending to be most pronounced in the INF group. However, a significant difference between IFN and teriflunomide could not be observed, not even with regard to fatigue gain, as reported in the TOWER study (Vermersch et al. 2014).

Finally, the global, multicenter, open-label, phase IV **Teri-PRO** trial collected data from RMS patients who were switched to teriflunomide from other immunotherapies in a real-word clinical setting using PROs ("patient-reported outcomes") (Coyle et al. 2018). One thousand patients received teriflunomide across a 48-week follow-up period. The primary outcome was patients' overall satisfaction with treatment as measured by the Treatment Satisfaction Questionnaire for Medication (TMSQ [Atkinson et al. 2004]). Fatigue was not assessed by a specific fatigue questionnaire, but was included in the MSPS (Multiple Sclerosis Performance Scale; Marrie and Goldman 2007; Schwartz et al. 1999) like other symptoms. After 48 weeks, there was a slight shift in fatigue severity towards less severe fatigue symptoms from the patients' perspective.

2 Immunotherapies for (Highly) Active Forms of MS

2.1 Fingolimod

Robust data that advocate an essentially neutral treatment-accompanying effect of fingolimod on fatigue in MS were obtained from the controlled phase III pivotal studies **FREEDOMS**, **TRANSFORMS,** and **FREEDOMS II.** In these studies, fatigue occurred with approximately the same frequency with fingolimod as in the placebo groups and even the comparative interferon beta-1a (i.m.) group of the TRANSFORMS study (Calabresi et al. 2014; Cohen et al. 2010; Kappos et al. 2010).

Evidence of favorable effects of fingolimod on fatigue come from a 6-month, placebo-controlled phase II study in which health-related quality of life (HRQoL) and depressive symptoms were examined as primary outcomes across 6 months in RRMS patients (Montalban et al. 2011). This study showed a significant positive effect of fingolimod 1.25 mg versus placebo on the fatigue/thinking subdomain of the Hamburg Quality of Life Questionnaire for MS (HAQUAMS). However, these data have not yet been replicated in a larger placebo-controlled study with fatigue as primary outcome measure.

However, there is a prospective, open-label l study in which the change in fatigue score was defined as the main outcome variable and analyzed in the context of 6 months of fingolimod therapy using several fatigue scales. The primary outcome parameter was the Modified Fatigue Impact Scale (MFIS), while the Fatigue Severity Scale (FSS) and the Visual Analogue Scale for Fatigue (VAS-F) were used as secondary outcome parameters. However, no significant change was found in the three fatigue scales at month 6 compared to baseline in the 54 patients who completed the study (Masingue et al. 2017).

On the other hand, there is evidence that a switch in therapy to fingolimod may have a positive effect in terms of fatigue. This is suggested by an open-label

American multicenter study **(EPOC),** which investigated the effects of a change from classic MS injection therapies to fingolimod (Fox et al. 2014). This study involved 1053 randomized patients with MS in a 3:1 ratio to fingolimod or to their previous injection therapy. In addition to benefits as expressed by better health-related quality of life and less depression, there was also minor fatigue sensation (FSS) after having switched to fingolimod. In the group that remained on their injection therapies, fatigue did not change. In a post-hoc analysis, the therapy change was reanalyzed in relation to the respective pre-medication (Calkwood et al. 2014). This showed that the reduction in fatigue was significant if the therapy change was made from subcutaneously applied beta-interferon preparations. A switch from intramuscularly applied beta-interferon only caused a tendency, but not a significant improvement in fatigue. Patients who switched from glatiramer acetate to fingolimod showed the least benefit.

From this data, it can be concluded that fingolimod is likely to have no relevant direct effect on MS-associated fatigue, but that switching therapy from beta-interferons to fingolimod may bring about a positive effect on fatigue.

2.2 Cladribine

No systematic investigations assessing the effect of cladribine on fatigue have been published. In ongoing studies (e.g., CladQoL, Clarity) with a focus on quality of life, fatigue is assessed alongside other PROs, so that information addressing the relationship between medication and fatigue will be available in the near future.

2.3 Natalizumab

Natalizumab (NTZ) was the first human monoclonal antibody that has been approved for the treatment of highly active relapsing-remitting MS in the following patient populations:

(a) patients with high disease activity despite appropriate treatment with an interferon beta preparation or glatiramer acetate.
(b) patients with rapidly progressive relapsing MS.

This restricts the evaluation of how natalizumab may act on fatigue to a special patient clientele and makes the comparison to first-line therapies difficult. Nevertheless, there is some interesting data concerning this topic.

Thus, in an observational study conducted by Putzki and colleagues (Putzki et al. 2007), 34 patients were treated with natalizumab and observed with regard to the medication effect on fatigue, depression, and quality of life across a period of 6 months. Fatigue was measured with the FSS (Krupp et al. 1989) and the MFIS (Multiple Sclerosis Council for Clinical Practice Guidelines 1998). While both scales showed no NTZ effect after 3 months of treatment, a significant reduction of

fatigue was demonstrated after 6 months. Interestingly, the MFIS showed the most significant NTZ effect for the motor subscale, while cognitive and psychosocial fatigue were much less positively affected. It can be assumed from this, that cognitive fatigue might be more refractory to the anti-inflammatory effect of natalizumab and that a longer observation period might have recorded a more positive effect on the cognitive fatigue dimension as well. The authors concluded that MS fatigue may significantly improve during treatment with natalizumab.

In another prospective, open-label and uncontrolled study, 42 MS patients (mean age 35.1 years, 60% female, mean EDSS 3.7) were followed across a period of 6 months. Fatigue was assessed with the MFIS and the FSS, and subjective well-being was assessed with a visual analogue scale (VAS). The mean total MFIS score was 45.8 (SD = 17.5) at baseline and decreased significantly to 40.1 (SD = 118.0) at 6 months follow-up ($p < 0.01$). Mean VAS scores for well-being increased from 5.5 (SD = 11.9) to 6.1 (SD = 12.1) at month 6 ($p < 0.01$). The annual relapse rate decreased from 2.2 prior to treatment to 0.2, and gadolinium-enhancing lesions were reduced by 96% with natalizumab. Interestingly, there was no correlation between gadolinium-enhancing lesions and fatigue scores. The conclusion from this study was that both fatigue and quality of life (well-being) may benefit after therapy initiation with NTZ.

The **ENER-G study** was a 12-month, open-label, single-arm observational study that monitored fatigue and cognition in patients with relapsing-remitting MS across 12 weeks. Primary endpoint was the VAS scale for fatigue (VAS-F); also MFIS and FSS were applied, as well as a cognitive test battery. Eighty-nine patients were included in the study who had at least used two previous MS therapies. At 12 weeks follow-up, significant improvement was observed in all fatigue scales, i.e., in the VAS-F, MFIS, and FSS (each $p = 0.0001$). These lasted up to 48 weeks (Wilken et al. 2013). However, a major limitation of the study was that no control group (placebo or active comparator group) was included so that no final conclusion can be drawn regarding the amount of the drug effect on fatigue.

Iaffaldano et al. (2012) monitored effects of NTC on fatigue and cognition in patients with relapsing forms of MS in a prospective, open-label, observational study across 2 years follow-up. Only after 1 year of treatment, there was a significant reduction in fatigue as measured by the FSS ($p = 0.008$) and in cognitive impairment ($p < 0.0001$). The positive effects were confirmed in a subgroup of patients across 2 years. Thus, evidence for at least a short-term positive effect of NTC on MS-associated fatigue were found in this observational study.

Another prospective, multicenter Scandinavian observational study with single-arm design is the **TYNERGY** trial. Here, patients with relapsing-remitting MS (RRMS) being treated with natalizumab for the first time showed a significant improvement in fatigue, defined as the primary endpoint, across a one-year observation period (Svenningsson et al. 2013). Fatigue was assessed using the Fatigue Scale for Motor and Cognitive Functions (FSMC [Penner et al. 2009]). In contrast to the other fatigue scales, the FSMC allows graduation of fatigue severity into mild, moderate, and severe. In the TYNERGY study, using this graduation was the first trial to describe a clinically relevant improvement in fatigue under NTZ therapy, in terms

of a change of the fatigue category after 1 year of treatment. Another study, based on the same study dataset, investigated whether the improvement in fatigue during NTZ therapy was related to depression and daytime sleepiness. It turned out that after a one-year treatment, the overwhelming majority of patients (>92%) remained stable or improved in their fatigue scores. In parallel, the proportion of patients without depression increased by 17% and those without relevant daytime sleepiness by 13%. Interestingly, the improved depression and sleepiness scores were significantly associated with reduced fatigue (Penner et al. 2015).

However, treatment with NTC does not seem to invariably improve fatigue in MS patients. Thus, in a small cohort of 19 MS patients, no improvement in fatigue was observed after 6 months of treatment, but no significant worsening neither (Khademi et al. 2008). Despite the small number of cases, this observation is interesting due to the fact that NTZ may also be associated with higher levels of proinflammatory cytokines (esp. TNF- and IFN-γ). This finding may illustrate that although we can empirically detect the overall positive effects of natalizumab on MS-associated fatigue and substantiate them in studies, we have not yet understood the CNS intrinsic processes responsible for this phenomenon.

2.4 Alemtuzumab

There is currently no data on alemtuzumab from which its effect on fatigue could be reliably derived. However, in the **CARE-MS II** study, in which alemtuzumab was compared with IFN-1a given after insufficient previous therapies, an improvement in various aspects of quality of life was found, which was also detectable after 2 years. Various scales were used to assess quality of life, such as the EQ5D, the SF-36, and the FAMS (Functional Assessment of Multiple Sclerosis [Cella et al. 1996]). In the FAMS, patients are also explicitly asked about fatigue, so that improved quality of life might also partly be attributed to reduced fatigue (Arroyo et al. 2020). The improvement in quality of life as assessed by FAMS could be confirmed after 5 years follow-up. However, robust data on fatigue, which were collected with a genuine fatigue instrument, are not yet available for alemtuzumab.

2.5 Ocrelizumab

Data about the therapeutic impact of ocrelizumab on fatigue in MS are also currently very sparse. While the two pivotal studies in relapsing-remitting MS **(OPERA I** and **II)** did not include a specific fatigue assessment, and no relevant adverse events concerning fatigue were reported, fatigue was specifically assessed in the **ORATORIO study,** the pivotal phase III study in primary progressive MS (PPMS), using the Modified Fatigue Impact Scale (MFIS). The MFIS score served as one of the secondary patient-reported outcomes (PROs) (Montalban et al. 2017). Thereby, in a post-hoc analysis of the PRO data, it was observed that the MFIS total score remained stable under ocrelizumab across the entire observation period of 120 weeks, while fatigue expression in the placebo group worsened significantly

($p = 0.009$) by approximately two grades on the MFIS scale (Wolinsky et al. 2017). This result provides preliminary evidence that ocrelizumab does not exert a negative effect on fatigue in broad clinical use. However, clinical experience also teaches that a proportion of MS patients on ocrelizumab may transiently develop moderate fatigue, particularly in close connection with the first ocrelizumab infusions. Currently, there is no data documenting an effect of ocrelizumab on fatigue as a direct outcome measure. However, several observational studies are underway in which this topic will be addressed.

2.6 Rituximab

Rituximab is a chimeric monoclonal antibody closely related to ocrelizumab. Rituximab is used as off-label therapeutic in Germany, and in particular for diseases from the neuromyelitis optica (NMO) spectrum (NMOSD) . In other countries, it has also been widely used as disease-modifying therapy of MS. It acts on the CD-20 antibody, thereby inducing a selective depletion of B cells. Controlled data on the effect of rituximab on fatigue in MS do not exist to date. In a Cochrane Review (He et al. 2013), only one randomized and placebo-controlled trial (RCT) with rituximab in 144 adult RRMS patients could be evaluated. Following this study, adverse events with rituximab, including fatigue, occurred particularly in the first 24 hours after the first rituximab infusion. Importantly, the fatigue events proved to be, in the vast majority, of mild to moderate severity.

However, rituximab was investigated in a randomized double-blind phase II study in 30 patients with chronic fatigue syndrome (CFS) (Fluge et al. 2011). Observations across 12 months and after two infusions (500 mg/m ^{2}KOF) showed statistically significant effects on various parameters, which were observed on average across 25 (8–44) weeks. However, the effect in this study occurred with a delay of 2–7 months after treatment onset and did not correlate with the immediately detectable therapeutically induced B-cell depletion. Thus, the primary endpoint, defined as the effect on self-perceived fatigue at 3 months, was not met. The same group reported sustained success across a 36-month follow-up period during maintenance therapy (3–6–10–15 months) in 2/3 of patients (Fluge et al. 2015). However, this effect could not be replicated in a multicenter, double-blind, placebo-controlled follow-up study of 151 patients with CFS (Fluge et al. 2019). Moreover, in a Swedish multicenter open-label phase II study, 75 patients previously on injection therapy were switched to rituximab while assessing fatigue in addition to treatment satisfaction. At 2 years follow-up, no effects on fatigue were detectable (de Flon et al. 2017).

3 Classic Immunosuppressants

In this group of medications, the most important one for MS is **Mitoxantrone**, which is approved for highly active relapsing MS associated with increasing disability. However, there is no controlled data answering the question whether and to

what extent mitoxantrone acts on fatigue. This is also true for **azathioprine,** which is still occasionally used as a back-up drug in MS therapy. For mitoxantrone, a small retrospective observational study is documented with 18 RRMS and SPMS patients who were treated with mitoxantrone for more than 1 year and in whom fatigue was assessed using the FSS scale. At the end of the observation period, fatigue was improved in eight of 18 patients, while it worsened in only three of 18. Secondary influencing factors, however, were not controlled for (Ostberg et al. 2005).

4 New Immunotherapeutics in MS

4.1 Siponimod

Siponimod is a sphingosine-1-phosphate (S1P) receptor modulator that selectively targets S1P1 and S1P5 receptors. In the MS therapeutic spectrum, siponimod is noteworthy as it has been approved in Europe since early 2020 for secondary progressive MS (SPMS) with disease activity as expressed by relapses and/or MRI activity. In the USA, siponimod has already been licensed in March 2019 for adults with all relapsing forms of MS including active secondary progressive MS. The **EXPAND** study (Kappos et al. 2018), which led to its approval, demonstrated a significant positive effect of siponimod on information processing speed as measured by the SDMT (Benedict et al. 2021). The endpoint fatigue was not collected in the EXPAND study. However, fatigue and depression were at the placebo level (9% and 5%, respectively) concerning side effects. Further data on the effect of the drug on fatigue are currently not available.

4.2 Ozanimod

Ozanimod is also a novel S1P receptor modulator that selectively binds with high affinity to sphingosine-1 phosphate receptor subtypes 1 and 5. Ozanimod has been licensed in March 2020 in the USA for the treatment of all relapsing forms of MS (RMS) including clinically isolated syndrome (CIS) and active secondary progressive MS (SPMS) and in May 2020 in the EU for patients with relapsing-remitting MS (RRMS) who have active disease as defined by clinical and/or imaging findings. In the 24-month phase III **RADIANCE** study, which enrolled 1320 patients with active RRMS, fatigue, as assessed in the adverse event spectrum, had a comparably low incidence of 3.9% (for ozanimod 0.5 mg) and 3.7% (for ozanimod 1.0 mg) as the comparator 30 µg interferon beta-1a i. m. (2.7%) (Cohen et al. 2019). However, a specific and objective fatigue instrument was not used in the study. The same holds true for the parallel phase III **SUNBEAM** trial, which followed an identical design as RADIANCE. In SUNBEAM, fatigue did not even appear among the relevant adverse events with an incidence lower than 2% (Comi et al. 2019).

4.3 Ponesimod

Ponesimod is the latest drug in the line of S1P-modulating agents against MS. It has most recently (March 2021) been approved in the USA for relapsing MS (RMS) including CIS syndrome and active secondary progressive MS (SPMS), and it has been licensed by the European Medicines Agency (EMA) in May 2021 for relapsing active forms of MS (RRMS). Like siponimod and ozanimod, ponesimod is a sphingosine-1-phosphate receptor modulator, but selectively targets the S1P1 receptor. In the **pivotal OPTIMUM study,** conducted in a multicenter, randomized, double-blind, parallel-group design against the active comparator teriflunomide in patients with RMS, secondary endpoints included fatigue explicitly assessed with a newly developed instrument, the FSIQ-RMS (Fatigue Symptoms and Impact Questionnaire-Relapsing Multiple Sclerosis). After 2 years of follow-up, ponesimod was significantly superior compared to teriflunomide on fatigue as assessed by FSIQ. The results of the phase III study were recently published (Kappos et al. 2021).

5 Summary

Although the number and the efficacy of immunotherapies available for the treatment of MS have increased significantly over the last decade, the data set on the effect of the various treatments on fatigue remains patchy and poorly supported by controlled data. From the studies reviewed in this chapter, it can be tentatively concluded that glatiramer acetate and natalizumab are most likely to have a positive effect on fatigue in MS patients. For beta-interferons, the study data do not provide consistent guidance. However, clinical experience teaches that one may face interferon therapy to bring about increased feelings of fatigue in individual patients. A discontinuation of interferon and a switch to glatiramer acetate or one of the other oral first-line drugs ("horizontal switch") can therefore be reasonable from the perspective of fatigue prevention. The modern antibody therapies seem to be rather uncritical with regard to triggering or worsening of fatigue. However, short-term fluctuations in fatigue may occur. The current data on ponesimod look promising, although it should be noted that the measurement instrument used for fatigue in the study was novel, and no comparative data are available to date comparing it to other compounds apart from the active comparator teriflunomide from the registration trial. It is therefore a high need for more controlled data to ensure that there is a "real superiority" of ponesimod in terms of fatigue compared to other therapies.

It was stated at the beginning of this chapter that fatigue and depression have a significant impact on the quality of life in people with MS. Therefore, it is important to pay more attention to the potential impact of immunotherapies on these aspects before making treatment decisions. Fatigue and depression should not be considered as secondary domains, but as an integral part of disease manifestation and therapy management. Thus, behavioral aspects should gain importance as primary parameters guiding therapeutic decisions.

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Symptomatic Drug Treatment of Fatigue

D. Woitalla

1 Introduction

Although cognitive impairment and fatigue are among the debilitating symptoms of MS, the evidence of benefit from drug therapies is considered low (Chen et al. 2020). Several reasons can be cited for this. First, most studies aim to reduce MS-specific progression markers, e.g., lesion burden, brain volume, disability level, which are defined as the primary targets of the studies for this reason. In contrast, cognitive impairment or fatigue is rarely considered as endpoints in phase III trials, and if so, only as secondary endpoints. At the same time, it should be noted that progression slowing does not automatically correlate with an improvement in cognitive symptoms and fatigue.

Also, most studies conducted to date on the question of drug therapy for MS fatigue are characterized by low case numbers or other design flaws. The use of patient-centered evaluation tools to analyze disorders that make it difficult to objectively assess findings, as is the case with MS-associated fatigue, is generally not well accepted in the scientific world and carries the risk of a high placebo effect, which can usually be demonstrated in all studies on the treatment of primary or secondary fatigue syndrome (Beth Smith et al. 2015). This is complicated by the lack of acceptance of an evaluation tool to assess the severity of fatigue, which would also need to take into account the specific characteristics of the disabilities associated with MS to allow an assessment adapted to the degree of motor disability (Braley et al. 2012; Walker et al. 2019).

Drug treatment of MS-associated fatigue should take into account the multicausality of fatigue. This includes in particular the occurrence of sleep disorders and

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depression, which must be taken into account in the selection of drug therapy methods. A careful evaluation of the patient is therefore the basis of every therapy in order not to overlook possible causal therapy options. An example of this is nocturnal urge incontinence, as a result of which night sleep is not restful and the resulting daytime tiredness can lead to confusion with fatigue symptoms.

For a better overview, the possible drug therapy approaches presented in the following have been classified in the context of the pharmacological principle. Strategies are also presented which did not show convincing evidence in the studies but which, in the author's opinion, can be considered in the context of individual case decisions.

2 Symptomatic Therapeutic Approaches

Outside of specific therapeutic procedures, the treatment of competing causes is the basis of any therapy. The following diseases/conditions should be excluded or causal treatment initiated:

Anemia
Hypothyroidism
Kidney function
Liver function
Infections
Vitamin D deficiency
Lung diseases
Drug effects (e.g., sedatives)
Restless legs syndrome
Difficulty falling asleep
Sleep apnea disorder
Nocturia

In particular, acute onset fatigue should lead to exclusion of an acute MS relapse by MRI scan (Veauthier et al. 2016).

Various medications used to treat MS and its accompanying symptoms can also cause fatigue. For this reason, critical reflection on the potential side effects of medications already prescribed is an important prerequisite for further therapeutic considerations.

3 Drug Treatment Approaches

A complete overview of all studies conducted to date on the treatment of fatigue is not possible, as the intention of the therapy is often hidden behind other neurocognitive parameters. The NIH (www.clinicaltrials.gov) lists a total of 59 completed

interventional studies in which the treatment of fatigue in MS is explicitly stated as a treatment goal. Of these, 19 studies investigated the effect of drug therapies, of which seven studies have published results (as of August 2020). In summary, on the basis of these and other studies not listed with the NIH, there are some promising treatment approaches, the evidence for which, however, has not yet been sufficiently proven.

4 Immunological Treatment Approaches

4.1 Cytokines

Among the immunomodulating signal substances, tumor necrosis factor-alpha (TNF-α) plays a prominent role. TNF-α acts essentially via two receptors (TNF-R1 and TNF-R2), which activate the transcription factor NF-B via various intermediate steps (Rahman and McFadden 2006). The effects of TNF activity vary from organ to organ. In the hypothalamus, stimulation of the hypothalamic-pituitary-adrenal axis results from increased release of CRH ("corticotropin-releasing hormone"). In the liver, it leads to increased formation of acute-phase proteins, which in turn result in cognitive modulatory effects in a range of immunological disease (Beste et al. 2014). Glial activation and secondary influences on mitochondrial homeostasis have also been causally related to fatigue (Morris et al. 2015). Ultimately, however, the undoubted link between the activity of immunomodulatory cytokines and their influence on neurocognition or fatigue remains unexplained.

Various drugs have an inhibitory influence on the release of TNF. These include in particular the substances used in rheumatism therapy, etanercept, infliximab, adalimumab, golimumab, and certolizumab. Positive effects have been identified with these substances in the treatment of rheumatism-associated fatigue (Almeida et al. 2016).

Based on the observation of increased TNF-mRNA expression in MS patients with fatigue (Heesen et al. 2006; Flachenecker et al. 2004) and the positive experience with the use of TNF inhibitors in isolated CFS (Vgontzas et al. 2004) as well as the abovementioned rheumatism-associated fatigue, a positive effect on fatigue could be assumed.

However, in a phase II study on the effect of Lenercept, this substance showed no effect over placebo in the three doses tested (10, 50, and 100 mg) over 4 weeks. On the contrary, the group treated with the substance showed a worsening of the disease parameters including fatigue (Group TLMSSG and TU of BCMA 1999).

No studies are available on the other substances.

In conclusion, it remains open which TNF inhibitors can contribute to an improvement of fatigue in MS, regarding different disease conditions. At present, there is insufficient evidence to justify the routine clinical use of these substances in MS.

Other MS-specific disease-modifying therapies have already been discussed in detail in Chap. 14.

5 Immunosuppressive Therapies

5.1 Cortisone

The effect of intravenous cortisone in the context of acute relapse treatment was also described by Flachenecker and Meissner (Flachenecker and Meissner 2008) in the context of a single case observation with regard to the positive effect on fatigue. Controlled studies on the prolonged use of cortisone are not available; the endocrine treatment aspects are discussed in the following chapter. Due to the spectrum of side effects of long-term cortisone therapy, the risk/benefit assessment speaks against the indication of such therapy to improve fatigue.

6 Endocrine Treatment Approaches

Among the endocrine mechanisms, strategies to compensate for the hypothalamic-pituitary-adrenocortical axis (HPA) (Cleare 2004) and the hormone dehydroepiandrosterone (DHEA) (Maes et al. 2005) have been particularly studied. Involvement of the HPA has been demonstrated in several autoimmune diseases linked to the occurrence of fatigue (Chen and Parker Jr 2004). Decreased serum DHEA concentrations have also been detected in MS with fatigue (Téllez 2006), so that a hormonal affection and its therapy must be counted among the hypothetical therapeutic approaches for the treatment of fatigue.

6.1 Hydrocortisone/Fludrocortisone

The substitution treatment with hydrocortisone pursues the compensation of a postulated cortisol lowering due to a primary disturbance of the hypothalamic-pituitary-adrenocortical axis (HPA). Although a positive effect on fatigue is reported by many patients on therapy with cortisone even at low doses, no effect was shown after administration of hydrocortisone (13 mg/m ^{2} KOF) and placebo over an observation period of 12 weeks in patients with CFS (McKenzie et al. 1998). Further studies could also show no effect on CFS symptoms in combination treatment with fludrocortisone (Blockmans et al. 2003), in contrast to preclinical non-blinded studies that investigated an effect of 0.1–0.2 mg fludrocortisone (n = 25) and showed a positive effect over 6 weeks (Petcrson et al. 1998).

In summary, therapy with hydrocortisone cannot be recommended with the exception of the proven disturbance of the HPA.

6.2 ACTH

In a smaller study (RCT; n = 8), the effect of ACTH (40 IU BW) over 28 weeks versus placebo on fatigue in MS was investigated and various variables were determined. The scales studied (MFIS, FSS) showed a significant effect of the

ACTH-treated group (MFIS: MW 56.50 [21–74] versus 29.00 [5–74]; FSS: MW 55.00 [25–63] versus 40.00 [25–57]) with positive effects in the secondary outcome variables (BDI-II [16.5 versus 40.00], ESS [11 versus 7], and SF-36 [39.5 versus 49.0]). The results are only available to date on the NIH site (NCT02315872).

6.3 Alfacalcidol

Alfacalcidol is a precursor of calcitriol (vitamin D), which is metabolized in the liver to the active vitamin.

In a smaller randomized double-blind placebo-controlled trial (n = 158), which included patients with significant fatigue listed in an MS registry (n > 600) as the cohort basis (Achiron et al. 2015), there was a positive outcome in the alfacalcidol (1 mcg/d) treated group. The FIS score improved by at least 30% (cut-off point) in the verum group in 41.6% compared to 27.4% of placebo-treated patients.

Taking into account that vitamin D levels are reduced in 90% of MS patients (Kępczyńska et al. 2016), another study confirmed the association between vitamin D supplementation and a positive effect on fatigue in 149 patients, 90% of whom were shown to be vitamin D deficient (Beckmann et al. 2020). It remains unclear whether the effect of vitamin D or its precursor alfacalcidol is more symptomatic or whether the substitution of vitamin D deficiency leads to an improvement in fatigue.

Substitution with vitamin D or its precursor should be considered in every patient and, in our opinion, is too rarely considered in practice.

7 Neurotransmitter-Oriented Treatment Approaches

A number of different neurotransmitters are involved in the regulation of the sleep/wake rhythm (e.g., adenosine, benzodiazepine, dopamine, GABA, histamine, melatonin, norepinephrine, orexin, and serotonin), the influence of which on medication has been investigated in various studies.

7.1 Amantadine

Amantadine is approved for the treatment of influenza and Parkinson's disease. The substance has a low potential for side effects (Khazaei et al. 2019) and is usually well tolerated. Amantadine blocks the NMDA receptor and thereby indirectly affects various transmitter systems. The effects on fatigue are not clear, a connection with the amphetamine-like effect is discussed (Generali and Cada 2014).

A beneficial effect of amantadine has been demonstrated in numerous MS fatigue trials (Khazaei et al. 2019, Generali and Cada 2014, Shaygannejad et al. 2012, Ledinek et al. 2013, Cohen and Fisher 1989). The 2010 Cochrane analysis had found superiority of amantadine over placebo, but the level of evidence was considered weak due to methodological weaknesses and small number of cases in most studies (Peuckmann-Post et al. 2010, Taus et al. 2003). The Cochrane analysis from

2015 evaluates amantadine as significantly better effective on fatigue symptoms than placebo (Mücke et al. 2015). Other authors conclude in a meta-analysis that amantadine does not show a significant effect against placebo in the studies examined and that the benefit is less than that of rehabilitative interventions (Asano and Finlayson 2014). Even taking into account new studies, the data on amantadine therefore remain inconsistent.

At the time of writing, the results of the comparative study between methylphenidate, modafinil, and amantadine (TRIUMPHANT-MS) (Nourbakhsh et al. 2018) had not yet been published, which may provide new insights into the benefits of amantadine therapy due to the primary endpoint and cohort size.

Despite the unclear data situation, a therapy trial with amantadine can be considered as an off-label therapy. The drug is well established in Parkinson's therapy and is characterized by a low side effect profile. Attention should be paid to QT time before starting treatment.

7.2 Ketamine

The effects of ketamine are based on blockade of the ionotropic NMDA receptor and therefore exert their effect via glutamatergic transmission. At the same time, it has a modulating and activating effect on GABA-A receptors and a weak agonistic effect on opioid receptors. Another effect is to inhibit the reuptake of catecholamines such as norepinephrine and dopamine. There are different theories about the cause of the rapid onset antidepressant effect (Yang et al. 2018 u. Artigas et al. 2018).

The intravenous administration (0.5 mg/kg) of ketamine versus midazolam (0.05 mg/kg) was investigated in a double-blind RCT in a total of 18 subjects (12: 6) (NCT03500289). The results of the study showed no significant benefit compared to midazolam, but this may be due to population size.

Ketamine, in the form of the eutomer (S)-ketamine (Spravato®), has been available in the EU for the treatment of treatment-resistant depression since December 2019.

7.3 Modafinil

Modafinil and the (R)-enantiomer armodafinil are substances that increase vigilance due to effects that have not yet been fully clarified. Armodafinil differs from modafinil in that its elimination half-life is three times longer; it has so far only been approved in the USA.

Modafinil improves alertness in a variety of species, including humans. The exact mechanism of action by which modafinil promotes wakefulness is unknown. Modafinil, unlike classic psychomotor stimulants, acts predominantly on brain regions responsible for the control of waking, sleep, wakefulness, and vigilance. The wakefulness-promoting effects of modafinil are antagonized by D1/D2 receptor antagonists, indicating that modafinil has indirect agonist activity at dopamine

receptors. Modafinil also binds to the norepinephrine transporter and inhibits norepinephrine reuptake.

The effect of the substances has been studied for various disorders with excessive sleepiness. These include idiopathic hypersomnia, obstructive sleep apnea syndrome, shift worker syndrome, and narcolepsy. Due to a more stringent risk assessment, the indication was limited to the use in adults with excessive sleepiness associated with narcolepsy, with and without cataplexy (BfArM communication of 18.03.2011).

The recommended daily dose to start is 200 mg. The total daily dose can be taken either as a single dose in the morning or divided into two doses (one in the morning and one at noon), according to the physician's assessment or the patient's response. The dose-response profile of modafinil appears to be non-linear according to various studies. In fact, no statistically significant difference was found in any of the measurements between the two applied doses of modafinil (200 mg and 400 mg) for the treatment of narcolepsy.

Modafinil shows a number of side effects, some of them serious, which led to a critical reassessment of the substance. These include in particular skin and hypersensitivity reactions (in part life-threatening), diseases of the nervous system (seizures, extrapyramidal symptoms, cerebrovascular events), psychiatric disorders (aggression, psychoses, depression), and cardiovascular diseases. In connection with the use of modafinil, dependence and the development of tolerance have been described in many cases.

Based on new findings, it is also suspected that the use of modafinil and armodafinil during pregnancy may lead to severe congenital malformations. Modafinil and armodafinil should therefore not be used during pregnancy. Patients of childbearing age who are treated with modafinil or armodafinil must use an effective method of contraception.

Two studies have been conducted on the treatment of fatigue in MS that showed no significant benefit against placebo (Stankoff et al. 2005, Rammohan et al. 2002). Another study ($n = 33$ DB RCT CO) (NCT 00981084) on the benefit of armodafinil showed a significant benefit on cognition (RVLT), but not on the other parameters investigated in the study.

Modafinil use is nevertheless recommended by some experts when other interventions fail. A 2017 analysis of modafinil prescribing patterns concluded that modafinil is prescribed in 30% to 59% of cases for off-label indications, of which 20% relate to multiple sclerosis and here presumably to the treatment of fatigue (Fritze et al. 2017). In any case, when prescribing modafinil, a careful benefit-risk assessment and appropriate patient education is required.

7.4 Ondansetron

The effect of ondansetron is based on its antagonistic action via selective blockade of the central 5-HT_3receptors. Due to its antiemetic effect, it is used for the treatment of tumor-associated nausea.

Considerations for the use of ondansetron for the treatment of fatigue result from the observation of a reduction in fatigue after administration of ondansetron in various liver diseases in which the substance is used to treat pruritus (Piche et al. 2005; Jones 2008).

Ondansetron was tested against amantadine in a comparative study (RCT CO; $n = 53$; 2 × 4 mg/die; 4 week) and showed a weaker, yet significant, benefit for the treatment of fatigue as measured by the FSS (Khazaei et al. 2019).

Ondansetron provides a therapeutic approach that requires further evaluation.

8 Treatment Approaches with Channel Blockers

8.1 Fampridine (Syn. 4-Aminopyridine)

Fampridine acts as a reversible potassium channel blocker, stabilizing intracellular potassium levels. Fampridine is approved as a drug to improve walking ability in all courses of MS. Due to its effects on various neurophysiological parameters (nerve conduction, action potential, synaptic transmission), positive effects on further clinical symptoms have been postulated (Kim et al. 1980; Shi and Blight 1997).

In an earlier study by Rossini et al. (2001), a positive effect on fatigue could only be observed in patients in whom a high serum concentration (>30 ng/ml) was detectable. Further studies also showed an effect only in a part of the investigated subjects. Fampridine shows positive effects on a variety of cognitive and psychological parameters (Allart et al. 2015; Pavsic et al. 2015; Ruck et al. 2014; Arreola-Mora et al. 2019). In contrast to the antidepressant effects, this effect correlates with the improvement in walking ability (Jongen et al. 2014).

An attempt at treatment appears to be justified; care should be taken to ensure an adequate dose.

9 Treatment Approaches with Stimulants

9.1 L-Amphetamine

A total of three studies were conducted on the benefit of amphetamines. In one RCT (n = 136) of cognitively impaired patients, no significant treatment effect was observed compared to placebo. Further data analysis showed effects in patients with significant impairment, so that it is possible to speculate about a dependence of therapy effects on the extent of pathological impairment. An RCT with a single dose of amphetamine (45 mg) showed significant effects on information processing tests (PASAT, SDMT, and Part A of the Trail-Making Test [Cohen's $d = 0.36–0.45$]), but no changes in memory function. Lower doses (15 mg, 30 mg) showed no effects on cognition in this study (Benedict et al. 2008; Sumowski et al. 2011).

9.2 Methylphenidate

Methylphenidate, like L-amphetamine, is used to treat ADHD.

The substance has so far only been investigated under the aspect of attention enhancement in MS and showed a significant effect in the 26 patients studied (Harel et al. 2009). To what extent the effects can be transferred to fatigue symptoms cannot be answered from the study.

In summary, contradictory results emerge from the various studies on the efficacy on fatigue under amphetamines. A benefit of the therapy cannot be excluded.

10 Antidepressant Therapy Methods

Depressive states can cause fatigue and should therefore always be excluded (Veauthier et al. 2016). The scales for assessing depression must be adapted to the specific conditions of MS (Patten et al. 2015).

The benefit of antidepressant therapy for the treatment of classic CFS has been widely investigated, but only a few conclusive studies are available for MS-associated fatigue. The indication for therapy is derived from the symptomatic effect of the depressive cardinal symptoms, which basically also include the disturbance of the drive. At the same time, the reactive depressive components are addressed, which result from the psychosocial consequences of an at least potentially disabling illness.

There are also no studies with high evidence for the treatment of depression in MS (Carta et al. 2018; Koch et al. 2011). The same applies to fatigue treated by antidepressants.

Drug-based antidepressant therapies can be subsumed under neurotransmitter-based therapies; for content considerations, they are presented here.

10.1 Selective Serotonin Reuptake Inhibitors (SSRI)

SSRIs are also considered a “first-line” treatment for depression in MS (Koch et al. 2011; Pérez et al. 2015). Studies on the change in fatigue in relation to studies of the motivational system (Behavioral Inhibition System and Behavioral Activation Scale [BIS/BAS]) were able to show a positive effect on fatigue under treatment with bupropion, demonstrating superiority over escitalopram (Pardini et al. 2013).

In a double-blind, placebo-controlled study over 12 weeks, no benefit of paroxetine over placebo could be demonstrated with paroxetine (Ehde et al. 2008). This also applies to fatigue, which was also investigated.

A double-blind, multicenter study of the benefits of fluoxetine, whose primary objective was to reduce disease progression, also failed to demonstrate an effect on fatigue symptoms over a 12-week period (Cambron et al. 2019). The authors explain this result with a different disease dynamic in the treatment groups, which possibly overlapped the effects.

In a three-arm study, sertraline was examined against cognitive behavioral therapy and a group-based psychotherapy approach (Mohr et al. 2003). The positive effect that this study demonstrated in the treatment arms was, according to the authors, caused by an influence on depression that correlated with the other parameters.

In summary, the studies conducted to date are not suitable to demonstrate an original effect of antidepressant therapy on fatigue symptoms.

11 Other Drug Therapy Approaches

11.1 Ginseng

The effects of ginseng (100 mg/die) were investigated in a smaller RCT. This showed no effect compared to placebo (Kim et al. 2011).

11.2 N-Acetylcysteine

Acetylcysteine acts as a radical scavenger and has antioxidant properties. It is a prodrug of the amino acid L-cysteine which is a component of the endogenous glutathione. Due to its property of cleaving disulfide bridges, it is used as a secretolytic. The antioxidant effect is derived from the reactive SH group of the molecule (Origuchi et al. 2000). Effects on psychiatric diseases have been investigated in various studies (Berk et al. 2008).

In a smaller study (DB RCT PG SC; n = 15 [10: 5]; study duration 4 weeks; 3 x 1250 mg/die, NCT 02804594), there was no effect under N-acetylcysteine in MFIS (−11.4 ± 14.9 versus −18 ± 15.4).

11.3 Pemoline

Pemoline is a drug with stimulant effects comparable to amphetamines. Pemoline was withdrawn from the market in 2009 due to liver toxicity. Two studies on the treatment of fatigue in MS showed no benefit over treatment with amantadine (Weinshenker et al. 1992; Krupp et al. 1995). Due to the withdrawal of the substance, it will not be discussed further here.

11.4 Carnitine

Carnitine has an essential role in energy metabolism. It reacts with fatty acids, whereby these are activated. Only in connection with carnitine they can be transported from the cytosol into cell organelles, with the mitochondria taking a prominent position in the context discussed here. Carnitine occurs in two isoforms, of

which L-carnitine is one. In the human body, carnitine is formed from the amino acids methionine and lysine. The effect of carnitine is linked to the presence of coenzyme A.

Metabolic studies show reduced phosphocreatine concentrations in patients with MS (Kent-Braun et al. 1994), this effect has been associated with muscular fatigability (Sharma et al. 1995) and secondarily perceived fatigue (Kent-Braun et al. 1993). The use of L-carnitine in the treatment of children with neurological disorders who have impaired drive (Plioplys et al. 1994) and the observation of a positive effect in the treatment of CFS (Plioplys and Plioplys 1997) encouraged the investigation of the effect in MS patients.

In a double-blind cross-over study, the effect of acetylated L-carnitine (1 g × 2/day) was compared with the effect of amantadine (100 mg × 2/day) over a period of three months with a three-month washout period ($n = 36$). Statistically significant effects ($p = 0.039$) were found in the FSS compared with amantadine, with L-carnitine being better tolerated overall, but not in the other scales studied (FIS, BDI) (Tomassini et al. 2004).

Even though this study has limitations regarding the number of subjects and the observation period, it supports the hypothetical benefit of carnitine substitution. Against the background of the scientific evidence of biochemical changes in MS patients, a symptomatic therapy trial with L-carnitine seems worth considering.

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Non-drug Treatment Approaches and Neurorehabilitation

M. Sailer, C. M. Sweeney-Reed, and J. Lamprecht

1 Introduction

Multiple sclerosis is characterized by a heterogeneous array of symptoms. Fatigue, reported by up to 80% of patients, is among the most frequent complaints (Simmons et al. 2010). The associated deficits described include memory and concentration disturbances, physical limb impairments, and sensitivity to heat. The effects of fatigue symptoms on physical and psychological functioning often result in a lasting negative impact on the quality of life of those affected and are among the leading causes for early retirement (Simmons et al. 2010).

Before fatigue can be treated, other potential causes must first be excluded. The differential diagnosis of fatigue includes sleep disorders, depression, medication side-effects, as well as other medical conditions (endocrinological, hematological, metabolic, etc.), all of which may result in secondary fatigue. Furthermore, a distinction should be made between fatigue ("trait fatigue") and fatiguability ("state fatigue" or "fatiguability"). Fatigue represents the general, global state of the patient, which changes little over time. Fatiguability, on the other hand, represents the current state during intense motor, cognitive or psychosocial stress and has been the subject of few studies to date. The instruments available for the assessment of fatigue predominantly measure the general condition ("trait fatigue") of the patient

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such as through self-evaluation scales. Objective measurement parameters that could also be used for therapy monitoring are the subject of current research.

As a result of the lack of systematic etiological classification as well as the ambiguous pathogenesis of fatigue, the primary aim of treatment is a successful, multidisciplinary symptom management based on a holistic approach.

Differentiation between motor and/or cognitive fatigue, as well as a distinction from fatigability, has not been consistently made so far when considering therapeutic concepts, especially given the lack of objective measurement instruments. The effectiveness of the treatment options for fatigue reported in the following is therefore chiefly presented in a global sense.

Current clinical treatment recommendations include pharmacological, educational, and rehabilitative interventions. The effectiveness of these three treatment options has been examined in a meta-analysis (Miho and Finlayson 2014). In a total of 18 rehabilitation and seven pharmacological studies focusing on fatigue, rehabilitative measures had a significantly greater impact on subjectively perceived fatigue severity than drug therapy (e.g., with amantadine and modafinil). Non-pharmacological treatment approaches for fatigue were concluded to represent the treatment of choice (Miho and Finlayson 2014; Henze et al. 2018). Recommended treatment options include exercise therapy, whole-body cryotherapy (WBC: lowering body temperature by cooling the body), and psychological and educational interventions. The National Institute for Health and Clinical Excellence (National Institute for Health and Care Excellence 2007) primarily recommends graded exercise therapy and cognitive behavioral therapy in the treatment of patients with mild to moderate fatigue. These findings have also been supported in Cochrane reviews (Price et al. 2008; Larun et al. 2019) and a large randomized, controlled trial (White et al. 2011).

2 Exercise Therapy

Various direct and indirect mechanisms of MS, as well as the frequently resulting physical inactivity, influence the extent of fatigue. Exercise therapies can induce physiological and psychological changes that counteract these mechanisms. On the one hand, improved cardiorespiratory fitness could result in an increase in available energy reserves. On the other hand, neuroprotective mechanisms and normalization of the hypothalamic-pituitary-adrenocortical axis may result in a reduction in MS-related fatigue (Heine et al. 2015). The prerequisite is that the exercise therapy is of sufficient duration, dose, and intensity. Exercise therapy is generally divided into resistance training and endurance training. Resistance training usually involves a training frequency of 2–3 days per week, is well-tolerated by patients, and leads to meaningful improvements (Dalgas et al. 2009). In general, a total body program comprising four to eight types of exercises is recommended, with priority given to the lower extremities (due to the greater strength deficit). The frequency of endurance training, on the other hand, should be two to three sessions per week, with an initial exercise duration of 10–40 min (Dalgas et al. 2009). For example, a

three-week training program, with five 60-min sessions per week, including 30 min of cycling at the individually determined lactate threshold, led to a significant reduction in fatigue.

A combination of both forms of training in equal proportions is particularly recommended. In a meta-analysis including a total of 45 studies, the effects of endurance training, muscle strength training, task-oriented training, as well as mixed and other forms of training (e.g., yoga, robot-assisted training, balance training, tai chi) on fatigue were investigated (Heine et al. 2015). A significant (moderate) effect was shown in favor of exercise therapy compared to control groups without exercise therapy. Taking into account the different types of exercise therapy, a significant effect was also demonstrated in favor of endurance training, mixed training, and special types of training (yoga, tai chi).

Exercise therapy presents difficulties for patients with limited movement capacity, however. Preliminary studies have indicated that cycling induced by functional electrical stimulation could result in a reduction in fatigue (Pilutti et al., 2019). Randomized, controlled trials are still required to investigate this possibility further. Additionally, further specific programs to reduce fatigue in patients with limited mobility are under evaluation, such as, for example, the use of imagined movements.

3 Cryotherapy

An increase in body temperature of 0.5 °C already leads to undesirable clinical symptoms in around 60–80% of MS patients (Guthrie and Nelson 1995). Furthermore, in a cross-sectional study including 50 patients with relapsing remitting MS (RRMS), the patients showed a raised body temperature compared to healthy, age-matched controls, which correlated with fatigue. Body temperature can be increased by physical exertion, sun, infrared light or hot baths, for example. Few studies have addressed interventions to reduce body temperature to date. Different approaches to WBC have been associated with subjective improvements in fatigue, however. Most studies have used cooling garments (with circulating cooling fluid or cooling packs) or skin contact with cooling fluids and surfaces. In a systematic review, exercise-induced hyperthermia was shown to be treated effectively with cold therapy (high-dose approximately 12.8 °C, low-dose approximately 21.1 °C) without side-effects, and significant improvements in physical functioning levels (especially walking) and fatigue were demonstrated (Kaltsatou and Flouris 2019). Core body temperature can be reduced between 0.37 and 1 °C within 30 min to 1 h after cooling. The effect on fatigue (outcome: “Modified Fatigue Impact Scale”; “Rochester Fatigue Diary”) before and after wearing a cooling vest for 1 h a day (in the morning) for 4 weeks with high-dose cooling was examined, among other things, in a randomized, controlled study (Schwid et al. 2003). Compared to the control group without cooling, the intervention group showed a significant decrease in subjectively-assessed fatigue symptoms.

4 Training and Empowerment

A diagnosis of MS is associated with a multitude of uncertainties regarding the course, prognosis, and disease-modifying therapies. Patients need adequate information in order to be able to participate actively in medical decision-making and, at the same time, to increase their sense of self-sufficiency. The latter factor ultimately also contributes to higher patient compliance. Approaches for improving disease-related knowledge were evaluated in a systematic review that included ten randomized controlled trials of information provision in MS with a total of 1314 participants (Köpke et al. 2014). With regard to fatigue, the greatest effect was achieved through special fatigue management programs. These programs provide, among other aspects, information regarding pharmacological treatment, nutrition, involvement of the social environment, sleep, exercise, relaxation, and cooling techniques, as well as advice on the use of assistive devices and adaptation options for the living or working environment (Kos et al. 2007). The essential core element of the training, however, is the teaching of strategies to save energy. The aim is to reduce energy consumption by modifying daily activities, which are systematically analyzed in advance (Mathiowetz et al. 2005). Usually, the training takes place for 2 h per week over a period of about 5 weeks. A randomized controlled trial showed that the trained energy-saving methods have a significant positive influence on the perceived physical and social effects of fatigue, as well as on quality of life and self-sufficiency (Jalón et al. 2013).

5 Cognitive Behavioral Therapy

Cognitive behavioral therapy (CBT) addresses the inter-relationship between physiological, behavioral, cognitive, emotional, and social factors that are considered instrumental in symptom management. The essence of CBT is to help patients understand and modify their behavioral and cognitive capabilities. The approach primarily involves changing avoidance behaviors, unhealthy sleep patterns, and negative beliefs related to the disorder (Burgess 2012). The basis for the development of CBT for the treatment of MS-related fatigue is the model of van Kessel and Moss-Morris (2006). The authors hypothesize that primary disease factors trigger initial fatigue, but the subsequent course of fatigue and the extent to which fatigue affects daily life depend on the interacting cognitive, emotional, behavioral, and biological responses of the individual. For example, people with MS who are more prone to perceiving events as catastrophic, are embarrassed by their condition, or believe that symptoms are always a sign of further physical impairment are more likely to perceive fatigue-related impairment (van Kessel and Moss-Morris 2006). Furthermore, two independent patterns of behavior have been recognized in dealing with fatigue: constant resting and limiting of activities, or all-or-nothing behavior, when sufferers are overly active at times when they are well (van Kessel and Moss-Morris 2006). A meta-analysis has been performed to examine the short- and longer-term effects of

CBT on the treatment of MS-related fatigue (van den Akker et al. 2016). The analysis encompassed four studies with a total of 403 MS patients and showed significant short-term effects (8–10 weeks after treatment). In three studies, a long-term effect (8–12 months after treatment) was also demonstrated. Whether the contact took place "face to face" or on the telephone was immaterial. The interventions included creating an activity plan (rest vs. activity phases), recognizing and dealing with stressors and difficult feelings, learning helpful thoughts, improving sleep behavior, and improving the patient's own understanding of their illness. Compared to the contents of the classical patient training, the contents taught here are practiced in a targeted manner in order to bring about a lasting change in behavior.

6 Nutrition

Obesity and excessive salt consumption have been shown to have a negative impact on the course of the disease (Gröber 2019). Although there are no robust data to date suggesting a specific dietary pattern for MS, there is evidence that an anti-inflammatory, vegan-oriented, low-carbohydrate diet can positively influence the course of the disease (Schwarz and Leweling 2005). Plant-based diets consisting of vegetables, legumes, and whole grains are particularly recommended, which stimulate the proliferation of protective bacteria and strengthen the intestinal barrier (Gröber 2019). A review of a total of 21 studies examined the extent to which anti-inflammatory diets have an impact on the inflammatory profile and can reduce fatigue symptoms (Haß et al. 2019). Although the available research provides clues rather than evidence, it showed that a balanced diet with whole grain products, high fiber content, and omega-3 fatty acids leads to a reduction in perceived fatigue symptoms. Specific nutrient deficiencies are also sought that may contribute to symptoms such as fatigue in MS, which could potentially be addressed through dietary supplements. Zinc is a trace element that is required for diverse proteins, enzymes, and transcription factors, and an association has been established between zinc and autoimmunity. Low zinc levels observed both in MS patients and also in patients suffering from chronic fatigue syndrome suggest the investigation of zinc as a potential supplement. A randomized controlled trial examined the clinical and metabolic effects of a low-fat, plant-based diet and its impact on fatigue and quality of life (Yadav et al. 2016). In both the control and intervention groups, patients were also instructed to perform 30 minutes of moderate-intensity activity five times per week. No differences were observed between the control and intervention groups in MRI, number of MS relapses, degree of disability, or adherence to physical activity. However, there was a significant improvement in blood lipids and insulin levels and a decrease in fatigue symptoms over a 12-month period. The adherence of patients in the intervention group to the diet was also good. However, it must be taken into account that recommendations regarding dietary behavior in MS should only be understood as supplementary.

7 Non-invasive Brain Stimulation

Non-invasive brain stimulation includes techniques to modulate cortical excitability and induce functional changes in brain structures and functional neural networks. A potential therapy using transcranial direct current stimulation (tDCS) or repetitive transcranial magnetic stimulation (rTCS) in fatigue has been mainly investigated in small studies (Liu et al. 2019; Tecchio et al. 2014; Liepert et al. 2005). The approach is based on the etiological concept that there is a link between fatigue symptoms and structural or functional changes in various neural networks. Despite some positive indications, there is as yet no generally applicable or evidence-based recommendation for the implementation of tDCS and rTCS for fatigue in MS (Iodice et al. 2017).

8 Neurorehabilitation

Non-pharmacological treatment approaches are usually delivered in a multimodal, structured neurological rehabilitation program that lasts several weeks. In this context, both outpatient and inpatient services may contribute equally to a longer-term improvement in activities and societal participation (Amatya et al. 2019). Inpatient medical rehabilitation is often of particular importance, however, due to the lack of MS-specific outpatient care structures. A distinctive feature of rehabilitative services is the compilation of an individually adapted, multidisciplinary, task- and goal-oriented therapy program through a comprehensive assessment of functional disorders and personal needs (Beer and Kesselring 2001). This approach is particularly important in the management of MS due to the different potential courses of the disease and the broad spectrum of disabilities. By using the entire spectrum of therapeutic services (physiotherapy, including sports and exercise therapy, occupational therapy, speech therapy, cognitive and psychological therapies, as well as provision of information about the disease and how to cope with it in the context of training sessions), the functional limitations of those affected can be reduced and the development of further, secondary sequelae potentially averted. The training sessions usually take place in groups and include sports and water therapies, adapted ergometer, movement, and walking training in the aerobic range (30 min a day for 4 weeks), as well as medical training therapies. The treatment effect may be longer-lasting compared to outpatient physiotherapy or individual forms of exercise alone (Beer and Kesselring 2001). In addition, neurological rehabilitation can contribute to a reduction in direct and indirect medical costs. Another new approach to address symptoms such as tiredness is the use of mobile electronic devices. A recent review, which included 30 studies and 3091 patients, concluded that a moderate effect on fatigue could be achieved (Bonnechère et al., 2021). The continued application in everyday life of the exercises learned and the information content acquired is also essential for the sustainability of rehabilitation. Here, special aftercare programs or targeted home training (e.g., Exergames, Thomas et al. 2015) can provide helpful support.

9 Summary

The complex and multifactorial etiology of fatigue in individuals with MS often permits only limited therapeutic options. The differential diagnosis includes a range of potential concomitant factors whose exclusion is relevant for optimizing the individual rehabilitation plan. Currently, an individual approach, based on a multidisciplinary therapy concept, in which non-pharmacological therapy is in the foreground, represents the therapy option of choice. The development and application of clinically meaningful assessments for more precise classification and objective quantification of symptoms and their evolution over time may enable further individualization of therapy in the future and thus improve its efficacy.

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